INCONTINENCE

EDITORS
PAUL ABRAMS - LINDA CARDOZO - SAAD KHOURY - ALAN WEIN

4th International Consultation on Incontinence, Paris July 5-8, 2008

4th EDITION 2009
Acknowledgement

We would like to thank:

• The Bristol Urological Institute and

• The Urology Department at La Pitié Hospital in Paris and its chairman Professor F. Richard

for kindly providing logistic assistance for the editing of this book.

We would also like to thank all the contributors for their enthusiastic support and help.

For information and orders:

Distributor: EDITIONS 21
76, rue de la Pompe - 75016 Paris - FRANCE
Fax: +33 1 45 04 72 89   E-mail: editions21@wanadoo.fr

© Health Publication Ltd 2009

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior permission of the publisher.

Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

The Publishers have made every effort to trace the copyright holders for borrowed material. If they have inadvertently overlooked any, they will be pleased to make the necessary arrangements at the first opportunity.

The great tragedy of science:
The slaying of a beautiful hypothesis by an ugly fact
Thomas Huxley (1825-1895)

ISBN 0-9546956-8-2

LAY-OUT: Stéphanie Taïeb
FOREWORD

The First International Consultation on Incontinence held in 1998 highlighted the plight of some 200 millions sufferers from urinary incontinence worldwide. Urinary incontinence represents a particular and severe problem in certain developing areas of the world, where labour and birth injuries lead to catastrophic leakage. Untreated vesico-vaginal fistula (VVF), particularly in sub Saharan Africa, affects millions of women causing ostracism from society. Because of the enormity of this particular problem, at the second consultation we added a specific committee to highlight the subject, to advance the understanding of the causes of birth injury, to lead to improved treatment for the many untreated women, and most importantly, to begin preventative programmes. At this Fourth Consultation we were delighted by the active participation of the WHO in our work on VVF.

There were two other new committees in the 2nd ICI: Pelvic Organ Prolapse and Faecal Incontinence. The first consultation stressed the importance of a multidisciplinary approach to continence care, and the new committees on pelvic organ prolapse and faecal incontinence recognize that, particularly in women, urinary incontinence coexists with prolapse and faecal incontinence in many instances. This is also true, to a more limited extent, in men with coexisting faecal incontinence. The task of these two committees was very considerable and they had to outline the basic science, and investigation and management techniques within a single chapter. The report of these two chapters laid the foundation for a broadening of the multidisciplinary approach to pelvic disorders which was further developed in the 3rd ICI and now in the 4th ICI. New patterns by which care is delivered are emerging and depend on the close collaboration between urologists, gynaecologists and coloproctologists, working within a multidisciplinary team with nurses and physiotherapists. From the research and investigation point of view, we are very dependent on our colleagues from other disciplines such as the basic sciences, epidemiology, social science and engineering.

The 4th Consultation on Incontinence was held in Paris in July 2008. In this consultation we gave a special attention the VV fistula in the developing world in collaboration with the WHO and many other associations working in this field. The structure of the consultation followed the successful formula developed by the ICUD and used for the previous 3 consultations. Once again an international faculty of over 150 individuals from a wide range of professions and specialities were grouped into a series of subcommittees, each with a specific area of responsibility. The spectrum of subcommittees spanned from Basic Science through assessment and investigation to therapy. These committees were further divided into specific patient groups for children, women, men, neurological patients and the frail elderly. In addition to fully integrating faecal incontinence and pelvic organ prolapse into the consultation, there was the renamed committee “Bladder Pain Syndrome”.

Subcommittee members were selected according to their academic reputation giving due recognition to the need to provide balance between specialities and geographical regions. A chairperson was selected for each subcommittee and was responsible for the drafting of that committees’ chapter. Most committees met at least once before the consultation in Paris, to progress their report.

Each chairperson presented his or her committees’ main discussions and recommendations in Paris. Their chapter was then modified accordingly, in the light of the consultation. This book details the evidence reviewed by each committee. Each committee used the ICUD System for evaluating evidence and providing recommendations with five levels of evidence (1 to 5) and four grades of recommendation (A to D).

This system worked well for the treatment committees but, as yet, it cannot be applied systematically to evaluate the evidence from the basic science and investigation committees. Nevertheless, the consultation feels that continued efforts to specify the evidence base for all recommendations are of vital importance.

The book’s final chapter is the Recommendations of the International Scientific Committee which includes all subcommittee chairs together with the members of the Steering Committee. This chapter has been expanded to include algorithms for the treatment of faecal incontinence, pelvic organ prolapse and bladder pain syndrome. Furthermore, the 2004 algorithms have been reconfigured in the light of new evidence and in order to facilitate their use.

These recommendations represent the evidence based opinion of a group of experts. They are not to be considered as guidelines or standards of care which are the responsibility of official organisations, governments and regulators.

We hope that the huge amount of effort put into the consultation and the production of this book will also be reflected in an increased prominence for all aspects of the consultation’s findings. We shall make the book more widely available and publish sections of the book in peer reviewed journals.

Paul Abrams and the Scientific Committee
Some of the members of the International
Committees Paris, France - July 5-8, 2008
**EDITORS**

P. Abrams, *U.K.*

L. Cardozo, *U.K.*

S. Khoury, *France*

A. Wein, *USA*

---

**MEMBERS OF THE COMMITTEES**

*(Alphabetical order - Chairmen in bold print)*

<table>
<thead>
<tr>
<th>No.</th>
<th>Chairmen</th>
<th>Members</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Deutkom</td>
<td>Daniel Amarenco</td>
<td>Sweden</td>
</tr>
<tr>
<td>2</td>
<td>Fry</td>
<td>Lori Bliss</td>
<td>USA</td>
</tr>
<tr>
<td>3</td>
<td>Griffiths</td>
<td>Ruud Bosch</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>4</td>
<td>Gajewski</td>
<td>Alain Bourcier</td>
<td>France</td>
</tr>
<tr>
<td>5</td>
<td>Grijzing</td>
<td>Wendy Bower</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>6</td>
<td>Happle</td>
<td>Katharine Brown</td>
<td>USA</td>
</tr>
<tr>
<td>7</td>
<td>Hango</td>
<td>Linda Brubaker</td>
<td>USA</td>
</tr>
<tr>
<td>8</td>
<td>Hapen</td>
<td>Brian Buckley</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>9</td>
<td>Hay</td>
<td>Kathryn Burgess</td>
<td>USA</td>
</tr>
<tr>
<td>10</td>
<td>Chang</td>
<td>Barry Caillier</td>
<td>USA</td>
</tr>
<tr>
<td>11</td>
<td>Chappel</td>
<td>Debuene Chang</td>
<td>USA</td>
</tr>
<tr>
<td>12</td>
<td>Chartier Kastler</td>
<td>Emmanuel Chartier</td>
<td>France</td>
</tr>
<tr>
<td>13</td>
<td>Comiter</td>
<td>Craig Comiter</td>
<td>USA</td>
</tr>
<tr>
<td>14</td>
<td>Cottenden</td>
<td>Alan Cottenden</td>
<td>UK</td>
</tr>
<tr>
<td>15</td>
<td>Cour</td>
<td>Nikki Cotteril</td>
<td>UK</td>
</tr>
<tr>
<td>16</td>
<td>Coyn</td>
<td>Karen Cruz</td>
<td>USA</td>
</tr>
<tr>
<td>17</td>
<td>Cruz</td>
<td>Francisco de Gennaro</td>
<td>Portugal</td>
</tr>
<tr>
<td>18</td>
<td>De Ridder</td>
<td>Dirk de Groot</td>
<td>Belgium</td>
</tr>
<tr>
<td>19</td>
<td>Denuk</td>
<td>John De Lancey</td>
<td>USA</td>
</tr>
<tr>
<td>20</td>
<td>Denuk</td>
<td>Daniel Altman</td>
<td>Sweden</td>
</tr>
<tr>
<td>21</td>
<td>Denuk</td>
<td>Gerard Amarenco</td>
<td>France</td>
</tr>
<tr>
<td>22</td>
<td>Denuk</td>
<td>Karl Eric Anderson</td>
<td>Sweden</td>
</tr>
<tr>
<td>23</td>
<td>Denuk</td>
<td>Walter Artibani</td>
<td>Italy</td>
</tr>
<tr>
<td>24</td>
<td>Denuk</td>
<td>Gerry Badlani</td>
<td>USA</td>
</tr>
<tr>
<td>25</td>
<td>Denuk</td>
<td>Kaven Baessler</td>
<td>Germany</td>
</tr>
<tr>
<td>26</td>
<td>Denuk</td>
<td>Clive Bartram</td>
<td>UK</td>
</tr>
<tr>
<td>27</td>
<td>Denuk</td>
<td>Barry Berghmans</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>28</td>
<td>Denuk</td>
<td>Lori Bider</td>
<td>USA</td>
</tr>
<tr>
<td>29</td>
<td>Denuk</td>
<td>Donna Bliss</td>
<td>USA</td>
</tr>
<tr>
<td>30</td>
<td>Denuk</td>
<td>Donna Bliss</td>
<td>USA</td>
</tr>
<tr>
<td>31</td>
<td>Denuk</td>
<td>Ruud Bosch</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>32</td>
<td>Denuk</td>
<td>Alain Bournier</td>
<td>France</td>
</tr>
<tr>
<td>33</td>
<td>Denuk</td>
<td>Wendy Bower</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>34</td>
<td>Denuk</td>
<td>Jeanette Brown</td>
<td>USA</td>
</tr>
<tr>
<td>35</td>
<td>Denuk</td>
<td>Andrew Bowning</td>
<td>Ethiopia</td>
</tr>
<tr>
<td>36</td>
<td>Denuk</td>
<td>Linda Brubaker</td>
<td>USA</td>
</tr>
<tr>
<td>37</td>
<td>Denuk</td>
<td>Homero Bruscini</td>
<td>Brazil</td>
</tr>
<tr>
<td>38</td>
<td>Denuk</td>
<td>Brian Buckley</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>39</td>
<td>Denuk</td>
<td>Kathryn Burgio</td>
<td>USA</td>
</tr>
<tr>
<td>40</td>
<td>Denuk</td>
<td>Barry Caillier</td>
<td>Australia</td>
</tr>
<tr>
<td>41</td>
<td>Denuk</td>
<td>Dough Canning</td>
<td>USA</td>
</tr>
<tr>
<td>42</td>
<td>Denuk</td>
<td>Ann Capewell</td>
<td>UK</td>
</tr>
<tr>
<td>43</td>
<td>Denuk</td>
<td>Linda Cardozo</td>
<td>UK</td>
</tr>
<tr>
<td>44</td>
<td>Denuk</td>
<td>David Castro</td>
<td>Spain</td>
</tr>
<tr>
<td>45</td>
<td>Denuk</td>
<td>Debunee Chang</td>
<td>USA</td>
</tr>
<tr>
<td>46</td>
<td>Denuk</td>
<td>Chris Chappel</td>
<td>UK</td>
</tr>
<tr>
<td>47</td>
<td>Denuk</td>
<td>Emmanuel Chartier</td>
<td>France</td>
</tr>
<tr>
<td>48</td>
<td>Denuk</td>
<td>Craig Comiter</td>
<td>USA</td>
</tr>
<tr>
<td>49</td>
<td>Denuk</td>
<td>Alan Cottenden</td>
<td>UK</td>
</tr>
<tr>
<td>50</td>
<td>Denuk</td>
<td>Nikki Cotteril</td>
<td>UK</td>
</tr>
<tr>
<td>51</td>
<td>Denuk</td>
<td>Karen Coyn</td>
<td>USA</td>
</tr>
<tr>
<td>52</td>
<td>Denuk</td>
<td>Francisco Cruz</td>
<td>Portugal</td>
</tr>
<tr>
<td>53</td>
<td>Denuk</td>
<td>Firouz Daneshgari</td>
<td>USA</td>
</tr>
<tr>
<td>54</td>
<td>Denuk</td>
<td>M. De Gennaro</td>
<td>Italy</td>
</tr>
<tr>
<td>55</td>
<td>Denuk</td>
<td>Chet De Groat</td>
<td>USA</td>
</tr>
<tr>
<td>56</td>
<td>Denuk</td>
<td>Dirk De Ridder</td>
<td>Belgium</td>
</tr>
<tr>
<td>57</td>
<td>Denuk</td>
<td>John De Lancey</td>
<td>USA</td>
</tr>
<tr>
<td>Number</td>
<td>Name</td>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KELLEHER Con</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>KISSLAR Vik</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>KIRSCHNER-HERMANNS Ruth</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>KLUIVERS K</td>
<td>The Netherlands</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>KOEHLER Heinz</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KOPP Z.</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>KOVINDHA Apichana</td>
<td>Thailand</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>KUCHEL George A.</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>KUSEK John</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>LANG Julie</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>LAPITAN Marie Carmela</td>
<td>Philippines</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>LAURBERG Soren</td>
<td>Denmark</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>LIN Alex Tong-Long</td>
<td>Taiwan</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>MAdERSBACHER Helmut</td>
<td>Austria</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>MADOFF Robert</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>MAHER Christopher</td>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>MATZEL Klaus</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MAYER Emeran</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>MELGREM A.</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>MELLGREN Anders</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MICHEL Martin</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MILLS Ian</td>
<td>Sweden</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>MILSOM Ian</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>MIMURA Toshiki</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>MOORE Katherine</td>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>MOORE Kate</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MORRISON John</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>N'DOW James</td>
<td>Ireland</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NELSON Richard</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>NEWMAN Diane</td>
<td>The Netherlands</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NUMAN Rien</td>
<td>Finland</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>NILSSON Karl Gustav</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>NISHIMURA Kaoru</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NITTI Victor</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>NORDLING Jorgen</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>NORTON Peggy</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>NORTON Christine</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>NORTON Nancy</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>NYBERG Leroy</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>NYGAARD Ingrid</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>OCONNELL Ronan</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>PALMER Mary</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>PATERSON Jan</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PATON Julian</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>PAYNE Chris</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>PAYNE Chris</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PERKASH I.</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>PFISTERER Mathias</td>
<td>Belgium</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>PIETERS Ronny</td>
<td>Slovenia</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PODNAR S.</td>
<td>Poland</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>RAdZISZEWSKI Piotr</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>RAJAMAHESWARI N.</td>
<td>India</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>RATNER Vicki</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ROBAIN Gilberte</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ROOSEN A.</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>RORTVEIT Guri</td>
<td>Norway</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ROSIER Peter</td>
<td>The Netherlands</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>ROWNER Eric</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>RUFFION Alain</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>SAKAKIBARA Stefano</td>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SALVATORE Peter K</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SAND Brigitte</td>
<td>Switzerland</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>SCHURCH Ulla</td>
<td>Sweden</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>SILEN P.B.</td>
<td>India</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>SMITH Tony</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>SOMBIE Issiaka</td>
<td>Burkina Faso</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>SRINIVASAN Vasan Satya</td>
<td>India</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>STASKIN David</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>STEERS William</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>STOTHERS Mary-Ann</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>SUBAK leslee</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SULTAN Abdul</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SZABO Laszlo</td>
<td>Hungary</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TAKEDA Masayuki</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TANNENBAUM Cara</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TEKUGUL Serdar</td>
<td>Turkey</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>THOM David H.</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>THOR Karl</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>TUBARO Andrea</td>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>UEDA Tomohiro</td>
<td>Japon</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>VAN KERREBOECK Philip</td>
<td>The Netherlands</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>VAN OPHOREN Arndt</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>VARMA M.E.</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>VIERHOUT David</td>
<td>The Netherlands</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>VODUSEK David</td>
<td>Slovenia</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>VON GONTHARD Alexander</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>VON THEOBALD Peter</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>WAGG Adrian</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>WAGNER Todd</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>WALL Lewis</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>WANG Alex</td>
<td>Taiwan</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>WEIN Alan</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>WHITEHEAD William</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>WILDE Mary</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>WILLIAMS Kate</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>WOOD Dan</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>WYNDAELE Jean Jacques</td>
<td>Belgium</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>YAMAGUCHI Osamu</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>YOSHIDA Masaki</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>ZIMMERN Philippe</td>
<td>USA</td>
<td></td>
</tr>
</tbody>
</table>
## Members of the Committees (by Committee)

1. Epidemiology
   - ALTMAN, Daniel Sweden
   - HERBISON, Peter New Zealand
   - LAPITAN, Marie C. Philippines
   - MILSOM, Ian Sweden
   - NELSON, Richard U.K.
   - SILLEN, Ulla Sweden
   - THOM, David H. USA

2. Cell Biology
   - FRY, Chris UK
   - KANAI, Tony USA
   - STEERS, William USA
   - TAKEDA, Masayuki Japan
   - ROOSEN, A. Germany
   - TAKEDA, Masayuki Japan
   - WOOD, Dan UK

3. Neural Control
   - BIRDER, Lori USA
   - DE GROAT, Chet USA
   - DRAKE, Marcus UK
   - FOWLER, Clare UK
   - GRiffithS, Derek USA
   - MAVER, Emeran USA
   - MILLS, Ian UK
   - MORRISON, John Arab Emirates
   - PATON, Julian UK
   - THOR, Karl USA

4. Pathophysiology
   - BAESSLER, Kaven Germany
   - BOURCIER, Alain France
   - KARRAM, Mickey U.K.
   - KOELBL, Heinz Germany
   - NITTI, Victor USA
   - SALVATORE, Stefano Italy
   - SULTAN, Abdul UK
   - YAMAGUCHI, Osamu Japan

5. Initial Assessment Including Quality of Life
   - AVERY, Kerry UK
   - BOSCH, Ruud The Netherlands
   - COTTERIL, Nikki UK
   - COYNE, Karen USA
   - EMMANUEL, Anton UK
   - HIRSCH, Mark USA
   - KELLEHER, Con UK
   - KOPP, Z. USA
   - STASKIN, David USA
   - YOSHIDA, Masaki Japan

6. Dynamic Testing
   - CAPEWELL, Ann UK
   - GAJEWSKI, Jerzy Canada
   - HOSKER, Gordon UK
   - ROBAIN, Gilberte France
   - ROSIER, Peter The Netherlands
   - SAND, Peter K USA
   - SZABO, Laszlo Hungary

7. Imaging, Neurophysiology and other Tests
   - AMARENCO, Gerard France
   - ARTIBANI, Walter Italy
   - BARTRAM, Clive UK
   - DE GENNARO, M. Italy
   - DELANCEY, John USA
   - KHULLAR, Vik UK
   - KLUIVERS, K. The Netherlands
   - PODNAR, S. Slovenia
   - TUBARO, Andrea Italy
   - VIERHOUT, M.E. The Netherlands
   - VODUSEK, David Slovenia

8. Drug Treatment
   - ANDERSSON, Karl Eric Sweden
   - CARDozo, Linda UK
   - CHAPPLE, Chris UK
   - CRUZ, Francisco Portugal
   - HAMPel, Christian Germany
   - HASHIM, H. U.K.
   - MICHEL, Martin The Netherlands
   - TANNENBAUM, Cara Canada
   - WEIN, Alan USA

9. Children
   - BOWER, Wendy Hong Kong
   - CANNING, Dough USA
   - HOEBEKE, Piet Belgium
   - NJIMAN, Rien The Netherlands
   - TEKGUL, Serdar Turkey
   - VON GONTHARD, Alexander Germany

10. Neurogenic Patients
    - CASTRO, David Spain
    - IGAWA, Yasuhiko Japan
    - KOVINDHA, Apichana Thailand
    - MADERSBACHER, Helmut Austria
    - PERKASH, I. USA
    - RADZISZEWSKI, Piotr Poland
    - RUFFION, Alain France
    - SAKAKIBARA, Ryuji Japan
    - SCHURCH, Brigitte Switzerland
    - WYNDaeLE, J-Jacques Belgium

11. Frail Elderly
    - DUBEAU, Catherine USA
    - HARARI, Danielle UK
    - JOHNSON, Ted USA
    - KUCHEL, George A. USA
    - PALMER, Mary USA
    - PFISTERER, Mathias Germany
    - WAGG, Adrian UK
12. Adult Conservative Management
BERGHMANS Bary The Netherlands
BURGIO Kathryn USA
DUMOULIN Chantale Canada
HAGEN Suzanne UK
HAY SMITH Jean New Zealand
MOORE Katherine Canada
N’DOW James UK
NYGAARD Ingrid USA

13. Surgery for Urinary Incontinence in Men
BRUSCHINI Homero Brazil
COMITER Craig USA
COUR Florence France
GRISE Philippe France
HANUS Tomas Czech Republic
HERSCHORN Sender Canada
KIRSCHNER-NERMANNS Ruth Germany

14. Surgery for Urinary Incontinence in Women
CHANG Debuene USA
CHARTIER KASTLER Emmanuel France
DMOCHOWSKI Roger USA
HILTON Paul UK
NILSSON Karl Gustav Finland
ROVNER Eric USA
SMITH Tony UK

15. Surgery for Pelvic Organ Prolapse
BRUBAKER Linda USA
GLAZENER Charis U.K
JACQUETIN Bernard France
MAHER Christopher Australia
MELGREM A. USA
NORTON Peggy USA
RAJAMAHESWARI N. India
VON THEOBALD Peter France
WANG Alex Taiwan

16. Conservative Treatment for Faecal Incontinence
BLESS Donna Z. USA
HARARI Danielle UK
LANG Julie UK
NORTON Christine UK
WHITEHEAD William USA

17. Surgery for Faecal Incontinence
LAURBERG Soren Denmark
MADOFF Robert USA
MATZEL Klaus Germany
MELLGREW Anders USA
MIMURA Toshiki Japan
O’CONNELL Ronan Ireland
VARMA Mika USA

18. Vesico-Vaginal Fistulas in the Developing World
BADLANI gopal USA
BROWNING Andrew Ethiopia
DE RIDDER Dirk Belgium

19. Painful Bladder Syndrome
HANNO Philip USA
LIN A.Tong-Long Taiwan
NORDLING Jorgen Long Denmark
NYBERG Leroy USA
PAYNE Chris USA
RATNER Vicki USA
UEDA Tomohiro Japon
VAN OPHOREN Arndt Germany

20. Technical Aspects of Continence Devices
BLISS Donna Z. USA
BUCKLEY Brian Irland
COTTENDEN Alan UK
FAKER Mandy UK
GETLIFE Kathryne UK
PATerson Jan Australia
PIETERS Ronny Belgium
WILDE Mary USA

21. Education and Continence Promotion
CAHILL Barry Australia
EE Chyehua Singapore
GORDON Barbara Australia
GORDON Deborah USA
GRIEBLING T. USA
NEWMAN Diane USA
NISHIMURA Kaoru Japan
NORTON Nancy USA
SRINI Vasan Satya India
WILLIAMS Kate UK

22. Economics of Incontinence
DEUTEKOM Marije The Netherlands
HAWTHORNE Graeme Australia
HU Teh-Wei USA
MOORE Kate Australia
SUBAK leslee USA
WAGNER Todd USA

23. Research
BROWN Jeanette USA
CASTRO David Spain
DANESHGARI Firouz USA
HAAB Francois France
IGAWA Yasuhiro Japan
KUSEK John USA
PAYNE Chris USA
RORTVEIT Guri Norway
STOTHERS Mary-Ann L. Canada
VAN KERREBOECK Philip The Netherlands
ZIMMERM Philippe USA
Dr. William C. de Groat is Professor of Pharmacology at the University of Pittsburgh Medical School. He received a Ph.D. in Pharmacology from the University of Pennsylvania Medical School in 1965 and then obtained postdoctoral training in Pharmacology at the University of Pennsylvania (1965-1966) and in Neurophysiology at the John Curtin School for Medical Research in Canberra, Australia (1966-1968).

He joined the faculty at the University of Pittsburgh in 1968 and was promoted to Professor in 1977. He has been a Visiting Scientist at the NIH (1988-1989) and at the University College London (1998).

He is an Honorary Member of the American Urological Association and the Japanese Urological Association. Dr. de Groat has published more than 400 papers primarily in the fields of autonomic neuroscience and neurourology. He has served on numerous editorial boards including: The Journal of Pharmacology and Experimental Therapeutics, American Journal of Physiology, Urology, Neuurology and Urodynamics, Autonomic Neuroscience, and Life Sciences.

Dr. de Groat has been Treasurer and a member of the Executive Council of the Society for Neuroscience and the Executive Vice President of the International Society for Autonomic Neuroscience. He is the recipient of a number of awards including: a National Institutes of Health (NIH) Method to Extend Research in Time (MERIT) Award, an NIH Research Career Development Award, a Lifetime Achievement Award from the Urodynamics Society and a Fellow of the American Association for Advancement of Science.

He has been recognized with the Carl Ludwig Distinguished Lectureship of the American Physiological Society, the University of Pittsburgh President’s Distinguished Research Award, the Pharmacia-ASPET Award for Experimental Therapeutics from the American Society for Pharmacology and Experimental Therapeutics, the Elsevier-JANS Lectureship of the International Society for Autonomic Neuroscience, the Sir Ludwig Guttman Lectureship of the International Society of Paraplegia and the University of Pittsburgh Chancellor’s Distinguished Teaching Award.

SYNOPSIS OF AREA OF INTEREST: Dr. de Groat is interested in the neural control of the lower urinary tract and the mechanisms underlying urinary incontinence and painful bladder conditions.
EVIDENCE-BASED MEDICINE OVERVIEW OF THE MAIN STEPS FOR DEVELOPING AND GRADING GUIDELINE RECOMMENDATIONS.

INTRODUCTION
The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years Consultations have been organised on BPH, Prostate Cancer, Urinary Stone Disease, Nosocomial Infections, Erectile Dysfunction and Urinary Incontinence. These consultations have looked at published evidence and produced recommendations at four levels; highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 http://minerva.minervation.com/cebm/docs/levels.html)

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly ‘mapped’ onto the Oxford system.

1. 1st Step: Define the specific questions or statements that the recommendations are supposed to address.

2. 2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.

   The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

   • Papers published, or accepted for publication in the peer reviewed issues of journals.

   • The committee should do its best to search for papers accepted for publication by the peer reviewed journals in the relevant field but not yet published.

   • Abstracts published in peer review journals should be identified. If of sufficient interest the author(s) should be asked for full details of methodology and results. The relevant committee members can then ‘peer review’ the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as “uninteresting” abstracts commonly do not progress to full publication.

   • Papers published in non peer reviewed supplements will not be included.

An exhaustive list should be obtained through:

I. the major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)

II. the table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How papers are analysed?

   Papers published in peer reviewed journals have differing quality and level of evidence.

   Each committee will rate the included papers according to levels of evidence (see below).

   The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution.

   is influenced by:

   • the type of study

   The hierarchy of study types are:

   - Systematic reviews and meta-analysis of randomised controlled trials
   - Randomised controlled trials
   - Non-randomised cohort studies
   - Case control studies
   - Case series
   - Expert opinion

   • how well the study was designed and carried out

   Failure to give due attention to key aspects of study methodology increase the risk of bias or confounding factors, and thus reduces the study’s reliability.

   The use of standard check lists is recommended to ensure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

   The objective of the check list is to give a quality rating for individual studies.

   • how well the study was reported

   The ICUD has adopted the CONSORT statement and its widely accepted check list. The CONSORT statement and the checklist are available at http://www.consort-statement.org

2.3 How papers are rated?

   Papers are rated following a «Level of Evidence scale». ICUD has modified the Oxford Center for Evidence-Based Medicine levels of evidence.

   The levels of evidence scales vary between types of studies (i.e. therapy, diagnosis, differential diagnosis/symptom prevalence study).

   the Oxford Center for Evidence-Based Medicine Website: http://minerva.minervation.com/cebm/docs/levels.html

3. 3rd Step: Synthesis of the evidence

   After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an Evidence Table.

4. 4th Step: Considered judgment (Integration of individual clinical expertise)

   Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration of individual clinical expertise with best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient: without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our “rules”
for exercising judgement, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency; applicability; generalisability; and clinical impact.

5. 5th Step: Final Grading
The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence and maintaining clarity for guideline users. The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine.

The levels of evidence shown below have again been modified in the light of previous consultations. There are now 4 levels of evidence instead of 5. The grades of evidence have not been reduced and a “no recommendation possible” grade has been added.

6. Levels of Evidence and Grades of Recommendation Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost effectiveness. It is accepted that at present little data exists on cost effectiveness for most interventions.

6.1 Levels of Evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn’t work). A level of evidence is given to each individual study.

- **Level 1** evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomised controlled trial, or ‘all or none’ studies in which no treatment is not an option, for example in vesicovaginal fistula.

- **Level 2** evidence (incorporates Oxford 2a, 2b and 2c) includes “low” quality RCT (e.g. < 80% follow up) or meta-analysis (with homogeneity) of good quality prospective ‘cohort studies’. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

- **Level 3** evidence (incorporates Oxford 3a, 3b and 4) includes:
  - good quality retrospective ‘case-control studies’ where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.
  - good quality ‘case series’ where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

- **Level 4** evidence (incorporates Oxford 4) includes expert opinion were the pinion is based not on evidence but on ‘first principles’ (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give ‘expert opinion’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘options’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2 Grades of Recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (don’t do the procedure). Where there is disparity of evidence, for example if there were three well conducted RCT’s indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgement as to the grade of recommendation given and the rationale explained.

- **Grade A** recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level 2 evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level 1 evidence.

- **Grade B** recommendation usually depends on consistent level 2 and or 3 studies, or ‘majority evidence’ from RCTs.

- **Grade C** recommendation usually depends on level 4 studies or ‘majority evidence’ from level 2/3 studies or Delphi processed expert opinion.

- **Grade D “No recommendation possible”** would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommend, that, as a minimum, any test should be subjected to three questions:

1. does the test have good technical performance, for example, do three aliquots of the same urine sample give the same result when subjected to ‘stix’ testing?
2. Does the test have good diagnostic performance, ideally against a “gold standard” measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out, in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

CONCLUSION

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system. There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost effectiveness, and also factors such as patient preference.

P. Abrams, S Khoury, A. Grant 19/1/04
CONTENTS

FOREWORD 3

PR WILLIAM C DE GROAT – President 10

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION 12

A Brief history of urinary incontinence and its treatment 19
Dirk Schultheiss (Germany)

Committee 1 : Epidemiology of Urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse (POP) 35
I. Milsom (Sweden) D. Altman (Sweden), M.C. Lapitan (The Philippines), R. Nelson (U.K), U. Sillén (Sweden), D. Thom (USA)

Committee 2 : Cell Biology 113
C.H Fry (U.K), A.J Kanai (USA), A. Roosen (Germany), M. Takeda (Japan), D.N Wood (U.K)

Committee 3 : Neural Control 167
L. Birder (USA), M. Drake (UK), W. de Groat (USA), C. Fowler (U.K), E. Mayer (USA), J. Morrison (UA.E), J. Paton (U.K)
Consultants : D. Griffiths (Canada), I. Mills (U.K), K. Thor (USA)

Committee 4 : Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse 255
H. Koelbl (Germany) V. Nitti (USA), K. Baessler (Germany), S. Salvatore (Italy), A. Sultan (U.K), O. Yamaguchi (Japan)

Committee 5 a : Initial Assessment of Urinary and Faecal Incontinence in Adult Male and Female Patients 331
D. Staskin (USA), C. Kelleher (U.K), K. Avery (U.K), R. Bosch (N.L), N. Cotterill (U.K), K. Coyne (USA), A. Emmanuel (U.K), M. Yoshida (Japan) Consultant : Z. Kopp (USA)

Committee 5 B : Patient-Reported Outcome Assessment 363

Committee 6 : Dynamic Testing 413
G. Hosker (U.K), P. Rosier (The Netherlands), J. Gajewski (Canada), P. Sand (USA) Consultants : L. Szabo (Hungary), A. Capewell (U.K)

Committee 7 A : Clinical neurophysiological Tests 523
D. Vodusek (Slovenia), G. Amarenco (France), S. Podnar (Slovenia)

Committee 7 B : Imaging and other Investigations 541
A. Tubaro (Italy), W. Artibani (Italy), C. Bartram (U.K), J. DeLancey (USA), V. Khullar (U.K), M. Vierhout (The Netherlands)
Consultants : M. De Gennaro (Italy), K. Kluivers (The Netherlands)

Committee 8 : Pharmacological Treatment of Urinary Incontinence 631
Karl-Erik Andersson (USA), C. R Chapple (U.K), L. Cardozo (U.K), F. Cruz (Portugal), H. Hashim (U.K), M.C. Michel (The Netherlands), C. Tannenbaum (Canada), A.J. Wein (USA)

Committee 9 : Diagnosis and management of urinary incontinence in childhood 701
S. Tekgul (Turkey), R. JM Nijman (The Netherlands), P. Hoebeke (Belgium), D. Canning (USA), W. Bower (Hong-Kong), A. von Gontard (Germany)

Committee 10 : Neurologic Urinary and Faecal Incontinence 793
J.J. Wyndaele (Belgium), A. Kovindha (Thailand), H. Madersbacher (Austria), P. Radziszewski (Poland), A. Ruffion (France), B. Schurch (Switzerland)
Consultants : D. Castro (Spain), Y. Igawa (Japan), R. Sakakibara (Japan)
Advisor : I. Perkash (USA)
Committee 11: Incontinence in the Frail Elderly
C.E. DuBeau (USA), G.A. Kuchel (USA), T. Johnson (USA), M.H. Palmer (USA), A. Wagg (U.K)

Committee 12: Adult Conservative Management
J. Hay Smith (New Zealand), B. Berghmans (The Nederlands), K. Burgio (USA), C. Dumoulin (Canada), S. Hagen (U.K), K. Moore (Canada), I. Nygaard (USA)
Consultant: J. N’dow (U.K)

Committee 13: Surgical Treatment of Urinary Incontinence in Men
S. Herschorn (Canada), H. Bruschini (Brazil), C. Comiter (USA), P. Grise (France), T. Hanus (Czech Republic), R. Kirchner-Hermanns (Germany)

Committee 14: Surgery for urinary incontinence in women
T. Smith (U.K), D. Chang (U.K), R. Dmochowski (USA), P. Hilton (U.K), C.G Nilsson (Finland), F.M Reid (U.K), E. Rovner (USA)

Committee 15: Surgery for pelvic organ prolapse
L. Brubaker (USA), C. Glazener (U.K), B. Jacquetin (France), C. Maher (Australia), A. Melgrem (USA), P. Norton (USA), N. Rajamaheswari (India), P. Von theobald (France)

Committee 16: Conservative and Pharmacological Management of Faecal Incontinence in Adults
C. Norton (U.K), W. Whitehead (USA), D. Z Bliss (USA), D. Harari (U.K), J. Lang (U.K)

Committee 17: Surgery for Faecal Incontinence
R.D. Madoff (USA), S. Laurberg (Denmark), K.E. Matzel (Germany), A.F. Mellgren (USA), T. Mimura (Japan), P.R. O’Connell (Ireland), M.G. Varma (USA)

Committee 18: Fistulas in the Developing World
D. De Ridder (Belgium), G. H. Badlani (USA), A. Browning (Ethiopia), P. Singh (India), I. Sombie (Burkina Faso), L. L. Wall (USA)

Committee 19: Bladder Pain Syndrome
P. Hanno (USA), A. Lin (Taiwan), J. Nordling (Denmark), L. Nyberg (USA), A. van Ophoven (Germany), T. Ueda (Japan)

Committee 20: Management Using Continence Products
A. Cottenden (U.K), D.Z.Bliss (USA), B. Buckley (Ireland), M. Fader (U.K), K. Getliffe (U.K), J. Paterson (Australia), R. Pieters (Belgium), M. Wilde (USA)

Committee 21: Continence Promotion, Education & Primary Prevention
D. K. Newman (USA), C. H. Ee (Singapore), D. Gordon (Australia), V. S. Srin (India), K. Williams (U.K) Consultants: B. Cahill (Australia), B. Gordon (USA), T. Griebling (USA), K. Nishimura (Japan) N. Norton (USA)

Committee 22: Economics of Urinary & Faecal Incontinence, and Prolapse
K. Moore (Australia), T. Wei Hu (USA), L. Subak (USA), T. Wagner (USA), M. Deutekom (The Netherlands)

Committee 23: Research
C. Payne (USA), J. Brown (USA), D. Castro (Spain), F. Daneshgari (USA), F. Haab (France), Y. Igawa (Japan), J. Kusek (USA), G. Rortveit (Norway), M-A Stothers (Canada), P. Van Kerreboreck (The Netherlands), P. Zimmerm (USA)

Recommendations of the International Scientific Committee:
Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence

Index
Committee 1

Epidemiology of Urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse (POP)

Chairman
I. MILSOM (Sweden)

Members
D. ALTMAN (Sweden),
M.C. LAPITAN (The Philippines),
R. NELSON (U.K),
U. SILLÉN (Sweden),
D. THOM (USA)
## CONTENTS

<table>
<thead>
<tr>
<th>A. INTRODUCTION</th>
<th>H. EPIDEMIOLOGY OF POP</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS</td>
<td>I. WHY DO PREVALENCE ESTIMATES DIFFER?</td>
</tr>
<tr>
<td>C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN</td>
<td>J. HELP SEEKING BEHAVIOUR</td>
</tr>
<tr>
<td>D. EPIDEMIOLOGY OF UI IN WOMEN</td>
<td>K. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT</td>
</tr>
<tr>
<td>E. EPIDEMIOLOGY OF UI IN MEN</td>
<td>L. RECOMMENDATIONS FOR FURTHER RESEARCH</td>
</tr>
<tr>
<td>F. EPIDEMIOLOGY OF OVERACTIVE BLADDER</td>
<td>REFERENCES</td>
</tr>
<tr>
<td>G. EPIDEMIOLOGY OF FAECAL INCONTINENCE</td>
<td></td>
</tr>
</tbody>
</table>

## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorders</td>
</tr>
<tr>
<td>ADL</td>
<td>Activity of Daily Living</td>
</tr>
<tr>
<td>AI</td>
<td>Anal Incontinence</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CAT</td>
<td>Childrens Apperception Test</td>
</tr>
<tr>
<td>CBCL</td>
<td>Childs Behaviour Check List</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DV</td>
<td>Dysfunctional Voiding</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>FI</td>
<td>Faecal Incontinence</td>
</tr>
<tr>
<td>IBD</td>
<td>Irritable Bowel Disorder</td>
</tr>
<tr>
<td>ICCS</td>
<td>The International Childrens Continence Society</td>
</tr>
<tr>
<td>ICI</td>
<td>International Consultation on Incontinence</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>LE</td>
<td>Level of Evidence</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower Urinary Tract Symptoms</td>
</tr>
<tr>
<td>MDS</td>
<td>Minimum Data Set</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental Status Examination</td>
</tr>
<tr>
<td>MNE</td>
<td>Monosymptomatic Nocturnal Enuresis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NE</td>
<td>Nocturnal Enuresis</td>
</tr>
<tr>
<td>NME</td>
<td>Non-Monosymptomatic Nocturnal Enuresis</td>
</tr>
<tr>
<td>OAB</td>
<td>Overactive Bladder</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>POP</td>
<td>Pelvic Organ Prolapse</td>
</tr>
<tr>
<td>POPQ</td>
<td>The ICS Pelvic Organ Prolapse Quantification Examination</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SUI</td>
<td>Stress Urinary Incontinence</td>
</tr>
<tr>
<td>TAH</td>
<td>Transabdominal Hysterectomy</td>
</tr>
<tr>
<td>TURP</td>
<td>Trans Urethral Resection of Prostate</td>
</tr>
<tr>
<td>UI</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>VD</td>
<td>Voiding postponement</td>
</tr>
<tr>
<td>VH</td>
<td>Vaginal hysterectomy</td>
</tr>
</tbody>
</table>
Epidemiology of Urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse (POP)

I. MILSOM, D. ALTMAN, M. C. LAPITAN, R. NELSON, U. SILLÉN, D. THOM

A. INTRODUCTION

In this report we focus on the epidemiology (distribution and determinants) of urinary incontinence (UI), faecal incontinence (FI), and pelvic organ prolapse (POP). We also discuss important topics such as differences between epidemiological and clinical approaches to health problems, help seeking behaviour, and methodological issues for this research.

Overactive bladder (OAB) is an evolving concept with close relationship to UI, and we have included a section on this topic. A worldwide estimation of the current and future number of individuals with lower urinary tract symptoms (LUTS)\[1\] including urinary incontinence and overactive bladder is also included at the end of this chapter.

The epidemiological population under study for this review will mainly be community dwelling non-institutionalized persons. The review will include discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences. We also review correlates and potential risk factors that have been revealed in epidemiological studies. Progress has clearly been made during the 4 years since our previous report when the 3rd International Consultation on Incontinence (3rd ICI) was published [2]. We are however greatly indebted to the authors of the previous chapter on epidemiology from the 3rd ICI who contributed important information which has in some instances been utilised in this chapter (S. Hunskaar, K Burgio and A Clark). Some new important areas have been studied with increasing regularity and quality. We have searched the literature for relevant new articles, thus reviewing a large number of high-quality and population based studies, as well as clinical trials that might include relevant epidemiological data. Because of an abundant number of studies, only a small fraction can be presented in a text like this. Other studies not presented here may have equally useful information, but lack of space precluded their inclusion.

Summary points:

- This review includes discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences in the epidemiology of UI, OAB, FI and POP.
- Correlates and potential risk factors that have been revealed in epidemiological studies are also reviewed.

B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS

Epidemiology is the scientific study of the distribution and determinants of disease in people. **Descriptive epidemiology** is the description of disease prevalence, incidence, (and mortality) by persons, place and time, while the term **analytical epidemiology** describes the search for determinants of disease risk. The discovery of risk factors and protective factors may then in turn lead to primary or secondary prevention.

In order to collect knowledge about risk factors or natural history, observational studies are needed. Cohort studies and case-control studies are the most common. However, caution is always needed when interpreting the results from such studies, as associations found in epidemiological studies may not be the same as causes. Longitudinal study designs and appropriate control for confounding factors are preferred, as these increase the validity of epidemiologic studies. For practical and ethical reasons, experimental designs are seldom used.

Recommendations and conclusions should always be based on the best available evidence. Studies of interventions, and studies of risk factors generally cannot be randomised because they relate to inherent human characteristics or practices, and exposing subjects to harmful risk factors is unethical. No uniform guidelines for assessing the results of observational studies exist, and the level of evidence for risk factors
from observational studies should be judged on the soundness of the exclusion of alternative explanations by statistical and other controls. But some initiatives for how to report meta-analyses of observational studies have been taken.[3]

Studies of disease frequency should rely on a very specific definition of the condition under investigation. The absence of unifying definitions for the conditions reviewed here is a fundamental problem which has not been resolved. Definitions used and problems associated with them are discussed in the subsections for the particular populations below.

**Prevalence** is defined as the probability of experiencing a symptom or having a condition or a disease within a defined population and at a defined time point. The concept is important for establishing the distribution of the condition in the population and for projecting the need for health and medical services.

**Incidence** is defined as the probability of developing the condition under study during a defined time period. Incidence is usually reported for one-, two- or five-year time interval.

Even in many of the recent studies reviewed analyses are very simple. Often only proportions or percentages are used to describe differences in different subgroups. Many analyses do not control for confounders (by stratification or multivariate analysis techniques). There is an obvious need for more advanced epidemiological analyses of risk factors and comorbidity, and strength of associations should be determined by relative risks and odds ratios.

**The relative risk (RR)** estimates the magnitude of an association between exposure and a condition, and indicates the likelihood of having the condition in the exposed group relative to those who are not exposed (e.g. do not have the risk factor). A RR of 1.0 indicates that the rates in the exposed and non-exposed groups are identical and thus that there is no association between the exposure and the condition in that specific dataset. A value greater than 1.0 indicates a positive association or an increased risk. A RR of 2.5 for UI indicates that there is a 2.5 times increased risk or that the persons in question are 150 percent more likely to have incontinence than those without the risk factor.

**The odds ratio (OR)** is the odds for having a risk factor in persons with a condition divided by the odds among those without the condition. An OR of 2.5 for UI my be interpreted as meaning that in this sample the odds in favour of having incontinence are 2.5 times higher among those with the risk factor than among those without.

For a condition with high prevalence, like UI or POP, OR and RR will not be identical, but in practice the results can be interpreted similarly. Results should always be given with a 95% confidence interval (CI).

Words like well established and established may be used about risk factors and findings with a high level of evidence in the literature. For less documented findings words like “indications of” or “data are suggestive” may be used.

**Summary points:**

- Descriptive epidemiology reports disease incidence, prevalence (and mortality) by persons, place and time.
- Analytical epidemiology searches for determinants of disease risk. There is a need for good longitudinal cohort studies.
- Variations in definitions and measurement issues are fundamental, and lead to problems with assessing the findings in epidemiological studies.
- There is a need for more advanced epidemiological analyses of risk factors and comorbidity using multivariable techniques, and strength of associations should be determined by relative risks and odds ratios.

---

**C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN**

---

**I. GENERAL COMMENTS AND DEFINITIONS**

The International Children's Continence Society (ICCS) has issued new recommendations regarding terminology of bedwetting or **nocturnal enuresis** (NE) [4]. NE is now the term for all urinary incontinence during sleep taking place in discrete episodes, regardless of the presence or absence of concomitant daytime symptoms. **Monosymptomatic nocturnal enuresis** (MNE) denotes bedwetting without any other lower urinary tract (LUT) symptoms, and **non-monosymptomatic nocturnal enuresis** (NMNE) should be used for those with any concomitant LUT symptom.

NE is caused by relative nocturnal polyuria [5] and/or nocturnal bladder over-activity [6], combined with the lack of arousal at the time when the bladder needs to be emptied. The most important cause is, of course, the lack of arousal, otherwise the child would have had nocturia.

Any other leakage of urine in children during both the day and night is referred to as **urinary incontinence** (UI), just as it is in the adult population. UI with no obvious cause, i.e. without neurological or congenital anatomic alterations, is often seen together with other
urinary symptoms such as frequency, urgency and infections. Altogether these symptoms are referred to as functional LUT dysfunction, which is the term used to describe the entire spectrum of functional filling-voiding disturbances. Several sub-classifications have been used for children who present with varying degrees of “functional” urinary symptoms. Some are based on urodynamic patterns, others on clinical presentation.

According to recent definitions by the ICCS [1], based on symptoms and flow-residual studies rather than invasive urodynamic investigations, incontinence as a result of a filling-phase dysfunction, is in most cases due to an overactive bladder (OAB), which can also be referred to as “urge syndrome” and “urge incontinence”. Children with OAB usually have detrusor overactivity, but this label cannot be applied to them without cystometric evaluation. When incontinence is the result of a voiding-phase dysfunction, the diagnosis is often dysfunctional voiding (DV), which is induced by increased activity in the sphincter and pelvic floor during voiding. It is subdivided into staccato and fractionated voiding, and the terms cannot be applied unless repeat uroflow measurements have been performed. Voiding postponement (VD) is another common LUT dysfunction causing UI in children, but differs from the other since it is induced by habitual postponement of voiding and not a LUT dysfunction per se.

NE and UI due to functional LUT dysfunction are the wetting problems addressed in this paper. Both can be either primary (the child has not been dry for more than six months) or secondary (the wetting has recurred after a dry period lasting more than six months). If the complaints are secondary, they may signify psychological, neurological or even structural anomalies and therefore require careful consideration.

The healthy infant is socially incontinent but physiologically continent, because micturitions (about once every hour) are discrete and there is no leakage of urine between micturitions [7]. Bladder control develops during the first four to six years of life and is a highly complex process, which is still not fully understood. Most children are toilet trained by the age of three years, although there is huge social and cultural variation. By the age of five years, the child is normally able to void at will and to postpone voiding in a socially acceptable manner [8]. By this age, nighttime and daytime involuntary wetting becomes a social problem and a cause for therapeutic intervention.

II. PREVALENCE OF NOCTURNAL ENURESIS (NE)

As bladder control is something that develops over time, longitudinal studies are the best way of defining the dynamics of this process. Studies giving us the prevalence for all children between five and 15 years of age, for example, are not appropriate, as all the developmental stages are clustered together. It is therefore better to give the prevalence for an age cohort, such as seven-year-olds. Furthermore, random sampling should preferably be used in order to be able to say anything about the population. These problems associated with understanding epidemiology were summarised by Krantz [9], who also reviewed the epidemiological studies that had been published by 1993.

One explanation for the variation in prevalence in different studies is the fact that some studies include only monosymptomatic enuresis (MNE), whereas others also include what is defined as nonmonosymptomatic enuresis (NMNE). Another explanatory factor is that the frequency of enuretic episodes differs or is not taken into account in some studies. Moreover, most epidemiological studies link primary and secondary enuresis together.

1. PREVALENCE OF ALL NIGHT WETTING (MNE+ NMNE) ACCORDING TO AGE

Longitudinal cohort studies should be the ideal when analysing epidemiology in childhood NE, as there is a successive reduction in prevalence. Only a few of these studies are available[10-14] and cross-sectional studies at different ages therefore have to be used.

Most studies investigate cohorts of children in an age span of six to 12 years of age, for example, and give the prevalence for the entire group. Some of them also give the age-related prevalence [12, 15-24] which is summarised in Table 1. Cross-sectional studies of a specific age are also included [25-29] in Table 1.

In most studies (Table 1), the prevalence for seven-year-olds was between 7% and 10%. In two studies, the prevalence was higher; 15.1% and 16.4% for Turkish [19] and Korean [20] children respectively, despite the fact that the inclusion criteria were very similar in all the studies dealing with seven-year-olds (NE=night wetting once/month or more), apart from the studies by Hellström [25] (once/3 months or more) and Järvelin [26] (once/6 months or more). The prevalence of more frequent wetting (once/week or more) was lower compared to the prevalence for all wetting (once/month or more) by age, which have been illustrated in Figure 1.

In nine studies at age seven years [13, 15, 18, 20-23, 25, 26] (Table 1) the numbers of both non-enuretic and enuretic children were given and the definitions for enuresis were similar (MNE and NMNE, wetting once/1-3 months or more). A prevalence of 10% was obtained by meta-analyses of these studies (cohort of 14372 seven-year-old children, of whom 1422 were enuretic). Only four studies included groups of children that were chosen at random from the population [15, 20, 23, 26].
At age 11-12 years, the prevalence of NE had decreased and from the studies shown in Table I the prevalence varied between 1.7% and 4.7%. In seven of the studies, the number of non-enuretics and enuretics were available and the definition of NE was similar (once/month or more), apart from Swithinbank’s study (once/3 months or more). In these studies, the total number of children included was 8947, while the number of children with NE was 278, giving a prevalence of 3.1%. So, of those children with NE at age seven years, almost 15% spontaneously grow out of the wetting every year. In a recent Japanese study a higher resolution rate was reported in children with MNE compared to NMNE in children 7 to 12 years of age (21% and 15%, respectively) [21]. Similar results was found in a study from Hong Kong in which the proportion of children with NMNE was significantly greater in adolescent boys than in boys aged 5-10 years (32% vs 14.6%), even if the total prevalence of NE was decreasing as in other studies [23].

The variation in the prevalence of NE at 11-12 years between the studies is less than that seen at age seven years. The highest prevalence is no longer found in Turkey or Korea, as was the case at age seven years, but instead comes from a non-randomised cross-sectional study of 11- to 12-year-old schoolchildren (n=1145) in the UK (4.7%). It can therefore be suggested that the high prevalence seen in the studies from Turkey and Korea at age seven is not due to differences in genetic predisposition, but rather to phenotypic differences, such as the age of toilet training and the subsequent attainment of bladder control, socio-economic status, or cultural differences.

At age 16-17, three cross-sectional studies show a further reduction in prevalence to 0.5-1.7%. Two of the studies re-investigate children who had previously been studied; at age seven years [27] and 11-12 years [28] respectively. The prevalence when the cohorts were added together was 1.3% (cohort=3819, NE=51) [23, 27, 29], which gives a spontaneous cure rate of 11% a year among those who wet at age 11-12 years. In a study of 13,081 adults randomly sampled in the Netherlands [30], an overall prevalence of NE of 0.5% was found. There was no significant difference between age groups. Primary NE was reported by 50% of the men and 19% of the women, indicating that a small group of the enuretic children remain enuretic as adults.

### Table 1. Prevalence of nocturnal enuresis (NE) ( = Monosymptomatic nocturnal enuresis (MNE) + Non-monosymptomatic nocturnal enuresis (NMNE) together) according to age

<table>
<thead>
<tr>
<th>Author and year</th>
<th>7 years</th>
<th>11-12 years</th>
<th>16-17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiozza [15]</td>
<td>6.8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Järvelin [26]</td>
<td>8</td>
<td>4.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Spee-van der Wekke [17]</td>
<td>8</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Cher [18]</td>
<td>9.3</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Hellström [25, 27]</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferguson [12]</td>
<td>10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanaheswari [24]</td>
<td>10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serel [19]</td>
<td>15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee [20]</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swithinbank [28, 29]</td>
<td>4.7</td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Soderstrom [22]</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kajiwara [21]</td>
<td>10.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeung [23]</td>
<td>10.1</td>
<td>2.0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

### Figure 1: Prevalence of nocturnal enuresis (NE) by frequency of enuretic episodes and age. The data were obtained from metaanalyses of the epidemiological studies included in table III.1. NE>1 episode/6months: at 7 years [15, 18, 20-26], 11-12 years [15, 18, 20-23, 28] and 16-17 years [23, 27, 29]. NE>1 episode/week: at age 7 years [22, 23, 25, 26], 11-12 years [22, 23, 28] and 16-17 years [23, 27].
2. PREVALENCE OF MONOSYMPTOMATIC ENURESIS (MNE)

Very few studies make a distinction between MNE and NMNE and it is therefore difficult to obtain relevant figures for MNE (Table 2). In two studies from Scandinavia dealing exclusively with seven-year-olds, there was agreement between the studies; 6.4% [26] and 7.4% [25]. Recently, a Japanese study gave similar figures for MNE: 6.2% at age 7 years. In this latter study MNE corresponded to approximately 60% of all NE in ages from 7 to 12 years [21]. When it comes to studies in which all ages were mixed (5-12 years), four studies were identified in which those without daytime voiding problems could be identified. However, the difference in prevalence of MNE varied in these studies; 3.5% [16], 6.9% [31], 9.4% [20] and 15% [32].

3. PREVALENCE OF NE VERSUS GENDER

Almost all epidemiological studies of NE report a higher prevalence in boys than in girls, with a ratio of 2:1 in western countries [15-22, 25, 26, 28, 31-33]. It appears that the gender difference diminishes with age and becomes less visible and less proven among older children [27, 29, 34] (Figure 2).

4. PREVALENCE OF NE VERSUS ETHNICITY

In a study from The Netherlands [17], a higher prevalence was reported in the Turkish/Moroccan group (14%) than in the Dutch children (6%) (OR 3.76 (95%CI 1.98-7.12)). An equally high prevalence was found in a Turkish study of children with NE [19] at age seven years (15.1%). In a study from Korea [20], the same high prevalence at age 7 years was identified (16.4%). However, other studies from South-East Asia had comparable [18, 21, 23] or even lower levels of prevalence to those in western countries. In fact, two Chinese studies have shown a low prevalence of nocturnal enuresis [16, 35], 3.6% and 4.3% for children aged 4-12 and 6-16 respectively, which they attribute to earlier nocturnal urinary control in Chinese children, due to earlier toilet training.

5. PREVALENCE OF NE VERSUS FREQUENCY OF WET NIGHTS AND AGE

Yeung et al [23] showed in a large epidemiological study that the relative proportion of subjects with frequent bed-wetting increased with age. Overall 82% of the adolescence had >3 wet nights/week versus enuretic children aged 5-10 (42%) (Figure 3).

### Table 2. Prevalence of Monosymptomatic nocturnal enuresis (MNE) at age seven years and overall (including all ages)

<table>
<thead>
<tr>
<th>Author</th>
<th>Prevalence of MNE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 7 years</td>
</tr>
<tr>
<td>Järvelin [26]</td>
<td>6.4</td>
</tr>
<tr>
<td>Hellström [25]</td>
<td>7.4</td>
</tr>
<tr>
<td>Kanaheswari [24]</td>
<td>9.0</td>
</tr>
<tr>
<td>Lee [20]</td>
<td>13.6</td>
</tr>
<tr>
<td>Yeung [16]</td>
<td>3.5</td>
</tr>
<tr>
<td>Neveus [31]</td>
<td>6.9</td>
</tr>
<tr>
<td>Bower [32]</td>
<td>15.0</td>
</tr>
<tr>
<td>Kajiwara [21]</td>
<td>6.2</td>
</tr>
</tbody>
</table>

IIII. POTENTIAL RISK FACTORS FOR NE

Several risk factors have been established or suggested by epidemiological studies and the most important ones will be discussed here.
1. FAMILY HISTORY

NE is a hereditary disorder and this has been demonstrated in many studies (for example, [15, 16, 19, 26, 31, 32, 36]). The mode of inheritance appears to be autosomal dominant. Järvelin [26] showed that, if both parents were enuretics as children, the RR (95% CI) for the child to have NE was 16 (6.3-20.1), while if only one was enuretic, the RR was 7.8 (5.1-9.8). Using molecular genetic methods, foci have been found on chromosomes 13, 12, 8 and 22 [37, 38]. A picture of pronounced heterogeneity for both genotype and phenotype emerges [39].

2. PSYCHOPATHOLOGY

There are evident connections between childhood enuresis and mental well-being [13, 14, 35, 36, 40-42]. Evidence is accumulating to show that psychological consequences are probably caused by the enuresis and not a cause of primary NE, which has been thought for a long time [41]. The findings presented by Feehan [14] support this latter statement, as he only found an association between psychopathology and secondary NE, while children with NE did not display a connection of this kind.

3. DEVELOPMENTAL DELAY AND MENTAL RETARDATION

Children with developmental delay and mental retardation have been shown to have a higher prevalence of NE [12, 17, 26, 43]. Spee-van der Wekke [17] found that children who were given special education, including both those with and without mental retardation, had an OR of 3.74 (95% CI 2.32-6.03) for NE.

Perinatal events such as toxaemia (pre-eclampsia) and low birth weight, possibly involving an increased risk of minor neurological dysfunction, have also been shown to be associated with NE [12, 26, 36]. A connection between NE and minor neurological dysfunction of this kind has also been shown by Lunsing [44] in 12-year-old enuretic children. Furthermore, children with attention deficit hyperactivity disorders (ADHD) are more likely to have enuresis than the general child population [42, 45, 46].

4. SLEEP AND AROUSAL

The main pathology behind NE in children is the inability to wake up to the sensation of a full bladder. Parents often say that their enuretic child “sleeps very deeply”. Some recent studies support this view. By using auditory signals [47], computerised EEG [48] or questionnaires [31], a defect in arousal has been largely validated. In the study by Neveus [31], the odds ratios were significantly higher for a high arousal threshold (2.7), pavour nocturnus (2.4) and confusion when awoken from sleep (3.4). Computerised EEG energy analysis has indicated both greater depth of sleep and impaired arousal in enuretics [49]. Difficulty in arousal from sleep has also been shown in children with NE compared to children with isolated day-wetting problems and controls, by using a scoring system in a questionnaire [50].

5. SOCIO-CULTURAL FACTORS

Differences in the prevalence of NE [16, 19, 20, 35, 51] at early ages in different parts of the world are probably partly due to socio-cultural differences and not to differences in genetic predisposition [17]. It has been suggested that socio-economic status correlates with NE in some studies [15, 42], whereas in others no correlation was found [12].

6. OTHER RISK FACTORS

Sleep apnoea has been associated with enuresis in some patients [52]. Upper airway obstruction due to large adenoids or tonsils also appears to be a cause of NE, as it has been reported that the removal of these obstructions significantly reduced or cured NE [53]. Constipation may cause secondary NE or make primary NE persist [54]. Sexual abuse must also be included among the factors that may lead to NE [55]. Organic conditions such as infravesical obstruction and neuropathic bladder may also present as NE. In most cases, however, additional symptoms are present to make detection possible. Type 1 diabetes was reported to be a risk factor for secondary MNE due to the polyuria seen at presentation [56].

IV. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN

In children with functional LUT dysfunction, the OAB is far more common than dysfunctional voiding. In a urodynamic study of 1,000 patients with functional LUT dysfunction, approximately two-thirds had an
overactive bladder and one-third had dysfunctional voiding [57]. Based on clinical information, another study comprising 226 children revealed that 76% were considered to have an overactive bladder and only 1% dysfunctional voiding. The difference illustrates that different inclusion criteria influence the rate of prevalence [58]. When considering the total prevalence of UI (all frequencies of UI included) (Table 3), there was a variation between 3.2% and 9% in different studies at the age of seven years. In the earliest studies the prevalence was lower (3.2%-5.0%), whereas in the studies performed later in the 2000 [20, 22, 59, 60], the prevalence was higher 6.3%-9.0%. One explanation for the difference was probably an increased recognition of the problem in the population through information via media etc. At 11-13 years the reported prevalence varied between 1.1% and 12.5%. Swithinbank’s study [28] showed a very high prevalence (12.5%) and differed most from the rest (1.1%-4.2%). The difference could probably partly be explained by different limits for frequency of UI (occasionally [28] vs once/month or more). The fact that the studies were performed in different parts of the world was also a possible explanatory factor (UK and Korea).

The frequency of UI decreased with age (Table 3), which was clearly demonstrated in the subjects with frequent episodes of UI (>1/week) (Figure 4). The prevalence at 7 years, 11-13 years and 15-17 years was 2.6%, 1.1% and 0.3% respectively. There were only two authors who investigated the same cohort of children on two occasions; Hellström [25, 27] in Sweden and Swithinbank [28, 29] in the UK. According to the studies by Hellström, the reduction from seven years to 17 years was 0.2% per year in those with wetting at least once a week and 0.3% when including all kinds of wetting. Swithinbank reported a far higher frequency for all kinds of wetting at age 11-12 years but not at 15-16 years and the reduction in her cohort of children was therefore approximately 2% per year. UI was more common in girls in most studies, especially in the older age groups (Table 3, fig.4). From the prevalence found in the different studies, daytime UI could be suggested to be 1.5 times more common in girls than in boys at age seven years, whereas at age 16 years the difference was even more pronounced: 5-10 times more common in girls than in boys (Table 3).

1. PREVALENCE OF OVERACTIVE BLADDER (OAB)

In a Japanese study [59], the prevalence in children between 7 and 12 years of age, OAB was seen in 17.8%, with no significant difference between boys and girls. There was a gradual decrease in prevalence from 19.8% at the age of 7 years to 12.8% at 12 years.

2. COMORBIDITY: PREVALENCE OF BOWEL PROBLEMS

Urinary and faecal incontinence often coexist in different combinations. Constipation in childhood is a very common condition and when functional faecal incontinence is seen, constipation is often the cause. The term enuresis can be used synonymously with functional faecal incontinence. Soiling, on the other hand, is a confusing term that is poorly defined and should therefore not be used [4].

An increasing number of epidemiological studies reporting the frequency of bowel problems are accumulating, either in terms of constipation or functional faecal incontinence, in children with daytime wetting. Table 4 shows that the prevalence of bowel problems in day-wetting children approximately corresponded to a third of the children (24%-35%) [22, 50, 59, 60, 62], with even higher prevalence in the subgroup with dysfunctional voiding (43%) [62]. A significant association between day-wetting and bowel problems was shown [22]. These results support the new treatment concept of day-wetting children, with treatment of bowel problems as the first step. Children with MNE, on the other hand, seldom have bowel problems (0%-1%), whereas in NMNE it is more

Figure 4 : Prevalence of day UI (including mixed day/night) >1 episode/week by age and gender. Data are from: at age 6 years [63], 7 years [22, 25], 11-12 years [22, 28] and 16-17 years [27]
### Table 3. Day urinary incontinence (UI) (including mixed day/night)

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Sample size</th>
<th>&lt;1/week</th>
<th>&gt;1/week</th>
<th>Total day+night</th>
<th>day only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children 7 years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Järvelin [26]</td>
<td>Total: 2,892</td>
<td></td>
<td></td>
<td>3.2&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Boys - 1,444</td>
<td></td>
<td></td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Girls -1,445</td>
<td></td>
<td></td>
<td>3.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Hellström [25]</td>
<td>Total: 3,555</td>
<td>2.3</td>
<td>2.5</td>
<td>4.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Boys - 1,834</td>
<td>1.7</td>
<td>2.1</td>
<td>3.8</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Girls - 1,721</td>
<td>2.9</td>
<td>3.1</td>
<td>6.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Bloom [61]</td>
<td>Total: 101</td>
<td></td>
<td></td>
<td>5.0&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Lee [20]</td>
<td>Total: 1,325</td>
<td></td>
<td></td>
<td>6.7&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3.9</td>
</tr>
<tr>
<td>Kajiwara [59]</td>
<td>Total: 984</td>
<td></td>
<td></td>
<td>9.0&lt;sup&gt;3&lt;/sup&gt;</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Boys: 532</td>
<td></td>
<td></td>
<td>9.2</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Girls: 452</td>
<td></td>
<td></td>
<td>8.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Söderström [22]</td>
<td>Total: 715</td>
<td>3.0</td>
<td>3.8</td>
<td>6.3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Boys: 367</td>
<td>3.0</td>
<td>3.8</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Girls: 348</td>
<td>3.2</td>
<td>2.6</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Joinson [60]</td>
<td>Total: 8213</td>
<td></td>
<td></td>
<td>7.8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Boys: 4222</td>
<td></td>
<td></td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Girls: 3991</td>
<td></td>
<td></td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>Children aged 11-13 years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom [61]</td>
<td>Total: 165</td>
<td></td>
<td></td>
<td>1.2&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Swithinbank [28]</td>
<td>Total: 1,171</td>
<td>11.9</td>
<td>0.6</td>
<td>12.5&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Boys: 510</td>
<td>7.0</td>
<td>0.2</td>
<td>7.2</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Girls: 661</td>
<td>15.7</td>
<td>0.9</td>
<td>16.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Lee [20]</td>
<td>Total: 913</td>
<td></td>
<td></td>
<td>1.1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.9</td>
</tr>
<tr>
<td>Kajiwara [59]</td>
<td>Total: 761</td>
<td></td>
<td></td>
<td>2.5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Boys: 366</td>
<td></td>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Girls: 395</td>
<td></td>
<td></td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Söderström [22]</td>
<td>Total: 763</td>
<td>1.8</td>
<td>2.3</td>
<td>4.2&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Boys: 398</td>
<td>1.8</td>
<td>2.3</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Girls: 365</td>
<td>3.0</td>
<td>1.3</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Children aged 15-17 years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom [61]</td>
<td>Total: 81</td>
<td></td>
<td></td>
<td>1.2&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hellström [27]</td>
<td>Total: 651</td>
<td>1.5</td>
<td>0.3</td>
<td>1.8&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Boys: 344</td>
<td>0.3</td>
<td>0.0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Girls: 307</td>
<td>2.9</td>
<td>0.7</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Swithinbank [29]</td>
<td>Total: 940</td>
<td></td>
<td></td>
<td>3.0&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Boys: 411</td>
<td></td>
<td></td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Girls: 529</td>
<td></td>
<td></td>
<td>4.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Episodes of UI: 1>1/6 months, 2>1/3 months, 3> 1/ month, 4>1/2 weeks, 5 occasionally.

### Table 4. Comorbidities. The prevalence of concomittant bowel problems in children with day-wetting and nocturnal enuresis

<table>
<thead>
<tr>
<th>Author</th>
<th>Number children bowel problems in day-wetting group</th>
<th>OR (95%CI)</th>
<th>Number children bowel problems in NE</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Söderström 2004 [22]</td>
<td>35%</td>
<td>7.2 (4.1-12.7)</td>
<td>1.2 (0.6-2.5)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.0 (0.6-6.3)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kajiwara 2004 [59]</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Gontard 2004 [62]</td>
<td>25%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0%-16%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Chandra 2004 [50]</td>
<td>24%</td>
<td>1%-24%&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joinson 2006 [60]</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 low value represents MNE, high value NMNE, 2OR for fecal incontinence, 3 OR for constipation, 4 Subgrouping of daywetting in OAB, VP and DV the prevalences are: 18%, 25% and 43%, respectively.
common (16%-24%) [50, 62]. In an epidemiological study from Japan including 5282 children, ages between 7-12 years, 81.5% were reported to have daily bowel movements. A significant higher prevalence of NMNE was found in those with constipation, compared to among those with regular daily bowel movements (3.4% vs 2.2%) [21].

V. POTENTIAL RISK FACTORS FOR DAY WETTING

1. FAMILY HISTORY

Day wetting, also including those subjects with mixed day and night wetting, has been shown to be correlated to hereditary factors, in parallel to what is known about children with NE. However, the number of studies are limited (Table 5).

2. PSYCHOPATHOLOGY

Children under stress as a result of marital separation, for example, have a higher incidence of diurnal or mixed UI, according to some authors [15, 36, 63]. Moreover, psychopathology investigated by Järvelin [36] using the Children’s Apperception Test (CAT) revealed a significant increase in the signs of repression, including an inability to express one’s emotions and feelings (p=0.027), when comparing day wetting children with controls. Neveus [31] found that day-wetting children had more difficulty falling asleep (OR 2.4, CI 1.4-4) and he interpreted them as “anxious children”. Lettgren [64] found a significant increase in attention problems and delinquent behaviour in a certain form of day-wetting children (voiding postponement) using the Child Behaviour Check List (CBCL, Achenbach). In a recent paper [65] similar results was found with the highest rate of psychiatric comorbidity in children with UI due to voiding postponement and the lowest in children with MNE. In the group with encopresis 65% were considered to have severe behavioural problems [62], meaning that children with both wetting and bowel problems are at the highest risk for psychopathology. In a population-based study investigating psychological problems associated with day UI, 8213 children were included of whom 643 suffered from daytime wetting at median age 7.5 years [60]. Overall the results indicated a rate of psychological problems that was twice the rate reported for children with no daytime wetting, particularly notable was the increase in externalising problems. After adjustment for developmental delay, gender, stressful life events, variables associated to family sociodemographic background and soiling, there was still an independent association of daytime wetting and behaviour problems (OR 2.04, CI 1.67-2.51). It is not clear whether the behavioural problems described are a cause or a consequence of daytime wetting.

3. MINOR NEUROLOGICAL DYSFUNCTION AND DEVELOPMENTAL DELAY

Children with minor neurological dysfunction have also been shown to have an increased rate of day wetting. Duel [45] found that children with ADHD are three times more likely to have day UI than controls (p<0.0005). Also in children with delayed maturation or with mental retardation, the risk of day wetting is increased (OR 1.9 and 4 respectively), according to studies by Järvelin [26]. Perinatal events, which can also be suggestive of minimal brain dysfunction, have also been shown to be over-represented in day-wetting children. For example, Järvelin [36] found that the children of mothers who had suffered from toxaemia had an RR of 8.5 (CI 1.4-51.9) for day UI.

4. OTHER RISK FACTORS FOR DAY UI

Sometimes, functional day UI is difficult to distinguish from UI due to organic anomalies. The most prominent examples are the adolescent form of posterior urethral

Table 5. Day wetting vs family history (including mixed day/night wetting)

<table>
<thead>
<tr>
<th>Author</th>
<th>RR (95%CI)</th>
<th>OR (95%CI)</th>
<th>Positive history (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Järvelin [36]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-enuresis in mother</td>
<td>10.1 (3.4-29.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-enuresis in father</td>
<td>5.9 (1.9-17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sureshkumar [63]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daytime wetting in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-male sibling</td>
<td>5.3 (1.6-18.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-paternal lineage</td>
<td>9.3 (3.2-27.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiozza [15]*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-enuresis in parents</td>
<td></td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Bower [29]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-family history of enuresis</td>
<td></td>
<td>70**</td>
<td></td>
</tr>
<tr>
<td>Neveus [28]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-family history</td>
<td>2.0 (1.1-3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Only children with mixed day and night wetting, **compared with 45% in dry children
valves in boys and epispadias in girls. In many papers, UTI is regarded as a risk factor for day UI. Järvelin [36] found an RR of 8.6 (2.3-32.3) for UTI in day UI children. Neveus [31] was able to demonstrate similar connections; OR 2.3 (1.3-3.9). However, these infections should probably be regarded as a consequence of the functional bladder disturbance with UI and not the other way round as a cause of the UI.

Nocturnal enuresis (NE)
- The prevalence of NE at age 7 seems to be around 10% for most countries, at age 11-12 years around 3% and at age 16 around 1.3%.
- The spontaneous cure rate seems to be around 15% annually between 7 and 12 years, and between 12 and 17 years 11%.
- In an adult population the prevalence of NE seems to be 0.5%. The prevalence was 0.1% when including only those with a history of NE during childhood. Thus the risk for NE as adult if having the condition at 7 years of age can be calculated to 1%.
- Potential risk factors for NE in children include OAB, polyuria, family history, psychopathology, developmental delay, mental retardation, socio-cultural factors, sleep and arousal problems, sleep apnoea, constipation, sexual abuse and organic conditions such as infravesical obstruction.

Functional incontinence
- Children who are and remain dry in the day seem to attain their diurnal continence already between age 4 and 5 years.
- Diurnal UI, or combined diurnal and nocturnal UI, in children is caused by overactive bladder in the great majority of cases.
- Prevalence for functional UI decrease with age. At age 7 years prevalence figures varies between 3.2% and 9%, with the highest prevalence in recent studies. At age 15-17 years the corresponding prevalence is 1.2-3%.
- Variation in prevalence figures is mainly dependant on differences in frequency of incontinence episodes in the studies.
- Potential risk factors for diurnal UI in children include bowel problems such as constipation and functional faecal incontinence, family history, psychopathology, socio-cultural factors, minor neurological dysfunction, developmental delay, organic anomalies such as infravesical obstruction in boys and sexual abuse.

VI. SUMMARY POINTS

D. EPIDEMIOLOGY OF UI IN WOMEN

UI is a common symptom that may affect women of all ages, and there is a wide range of severity and nature of symptoms. UI is not a life-threatening disease, but the symptoms may seriously influence the physical, psychological, and social well being of the affected individuals.

Virtually all epidemiologic studies rely on participant self-report of UI. Multiple studies have examined the association between self-reported incontinence and clinically demonstrable incontinence, and by type of incontinence based on self-reported compared to type based on clinical diagnosis. While self-report and clinical diagnosis are highly correlated, they are inherently different. For example, Sandvik and coauthors [66] validated diagnostic questions used in a survey against a final diagnosis made by a gynaecologist after urodynamic evaluation. The percentage of stress only incontinence increased from 51% to 77%, mixed incontinence was reduced from 39% to 11% while the proportion with urge only UI remained virtually the same (10% vs. 12%). For public health purposes, self-report has the advantage of reflecting the woman’s experience and allows further characterisation of the incontinence by frequency and quantity of urine loss. Despite the uncertainty in determining type of incontinence, the differences in the epidemiology of urge and stress incontinence are potentially important given the presumed differences in underlying pathophysiology. Differences in the association of stress and urge UI (based on self-report) with respect to age, race/ethnicity, and risk factors suggest that questionnaire-based determination of UI type is useful and should be included in all epidemiologic studies of UI [67].

Usually incontinence is defined by the episode frequency, for example one or more episodes in the past year or past month, or typically leaking at least once a week or daily. UI can also be defined by severity (a combination of frequency and quantity). Probably the most widely used measure of severity is the Sandvik Severity index [68-69] which is calculated by multiplying the reported frequency (four levels) by the amount of leakage (three levels). Incontinence can also be characterized by impact, with is usually assessed either in terms of bothersomeness, or by the degree to which it restricts a woman’s activity (for example, the Incontinence Impact Questionnaire) [70].

The vast majority of epidemiological studies of female UI have been conducted in the U.S, Canada, Europe,
Australia or Japan. A few additional studies have been reported from other Asian countries. Thus we know very little about the prevalence, incidence and risk factors for UI in Africa or other parts of the developing world.

II. PREVALENCE

Estimates of UI prevalence differ for a variety of reasons other than variation in true prevalence:

1. Sampling frame. Representative samples drawn from a large, usually geographically defined, population (e.g. via random digit dialling) are thought to provide prevalence estimates that are the most generalisable. In contrast, studies of hospitalized patients or patients seen in specialty clinics are likely to provide estimates biased by self-selection and local referral patterns. In this chapter, we will cite population-based studies unless otherwise stated.

2. Response rates. Even population-based studies can provide biased prevalence estimates due to poor response rates [71]. Women with incontinence may be more predisposed to enroll in studies of incontinence or women’s health. One study that asked about continence status among women declining to enroll did find a higher proportion of enrollment by women who were incontinent compared to those who were continent, particularly among minority women [72]. While the degree of bias is often unknown, as a general rule response rates above 80% are considered good, while those between 60 and 80% are marginal.

3. Threshold definition of UI. Usually incontinence is defined by a threshold frequency, for example one or more episodes in the past year or past month, or typically leaking at least once a week or daily. Severity of degree of bother may also be used. The threshold chosen to define UI obviously affects the prevalence and incidence.

4. Types of UI. UI in women is typically classified as stress, urge or mixed. Stress UI is urine leakage resulting from increased intra-abdominal pressure (e.g., coughing, standing up) while urge UI is leakage immediately preceded and accompanied by a strong physical ‘urge’ to urinate, while mixed UI is a combination of the two. Other UI – neither stress or urge – is uncommon in women. Prevalence estimates for each type of UI are sensitive to the wording of the questions and to definitions of stress and urge UI, with some definitions requiring all UI episodes to be of one type to be classified as stress or urge, while other definitions may require only that the majority of episodes be of that type.

5. Survey methods. While there are few data comparing differences in prevalence based on method of ascertainment [73-74], variation it ascertainment (e.g., in person interviews, phone interviews, mailed questionnaires, or diaries) have been shown to affect prevalence estimates for other socially sensitive conditions.

6. Culture and language. While this area has not been investigated, it is likely that there are cultural differences in the perception of and terms used to describe UI that may affect prevalence estimates. Similarly, differences in language may lead to differences in ascertainment.

In the following sections, we attempt to account for variation from the above sources by using population-based estimates with high response rates whenever possible and examining prevalence by age, by type of incontinence, and among major subgroups of interest (pregnant and post-partum women, women in long term care, and by race/ethnicity). Even so, there remain substantial variations in prevalence estimates likely related to remaining differences in study methods or sample characteristics.

1. PREVALENCE IN GENERAL POPULATION OF ADULT WOMEN

A review of 36 general population studies from 17 countries in the 2004 3rd ICI edition found that the prevalence estimates for the most inclusive definitions of UI (‘ever’ ‘any’ or ‘at least once in the past 12 months’) ranged from 5% [75] to 69% [76], with most studies reporting a prevalence of any UI in the range of 25% to 45%. For daily incontinence, prevalence estimates typically range between 5 and 15%.

As seen in Table 6, studies since 2004 have added important information on prevalence of incontinence in women younger than 30 and older than 80 years of age, particularly for prevalence of incontinence by type. These studies are consistent with previous studies reporting that older women are more likely to have mixed and urge incontinence [103-106] while young and middle-aged women generally report stress incontinence [78-79, 107-109]. Overall, approximately half of all incontinent women are classified as stress incontinent. A smaller proportion are classified as mixed incontinent and the smallest fraction as urge incontinent. A recent study which included the entire adult age range by Hannested et al.[79] demonstrated a fairly regular increase in prevalence of mixed incontinence across the age range, and a decrease in prevalence of stress incontinence from the 40-49 year old age group through the 60-69 year old group.
Table 6. Prevalence of “any” ‘current’ or ‘ever’ incontinent UI, and of daily UI, in the general population by age of women and type of incontinence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Size</th>
<th>Survey Method</th>
<th>Ages (yrs)</th>
<th>Prevalence of ‘any’ UI (%)</th>
<th>Prevalence of daily UI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irvin [83]</td>
<td>Multiple</td>
<td>9605</td>
<td>Interview</td>
<td>18+</td>
<td>13 (all)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;39</td>
<td>7 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>14 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (mixed)</td>
<td></td>
</tr>
<tr>
<td>Zhu [84]</td>
<td>China</td>
<td>5221</td>
<td>Interview</td>
<td>20+</td>
<td>49 (all)</td>
<td>21 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-29</td>
<td>25.5 (all)</td>
<td>6 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 (stress)</td>
<td>5 (stress)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (urge)</td>
<td>1 (urge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (mixed)</td>
<td>1 (mixed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>37 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (urge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>59 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34 (stress)</td>
<td></td>
</tr>
<tr>
<td>Minassian [85]</td>
<td>USA</td>
<td>2577</td>
<td>Interview</td>
<td>20+</td>
<td>81 (all)</td>
<td>25 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 (stress)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 (all)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 (mixed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 (all)</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. (Ctd) Prevalence of “any” ‘current’ or ‘ever’ incontinent UI, and of daily UI, in the general population by age of women and type of incontinence (To be continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Size</th>
<th>Survey Method</th>
<th>Ages (yrs)</th>
<th>Prevalence of ‘any’ UI (%)</th>
<th>Prevalence of daily UI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togerstedt [66]</td>
<td>Sweden</td>
<td>549</td>
<td>Postal</td>
<td>30-79</td>
<td>63 (stress)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-33</td>
<td>51 (urge)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>65 (stress)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>70 (stress)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>88 (stress)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>65 (stress)</td>
<td>-</td>
</tr>
<tr>
<td>Melville [87]</td>
<td>USA</td>
<td>353</td>
<td>Postal</td>
<td>30-80</td>
<td>42 (all)</td>
<td>11 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>41 (all)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>48 (all)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>51 (all)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>55 (all)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80-90</td>
<td>54 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Corcos [88]</td>
<td>Canada</td>
<td>3249</td>
<td>Interview</td>
<td>35+</td>
<td>13.6 (stress)</td>
<td>-</td>
</tr>
<tr>
<td>Danforth [89]</td>
<td>USA</td>
<td>83355</td>
<td>Postal</td>
<td>37-54</td>
<td>43 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Homma [90]</td>
<td>Japan</td>
<td>54016</td>
<td>Postal</td>
<td>40+</td>
<td>-</td>
<td>12 (any)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (stress)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (urge)</td>
</tr>
<tr>
<td>Thorn [72]</td>
<td>USA</td>
<td>2109</td>
<td>Interview</td>
<td>40-69</td>
<td>70 (all)</td>
<td>10 (all)</td>
</tr>
</tbody>
</table>
Table 6. (Ctd) Prevalence of “any” ‘current’ or ‘ever’ incontinent UI, and of daily UI, in the general population by age of women and type of incontinence.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Size</th>
<th>Survey Method</th>
<th>Ages (yrs)</th>
<th>Prevalence of ‘any’ UI (%)</th>
<th>Prevalence of daily UI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waelten [91]</td>
<td>USA</td>
<td>3302</td>
<td>Interview</td>
<td>42-52</td>
<td>47 (any) 31 (stress) 9 (urge) 14 (mixed)</td>
<td>-</td>
</tr>
<tr>
<td>Rohr [92]</td>
<td>Denmark</td>
<td>5795</td>
<td>Interview</td>
<td>46+</td>
<td>33 (all) 24 (stress) 20 (urge) 20 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Mogeheidas [93]</td>
<td>Sweden</td>
<td>6642</td>
<td>Postal</td>
<td>50-64</td>
<td>31 (any)</td>
<td></td>
</tr>
<tr>
<td>Lewis [94]</td>
<td>USA</td>
<td>10,678</td>
<td>Interview</td>
<td>50-90</td>
<td>22 (all)</td>
<td>9 (all)</td>
</tr>
<tr>
<td>Mardon [95]</td>
<td>USA</td>
<td>144,265</td>
<td>Postal</td>
<td>65+</td>
<td>44 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Guoode [96]</td>
<td>USA</td>
<td>490</td>
<td>Interview</td>
<td>65+</td>
<td>41 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Anger [97]</td>
<td>USA</td>
<td>Not reported</td>
<td>Interview</td>
<td>60+ 60-69 70-79 80+ 80+</td>
<td>38 (all) 7 (all) 40 (all) 37 (all) 14 (all)</td>
<td>11 (all) 15 (all) 19 (all)</td>
</tr>
<tr>
<td>Hsieh [98]</td>
<td>Taiwan</td>
<td>1517</td>
<td>Interview</td>
<td>60-69 70+ 60+</td>
<td>25 (all) 36 (all) 30 (all)</td>
<td>13 (all) 9 (all) 17 (all)</td>
</tr>
<tr>
<td>Ostbye [99]</td>
<td>Canada</td>
<td>5133</td>
<td>Interview</td>
<td>65+ 65-69 70-74 75-79 80-84 85-89 90+</td>
<td>19 (any) 14 (any) 16 (any) 20 (any) 25 (any) 25 (any) 29 (any)</td>
<td>-</td>
</tr>
<tr>
<td>Adelman [100]</td>
<td>USA</td>
<td>747</td>
<td>Interview</td>
<td>65+ 65-74 75-84 85+</td>
<td>45 (all) 37 (all) 48 (all) 62 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Holroyd-Leduc [101]</td>
<td>USA</td>
<td>4099</td>
<td>Interview</td>
<td>70+</td>
<td>19 (all)</td>
<td>-</td>
</tr>
<tr>
<td>Stenzelius [102]</td>
<td>Sweden</td>
<td>2638</td>
<td>Postal</td>
<td>75+ 75-79 80-84 85-89 90+</td>
<td>42 (all) 33 (all) 40 (all) 45 (all) 56 (all)</td>
<td>-</td>
</tr>
</tbody>
</table>
The prevalences shown in Table 6 generally fall into ranges previous reported. There is no hard evidence for different prevalences of UI among Western countries. Comparing prevalence between countries based on separate studies is difficult due to differences in methods and definitions, as well as language, cultural and social differences. One of the few studies to estimate the prevalence of UI in more than one country found similar prevalences of any UI (41% to 44%) in 3 of the 4 countries examined (France, Germany and UK) but a lower prevalence (23%) in the fourth country (Spain) [110]. There was no apparent reason for the lower prevalence in Spain. Virtually no population based studies of UI prevalence have been done in developing countries.

Only 3 population-based studies were located which reported prevalence of UI based on the Sandvik severity score. In one US study of over 3300 women age 42 to 52, the prevalence of severe UI was 10% [111], while in another US study of over 3500 women age 30 to 90, the prevalence was 18% [87]. In the Norwegian EPINCONT study, the prevalence of UI was moderate to severe by the Sandvik score and of at least some bother was 7%. Unfortunately, while there is wide recognition that ‘any incontinence’ which has a prevalence of 40 to 70 percent among middle aged and older women, is overly broad for many purposes, including estimating economic and health burden, there is no generally agreed upon criteria for what might be called “significant incontinence.” Frequency, severity, impact and bother all have their own drawbacks as the sole basis for defining significant incontinence. Reporting UI prevalence using different threshold definitions, including severity, bothersomeness, impact, and desire for treatment or treatment seeking allows for flexibility, but by itself does not move us toward consensus.

2. PREVALENCE IN SPECIFIC POPULATIONS

The following section reviews UI prevalences among women living in long term care facilities, during pregnancy and post-partum period, and among women of different race/ethnicity.

3. PREVALENCE IN LONG TERM CARE FACILITIES

Several studies have documented a higher prevalence of UI in women residing in long-term care facilities compared to community dwelling women [112-116]. Because UI is associated with dementia, limited mobility and other co-morbid conditions, prevalence of UI is higher in facilities with residents requiring a higher level of care. In addition to being more frequent, UI in long term care residents tends to be more severe, costly, and have greater burden on caregivers compared to UI in the community [117].

Estimating the prevalence of UI women in institutions is complicated by the variety of definitions of long term care, ranging from supervised residential living facilities to nursing homes specialising in patients with advanced dementia. Some facilities offer a mixture of levels of care. In addition, differences in methods used to ascertain incontinence in nursing home residents resulting in wide differences in prevalence estimates. For example, a US study found a prevalence of just 1.4% based on medical record diagnosis, compared to 56% of patients with UI documented by the nursing staff [118]. Another study which analysed nearly 30,000 nursing home residents in US found that 30% had UI recorded (usually at admission) in the required ‘minimum data set’ (MDS) [119], similar to the prevalence of 34% found in smaller, study in Switzerland [113]. Studies that directly survey patients, family and/or staff consistently generally find higher prevalences of 50% to 80% among current residents [100, 112, 114].

4. PREVALENCE DURING PREGNANCY AND POST-PARTUM

Studies of UI during pregnancy have reported period prevalences of 32% to 64% for all UI and 40% to 59% for stress (including mixed) UI as documented in the 3rd ICI edition. Period prevalence is higher in parous than in nulliparous women [120-123], whereas new onset of UI (cumulative incidence) during pregnancy is higher in primagravida [121-123]. Point prevalence of UI is low in the first trimester, rising rapidly in the second trimester and increasing further, though less rapidly, in the 3rd trimester [121-122]. Severity of incontinence appears to increase during pregnancy as well [124]. Data recently reported from the Norwegian Mother and Child Cohort Study, a large (N=43,279) population-based study, confirms these observations [125]. In this study, the prevalence of stress incontinence from before to during pregnancy, rose from 9% to 31% in nulliparous women, and from 24% to 42% in parous women. In contrast, mixed incontinence showed a similar rise in both groups (from 6% to 16% and from 8% to 20%, respectively). Urge incontinence remained virtually unchanged in both groups at less 5%.

Estimating the post-partum prevalence of urinary incontinence is complex because in addition to differences in study design, method of ascertainment and choices of definition of incontinence, prevalence may also depend on number of previous births, type of delivery, and history of previous incontinence. The table below summarizes studies which report the prevalence of UI in the first year post-partum for primiparous women by mode of delivery. These studies were chosen because they enrolled consecutive women delivered at one or more large hospitals serving a defined population, and were able to recruit and evaluate over 50% of women.

As shown in Table 7, nearly all post-partum UI is stress related. Most studies did not provide information
Table 7. Prevalence of urinary incontinence in the first post-partum year among primiparous women by type of delivery.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Type of delivery</th>
<th>N</th>
<th>Type of UI</th>
<th>Freq. of UI</th>
<th>1 to 3 months</th>
<th>4 to 6 months</th>
<th>7 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altman [128]</td>
<td>Sweden</td>
<td>VD</td>
<td>287</td>
<td>Stress</td>
<td>Any</td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Chaliha [129]</td>
<td>UK</td>
<td>VD</td>
<td>289</td>
<td>All</td>
<td>Any</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eason [130]</td>
<td>Canada</td>
<td>VD</td>
<td>467</td>
<td>All</td>
<td>Any</td>
<td>31</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Effekhar [131]</td>
<td>Iran</td>
<td>VD</td>
<td>357</td>
<td>Stress</td>
<td>Any</td>
<td>16*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekstrom [132]</td>
<td>Sweden</td>
<td>VD</td>
<td>197</td>
<td>Stress</td>
<td>Any</td>
<td>20</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Pregazzi [133]</td>
<td>Italy</td>
<td>VD</td>
<td>379</td>
<td>Stress</td>
<td>Any</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Farrell [134]</td>
<td>Canada</td>
<td>SVD</td>
<td>313</td>
<td>All</td>
<td>Any</td>
<td>23*</td>
<td>22*</td>
<td></td>
</tr>
<tr>
<td>Grouetz [135]</td>
<td>Israel</td>
<td>SVD</td>
<td>145</td>
<td>Stress</td>
<td>2+mo.</td>
<td></td>
<td></td>
<td>10*</td>
</tr>
<tr>
<td>Pregazzi [136]</td>
<td>Italy</td>
<td>SVD</td>
<td>218</td>
<td>Stress</td>
<td>Any</td>
<td>16</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Wijma [137]</td>
<td>Netherlands</td>
<td>SVD</td>
<td>62</td>
<td>All</td>
<td>Any</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Arya [138]</td>
<td>USA</td>
<td>SVD</td>
<td>150</td>
<td>Stress</td>
<td>Any</td>
<td>7*</td>
<td>12*</td>
<td>3</td>
</tr>
<tr>
<td>Glazener [126]</td>
<td>New Zealand,</td>
<td>VD/SVD</td>
<td>2805</td>
<td>Stress</td>
<td>Any</td>
<td>32, 29*</td>
<td>31, 28*</td>
<td>33, 30*</td>
</tr>
<tr>
<td></td>
<td>Scotland,</td>
<td></td>
<td>19548</td>
<td>Urged</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>England</td>
<td>VD</td>
<td>51</td>
<td>All</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schytt [139]</td>
<td>Sweden</td>
<td>VD/SVD</td>
<td>750</td>
<td>SUI</td>
<td>Any</td>
<td>20</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Chaliha [129]</td>
<td>UK</td>
<td>CS</td>
<td>131</td>
<td>All</td>
<td>Any</td>
<td>9</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Eason [130]</td>
<td>Canada</td>
<td>CS</td>
<td>104</td>
<td>All</td>
<td>Any</td>
<td>12</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Glazener [126]</td>
<td>New Zealand,</td>
<td>CS</td>
<td>569</td>
<td>All</td>
<td>Any</td>
<td>16, 12*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scotland,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>England</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekstrom [132]</td>
<td>Sweden</td>
<td>CS</td>
<td>192</td>
<td>Stress</td>
<td>Any</td>
<td>4</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Grouetz [135]</td>
<td>Israel</td>
<td>ECS/CSL</td>
<td>118</td>
<td>Stress</td>
<td>2+mo.</td>
<td></td>
<td></td>
<td>3*</td>
</tr>
<tr>
<td>Borello-France [127]</td>
<td>USA</td>
<td>ECS</td>
<td>116</td>
<td>All</td>
<td>Any</td>
<td>12*</td>
<td></td>
<td>11*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stress</td>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Restricted to women with no UI prior to pregnancy

VD=all vaginal deliveries; SVD=spontaneous (non-instrumental) vaginal delivery; IVD=instrumental vaginal delivery (forceps and/or vacuum); CS=all Cesarean sections; ECS=elective Cesarean section (prior to labor); CSL=Cesarean section after onset of labor
on frequency of leakage or degree of bother. Overall, it appears that any incontinence is reported by 15% to 30% women during the post-partum year, while weekly or greater incontinence is reported by 5% to 10% and daily UI by less than 5% of women. Excluding women with UI prior to pregnancy reduced the prevalence of post-partum incontinence by 3% to 4% in the one study reporting separate prevalences for each group [126].

Studies which included women delivered by Caesarean section and delivered vaginally consistently found a lower prevalence in those delivered by Caesarean section. Studies reporting prevalence in women delivered by elective Caesarean section and by Caesarean section after initiation of labor showed a substantially lower prevalence of post-partum UI in the elective Caesarean section group. The relatively high prevalence of post-partum incontinence among women having had an elective Caesarean section in the study reported by Borello-France is not consistent with other studies [127].

5. PREVALENCE IN DIFFERENT RACIAL AND ETHNIC GROUPS

While most epidemiological studies of UI have been conducted on Caucasian populations in the US, Canada and Europe, there are now a substantial number of studies in Asian countries [73, 91, 118-126], and among other racial/ethnic groups in the US [72, 89, 91, 97, 108, 111, 140-147]. Because of the substantial variation in prevalence of incontinence between studies, it is best to examine differences by race and ethnicity in the same study. Several population-based studies comparing the prevalence of UI among white women and women from one or more racial or ethnic groups are summarised in the table below. Most striking is the lower prevalence of stress UI in Black and Asian compared to White women. In most studies, Blacks have half to a quarter the prevalence of stress UI compared to White women but the same or slightly higher prevalence of urge UI and a slightly lower prevalence of mixed UI. Thus the difference in prevalence of UI between White and Black women appears to be almost entirely the result of a markedly lower prevalence of stress UI symptoms in Black women. The consistency of this difference across all studies and different frequencies and severities of UI suggest this is a real difference and not simply reporting bias. In contrast, the lower prevalence of UI seen in Asian women compared to White women reflects a lower prevalence of both stress and urge UI. The comparison of prevalences between Hispanic and non-Hispanic White women is complex in that some studies have found a lower prevalence of UI in Hispanic women while others have reported the prevalence to be higher in this group. This heterogeneity may be explained, at least in part, by differences in prevalence among sub-population of Hispanic women. Studies, such as the SWAN study, [46] that include Hispanic women who are primarily of Caribbean origin have reported lower UI prevalence, while those enrolling primarily Mexican-American women have reported higher UI prevalences [72, 144, 148]. This relationship is further supported by the NHANES data reported by Anger et al which found prevalences of any UI to be 36% in Mexican-American women and 30% in other Hispanic women [97, 148] (Figure 5).

Most studies used multivariate analysis to adjust for differences in parity, age, BMI, hysterectomy, oestrogen use, and other variables potentially related to both race and UI and have found that White women continue to have a significantly elevated risk of UI compared to Blacks or Asians [72, 89, 91, 140-145]. For studies in which Hispanic women report a higher prevalence of UI, adjusting for these variables reduces the difference with White women [72, 144, 148] (Table 8).

A few studies have compared physiological parameters between Black and White women to try to explain the lower prevalence of stress incontinence in Black women. These studies have reported Black women to have higher urethral closure pressures, greater urethral length and puboccocygeal muscle strength, larger urethral volumes and, paradoxically, greater vesical mobility [150-151]. The extent to which these differences, if confirmed, can explain differences in the prevalence of stress incontinence is not yet clear.

III. INCIDENCE AND REMISSION

In summarizing rate data, several factors should be borne in mind. Incontinence is a dynamic condition and both remission and reoccurrence are possible. As a practical matter, incidence is usually defined as the percent of continent women who later report incontinence. Some women who are continent at the time of enrollment may have been incontinent in the
### Table 8. Prevalence (%) of UI by Race/Ethnicity in Population-based Studies

<table>
<thead>
<tr>
<th>Reference/Study name</th>
<th>Age</th>
<th>Size</th>
<th>% white</th>
<th>Definition of UI</th>
<th>White</th>
<th>Hispanic</th>
<th>Black</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller [140] AHEAD</td>
<td>70+</td>
<td>3991</td>
<td>85</td>
<td>any in past year</td>
<td>23</td>
<td>-</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Nygaard [141] HRS</td>
<td>50-69</td>
<td>5701</td>
<td>72</td>
<td>any ≥1/year</td>
<td>17</td>
<td>10</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Burgio [138]</td>
<td>42-56</td>
<td>541</td>
<td>91</td>
<td>any ≥1/month</td>
<td>32</td>
<td>-</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Grodstein [142] N+H</td>
<td>50-75</td>
<td>92,936</td>
<td>77</td>
<td>any ≥1/month</td>
<td>35</td>
<td>28</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Danforth [88] N+H+II</td>
<td>37-54</td>
<td>85,670</td>
<td>52</td>
<td>any ≥1/month</td>
<td>44</td>
<td>45</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Sampselle [111] SWAN</td>
<td>42-52</td>
<td>3258</td>
<td>47</td>
<td>any in past year</td>
<td>66</td>
<td>42</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Anger [97] N+ANES</td>
<td>60+</td>
<td>23,477,725*</td>
<td>60</td>
<td>any ≥1/month</td>
<td>41</td>
<td>31</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Jackson [143] Health ABC</td>
<td>70-79</td>
<td>1558</td>
<td>54</td>
<td>any ≥1/month</td>
<td>27</td>
<td>27</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Westen [91] SWAN</td>
<td>42-52</td>
<td>3002</td>
<td>47</td>
<td>any ≥1/month</td>
<td>57</td>
<td>28</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Dooley [144] N+ANES</td>
<td>20+</td>
<td>4229</td>
<td>58</td>
<td>any ≥1/month</td>
<td>53</td>
<td>30</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Fenner [145] EPIS</td>
<td>35-64</td>
<td>2814</td>
<td>68</td>
<td>any ≥1/month</td>
<td>33</td>
<td>21</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Thom [72] RRISK</td>
<td>40-60</td>
<td>2109</td>
<td>48</td>
<td>any ≥1/month</td>
<td>45</td>
<td>51</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Markland [116] SALSA</td>
<td>65+</td>
<td>421</td>
<td>45</td>
<td>“Difficulty holding urine” at least some of the time</td>
<td>45</td>
<td>29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Markland [147] UABSA</td>
<td>65+</td>
<td>490</td>
<td>50</td>
<td>any ≥1/month</td>
<td>41</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
</tbody>
</table>

HRS = Health and Retirement Study, AHEAD = Asset and health Dynamics Among the Oldest Old Study, Health ABC = Health, Aging, and Body Composition Study, SWAN = Study of Women’s Health Across the Nation, NHS = Nurses’ Health Study, NHANES = National Health and Nutrition, EPIS = EPI Study, RRISK = Reproductive Risks for Incontinence Study at Kaiser, UABSA=University of Alabama at Birmingham Study on Aging; SALSA = San Antonio Longitudinal Study of Aging; # Chinese and Japanese combined
past. Also, women who are continent at baseline may develop incontinence which then remits (either spontaneously or due to treatment) prior to the follow-up survey. Depending on the study design, such women may or may not be counted as incident cases. For follow-up periods of a few years, the impact of such development and remission on estimates of new incontinence, particularly incontinence at least weekly, is probably negligible. The one study of more than 5 years duration included cases where new incontinence remitted as a part of the cumulative incidence [152]. As with prevalence, incidence will depend on the exact definition of UI used. It is worth noting that remission rates are usually higher than incidence rates even if the overall prevalence of incontinence is increasing, because the denominator for remission, the number of continent women, is usually smaller than the denominator for incidence of new incontinence (continent women).

Table 9 summarises population based studies reporting incidence and remission; 6 are new since 2004. Several studies report rates by age groups, frequency of UI, and type of UI. Annual incidence of any new UI ranged from 3 to 11% and increased with age. Rates of complete remission ranged from 0 to 13% per year and tended to increase with age, though not as consistently as did incidence.

IV. POTENTIAL RISK FACTORS

Many epidemiological studies have investigated potential risk factors for UI. The design of most of these studies has been cross-sectional using prevalent UI. In cross-sectional studies, the temporal relationship between some potential risk factors such as diet, physical activity, medications or body weight is ambiguous as the development of UI can lead to changes in behaviour. Since 2004, there have been several prospective studies looking at risk factors for incident UI which have alloweds for evaluation of the temporal relationship. Associations in all observational studies are subject to potential confounding, necessitating multivariate analysis to estimate the independent association between risk factors and UI. The risk factors of oestrogen use and body mass (obesity) have been examined in randomised controlled trials. With the exception of age, the following risk factors are considered to be at least potentially modifiable.

1. AGE

Virtually all studies have found an increase of UI prevalence with age [66, 77, 79, 81, 112, 159-168]. While incontinence is not considered to be an inevitable part of aging; there are changes in the bladder and the pelvic structures that occur with age and which can contribute to UI [169-170]. Further, UI is often attributable to medical problems or diseases that can disrupt the mechanisms of continence (e.g., diabetes mellitus, cognitive impairment, physical disability), many of which are more common among older adults. Several investigators have noted that the prevalence of any UI appears to increase up to middle age, with a leveling off between ages 50 and 70, followed by a steady increase among the aged [79, 110, 160]. Cross-sectional studies suggest that this pattern reflects an increase in the prevalence of stress incontinence during middle age followed by little increase or even a decline after age 50. In contrast, urge and mixed UI continue to rise after age 50. As a result, while stress incontinence predominates in younger and middle aged women, urge and mixed incontinence are more common in older women [79].

2. PREGNANCY, PARITY AND PARTURITION EVENTS

Stress UI is reported by most women at some time during pregnancy, usually in the third trimester, but is generally self-limited and resolves after delivery. For some women, UI that began during pregnancy persists after delivery as chronic UI [171-173]. In addition, women who are incontinent during pregnancy, even if they become continent after delivery, are more likely to develop incontinence later [128, 174]. The interpretation of this association is not clear. It may be that physiological changes during pregnancy cause incontinence later in life, but it is also possible that the temporary physiological changes during pregnancy may ‘uncover’ women with a predisposition to incontinence who are destined to become incontinent later in life regardless of the effects of pregnancy.

The vast majority of studies have found an association between parity and later UI [78, 124, 160, 167-168, 175-187]. Some studies have reported a threshold effect at one delivery and little or no additional risk with increasing parity [78, 185-186, 188]. However, other studies suggest that increasing parity increases the risk of UI [179, 185, 187, 189-190].

The effect of parturition on risk of incontinence is difficult to separate from the effect of pregnancy. Possible mechanisms by which vaginal birth could lead to incontinence include stretching damage to pudendal and other nerves and tearing of connective tissue reducing pelvic floor support for urethral competence [191]. One approach to estimating the impact of vaginal delivery separately from the impact of pregnancy itself is to compare the risk of incontinence in women who deliver vaginally compared to those who have a Caesarean delivery. Most such studies have found vaginal delivery to be a risk factor for both post-partum incontinence and incontinence in later life, particularly for stress incontinence, compared to delivery by Cesarean section [134, 167-168, 171-172, 192-200]. For example, in a large study of over 15,000 women under the age of 65 years,
### Table 9. Incidence of new UI in community-dwelling women from 11 population-based prospective studies since 2000

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of study (yrs)</th>
<th>Number without UI at baseline</th>
<th>Number with UI at baseline</th>
<th>Definition of UI</th>
<th>Age Group (yrs)</th>
<th>Average annual incidence (%)</th>
<th>Average annual remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samwesson [153]</td>
<td>6</td>
<td>202</td>
<td>90</td>
<td>any</td>
<td>20-59</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Haggflund [154]</td>
<td>4</td>
<td>135</td>
<td>113</td>
<td>any stress</td>
<td>22-55</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Wehrberger [152]</td>
<td>6.5</td>
<td>300</td>
<td>141</td>
<td>any 1+4 weeks</td>
<td>20+</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>any 2+week</td>
<td>20-39</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Townsend [155]</td>
<td>2</td>
<td>33,852</td>
<td>30,686</td>
<td>any 1+month</td>
<td>36-55</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>NHS</td>
<td></td>
<td></td>
<td></td>
<td>any 1-3/month</td>
<td>36-45</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>any 1+week</td>
<td>36-45</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe*</td>
<td>36-45</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Dettosso [156]</td>
<td>1</td>
<td>8,224</td>
<td>-</td>
<td>stress &quot;at least several times per month&quot;</td>
<td>40+</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>MRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70+</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>McGrother [157]</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>any</td>
<td>40+</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>MRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80+</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Waagen [31]</td>
<td>6</td>
<td>1439</td>
<td>-</td>
<td>any 1+month</td>
<td>42-52</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>SWAN</td>
<td></td>
<td></td>
<td></td>
<td>any 1+week</td>
<td></td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stress 1+month</td>
<td></td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>urge 1+month</td>
<td></td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mixed 1+month</td>
<td></td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Liu [158]</td>
<td>2</td>
<td>733</td>
<td>300</td>
<td>any stress</td>
<td>65+</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>804</td>
<td>429</td>
<td>any urge</td>
<td></td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Oodedie [96]</td>
<td>3</td>
<td>230</td>
<td>150</td>
<td>any 1+month</td>
<td>65+</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>USMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65-74</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>CSHA</td>
<td>5</td>
<td>4291</td>
<td>1020</td>
<td>any in past year</td>
<td>75-84</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85+</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

CSHA = Canadian Study of Health and Aging, SWAN = Study of Women's Health Across the Nation, NHS = Nurses' Health Study, MRC = Leicestershire MRC Incontinence Study, USMB = US Medicare Beneficiaries
* 1+ / month of sufficient quantity to at least soak underwear
Rortveit et al demonstrated that women who had delivered only by cesarean section were at increased risk of stress or mixed UI compared to nulliparous women (OR = 1.5) [198]. Further, those who had delivered vaginally only were at even greater risk of stress UI compared to those who had a Caesarean section only (OR = 2.4). Other studies of primiparous women have shown similar results with odds ratios (or relative risks) for UI in later life ranging from 1.7 to 2.8 [134, 167-168, 171, 201] for vaginal delivery compared to Caesarean section only.

Studies of maternal and fetal factors have found conflicting evidence regarding older maternal age at delivery and birth weight to be independent risk factors for UI. Foldspang et al found increased risk of UI with increasing age at the last childbirth for women aged 30-44 years [182]. Other studies have reported that older age at first birth is associated with an increased risk of later UI [183, 202-203]. Greater birth weight may also predispose the mother to UI [165, 193].

Studies have also examined the association between specific parturition factors during vaginal delivery and the risk of both post-partum UI and UI in later life. While several studies have reported forceps delivery [134, 171, 204], induced labour [190, 205], and episiotomy [206] to increase the risk of incontinence, these associations tend to become non-significant in multivariate analyses [138, 171-172, 183, 187, 189-190, 193, 205, 207-208] suggesting that risk of UI associated with vaginal delivery is not primarily the result of any single aspect of delivery or limited to any subset of women. Virtually all these studies have been conducted in developed countries. For women in developing countries with limited access to modern obstetrical care, traumatic vaginal delivery is a major cause of UI, including vesico-vaginal fistula [209].

Importantly, the association between parity, as well as between mode of delivery and specific parturition variables, appears to diminish and even disappear over time [160, 182, 185, 200]. A large study in Australia found that parity was strongly associated with UI for young women (18-23 years). For women 45-50 years there was only a modest association, and for older women (70-75 years) the association disappeared [160]. In a Norwegian study [185], the relationship between UI and parity was significant for younger women (age 20-34 years), weaker in middle-aged women, (35-64) and absent in older women (> 65 years).

3. OBESITY AND BODY MASS

Obesity is well established as a factor that can cause UI or contribute to the severity of the condition. It is believed that the added weight of obesity, like pregnancy, may bear down on pelvic tissues causing chronic strain, stretching and weakening of the muscles, nerves, and other structures of the pelvic floor. Some studies have found central obesity, measured by waist to hip ratio, to be more strongly associated with UI than is the traditional body mass index (BMI) [91, 210]. Because obesity has also been associated with urge UI it is thought that obesity may also act via pathways other than increased intra-abdominal pressure.

Data from numerous cross-sectional studies indicate that UI in women is associated with higher body mass index and greater weight [85, 87, 89, 92-94, 108, 111, 140, 160, 162, 165-166, 168, 171, 178, 180, 183-184, 187-188, 204-205, 211-222]. The relationship between BMI and UI has been reported in studies of younger women [160], middle aged women [111, 160, 184, 204], older women [160], and both parous and nulliparous women [171, 216]. Several studies have reported an association between body mass and all 3 major incontinence types (stress, urge and mixed) [188, 213, 218]. The association appears to increase with increasing body mass with women in the highest body mass quartile being 2 to 4 times more likely to have UI compared to women in the lowest quartile. One large cross-sectional study estimated that the risk of UI increased by 60% for every 5 unit increase in body mass index (BMI) [143]. In another study, risk of UI increased by about 50% and risk of severe UI increased by approximately 100% for each 5 unit increase in body mass [218].

In addition to cross-sectional data, several longitudinal studies have found that weight at baseline predicts later incontinence, and that an increase in body weight is associated with an increased risk of new incontinence or progression of existing incontinence [91, 223]. In one study, a weight gain of 5-10 kg increased the risk of incontinence by nearly 50% while in another, a gain of 5 units on the body mass index (BMI) was associated with a 30% increase in risk of stress UI and a 15% increase in risk of urge UI [91].

Finally, intervention studies for weight reduction have reported that loss of weight is associated with partial remission or complete resolution of UI. Several studies of incontinent women who sustained substantial weight loss from bariatric surgery found that a majority experienced resolution of stress and urge incontinence with the probability of resolution strongly correlated to the degree of weight loss [224-226]. Weight reduction has also resulted in a significant reduction in UI frequency in a randomized controlled trial of nonsurgical weight reduction for obese women [227] and in a large intervention trial for women with type 2 diabetes [228]. Thus, there is strong evidence to support the causal role of excess weight in the development of UI.

4. HORMONES

Oral oestrogen replacement therapy has been widely used to treat urinary incontinence during or after menopause for many years, despite equivocal data from clinical trials. The positive association between
oestrogen use and incontinence noted in cross-sectional studies [205, 229-230] was generally assumed to be the result of women with incontinence receiving estrogen for treatment of their incontinence. In 2001, Grady et al published data from the Heart Estrogen/Progestin Replacement Study (HERS), a large placebo-controlled randomized trial of estrogen replacement therapy which showed that postmenopausal women randomized to conjugated oral estrogen plus medroxyprogesterone were more likely then women taking the placebo to experience worsening of their incontinence over 4 years (39% vs 27%, p<.001) [231-232] A similar association was later found in women age 50-79 enrolled in the Womens’ Health Initiative (WHI) Hormone Replacement Trial [233]. In this large randomized controlled trial, continent women receiving estrogen, with or without progestogen, were approximately twice as likely to have developed stress incontinence at 1 year (16% vs 9%, p<.0001). The risks of mixed and urge incontinence were also significantly increased, though more modestly. The effect was seen primarily in women 55 and older. Thus, while oral estrogen as a risk factor for stress UI may be unexpected, the evidence from these 2 large randomized controlled trials supports this conclusion for stress UI, at least in women age 55 and older. The effect of estrogen on urge incontinence, and on incontinence in women less 55 years of age, is less clear.

While relatively little is known about the effects of the newer class of selective estrogen receptor modulators (SERMs) on incontinence, two SERMs, levormeloxifene and idoxifene have been associated with an increased risk of pelvic organ prolapse surgery in clinical trials [234], and women taking levormeloxifene have experienced a 4-fold increase in urinary incontinence [235]. In contrast, no increase in UI was seen an a randomized controlled trial of raloxifene [236].

5. DIABETES

Many, though not all, cross sectional studies have reported urinary incontinence to be more common in women with type 2 diabetes than among women with normal glucose levels even after adjusting for common risk factors, including age and obesity [87, 89, 91, 111, 143, 228, 237-238]. In the analysis of the large, prospective Nurses’ Health Study cohort, diabetes was a significant predictor for new incontinence [237], and the strength of the association increased after 5 years of diabetes and by severity of incontinence. Women with diabetes of more than 5 years duration had approximately 50% more risk of severe UI and twice the risk of very severe UI. Data from another prospective cohort study did not find an association between new diagnosis of diabetes and UI up to 1 year later [239], suggesting that diabetes needs to have been present for more than a year to substantially increase the risk of UI.

6. HYSTERECTOMY

Approximately 600,000 women have hysterectomies in the U.S. each year, usually for non-cancerous conditions. There has been concern that hysterectomy may be associated with development of urinary incontinence via damage to the pelvic nerves and pelvic supportive structures [240-242]. However, most studies have not found an increase in reported incontinence in the first two years following hysterectomy [243-247] and at least two studies have reported a statistically significant decrease in incontinence following hysterectomy [248-249]. Most of these studies have been uncontrolled and limited by small sample sizes (fewer than 35 patients per study). However, a larger (n=158) prospective study that did include a control group (women undergoing a dilatation and curettage), also found no increase in incontinence 3 to 21 months after hysterectomy [250]. A 2-year, randomized controlled trial of 160 women who had undergone either hysterectomy or endometrial ablation for menorrhagia found no difference in incontinence or in cystometric abnormalities between the two groups [251]. A third, large, retrospective study, of 415 hysterectomised women and 335 women who had undergone laparoscopic sterilization, also found no difference in the prevalence of urinary incontinence between the two groups 2 to 8 years after hysterectomy [252].

While most prospective studies have failed to find an association between hysterectomy and subsequent incontinence, several epidemiologic studies have reported an association between a history of hysterectomy and current UI, with relative risks ranging from 1.2 to 2.1 after controlling for other variables using multivariate analysis [87, 89, 93, 145, 205, 229]. In two studies, the association between hysterectomy and incontinence was found to be stronger if the hysterectomy was performed before age 50 [81,205].

Some studies have reported an increased prevalence of UI in women receiving a subtotal, compared to a total, hysterectomy [253-254] while others found no difference by techniques [255]. Additional factors, such as indication for hysterectomy (fibroids, endometriosis, or prolapse) and concomitant oophorectomy, have not been well studied.

Prospective studies of the association between a history of hysterectomy and incident UI have provided conflicting results. One prospective study reported a significant association between history of hysterectomy at baseline and subsequent incidence of new urge, but not stress, UI [221]. In contrast, two other studies failed to find a significant association between baseline hysterectomy status and UI [153, 256].

Based on the available data, hysterectomy does not appear to increase the risk of UI in the short term. While several cross-sectional studies have reported an association between a history of hysterectomy and
current UI, the strength of the adjusted association has been weak to moderate. The few prospective studies have given mixed results on whether a history of hysterectomy is an independent risk factor for new onset UI. While two studies have suggested that hysterectomy at a younger age may be a stronger risk factor, this needs to be confirmed in future studies.

7. URINARY TRACT INFECTIONS AND LOWER URINARY TRACT SYMPTOMS

Urinary tract infection (UTI) has long been considered to be a cause of transient UI. The role UTIs with respect to the development of chronic UI is less clear. While several cross-sectional epidemiologic studies have found that women with UI are more likely to report having had one or more UTIs [73, 145, 159, 164, 211-213, 219, 221, 257-265] these results should be treated cautiously. UTIs are often diagnosed and treated based on symptoms without culture confirmation and therefore in some cases women may have received a diagnosis of a UTI for what is actually urge incontinence. In addition, lower urinary tract symptoms, including burning on micturition, frequency and nocturia may increase the likelihood of being diagnosed with a UTI in addition to being associated with UI. UI may also be a risk factor for UTI. A recent prospective 2 year study of 913 women age 55-75 found that baseline prevalence of UI was nearly twice as high in women who subsequently developed a UTI compared to those who did not [266]. Without additional data, it is not possible to say if UTIs actually increase the risk of later UI, if UI increases the risk of being diagnosed with a UTI, or if both UI and UTIs are manifestations of a common underlying process.

8. IMPAIRED PHYSICAL FUNCTION

Functional impairments, particularly mobility limitations, a history of falls, arthritis, dizziness, need to use walking aid, and poor lower extremity strength, have been correlated with UI in many community-based and nursing home studies [102-103, 112, 115, 140-141, 146-147, 159, 161, 165, 219, 221, 262, 267-274]. Odds ratios for UI from a study of 839 nursing home residents demonstrated the increasing likelihood of incontinence with an ORs=1.8, 5.6 and 7.4 for needing partial assistance, needing full assistance, or being wheelchair or bed bound, respectively [112]. A study of 2025 older women indicated that several functional impairments, particularly mobility limitations, may have received a diagnosis of a UTI for what is actually urge incontinence. In addition, lower urinary tract symptoms, including burning on micturition, frequency and nocturia may increase the likelihood of being diagnosed with a UTI in addition to being associated with UI. UI may also be a risk factor for UTI. A recent prospective 2 year study of 913 women age 55-75 found that baseline prevalence of UI was nearly twice as high in women who subsequently developed a UTI compared to those who did not [266]. Without additional data, it is not possible to say if UTIs actually increase the risk of later UI, if UI increases the risk of being diagnosed with a UTI, or if both UI and UTIs are manifestations of a common underlying process.

9. COGNITIVE IMPAIRMENT

Research on UI in nursing home residents has consistently supported an association between UI and dementia [99,112,267,270, 275-279]. In studies using multivariate analyses, patients lacking mental orientation had a 3.6 times greater risk of being incontinent than those with normal mental status [112] and the presence of dementia increased the odds of UI by 1.5 to 2.3 [267, 270]. A link between incontinence and mental status has also been demonstrated in the acute care setting. In a sample of women admitted to the hospital for hip fracture, presence of confusion increased the odds of developing UI during the hospitalization (OR = 3.4) [272]. In the Canadian Study of Health and Aging a strong association was found between severity of dementia and UI in elderly women [115]. Odds ratios were 1.2, 4.0, and 12.6 for mild, moderate and severe dementia, respectively, after controlling for age, residence, and ambulatory function. However, in a study of community dwelling women, no relationship was found between mental status and difficulty holding urine [280]. Another, more recent community-based study found an association between cognitive impairment, defined as a score of < 24 on the mini mental status exam (MMSE), and prevalent UI, though after adjusting for physical functioning and other variables the association became substantially weaker and of borderline statistical significant (OR=1.3, 95% CI-1.0-1.6) [279]. A recent longitudinal study of 6349 community women found that a decrease in mental functioning more than 1 standard deviation, as measured by the modified mini mental status exam (MMSE) and by Trails making A and B, was not associated with increased risk of UI; however it did predict a greater impact of UI [275]. Another study of over 5000 women age 65 and older found no significant association between moderate or severe cognitive impairment, defined by the modified
MMSE, and incident UI over 10 years [99]. Together these studies suggest that mild dementia in community dwelling women is at most weakly associated with UI, while moderate to severe dementia has a consistent moderate to strong association. No studies were found which investigated whether an intervention to maintain or improve mental functioning would also improve or prevent UI.

10. DEPRESSION

Several cross-sectional studies have documented an association between depression and incontinence with estimates of the relative risk ranging from 1.4 to 2.7 [87, 91, 93, 141, 143, 147, 259, 261]. The cross-sectional and observational nature of studies linking depression and incontinence means that while depression may predispose a woman to developing UI, it is also possible that UI leads to depression (for example by reducing a woman’s social network), that depression and UI share one or more common neurochemical or hormonal pathways [281], or that women with depression are more likely than non-depressed women to be bothered by, and hence report, having incontinence. One prospective cohort study found no association between baseline depression or new depression and subsequent UI [91, 239, 281]. A second prospective study reported a weak association between baseline depression and subsequent UI over 3 years (OR=1.2, 95% CI=1.0-1.4) [96].

11. MENOPAUSE

Historically, menopause has been considered a risk factor for UI. However, establishing a relationship between menopause and UI has been difficult, probably in part because changes in endogenous hormone levels vary over a period of at least several years and only approximately correspond to amenorrhea or vasomotor symptoms used to define clinical menopause. Many cross-sectional studies have found that the prevalence of incontinence does not increase with natural menopause [81, 177, 179, 188, 145, 164, 282] and some studies have found a significantly lower prevalence of UI among postmenopausal women than among premenopausal women [108, 177, 179, 188]. Two recent longitudinal studies have confirmed this neutral or protective effect of the natural menopausal transition (without hormone replacement therapy) on UI [222, 239]. There is evidence that menopause may have a different association with stress incontinence than with urge incontinence [76, 175]. In one study, the prevalence of urodynamic stress incontinence decreased from 21% to 12% after menopause while the prevalence of detrusor overactivity increased from 9% to 19% [283].

12. PHYSICAL ACTIVITY

Evaluating physical activity as a potential risk factor or protective factor for incontinence has been difficult. Incontinence, particularly stress UI, can be a barrier to exercise [284], which could lead to the spurious appearance of a protective effect of physical activity on UI. Alternatively, engaging in physical activity could ‘unmask’ an existing propensity toward stress incontinence by increasing intra-abdominal pressure, resulting in physical activity being identified as a risk factor in the short term even if it is protective in the long term. Some cross-section studies have found a protective association between exercise and UI [84, 229, 262]. However establishing physical activity as a risk factor for incontinence using observational data is challenging due to difficulties in measuring and classifying physical activity prospectively over sufficient time to see an effect. In a longitudinal study of 4291 women age 65+ “regular exercise” at baseline was not associated with either prevalent UI or new UI 10 years later in multivariate analysis [99]. In contrast, a study of over 80,000 US nurses age 54-79 found that a higher level of physical activity, averaged from 7 reports over 14 years, was associated with a reduced risk of new UI [285]. Specifically, the investigators found that that being in the top quintile for overall physical activity reduced the risk of new UI by about 20% (OR=0.81, 95% C=0.71-0.93) compared to the bottom quintile. For walking, being in the top quintile reduced the risk of UI by about 25% (OR=0.74, 95% CI=0.63-0.88). Both total activity and walking significantly reduced stress UI, but not urge or mixed UI.

13. SMOKING, COUGH AND CHRONIC LUNG DISEASE

Smoking has been reported to be an independent risk factor for incontinence in women in some cross-sectional studies [85, 89, 109, 111, 141, 171, 189, 204, 218, 222, 285-287] but not in others [87, 93, 165-166, 186, 207, 211-213, 262, 288] possible mechanisms by which smoking could be associated with UI is by increased intra-abdominal pressure due to increased coughing among smokers. Other mechanisms, such as inhibition of collagen formation [286], also have been suggested.

Recent data from the Nurses’ Health Study II, with over 83,000 US women age 37 to 54 years old, supports smoking as a weak risk factor for UI, with the odds ratio for current smoking vs. never smoking increasing 0.91 to 1.20 to 1.34 for occasional, frequent and severe incontinence respectively, by multivariate analysis [89]. Former smokers had a risk intermediate between never and current smokers. In contrast, four prospective cohort studies failed to find a significant association between either past or current smoking and incident UI in multivariate analysis [99, 153, 239, 256].

The conflicting data from cross-sectional studies and lack of association between smoking and incident UI
14. DIET

Studying diet as a risk factor for UI is challenging. While some dietary constituents such as coffee, alcohol or carbonated beverages have been suspected as worsening UI, there is little reason to suspect other dietary constituents as causing, or protecting from, UI. Studies of dietary factors must adjust for confounders, notably age and body mass, and should consider the tradeoffs made with other constituents. Dietary data are difficult to obtain reliably. Finally, women may change dietary intake in response to UI, making cross-sectional studies of diet and UI difficult to interpret.

Several studies have examined the consumption of alcohol, coffee as risk factors for UI. While a few studies have reported coffee drinking to be associated with an increased risk of UI [99, 289], others have not found an association [211, 218, 229, 262]. Similarly, a positive association between alcohol consumption and UI has been reported by some [166, 290] but not others [211, 218, 222, 229]. Drinking 1 or more carbonated beverage daily compared to less than 1 per week was associated with a higher incidence of stress UI in one study (adjusted OR= 1.6, 95% CI =1.2-2.2) [291]. Tea drinkers were found to be at slightly higher risk of all types of incontinence in another study [218].

15. FAMILY HISTORY AND GENETICS

Since 2004 several family and twin studies of UI have been published. One twin study of 161 monozygotic (identical) and 249 dizygotic (fraternal) twins age 75+ found evidence for significant inheritability for urge, but not for stress UI [292]. Another twin study estimated that genetics accounted for nearly 60% of the variation in bladder neck descent as measured by ultrasound [293]. Several family history studies have found a two to three fold greater prevalence of stress UI among first degree relatives of women with stress UI compared to first degree relatives of continent women [294-296]. In one study, relative risks for stress UI was 2.8, 2.9, and 2.3, respectively, for mothers, sisters, and daughters of women with stress incontinence compared to women without first degree relatives with stress UI [294]. A large study of sisters, daughters, mothers and grandmothers of women with UI found an association between incontinence status in first-degree relatives with an increased risk for stress and mixed UI after adjustment for body mass index and parity [297]. In general the risk was somewhat higher for sisters of a woman with UI than for daughters.

16. ISCHEMIC HEART DISEASE

A recent community-based study of urinary tract symptoms reported an adjusted association between UI and ischemic heart disease in Black, but not White or Hispanic women [298] an association previously reported, though unadjusted [94]. However, at least 3 other cross-sectional studies have not found an association between coronary heart disease and UI [143, 299-300]. In a prospective cohort study, “heart attack/angina” was associated with stress UI cross-sectionally but not longitudinally in age-adjusted analysis, and became non-significant after adjusting for other variables [273]. In contrast, a prospective analysis of the Nurses’ Health Study found that coronary heart disease was associated with frequent UI (OR=1.5, 95% CI=1.2-1.8) and severe UI (OR=1.8, 95% CI=1.3-2.4) [256]. Given these mixed associations and the difficulty of completely controlling for common risk factors for heart disease and UI, it is not clear if heart disease is an independent risk factor for UI.

17. OTHER FACTORS

Additional variables reported as associated with UI include constipation [84, 160, 184, 187, 270], faecal incontinence [103, 112], genit al prolapse [107, 189], congestive heart failure [301], use of diuretics [138, 187, 262], benzodiazepines [302], and other drugs [161, 303-304], and childhood enuresis [188, 215, 305-306]. In a review of medical records of 5986 members aged 65+ of a large health maintenance organization in California an increased risk of UI was associated with Parkinson’s disease, dementia, stroke, depression, and congestive heart failure [307].

V. IMPACT AND CONSEQUENCES

The impact of urinary incontinence is typically assessed by degree of bother or by scales that measure the impact of incontinence on functional status and quality of life. A single question asking patients to report the degree of bother they experience from their incontinence provides an important dimension to characterising UI in addition to frequency and amount of urine lost. Typically incontinence that is more severe, of longer duration, and is urge or mixed, is also more bothersome [308]. There are validated scales that measure the impact of UI. One of the first scales, the Incontinence Impact Questionnaire [70], uses 30 items asking whether incontinence limits activities in 4 domains. There are several other similar scales, some specific for urge or stress incontinence or for overactive bladder [70, 309-314]. In addition to severity of UI, interference with sexual activities and incontinence at night are associated with greater reported impact on quality of life [315]. Incontinence has been identified as a potential risk factor for falls and nursing home admissions. In a prospective study of over 6000 older women, women with weekly urge, but not stress, incontinence were more likely to fall during the 3 year follow-up, adjusting
for multiple other factors (adjusted OR=1.3, 95% CI=1.1-1.4) [316]. Similarly, in a study of 472 long term care residents in Germany, UI at baseline predicted falls over the next 12 months after adjusting for a variety of patient factors and co-morbid conditions [317]. UI was the second strongest predictor of falls (a history of falls being first). However, it is possible that both falls and UI are markers for frailty that cannot completely be adjusted for. Whether treatment of UI would reduce the number of falls has not been established.

UI has also been reported as a risk factor for nursing home admissions even after adjusting for multiple co-morbid conditions [301,326]. However, another study that also adjusted for additional measures of frailty, including activities of daily living, found that the association became weaker and non-significant [101].

UI has substantial, well documented, economic consequences as well. Annual costs of urinary incontinence are estimated to be over $20 billion in direct costs (primarily costs of routine care, including out of pocket costs) [318] which is greater than the annual costs for breast, cervical, uterine and ovarian cancer combined [319]. There are also substantial indirect costs from work loss and missed volunteer work as well [320].

VI. TREATMENT SEEKING AND TREATMENT

Since 2004, at least 8 papers have been published which report the proportion of women with incontinence who have sought treatment [84, 95, 98, 110, 321-325] (Table 10). Combined with previously published studies [78, 81, 105, 111, 308, 322, 326-328], the proportion of women with any UI in the past 12 months who report having sought medical treatment ranges from 12% [46] to 53% [30] with about half the studies showing 25% to 30% [81, 98, 322, 326]. All studies that have examined treatment seeking by type of incontinence have found that a women with urge or

Table 10. Percent of women with UI in the general population who have sought help from a physician

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Age (years)</th>
<th>Definition of UI</th>
<th>N</th>
<th>Sought help (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannestad [322]</td>
<td>Norway</td>
<td>20+</td>
<td>In past 12 mos</td>
<td>6625</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any</td>
<td>3300</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stress</td>
<td>3085</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urge or mixed</td>
<td>1201</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daily</td>
<td>1538</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>2201</td>
<td>50</td>
</tr>
<tr>
<td>Roberts [105]</td>
<td>USA</td>
<td>50+</td>
<td>Any in past 12 mos</td>
<td>356</td>
<td>13</td>
</tr>
<tr>
<td>Hagglund [326]</td>
<td>Sweden</td>
<td>23-51</td>
<td>Persistently incontinent for &gt;4 years</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>Rekers [81]</td>
<td>Belgium</td>
<td>35-79</td>
<td>Any</td>
<td>344</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minor*</td>
<td>242</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serious*</td>
<td>97</td>
<td>44</td>
</tr>
<tr>
<td>Kinchen [327]</td>
<td>USA</td>
<td>18+</td>
<td>Any in past 30 days</td>
<td>1970</td>
<td>45</td>
</tr>
<tr>
<td>Diokno [329]</td>
<td></td>
<td></td>
<td>4+ days/week</td>
<td>632</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>453</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bothersome</td>
<td>877</td>
<td>62</td>
</tr>
<tr>
<td>Holst [78]</td>
<td>New Zealand</td>
<td>18+</td>
<td>Any in past 12 mos</td>
<td>142</td>
<td>35</td>
</tr>
<tr>
<td>Van der Vaart [308]</td>
<td>Netherlands</td>
<td>20-45</td>
<td>Any stress</td>
<td>365</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any urge</td>
<td>143</td>
<td>11</td>
</tr>
<tr>
<td>Mardon [95]</td>
<td>USA</td>
<td>65+</td>
<td>Any in past 6 mos</td>
<td>37,805</td>
<td>53</td>
</tr>
<tr>
<td>Sampselle [111]</td>
<td>USA</td>
<td>42-52</td>
<td>Any in past 12 mos</td>
<td>1854</td>
<td>12</td>
</tr>
<tr>
<td>Hsieh [98]</td>
<td>Taiwan</td>
<td>60+</td>
<td>Any</td>
<td>485</td>
<td>30</td>
</tr>
<tr>
<td>Gasquet [325]</td>
<td>France</td>
<td>18-70</td>
<td>Stress in past 30 days</td>
<td>980</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild severity*</td>
<td>729</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate severity*</td>
<td>198</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High severity*</td>
<td>53</td>
<td>81</td>
</tr>
<tr>
<td>Harris [324]</td>
<td>USA</td>
<td>30-79</td>
<td>Any 1+ /week</td>
<td>331</td>
<td>45</td>
</tr>
<tr>
<td>Zhu [84]</td>
<td>China</td>
<td>20+</td>
<td>Any in past month</td>
<td>2110</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any SUI in past month</td>
<td>1196</td>
<td>7.4</td>
</tr>
<tr>
<td>Hunskaar [110]</td>
<td>France, Germany,</td>
<td>18+</td>
<td>Any in past 30 days</td>
<td>5976</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Spain, UK</td>
<td></td>
<td>France</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Germany</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spain</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UK</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

* Serious defined as >weekly and > few drops; minor defined as other then serious
# low severity = minor amount of urine loss less than daily; moderate = either more then a minor amount of urine loss or daily urine loss; severe = daily loss of greater than a minor amount of urine
mixed incontinence are more likely to seek treatment than women with stress incontinence [84, 89, 322]. As expected, the proportion of women seeking treatment is strongly associated with frequency, severity and bothersomeness, with several studies reporting proportions of 50% to 80% of women with daily, moderate to severe, or bothersome incontinence [321-322, 325, 327].

Reasons given by people for not seeking help include: not regarding incontinence as abnormal or serious [78, 330-331], embarrassment [332-334], considering incontinence to be a normal part of ageing [331, 335], having low expectations of treatment [78, 330] and thinking they should cope on their own [332, 335]. Several studies have identified factors associated with seeking care for UI, including severity, duration and type of UI, nocturnal symptoms, and the bother or impact of UI [78, 105, 322, 326-327, 330-331]. Other characteristics such as age, general health, or attitude toward health care may also play a role [327].

Even when women seek care for incontinence, treatment is often limited or not provided at all [336-337]. For those receiving medical treatment, most discontinue within 12 months. Probably less than 20% of women with mild to moderate incontinence are actively being treated for incontinence [325]. In a study of management of incontinence in general practice, 30% of the women who had told their doctor about their symptoms perceived that they were offered no help [335]. It is probable that many primary health care providers lack confidence in managing UI, and that this contributes to under treatment in those seeking help [338].

Only a small proportion of incontinent community-residing women have had surgery, medication, or exercise regimens [110, 327, 339-341]. In addition to seeking help from the formal health care system, common responses to symptoms of illness are self-management and self-treatment behaviour. The major method of actively managing UI among community residents is the use of absorbent products [339, 342-345]. For many women with very mild or occasional UI it is probably adequate not to seek help from the health care system. Others are satisfied with information and understanding about the causes and in many cases self-care may be quite appropriate. A Danish study has shown that simple information and advice was adequate “treatment” for 23% of the women seeking an open access incontinence clinic [346]. A Swedish study found that among 136 women with UI, 36% wanted clinical evaluation, and only 24% subsequently started treatment [109].

Both epidemiological and qualitative research in this field should be encouraged in order to understand cultural, religious, and personal factors including attitudes and perceptions of health care, for help seeking behaviour world wide [331, 333, 337].

VII. SUMMARY POINTS

1. The estimated prevalence of UI in middle-aged and older women in the general population appears to be in the range of 30% to 60% (increasing with age); while the prevalence of daily UI ranges from 5% to 15%, rising to over 15% in women over age 70 who are institutionalized. Some studies have found prevalences outside theses ranges, demonstrating that there remains a large variation in the estimated prevalence of urinary incontinence in women, even after taking into account differences in definitions, ascertainment, and demographic characteristics. At least part of this variation is likely to be due to the sensitivity of the subject and subtle differences in the conduct of studies. (LE 1)

2. Multiple observational studies have confirmed that White, non-Hispanic women have a substantially higher prevalence of stress UI than Black or Asian women that is not explained by differences in known risk factors for UI. (LE 1)

3. Pregnancy, labour and vaginal delivery (vs C-section) are significant risk factors for later UI, but the strength of this association diminishes substantially with age. (LE 1)

4. While several specific parturition factors such as instrumental delivery and birth weight are risk factors for UI in the post-partum period, their association with UI in later life is weak or nonexistent, suggesting that changes in birthing practices in developed countries are unlikely to affect UI in older age. (LE 2)

5. Additional evidence has now established body mass as an important, modifiable risk factor for UI. (LE 1)

6. Physical function also appears to be an independent risk factor for UI in older women. Whether improvement in physical function leads to a reduction in UI remains to be established. (LE 2)

7. Evidence from 2 blinded, randomised controlled trials indicate that oral oestrogen, with or without progestogen, is a significant risk factor for UI in women age 55 and older (LE 1).

8. Diabetes is a risk factor for UI in most studies. While diabetic neuropathy and/or vasculopathy are possible mechanisms by which diabetes could lead to UI, no mechanism has been established, nor is it clear whether prevention or treatment of diabetes, separate from weight reduction, will reduce the risk of UI. (LE 2)

9. Menopause, as generally defined, does not appear to be an independent risk factor for stress UI. (LE 2)
10. Hysterectomy remains a possible risk factor for later UI, but the evidence is inconsistent. (LE 2) 

11. Moderate to severe dementia in older women is a moderate to strong independent risk factor for UI (LE 2). Whether interventions to maintain or improve cognitive functioning also reduce UI has not been evaluated.

12. Mild loss of cognitive function in community-dwelling women, separated from physical function and other factors, increases the risk of UI slightly if at all, but may increase the impact of UI. (LE 2)

13. Data from twin studies suggests that there is a substantial genetic component to UI. (LE 1)

14. Other potential risk factors, including smoking, diet, depression, constipation, UTIs, and exercise, while associated with UI, have not been established as etiologic risk factors and are in fact difficult to study with observational data because of the potential for unmeasured confounding and questions of direction of the association. (LE 3).

Since the 3rd ICI in 2004, the quantity and quality of epidemiologic studies of UI has continue to increase. Most notable are the availability of prospective data from several studies that can examine risk factors for incident incontinence and a growing number of studies comparing the prevalence and incidence of UI among Caucasian, Black, Asian and Hispanic women using population-based samples and multivariate analysis. Below are several suggestions for research over the next 5 years.

- Obesity is now an established, modifiable risk factor for UI. Investigation and dissemination of strategies to reduce the risk of UI through weight control or reduction should be a priority.

- Poor physical function is a consistent risk factor for incontinence, particularly in the elderly. Whether or not it is modifiable is not clear. Intervention studies are needed to assess the impact of improvement of physical function on prevention or reduction of UI in frail elderly.

- Moderate to severe dementia is also a consistent risk factor for incontinence. Studies aimed to maintain or improve cognitive functioning should assess change in UI as an outcome variable.

- The higher prevalence and incidence of UI, particularly stress UI, among Caucasian women, compared to Black or Asian women remains unexplained. Further studies are needed to identify additional exposures or biological factors that could explain these differences.

E. EPIDEMIOLOGY OF UI IN MEN

I. GENERAL COMMENTS

The epidemiology of UI in men has not been investigated to the same extent as for females. However, progress has been made during recent years, particularly in the reporting of population-based studies of urinary incontinence among men and more specifically, of urinary incontinence associated with prostatectomy. In addition, more reports have been published on the risk factors for the development of UI in men.

In almost all community based studies, the prevalence rates of UI continue to be reported to be less in men than in women by a 1:2 ratio. The type and age distribution of UI appear to be different between the sexes, and risk factors, although less investigated in men, seem to be different from women. It is also important not to consider UI as an isolated problem in men, but rather as a component of a multifactorial problem. Often other urogenital symptoms (LUTS) such as weak stream, hesitancy, and dribbling, or erectile dysfunction, exist.

Post-prostatectomy incontinence has been studied and reported with increasing regularity in the last few years. Since radical prostatectomy is being performed with increased frequency, and incontinence is one of the main complications of the procedure, a specific review of UI in the postprostatectomy patient population is presented in this section. In addition to epidemiological studies, we included clinical trial data on postprostatectomy incontinence.
II. PREVALENCE

Several surveys from the general population have been conducted to determine the prevalence of UI in men (Table 11). Prevalences ranging from 1 – 39% have been published. The wide span of results may be explained by the variation in the population studied, the definition of incontinence used and the methods used in the surveys. A systematic review of 21 studies reported a prevalence of UI in older men ranging from 11-34% (median = 17, pooled mean = 22%). In the same review, the prevalence of daily UI in men ranged from 2-11% (median = 4%, pooled mean = 5%) [347]. A wide definition of UI, older age, inclusion of institutionalized men, and the use of self-reporting methods tend to result in higher prevalence rates [347-348].

For any definition of UI, there is a steady increase in prevalence with increasing age (Table 12).

1. INCONTINENCE SUBTYPES

Due to differences in pathological anatomy and pathophysiology of UI in men and women, there is a different distribution in incontinence subtypes. Recent studies confirmed our previous reports of the predominance of urge incontinence (40-80%), followed by mixed forms of UI (10-30%), and stress incontinence (<10%) [376] (Table 13).

The higher percentages of the urge and mixed types of incontinence are more significant in studies involving older people. In fact, the increasing prevalence of any UI by age in men is largely due to the contribution of urge incontinence rather than stress incontinence. One study demonstrated an increasing rate of urge UI from 0.7% between age 50-59, 2.7% between 60-69 and 3.4% for 70 years and older respondents. Stress UI was steady at 0.5%, 0.5% and 0.1% for the above groups respectively [356]. On the other hand, Maral and coworkers reported increasing prevalence also of SUI with age, from 0.9% between age 35-44, to 1.2% between 45-54, 3.8% between 55-64, and 4.9% at age 65 and older [353].

Most studies report a significant fraction of other/unclassified type of urinary incontinence. One study reported that a majority of men with UI had overflow and functional types of incontinence [354], while another found constant dribbling in 7% of their respondents [373]. Terminal dribbling or postvoid dribbling is another type of leakage in men that is difficult to assign to the conventional subtypes of UI. In an Australian survey, 12% of respondents reported frequent terminal dribbling [387].

2. SEVERITY

When it comes to severity, the distribution in men follows that of the women. Estimates for severe UI in older women tend to be about twice as high as for older men [376].

3. RACE-ETHNICITY

Very few studies have looked at the impact of race or ethnicity on the prevalence of UI among men. A four-country study presented lower prevalences of reported UI among men from Korea (4%) and France (7%) than in men from Britain (14%) and Denmark (16%) [349]. On the other hand, unpublished data from the MESA study did not indicate differences in prevalence among white male respondents compared to African American respondents.

4. INCIDENCE AND REMISSION

Literature on the incidence of male UI is very scarce. The MESA study [376] found a one-year incidence rate for men older than 60 years of 9-10%. In a population-based survey in the UK among men at least 40 years of age, the one-year incidence of UI was noted to be 3.8% [364]. A review of a health organization database of males at least 65 years old revealed an UI incidence of 23.8 per 1000 person years. Malmsten [360] analysed the age of onset of UI for each age cohort. Mean starting age for all men was 63 years. The mean duration was about 8-10 years in the cohorts.

Substantial remission rates for UI in males were noted by the MESA study, higher among men (27-32%) than women (11-13%) [376]. A similarly high one-year remission rate of 39.6% was noted among British males [364].

One possible explanation for the difference in the published incidence and remission rates in men compared to women, is the predominance of urge type incontinence among men, and its close relation to overactive bladder with and without incontinence. Another factor is the close association between urge UI and prostate gland disease, infections, or bowel dysfunction, all of which are relatively amenable to treatment or may improve even without treatment.

III. POTENTIAL RISK FACTORS FOR UI

There is relatively little research concerning conditions and factors that may be associated with UI in men, and clear risk factors are more seldom scientifically documented. However, a few available studies have identified potential risk factors, which are described below.

1. AGE

As in women, increasing age is correlated with increasing prevalence of UI (Table 12). Multivariate analysis in several studies has shown that age is an independent risk factor for incontinence [349, 378,
### Table 11. Examples of prevalence studies of UI among men

#### A. General Population Sampling, all adult age groups

<table>
<thead>
<tr>
<th>Author and year [ref]</th>
<th>N</th>
<th>Response rate (%)</th>
<th>Population (age)</th>
<th>Definition of UI used</th>
<th>Method of assessment</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle 2003 [349]</td>
<td>4979</td>
<td>28–72%</td>
<td>40–79</td>
<td>Lack of control over bladder function which caused urine leakage at times</td>
<td>Self-administered questionnaire</td>
<td>7 (France), 16 (The Netherlands), 14 (UK), 4 (Korea)</td>
</tr>
<tr>
<td>Engstrom 2003 [350]</td>
<td>7806</td>
<td>86</td>
<td>60</td>
<td>Self-administered questionnaire</td>
<td>2 (SUI)</td>
<td></td>
</tr>
<tr>
<td>Van Oyen 2002 [351]</td>
<td>7266</td>
<td>-</td>
<td>&gt; 15</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 2001 [362]</td>
<td>1236</td>
<td>-</td>
<td>Mean 49</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maral 2001 [363]</td>
<td>1000</td>
<td>90</td>
<td>&gt; = 15</td>
<td>1 (SUI), 3 (IUI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortolotti 2000 [354]</td>
<td>2721</td>
<td>-</td>
<td>&gt; 50</td>
<td>Telephone interview</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Liotta 2000 [360]</td>
<td>3500</td>
<td>52.5</td>
<td>&gt; 40</td>
<td>Mailed self-administered questionnaire</td>
<td>10.5 (IUI)</td>
<td></td>
</tr>
<tr>
<td>Roberts 1999 [357]</td>
<td>778</td>
<td>-</td>
<td>&gt; 50</td>
<td>25.5 (95CI 22.5 28.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts 1998 [358]</td>
<td>2150</td>
<td>-</td>
<td>&gt; 40</td>
<td>Self-administered questionnaire</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Schulman 1997 [359]</td>
<td>2489</td>
<td>-</td>
<td>&gt; 30</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marniesten 1997 [360]</td>
<td>10458</td>
<td>74</td>
<td>&gt; 45</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drokichurst 2003 [361]</td>
<td>1883</td>
<td>-</td>
<td>&gt;=30</td>
<td>Interview</td>
<td>6.0% overall, 3.8% incontinent in the previous year, 2.8% in the previous 2 months</td>
<td></td>
</tr>
<tr>
<td>Irwin 2006 [362]</td>
<td>19165</td>
<td>33%</td>
<td>&gt;=18</td>
<td>ICS 2002 definition</td>
<td>5.4 (1.9-9.0)</td>
<td></td>
</tr>
<tr>
<td>Legace 1993 [363]</td>
<td>2830</td>
<td>86%</td>
<td>&gt; 20</td>
<td>Self-administered questionnaire</td>
<td>11 (9-13)</td>
<td></td>
</tr>
<tr>
<td>McGrother 2004 [364]</td>
<td>90491</td>
<td>60.2</td>
<td>&gt;=40</td>
<td>Postal questionnaire</td>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>O’Brien 1991 [365]</td>
<td>2496</td>
<td>79</td>
<td>Self-administered questionnaire</td>
<td>7.4 (95CI 6.4 – 8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farnacci 2002 [366]</td>
<td>9613</td>
<td>97.5</td>
<td>&gt;=50</td>
<td>Involuntarily leaked in the past 3 months</td>
<td>8.3 (7.7-8.9)</td>
<td></td>
</tr>
<tr>
<td>Roc 1999 [367]</td>
<td>12529</td>
<td>53</td>
<td>5.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diokno 1986 [368]</td>
<td>805</td>
<td>85.1</td>
<td>60 older</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11. Examples of prevalence studies of UI among men (Continued)

<table>
<thead>
<tr>
<th>Author and year [ref]</th>
<th>N</th>
<th>Response rate (%)</th>
<th>Population (age)</th>
<th>Definition of UI used</th>
<th>Method of assessment</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dice-Diaz 2003 [389]</td>
<td>350</td>
<td>-</td>
<td>&gt; 64</td>
<td>-</td>
<td>-</td>
<td>7 (95CI: 15-28)</td>
</tr>
<tr>
<td>Stoddart 2001 [370]</td>
<td>1 000</td>
<td>79</td>
<td>&gt; 65</td>
<td>Incontinence in the previous month</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Aggazzotti 2000 [371]</td>
<td>693</td>
<td>90</td>
<td>&gt; 65, Community and residential homes</td>
<td>Involuntary loss of urine at least 2x/month</td>
<td>Questionnaire, review of clinical record</td>
<td>39.2</td>
</tr>
<tr>
<td>Gavras-igloias 2000 [372]</td>
<td>827</td>
<td>-</td>
<td>≥ 65</td>
<td>-</td>
<td>-</td>
<td>29 (25-36 95CI)</td>
</tr>
<tr>
<td>Simoger 2000 [355]</td>
<td>840</td>
<td>85</td>
<td>25-83, VA clinic</td>
<td>Incontinence in the past 12 months</td>
<td>Self administered questionnaire</td>
<td>32.3</td>
</tr>
<tr>
<td>Damian 1998 [373]</td>
<td>589 (including women)</td>
<td>78</td>
<td>≥ 65</td>
<td>Current experience of difficulty in controlling urine or urine escaping involuntarily</td>
<td>Interview</td>
<td>15</td>
</tr>
<tr>
<td>Umlauf 1996 [374]</td>
<td>1 480</td>
<td>53</td>
<td>Elderly</td>
<td>Uncontrolled urinary leakage of any amount the month before</td>
<td>Mailed self administered questionnaire</td>
<td>29</td>
</tr>
<tr>
<td>Nyulio 2003 [375]</td>
<td>171</td>
<td>-</td>
<td>≥ 70</td>
<td>-</td>
<td>-</td>
<td>24 (UUI)</td>
</tr>
<tr>
<td>Horzeg 1990 (MBSA study) [376]</td>
<td>66% - 72%</td>
<td>&gt;=60</td>
<td>In the past 12 months about on how many days have you lost any urine, even a small amount beyond control</td>
<td>Interview</td>
<td>16.9%</td>
<td></td>
</tr>
<tr>
<td>Janssen 2007 [377]</td>
<td>57%</td>
<td>&gt;= 65</td>
<td>Leaked or lost control of urine in the past year</td>
<td>Interview</td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td>Landi 2003 [378]</td>
<td>5372</td>
<td>&gt;= 85</td>
<td>MDS urinary incontinence scale of &gt;=1</td>
<td>Health care professional assessment</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Thom 1997 [379]</td>
<td>1420</td>
<td>NA</td>
<td>&gt;=85</td>
<td>Review of database</td>
<td>-</td>
<td>5.3</td>
</tr>
</tbody>
</table>

5UI: Stress UI, UUI: Urga UI, MUI: Mixed UI
Table 12. Examples of prevalence of UI across age spectrum in men

<table>
<thead>
<tr>
<th>Author and year [ref]</th>
<th>N</th>
<th>Distribution by age</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yarnell, 1979 [380]</td>
<td>169</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 – 80</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80+</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 – 64</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65 – 74</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75+</td>
<td>18</td>
</tr>
<tr>
<td>Diokno, 1986 [103]</td>
<td>805</td>
<td>60+</td>
<td>19</td>
</tr>
<tr>
<td>Malmsten, 1997 [360]</td>
<td>10458</td>
<td>45</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90+</td>
<td>28.2</td>
</tr>
<tr>
<td>Schulman, 1997 [342]</td>
<td>2499</td>
<td>50 – 54</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 – 64</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70+</td>
<td>14</td>
</tr>
<tr>
<td>Bortolotti, 2000 [211]</td>
<td>2721</td>
<td>51 – 60</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61 – 70</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70+</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 – 69</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70+</td>
<td>4</td>
</tr>
<tr>
<td>Aggazzotti, 2000 [371]</td>
<td>839</td>
<td>&lt;65</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65 – 74</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 – 84</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85+</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;=95</td>
<td>57</td>
</tr>
<tr>
<td>Temml, 2000 [382]</td>
<td>1236</td>
<td>20 – 39</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 – 59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 – 69</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70+</td>
<td>12</td>
</tr>
<tr>
<td>Smoger, 2000 [355]</td>
<td>840</td>
<td>&lt;40</td>
<td>25.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41 – 50</td>
<td>30.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51 – 60</td>
<td>31.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61 – 70</td>
<td>36.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71 – 80</td>
<td>33.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;80</td>
<td>20.0</td>
</tr>
<tr>
<td>Mariappan 2006 [383]</td>
<td>353</td>
<td>40-49</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-59</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-69</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;=70</td>
<td>10.3</td>
</tr>
<tr>
<td>McGrother 2004 [157]</td>
<td>92491</td>
<td>40-49</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-59</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-69</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;=80</td>
<td>30.5</td>
</tr>
<tr>
<td>Obrien 1991 [365]</td>
<td>2496</td>
<td>35-44</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45-54</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55-64</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65-74</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;=75</td>
<td>15.4</td>
</tr>
<tr>
<td>Thom 1997 [379]</td>
<td>1420</td>
<td>65-74</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-79</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;=80</td>
<td>7.6</td>
</tr>
</tbody>
</table>
Compared to women, however, there seems to be a more steady increase in prevalence in men with increasing age.

2. LOWER URINARY TRACT SYMPTOMS (LUTS) AND INFECTIONS

In postal and telephone surveys of community-living incontinent men, a majority has experienced a variety of other medical conditions, many of which may cause or aggravate UI. LUTS like urgency, nocturia, feeling of incomplete voiding and reduced flow are typically associated with UI [352,368, 394]. In one study, UI was reported by 15% of men without voiding symptoms, frequency or urgency and by 34% of those with such symptoms [368].

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI [356, 373], with an odds ratio of 3.7 for UI in men reporting cystitis [356] and an odds ratio of 12.5 among men with recurrent infections [354]. It should be noted that reports indicating a positive association between UTI and incontinence involved men aged older than 60 years.

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI [356, 373], with an odds ratio of 3.7 for UI in men reporting cystitis [356] and an odds ratio of 12.5 among men with recurrent infections [354]. It should be noted that reports indicating a positive association between UTI and incontinence involved men aged older than 60 years.

3. FUNCTIONAL AND COGNITIVE IMPAIRMENT, PHYSICAL ACTIVITY

Mobility problems such as use of a wheelchair or aids to walking, as well as diagnosed arthritis or rheumatism or having a fall during the last year, were significantly greater among incontinent than continent men [373, 395]. A Japanese study of community dwelling men noted that UI is more likely among men whose activities of daily living (ADL) are impaired, specifically those who are unable to change clothes and unable to walk outside, with odds ratio of 17.4 and 4.36 respectively [356]. A Canadian study found odds ratios of 1.8 and 6.4 for partially and totally immobile men aged 65+, respectively, for daily UI compared to those with normal ambulatory function. Similarly, the Silver Network Home Care project among the frail older persons in Italy showed that those with higher ADL scores (i.e., greater functional impairment) had 2-4x higher odds of having UI. A survey of nursing home residents in Wisconsin identified dementia and poor ADL as risk factors for the occurrence of UI [390]. In general, most studies find similarities between men and women (see subsection on women) for functional and cognitive impairment as risk factors for UI.

Corollary to this, the association between physical activity and UI has been studied by Kikuchi and co workers among the elderly, community-based population in Japan [391]. They found that men with middle level physical activity was associated with a lower UI prevalence compared to those with low level physical activity, with an odds ratio of 0.17-0.78. High level physical activity showed similar relations but was not statistically significant.

4. NEUROLOGICAL DISORDERS

Many specific neurological diseases may lead to UI [392]. Neurogenic detrusor overactivity is seen commonly in meningo-myelocele patients and in spinal injuries, Parkinson’s disease and multiple sclerosis. Underactive bladder dysfunction due to a cauda equina lesion or diabetes might cause overflow or a paralysed pelvic floor and hence stress incontinence. Men who have suffered a stroke were at increased risk for incontinence with an odds ratio of 7.1 [356]. A case control study of age-matched long-term stroke male survivors with controls showed a higher prevalence of UI among stroke survivors compared to controls (17% vs 9%). In addition, among UI sufferers, the stroke survivors were found to have higher frequency and more leakage than controls. In a study of 235 stroke patients, the occurrence of UI correlated with motor weakness (OR 5.4), visual defects (OR 4.8, and dysphagia (OR 4.0).

5. PROSTATECTOMY

A well known iatrogenic cause of male incontinence is prostatectomy, but we do not know the attributable risk for this factor in the population of men with UI. In a Norwegian survey of elderly men with UI almost a third had undergone prostatectomy. [394].

In a cross sectional study among men in Vienna, Schmidbauer and associates identified previous prostatectomy to be associated with UI [352].

TURP seems to be followed by an incidence of stress incontinence of about 1%. A randomized controlled trial
comparing TURP, laser prostatectomy and evaporization of the prostate for benign disease showed comparable incontinence rates immediately and up to 12 months postoperatively [396].

**Radical prostatectomy** seems to induce UI at a much higher rate than TURP. The overall prevalence of post- radical prostatectomy incontinence ranges from 2 to nearly 60% (Table 14). This wide range may be explained by many factors, including differences in study characteristics, population characteristics, study site, the definition used, and the timing of assessment of continence in relation to the surgery. The era in development of the procedure has also been found to be associated to the prevalence rates [411], as well as the various procedural modifications of the surgery (see below).

Post-prostatectomy incontinence rates elicited from symptoms reported by patients are generally 2-3x higher than those from physicians’ observations. Studies that have performed both assessments in the same population confirm this observation that doctors underestimate postprostatectomy incontinence by as much as 75% [419,422-424].

Incontinence rates after prostatectomy seem to steadily decline with time and plateaus 1 - 2 years after surgery [400, 404,407-410] (Table 15). This emphasizes the need of a long follow-up period to establish continence status postprostatectomy. An actuarial study among 647 postprostatectomy men estimated UI rate of 13% at one year and 7% at two years postsurgery [425].

The **technique of radical prostatectomy** impacts on UI rates. Modifications associated with lower UI rates include the perineal approach [416, 418] and preservation of neurovascular bundle [431-433]. Bladder neck preservation affords earlier return to continence compared with bladder neck resection, but with similar UI rates after one year [405, 434]. One study showed earlier recovery of UI after tennis racquet reconstruction and bladder neck preservation compared with bladder neck resection with puboprostatic ligament preservation, but with similar UI rates at one year [410,435]. However, continence status assessed more than 12 months after surgery showed even lower rates of UI after bladder neck preservation (11.6%) compared to resection (4.9%) in one study [410]. UI after laparoscopic procedures seems to be higher initially but approximates that of open techniques by one year [427].

Older age at time of surgery has been found to be associated with a higher prevalence of post-prostatectomy UI [398, 408, 418, 43-433], one study showed a doubled risk for every 10 years of age beginning at age 40 [406]. Another study suggested that rather than absolutely affecting final continence prevalence, elderly men need a longer time to achieve continence after surgery [407]. Two studies found no relation between age at surgery and UI [423, 436].

Other factors have been found to be associated with a higher prevalence of post-prostatectomy UI, although not consistently. Such factors include prior TURP, preoperative lower urinary tract symptoms, obesity, clinical stage, PSA, prostate volume and Gleason score [398, 432-433, 437-438]. A retrospective analysis of 156 patients who had undergone preoperative MRI of the prostate and were followed up post-prostatectomy showed that time to return to continence was associated with the variation in the shape of the prostatic apex. The prostatic apex that do not overlap with the membranous urethra was found to be significantly associated with an early return of continence [438 The 5-year cohort study of the Prostate Cancer Outcomes Study found that among prostatectomy patients, race and ethnic differences was related to urinary incontinence, with African-Americans having better recovery compared to non-hispanic whites and Hispanics [439].

Adjuvant radiotherapy has not been found to affect post-prostatectomy incontinence rates when assessed beyond 1 year [Formenti 2000, Hofmann 2003, Kundu 2004].

### IV. FACTORS OF UNCLEAR ASSOCIATION WITH UI IN MEN

A 9 year study of Janssen (377) showed increasing rates of UI with increasing BMI among the older men and women. However, multivariate analysis failed to show increased BMI (overweight and obese levels) as an independent risk factor for the development of UI.

In a study including a younger population in Australia, obesity was noted to be associated with UI with an odds ratio of 3.2 (1.2-9.0) [389]. In this study, however, being merely overweight was not associated with UI.

Several studies in the older persons have shown an association between physical activity and UI among women that is not seen among men [349, 391].
### Table 14. Examples of studies on the prevalence of post-prostatectomy incontinence

<table>
<thead>
<tr>
<th>Author/Ref</th>
<th>Procedure</th>
<th>N</th>
<th>Follow up (months)</th>
<th>Definition</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demirkesen 2007</td>
<td>RRP</td>
<td>72</td>
<td>&gt;12</td>
<td>More than once a day leakage</td>
<td>8</td>
</tr>
<tr>
<td>Kundu 2004</td>
<td>RRP</td>
<td>2737</td>
<td>&gt;= 18</td>
<td>Use of pads</td>
<td>7</td>
</tr>
<tr>
<td>Salomon 2003</td>
<td>RRP</td>
<td>205</td>
<td>12</td>
<td>Use of pads</td>
<td>34</td>
</tr>
<tr>
<td>Moizadeh 2003</td>
<td>RRP</td>
<td>200</td>
<td>12-15</td>
<td>Use of pads</td>
<td>2</td>
</tr>
<tr>
<td>Maffezzini 2003</td>
<td>RRP</td>
<td>300</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Deliveliotis 2002</td>
<td>RRP</td>
<td>149</td>
<td>12</td>
<td></td>
<td>6-8</td>
</tr>
<tr>
<td>Benoit 2000</td>
<td>RRP</td>
<td>25 651</td>
<td>12</td>
<td>Use of pads</td>
<td>8</td>
</tr>
<tr>
<td>Walsh 2000</td>
<td>RRP</td>
<td>64</td>
<td>12-18</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Poon 2000</td>
<td>RRP</td>
<td>220</td>
<td>Mean &gt;12</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Catalona 1999</td>
<td>RRP</td>
<td>1 870</td>
<td>&gt;12</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Horie 1999</td>
<td>RRP</td>
<td>104</td>
<td>12</td>
<td>Use of pads</td>
<td>22</td>
</tr>
<tr>
<td>Golutuboff 1998</td>
<td>RRP</td>
<td>480</td>
<td>12</td>
<td>Any UI Daily or pad use</td>
<td>57</td>
</tr>
<tr>
<td>Weldon 1997</td>
<td>RRP</td>
<td>220</td>
<td>18</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Lowe 1996</td>
<td>RRP</td>
<td>180</td>
<td>12</td>
<td>Any protection</td>
<td>12</td>
</tr>
<tr>
<td>Hu 2003</td>
<td>RP</td>
<td>12 079</td>
<td>&gt; 36</td>
<td></td>
<td>4-20</td>
</tr>
<tr>
<td>Augustin 2002</td>
<td>RP</td>
<td>674</td>
<td>&gt; 24</td>
<td>Use of pads</td>
<td>32</td>
</tr>
<tr>
<td>Sebesta 2002</td>
<td>RP</td>
<td>24</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Potosky 2000</td>
<td>RP</td>
<td>60</td>
<td>12</td>
<td>Use of pads</td>
<td>3-19</td>
</tr>
<tr>
<td>Arai 1999</td>
<td>RP</td>
<td>907</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egawa 1997</td>
<td>RP</td>
<td>94</td>
<td>18</td>
<td>Use of pads</td>
<td>27</td>
</tr>
<tr>
<td>Gray 1999</td>
<td>RRP/RPP</td>
<td>209</td>
<td>Median 32</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Olsson 2001</td>
<td>Lap RP</td>
<td>228</td>
<td>12</td>
<td>Use of pads</td>
<td>21.6</td>
</tr>
<tr>
<td>La Fontaine 2000</td>
<td>Lap RP</td>
<td>522</td>
<td>Mean 31</td>
<td>Use of pads</td>
<td>15</td>
</tr>
<tr>
<td>Galli 2006</td>
<td>Lap RP</td>
<td>150</td>
<td>12</td>
<td>Use of pads</td>
<td>8.3</td>
</tr>
</tbody>
</table>

RRP: radical retropubic prostatectomy
RPP: radical perineal prostatectomy
RP: radical prostatectomy, unspecified or combined
Lap RRP: laparoscopic retropubic prostatectomy

### Table 15. Examples of studies on postprostatectomy UI rates at different times of assessment

<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>N</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobson 2007</td>
<td>RRP, Lap RP</td>
<td>210</td>
<td>48</td>
<td>29</td>
<td>15</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Galli 2006</td>
<td>Lap RRP</td>
<td>150</td>
<td>45</td>
<td>26.2</td>
<td>12.1</td>
<td>8.3</td>
<td>-</td>
</tr>
<tr>
<td>Link 2005</td>
<td>Lap RRP</td>
<td>122</td>
<td>-</td>
<td>83.0</td>
<td>47.8</td>
<td>33.3</td>
<td>-</td>
</tr>
<tr>
<td>Minzadeh 2003</td>
<td>RRP</td>
<td>-</td>
<td>18</td>
<td>9</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jonier 1996</td>
<td>RP</td>
<td>24</td>
<td>87</td>
<td>67</td>
<td>63</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pensco 2005</td>
<td>RP</td>
<td>-</td>
<td>1213</td>
<td>-</td>
<td>33</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

1 - continence defined as 0 pads
2 - continence defined as <= 1 pad daily
Overactive bladder (OAB) is defined as the presence of urgency and frequency (either daytime or nighttime), with or without urinary incontinence (UI) [1]. OAB is often divided into OAB without UI (OABdry) and those with OAB and UI (OABwet). To find studies looking for the prevalence of OAB a search was carried out on Medline with the strategy (((Overactive bladder.mp) or (OAB$.mp)) and ((prevalence.mp) or (incidence.mp))). The studies identified in the search were then scanned to be sure they were population based (i.e. not based on doctor attendances or similar). The references to the studies found were searched for further applicable studies. The studies often used different populations and ways of selecting samples, and the definition of OAB changed slightly, although this was standardised after the 2002 ICS standardization report. The results of these studies are summarized in the table.

The prevalence of OAB in adult males varies from 10.2% to 17.4% and in females from 7.7 to 31.3 (Table 16). Clearly different definitions, the different age groups studied and maybe cultural differences affect the rates (LE 2). OABwet was less prevalent than OABdry except for one implausible looking result. The response rate was quite low in many of these studies, and sometimes it was impossible to know the response rate (e.g. when quota sampling was used).

A common finding was that the rates increased with age, but this was not universal (LE 2). Some studies found that after adjusting for state of health then the relationship with age went away, and some found that it only applied to OABwet. Usually OAB was more prevalent in females, and this was very much more pronounced for OABwet which sometimes meant that OABdry was the same for males and females. OAB was related to general health problems and in particular diabetes. It is likely to be related to urinary problems in childhood.
Faecal Incontinence (FI) is the involuntary loss of faeces – solid or liquid. Anal Incontinence (AI) includes these events as well as the involuntary loss of flatus, which is felt by many patients to be an equally disabling disorder. The discussion below will therefore focus on the broader definition: AI. A third cause of soiling or embarrassment is anal mucoid seepage, a condition that cannot be deferred by an able sphincter and intact cognition, most often caused by an organic colonic disease or dietary sensitivity, and more rarely by faecal impaction. This is the loss of fluid, sometimes feculent, often following a normal continent defecation. This is an important condition to distinguish from true incontinence because authors that report very high prevalence rates of AI include leakage in their questionnaires and thus may include these individuals with this very common symptom. However in this case there is no detectable sphincter abnormality and it is not treatable by any of the standard therapies for true incontinence: sphincter repair, neuromuscular re-education or even faecal diversion. It is in fact why we wear underclothes.

Older reports of AI prevalence have come from single institutions, and the patients described therein have been subject to referral bias when demographics and aetiology are discussed. The accuracy of AI prevalence estimates may also be diminished by difficulty in ascertaining those figures due to the common underreporting of AI and patients’ reluctance to report symptoms or to seek treatment. It has been shown that women are more willing to report AI than men. In addition, the character (incontinence of solid faeces, diarrhoea, or flatus, or merely anal seepage) and frequency (daily versus episodic) of reported AI varies greatly in each report, and indeed between individuals. So, prevalence depends heavily on the definition of AI.

**Data Sources and Level of Evidence**

Since ICI 3, New studies were sought using Medline and EMBASE using the search terms faecal, faecal, anal, incontinence, epidemiology. In addition systematic reviews were specifically sought in Medline, EMBASE and the Cochrane Library.
Because therapeutic interventions are not the subject of this chapter, and so the epidemiology is descriptive and not derived from randomised clinical trials, the level of evidence will be at best 2, and the strongest evidence will come from systematic reviews in which there was a predefined search strategy and application of quality assessment tools that were designed specifically to minimise bias in referral or ascertainment.

II. PREVALENCE

1. ADULTS

In an effort to resolve the widely varying reported prevalence figures (Table 17), two systematic reviews of the published frequencies have been done of community dwelling adults (above age 15 in the second). A summary frequency was not calculated in the first because of the marked clinical heterogeneity between reports (Table 18). The three reports that the authors judged most free of potential biases had frequencies between 11% and 15%, though only one of these three used a validated assessment instrument [461]. The degree of disability present in these 11%-15% is not known, nor even if a portion of them had only anal seepage. These high prevalences were obtained in surveys that employed anonymous self-administered questionnaires, which may not allow objective confirmation of AI or assessment of degree of disability associated with AI. The second systematic review found a range of solid and liquid anal incontinence of 0-15.2% for solid and liquid faeces, with an average across both genders and all age groups of 4.3% [462].

2. CHILDREN

The reported prevalence of AI in children can be broadly divided into two facets: in those children born with congenital anomalies of the anus and rectum - either congenital aganglionosis (Hirschprung’s Disease) or imperforate anus - and those children without congenital anomalies. Among those children and adults who were born with defects, despite surgical correction of the defect, life long defaecation difficulties are common, occurring in roughly half of affected children [463-465]. Problems with psychological health and development because of the defaecation disorder is also common in this group, as is a generally depressed quality of life [466]. These disorders are not horribly rare, occurring in 3 to 5 per 10,000 live births [467].

Among children without congenital defects of the anal canal, bowel control has been found to be complete in one Swiss cohort in 33% by age 1 year, 75% by age two and 97% by age three. Nevertheless in this longitudinal study, a quarter of the boys and one tenth of the girls had a major period of incomplete bowel or bladder control between the ages of 6 and 18. At least annual encopresis occurred in 2-3% of these children, boys more frequently than girls [468]. In the Wisconsin Family Health Survey the prevalence of AI in children from the ages of 5 and 16 years was 12/1367 (0.88%) with the gender distribution being 7 boys and 5 girls (Wisconsin Family Health Survey: unpublished data). The common disorder for all children and then adults in this discussion is faecal retention with overflow and seepage.

III. INCIDENCE

Clinical trials have provided incidence data after a therapeutic interventions, but usually without a preliminary continence assessment. This is best seen in two Cochrane reviews of therapy for anal fissure [469-470]. AI incidence rates varied widely from 0% to 30%, to flatus only, and the duration was unspecified in the trials. Medical therapy was less likely than surgery to cause AI (0.23, 0.02-2.1), and certain operations (anal stretch) were more likely to cause AI than others (sphincterotomy) (4.2, 1.9-9.4).

IV. RISK FACTORS

1. AGE

Two systematic reviews have analyses of the association of age and anal incontinence and found age to be the most significant of all assessed associations [462,471].

2. GENDER

Most discussions of the aetiology of AI have been based upon the assumption that women, particularly for individuals under the age of 65 years, are far more at risk for AI than men. Injury to the pudendal nerve or sphincter muscle from prior obstetric trauma is described as the primary risk factor [472-474], followed by irritable bowel syndrome (a disease thought to be more prevalent in women) [475], and other aetiologies such as diabetes a distant third [476]. Yet each population based-survey of the prevalence of AI has shown a surprisingly high prevalence in males (Table 17) [459-460, 477-508]. Of the two systematic reviews that looked specifically at prevalence, only one assessed the role gender played and in that review gender was not associated with incontinence in any age group [462]. Clearly, aetiologies other than childbirth must be sought.

3. OBESITY

Three recent reports have demonstrated an increased risk of AI in obese women, a Kaiser cohort, a cross sectional survey in a specialty clinic and a case control study [508-510]. One longitudinal study found a reduction in anal leakage (again not necessarily a
### Table 17. Population-based Surveys of Prevalence of Anal Incontinence

<table>
<thead>
<tr>
<th>COUNTRY (ref)</th>
<th>POPULATION</th>
<th>N</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.K. [459]</td>
<td>Community Service</td>
<td>4 844</td>
<td>1.9%</td>
</tr>
<tr>
<td>France [476]</td>
<td>All &gt;45 years</td>
<td>1 100</td>
<td>11%, 6% to faeces, 50% are women</td>
</tr>
<tr>
<td>U.S.A. [476]</td>
<td>Market mailing</td>
<td>5 430</td>
<td>7% stooling, 0.7% to faeces</td>
</tr>
<tr>
<td>U.S.A. [460]</td>
<td>Wisconsin households</td>
<td>6 959</td>
<td>2.2%, 63% women</td>
</tr>
<tr>
<td>Australia [475]</td>
<td>Household survey</td>
<td>3 010</td>
<td>6.8% in men, 10.3% in women &gt;age</td>
</tr>
<tr>
<td>Germany [461]</td>
<td>&gt;18 years</td>
<td>500</td>
<td>4.4%-6.7% (by health)</td>
</tr>
<tr>
<td>Australia [480]</td>
<td>&gt;18 years</td>
<td>618</td>
<td>11-20% (gender M&gt;F)</td>
</tr>
<tr>
<td>Australia [482]</td>
<td>&gt;18 years</td>
<td>651</td>
<td>11.3%</td>
</tr>
<tr>
<td>New Zealand [484]</td>
<td>&gt;18 years old</td>
<td>717</td>
<td>8.1% for solid and higher for gas</td>
</tr>
<tr>
<td>U.K. [485]</td>
<td>&gt;40 years</td>
<td>10 116</td>
<td>1.4%</td>
</tr>
<tr>
<td>U.K. [488]</td>
<td>Postpartum women</td>
<td>549</td>
<td>5.5%</td>
</tr>
<tr>
<td>Canada [487]</td>
<td>Postpartum women</td>
<td>946</td>
<td>3.1% solid, 25.5% flatus</td>
</tr>
<tr>
<td>Denmark [468]</td>
<td>Postpartum women</td>
<td>1 726</td>
<td>6.6% in post partum, 6.6% to solid stool</td>
</tr>
<tr>
<td>Nigeria [468]</td>
<td>Gynecology patients</td>
<td>3 963</td>
<td>6.9%, 2.3% to solid stool</td>
</tr>
<tr>
<td>United Arab Emirates [490]</td>
<td>Women multipara</td>
<td>450</td>
<td>11.3%, 5.5% to solid stool</td>
</tr>
<tr>
<td>Canada [491]</td>
<td>Teenage females</td>
<td>228</td>
<td>3.5% flatus, 3% FI</td>
</tr>
<tr>
<td>Czech Republic [492]</td>
<td>Gynecology patients</td>
<td>2 212</td>
<td>5.6%, 4.4% in the</td>
</tr>
<tr>
<td>Japan [493]</td>
<td>Ureterosigmoidostomy</td>
<td>23</td>
<td>60.7% post</td>
</tr>
<tr>
<td>Sweden [494]</td>
<td>Prostate cancer</td>
<td>864</td>
<td>RR 1.3-4.5</td>
</tr>
<tr>
<td>Australia [495]</td>
<td>Diabetics</td>
<td>8 857</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Holland [496]</td>
<td>Women &gt;60 years</td>
<td>710</td>
<td>4.2% to 16.9% with rising age</td>
</tr>
<tr>
<td>U.S.A. [497]</td>
<td>&gt;65 years at home</td>
<td>326</td>
<td>3.7% (M&gt;F)</td>
</tr>
<tr>
<td>Japan [498]</td>
<td>&gt;65 years at home</td>
<td>1 405</td>
<td>6.6-6.7% (by age)</td>
</tr>
<tr>
<td>U.S.A. [499]</td>
<td>&gt;50 years</td>
<td>1 440</td>
<td>11.1 - 15.2% (F &gt; M)</td>
</tr>
<tr>
<td>U.K. [500]</td>
<td>&gt;65 years at home</td>
<td>2 818</td>
<td>3%</td>
</tr>
<tr>
<td>Holland [501]</td>
<td>&gt;60 years</td>
<td>3 345</td>
<td>6%, (M = F)</td>
</tr>
<tr>
<td>Czech Republic [502]</td>
<td>Nursing homes</td>
<td>1 162</td>
<td>54.4%</td>
</tr>
<tr>
<td>U.S.A. [503]</td>
<td>Nursing homes</td>
<td>18 170</td>
<td>47% FI</td>
</tr>
<tr>
<td>Canada [504]</td>
<td>Nursing homes</td>
<td>447</td>
<td>46% FI, 44% both UI and FI</td>
</tr>
<tr>
<td>France [505]</td>
<td>&gt;18 years</td>
<td>713</td>
<td>30% response rate, 11% gas, 4% feces, Women&gt;Men</td>
</tr>
<tr>
<td>France [507]</td>
<td>Women &gt;50 years</td>
<td>2 640</td>
<td>85% response rate. 9.5% FI, but Incontinence</td>
</tr>
<tr>
<td>U.S.A. [508]</td>
<td>Obesity</td>
<td>4 103</td>
<td>37% response rate. 25% AI</td>
</tr>
</tbody>
</table>
direct correlate with incontinence) in women after bariatric surgery and weight loss, though other factors including dietary and activity change may have been responsible for the improvement [511].

4. CHILDBIRTH AND MODE OF DELIVERY

A meta-analysis of published reports that assessed anal sphincter integrity after vaginal delivery and correlated this with continence stated that 77%-83% (depending on parity) of anal incontinence in parous women was due to sphincter disruption [512]. Three things are implied by this conclusion: first, that incontinence in men, children, of elderly onset (or even in middle aged women) and in nulliparous women, or women having Caesarean section has a completely different cause than in women who have ever delivered vaginally. There is scant epidemiologic evidence that this is the case [513]. Second, it is implied that sphincter repair would be effective treatment for anal incontinence in almost all parous women. Yet repair of disrupted sphincter has less than a perfect track record. Even more importantly, there is a reported rapid decay in function after repair that is far too great to be explained by age alone [515-522]. Third, if direct trauma to the anal sphincter (and not intra-pelvic nerves) were the major cause of anal incontinence, then Caesarean section should be effective in preventing incontinence (Figs 6 & 7).

However a systematic review has shown that this is not the case [471]. Seventeen reports have been found eligible for inclusion in the review, encompassing 16,036 women having had 3,101 Caesarean deliveries and 12,935 vaginal births as the index event prior to anal continence assessment. None of these reports demonstrated a significant benefit of Caesarean section in the preservation of anal continence. The greater the quality of the report, the closer its Odds ration approached 1.0. There was no difference in continence preservation in women who had Cesarean section versus vaginal delivery. Among the seven best studies, the NNT is 339, i.e. 339 Caesarean section would have to be performed to prevent a single case of fecal incontinence. Surprisingly, in the only reported cohort that included nulliparous women, there is an increased risk of anal incontinence in women who have had Cesarean section [480] that approaches that of women who had a vaginal delivery (Figures 6,7,8).

Forrest plots demonstrate the meta-analyses of the 7 best studies providing data on post partum fecal incontinence (quality in this instance being defined as age and parity adjustment of data, no prior vaginal delivery in the Caesarean section cohort, and assessment a long enough time after parturition to allow for perineal healing), comparisons of elective versus emergency Cesarean section and elective Caesarean section versus vaginal delivery. Summary data are presented in Table 18.

But why doesn’t Caesarean section prevent anal incontinence, especially when associating perineal trauma with loss of bowel control is not just intuitive, but sometimes visibly obvious? Certain aspects of vaginal delivery are clearly causally related to anal incontinence: significant laceration, forceps, and some episiotomies [523-524]. However this review demonstrates that other factors need to be explored. So one must look to pregnancy and not just labour and delivery as an initiating factor. Further evidence in
Figure 6: Seven of the published studies that compare fecal incontinence rates after C-section compared to vaginal delivery that are adjusted for age, parity, primipara or prior C-section only and have adequate follow up to allow for perineal healing.

Figure 7: Studies that provide data allowing comparison of fecal incontinence rates in women having elective versus emergent C-section.

Figure 8: Studies with data that allowed comparisons of fecal incontinence rates in women have only elective C-section versus vaginal delivery.
favour of this comes from the sphincter repair literature cited above. The rapid decay in function suggests that another defect is present besides a gap in the sphincter that remains after the early effects of sphincter repair wear off. What this is is not yet known, though trauma at the pelvic inlet during pregnancy or in early labour [525] seems likely.

Indirect evidence for the possibility that injury higher in the pelvis may be related to AI in pregnant women can be found in the association of hysterectomy with AI, an association seen more prominently with abdominal hysterectomy (TAH) than vaginal hysterectomy (VH), and for flatus only [526] (Odds Ratio of TAH vs. VH for faeces: 1.2, 0.3-4.7, Odds Ratio for gas: 18.9, 1.1-327). Pelvic nerve injury during surgery is the postulated reason for this difference.

5. NURSING HOME RESIDENCE

The most prominent association with AI by far is nursing home residence. Whereas the prevalence of AI is probably around 2% to 5% for community-dwelling persons, and may rise with increasing age to greater than 10%, among nursing home residents the prevalence approaches 50% [502-504]. This is partly explained by FI being one of the most common reasons for nursing home admission. In a large survey of 18,000 Wisconsin nursing home residents, risk factors for fecal incontinence (FI) were directly observed by nursing home personnel [503]. Urinary incontinence (UI) was the greatest risk factor for FI (OR = 12.6, 11.5-13.7), followed by the loss of ability to perform daily living activities (6.0, 4.7-7.7), tube feeding (7.6, 5.6-10.4), physical restraints (3.2, 4.7-7.7), diarrhoea (3.3, 2.7-4.2), dementia (1.5, 1.4-1.7), impaired vision (1.5, 1.4-1.7), constipation (1.4, 1.3-1.6), fecal impaction (1.5, 1.1-2.1), stroke (1.3, 1.2-1.5) male gender (1.2, 1.1-1.3), age and body mass index. Inverse associations were noted with heart disease, arthritis and depression.

6. DIARRHOEA

The importance of diarrhoea of liquid stool in FI cannot be overemphasized. One case series noted that 51% of individuals with chronic diarrhoea were incontinent [458]. In the Wisconsin Family Health Survey of AI [560], 10 of the 25 subjects with FI lived in Milwaukee when the city experienced an outbreak of waterborne disease [527]. Non-infectious causes of diarrhoea must also be considered, including those initiated by leisure activities such as running [528].

7. SURGERY

AI originating from surgery would seem fairly insignificant in the general population, since prior anal surgery has not been an apparent risk factor in the larger surveys. Several operations nonetheless frequently can result in AI. Examples are midline internal sphincterotomy, lateral internal sphincterotomy, fistulectomy, fistulotomy, ileo-anal reservoir reconstruction, low anterior rectal resection, total abdominal colectomy, and ureterosigmoidostomy. The risk of lateral internal sphincterotomy for anal fissure causing AI was previously thought to be insignificant when compared to midline sphincterotomy, but a recent reappraisal of this operation has shown an AI risk may be 8% [529]. The risk of AI after fistulotomy has been reported to be as high as 18% to 52% [530]. New approaches to fissure and fistula have recently been developed specifically to lower this risk [530-531]. However incontinence after haemorrhoidectomy has also been reported to be as high as 33%, an operation in which no sphincter is divided [532]. This suggests either that division of the anoderm, not the sphincter may be affecting continence, or that the method of ascertainment used in published surveys is not accurate. Mixing urine and stool has been found to have a predictable effect on anal sphincter control, as does diarrhoea, in patients having uretero-sigmoidostomy after urinary bladder resection [493].

8. SPECIFIC NEUROLOGICAL AND OTHER DISEASES

Several specific diseases have been anecdotally associated with AI in case series, and mechanisms to explain the associations have been investigated [533]. Examples are diabetes, stroke [534-535], multiple sclerosis, Parkinson’s disease, systemic sclerosis, myotonic dystrophy, amyloidosis, spinal cord injury, perforate anus, Hirschsprung’s disease, retarded or interrupted toilet training, procidentia, and any illness causing diarrhoea (HIV, IBD, radiation, infection). Many of these conditions directly affect patient mobility and ability to perform daily living activities or they cause diarrhoea or faecal impaction.

9. OTHER FACTORS AND PROSPECTIVE ASSESSMENT OF RISK FACTORS

Because of a paucity of clinical trials that specifically address risk factors and prevention of AI, the strongest available data to identify risk come from cohorts that collected data on potential risk factors prior to the onset of incontinence. The only prospectively collected risk assessments for FI have occurred in three nursing home cohorts. Porell combined UI and FI into a single outcome variable and found many positive associations in a cohort of 60,000 nursing home residents in Massachusetts [536]. Age, African American race, cognitive and ADL impairments predicted the outcome, though specific relative risks for incidence are not presented. Chassange followed 234 previously non-FI residents in France for 10 months, during which 20% had FI episodes, but only 7.5% developed long lasting FI [537]. The others had acute episodes due to diarrhoea or impaction. The factors associated with the development of long lasting FI were urinary incontinence (UI) (2.9, 1.8-4.6), decreased mobility (1.8, 1.1-3.0), and cognitive defects:
either as seen in an MMSE score <15 (2.5, 1.4-4.4) of history of dementia (2.1, 1.2-3.5). Neither gender nor age were risk factors. Nelson reported, in a cohort of 18,000 nursing home residents in Wisconsin, a subgroup of 3,850 continent of both urine and faeces in 1992 and were assessed one year later [538]. 15% developed FI. Positive associations were seen for ADL loss (3.4, 2.4-4.5), trunk restraints (2.5, 1.7-3.6), dementia (1.7, 1.4-2.0), African American race (2.1, 1.3-3.4) and age (1.02, 1.0-1.0). UI was not investigated as a risk factor because it was felt to be a co-morbid condition.

Lastly, in a broadly based cross sectional survey, it was apparent that factors that affect an individual’s general health or physical capabilities, independent of age and gender, place that individual at greatest risk for AI [475], though all four are significantly associated with AI [460]. Among obstetrical patients age has also been a consistent association, with less consistent associations noted for chronic bronchitis (OR =6.5, 1.1-3.8), symptoms of pelvic prolapse (5.0, 3.0-8.7) and obesity (3.0, 1.0-3.4) [539].

VI. PREVENTION

This discussion is by necessity descriptive, so preventive measures are only relevant insofar as they provide insight into aetiology of incontinence. By far the most frequently applied preventive measure is Caesarean delivery, discussed above. Its lack of effectiveness in preventing anal incontinence provides a valuable insight into the relationship of pregnancy and AI – that the focus may need to be more on the pregnancy rather than the delivery and how it effects defecation afterwards. A decision analysis study suggests specific obstetrical indication for elective C. section that may be cost effective [540]. Another study related to birth trauma randomized mothers to immediate post-partum anal ultrasound with repair of occult defects in the sphincter and continence assessed in follow-up, demonstrating an improved outcome with this intervention [541].

The AHRQ recently published a monograph on prevention of incontinence, though the strategies listed for AI were therapies for existing AI, such as pelvic floor exercises and retraining, rather than established mechanisms for prevention [542].

VI. SUMMARY POINTS

- Anal and urinary incontinence commonly coexist, particularly in the elderly and in nursing home residents (LE 1).
- The prevalence of anal incontinence increases with age, but is present in all age groups and both genders varying from 1.5% in children to more than 50% in nursing home residents (LE 1).
- AI is almost as common in men as in women (LE 2).
- Mode of delivery does not seem to be a significant factor in the development of obstetric anal incontinence, i.e., AI develops after Caesarean delivery as often as after vaginal delivery (LE 2).
- Obesity is perhaps the most modifiable risk factor for AI (LE 2).
- As populations age, co-morbid disease becomes a significant component of fecal incontinence risk. Surgery, neurological diseases, and stroke are examples.
- Cognitive and ADL impairment are associated with fecal incontinence.
- More population based prevalence surveys have been published.
- More analyses comparing AI after Caesarean section and vaginal delivery have been published.
- Systematic reviews of prevalence, including the role of age and gender, Caesarean delivery and decision analyses for the application of Caesarean delivery in macrosomia have been published, providing needed aggregation of data with quality assessment of existing literature.

VII. FUTURE NEEDS

- Risk factors for AI in each age group are still poorly defined
- Prevention research, much less policy, are therefore still a great distance away.
H. EPIDEMIOLOGY OF POP

I. GENERAL COMMENTS AND DEFINITIONS

Pelvic organ prolapse (POP) refers to loss of support for uterus, bladder, colon or rectum leading to prolapse of one or more of these organs into the vagina. Prolapse is thus a continuous condition when measured by visual inspection of the vaginal wall during valsalva. For clinical purposes, the degree of POP is commonly described as above the introitus, at the introitus, or beyond the introitus with or without valsalva. The International Continence Society first developed a standardised definition for the condition of POP in 1996 [543]. The ICS Pelvic Organ Prolapse Quantification (POPQ) examination defines prolapse by measuring the descent of specific segments of the reproductive tract during valsalva strain relative to a fixed point, the hymen. The POPQ system describes the anatomic findings of pelvic organ prolapse without consideration for symptoms and bother perceived by the woman. Validation of this system has shown it to be highly reliable [544]. The stages of prolapse severity are arbitrarily defined, and there is no clear differentiation between normal anatomic variation and mild POP. For research purposes there is consensus for use of the POPQ system until further evidence might clarify the distinction between normal variation and mild prolapse [545].

Determining POP based on self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms attributed to pelvic organ prolapse [546] and the fact that prolapse above the level of the hymeneal ring is usually asymptomatic [547]. The only exception appears to be a sensation of bulging into the vaginal [6] which is most strongly associated with prolapse at or below the hymeneal ring [549-550]. A recent study of 110 women found that a question asking about a feeling of something bulging in or dropping out of their vagina had a sensitivity of 84% and a specificity of 94% for POP at or beyond the hymeneal ring on examination [547]. Seeing prolapse would presumably be even more specific, but is too uncommon to be useful as a definition.

While not actually population-based, the women in the trial were recruited from the community rather than from women seeking gynaecological care, and provide important information on the prevalence of POP based on pelvic examination.

The prevalence of POP based on a sensation of a mass bulging into the vagina was remarkably consistent, ranging between 5 and 10 percent. The study by Eva et al., which reported a substantially higher prevalence included in the definition of POP, pelvic heaviness or digital pressure on the perineum or in the vagina to aid with defaecation [557]. The prevalence of observed prolapse in women enrolled in the WHI trial is similar to the prevalence found in the one population-based study that also used pelvic examination [558], although the prevalence of each type of prolapse was higher in the WHI study [550]. In both studies, prolapse occurs most frequently in the anterior compartment, next most frequently in the posterior compartment, and least in the apical compartment (Table 19).

Two studies that examined prolapse by race found that Black women had the lowest prevalence and Hispanic women the highest after controlling for multiple other factors in multivariate analysis [550,556]. The study reported by Rortveit et al based on symptoms found adjusted odds ratios of 0.4 (95% CI=0.2-0.8) for Black and 1.3 (95% CI=0.8-2.2) for Hispanic women, with White women as the referent group [556] [20]. Hendrix et al reported adjusted odds ratios of 0.6 (95% CI=0.5-0.8) for Black and 1.2 (95% CI=1.0-1.5) for Hispanic women compared to White women for POP based on genital examination [551].

II. PREVALENCE OF POP

Since the 3rd ICI, several additional studies have reported the prevalence of POP in a general population [551-556]. Reports from the Women’s Health initiative (WHI) Oestrogen Plus Progesterone trial, and randomized controlled trial, have been included [551,553-554].

III. INCIDENCE

Only two studies could be located that reported the incidence of new POP. Both studies were done on sub-groups of women enrolled in the WHI Oestrogen Plus Progestin Trial. The first study of 412 women enrolled at the University of California, Davis site, used a standardised pelvic examination repeated every 2 years over 8 years [551]. The incidence of new cystocele, rectocele and uterine prolapse was 9%, 6% and 2%, respectively. Annual rates of remission from grade 1 (prolapse to above introitus) was relatively common for each type of POP (24%, 22% and 48%, respectively) but less common from grade 2 or 3 (prolapse to or beyond introitus) (9%, 3% and 0%, respectively). In a second study of 259 women post-menopausal women with a uterus were examined using the POP-Q at baseline and annually for 3 years. POP was defined as prolapse to or beyond the hymeneal ring. The incidence of new POP was 26% at 1 year and 40% at 3 years, with remission rates of 21% at 1 year and 19% at 3 years [553].
## Table 19. Prevalence of pelvic organ prolapse (POP) defined by symptoms or observed on pelvic examination in the general population

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Definition of POP</th>
<th>Ages (years)</th>
<th>N</th>
<th>Prevalence Subgroup: %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumari [559]</td>
<td>India</td>
<td>“a mass of flesh in the vagina” or equivalent using local terminology</td>
<td>15+</td>
<td>2990</td>
<td>15-24: 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-34: 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35-44: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45-54: 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55-64: 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65+: 3</td>
</tr>
<tr>
<td>McLennan (560)</td>
<td>Australia</td>
<td>A feeling of something coming down in the vagina</td>
<td>15-97</td>
<td>1546</td>
<td>8</td>
</tr>
<tr>
<td>Tegerstedt (555)</td>
<td>Sweden</td>
<td>Validated 5 item questionnaire</td>
<td>30-79</td>
<td>5489</td>
<td>8</td>
</tr>
<tr>
<td>Eva [557]</td>
<td>Sweden</td>
<td>Any symptom of pelvic heaviness, genital bulge, or use of fingers in vagina or on perineum for defecation</td>
<td>40</td>
<td>641</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>663</td>
<td>28</td>
</tr>
<tr>
<td>Samuelsson [558]</td>
<td>Sweden</td>
<td>Standardized pelvic examination</td>
<td>20-59</td>
<td>487</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=39)</td>
<td></td>
<td>To introitus: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystocele: 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectocele: 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterocele*: 5</td>
</tr>
<tr>
<td>Rortveit [556]</td>
<td>USA</td>
<td>Feeling of bulging, pressure or protrusion or visible bulge or protrusion</td>
<td>40-73</td>
<td>2109</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawrence [552]</td>
<td>USA</td>
<td>Sensation of bulge in vagina or something falling out of vagina with a degree of bother of at least 33 on a 1-100 visual analogue scale (validated)</td>
<td>25-84</td>
<td>4103</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hendrix [550]</td>
<td>USA</td>
<td>Standardized pelvic examination</td>
<td>50-79</td>
<td>27,342</td>
<td>Any prolapse: 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=83)</td>
<td></td>
<td>Cystocele: 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectocele: 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterocele*: 14</td>
</tr>
<tr>
<td>Handa [551]</td>
<td>USA</td>
<td>Standardized pelvic examination</td>
<td>50-79</td>
<td>412</td>
<td>Any prolapse: 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=63)</td>
<td></td>
<td>Cystocele any: 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystocele grade 1: 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystocele grade 2: 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectocele any: 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectocele grade 1: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectocele grade 2: 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterocele any: 4 Uterocele grade 1: 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterocele grade 2: 1</td>
</tr>
<tr>
<td>Nygaard [554]</td>
<td>USA</td>
<td>POP-Q**</td>
<td>50-79</td>
<td>270</td>
<td>Stage 0: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=68)</td>
<td></td>
<td>Stage 1: 33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage 2: 63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage 3: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage 4: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; hymeneal ring: 26</td>
</tr>
<tr>
<td>Bradley [553]</td>
<td>USA</td>
<td>POP-Q</td>
<td>50-79</td>
<td>270</td>
<td>≥ hymeneal ring: 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mean=68)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denominator is women with a uterus

** Stages defined as 0: no prolapse, 1: prolapse to 1 cm above hymen, 2: prolapse to between 1 cm above and 1 cm below hymen, 3: prolapse between 1 cm below hymen and 2 cm above introitus, 4: prolapse beyond 2 cm above introitus.

Note: Studies reported by Handa, Nygaard and Bradley are all subsets from study reported by Hendrix.
Several studies have reported the annual incidence of surgery for POP in the US and at least one in the UK. A longitudinal study of over 17,000 women in the U.K., age 25 to 39 at baseline, reported an annual rate of prolapse surgery of 0.16% [561]. This rate is consistent with the rate of approximately 0.2% per year reported in the US [562-563]. One US study reported an annual incidence rising with age from 0.05% in women age 30-39 to 0.5% in women age 70-79 with an estimated lifetime cumulative risk of surgery from prolapse of 7% to 11% [564]. A recent US study reported similar surgical rates: 0.07% for women 18-39, 0.24% for women age 40-59, and 0.31% for women age 60-79 [565]. Surgical rates drop substantially after age 80 [564-565]. Estimating rates of prolapse surgery has the advantage of use of hospital discharge data on procedures, which is highly accurate for the procedure performed, but less accurate for the indications for the procedures, particularly when a procedure may have more than one indication.

### IV. POTENTIAL RISK FACTORS

#### 1. BOWEL DYSFUNCTION AND PELVIC ORGAN PROLAPSE

Bowel dysfunction is highly prevalent in women and comprises a wide variety of symptoms including constipation, rectal emptying difficulties, incomplete defecation, manually assisted defecation and faecal urgency. It has been estimated that up to 27 percent of the population in industrialised countries is affected by constipation. The overall prevalence of constipation and associated symptoms in women with pelvic organ prolapse range between 20-53% depending on definition of disorders[566-568]. Neurophysiological assessments have shown that damage to the pelvic floor musculature and nerve supply can occur in women with chronic constipation [569]. Although definitions of disease differ between studies, it is widely acknowledged that bowel dysfunction is a complex condition with a multifactorial aetiology. Predisposing factors comprise low socio-economic status, pelvic floor surgery, depressive disorders, thyroid dysfunction, physical disability and inactivity, and food habits [570].

Current epidemiological evidence on the association between bowel dysfunction and pelvic organ prolapse are at odds. A number of studies suggest that women with pelvic organ prolapse are significantly more likely to experience constipation and other symptoms of bowel dysfunction [568, 571-574], whereas others show a weak or non-existent association [567, 575-577]. In a case-control study, manually assisted defaecation was present in 19.7% of women with prolapse compared to 4.4% of control subjects (p<0.001) [568]. In a randomly selected population-based study, irritable bowel syndrome and constipation were both strongly associated with pelvic organ prolapse (OR 2.9 95% CI 1.7-4.8, and OR 2.5 95% CI 1.7-3.7 respectively) [573]. Varma et al. [574], suggested that among randomly selected women, having symptomatic pelvic organ prolapse more than doubled the risk of obstructed defecation (OR 2.3 95% CI 1.5-3.7). A retrospective questionnaire based survey of women with and without prolapse concluded that constipation as a young adult was an important factor in the development of uterovaginal prolapse [571]. In a case-control study, women with prolapse were at increased risk of constipation also after adjustment for dietary fibre intake (OR 2.9, 95% CI 1.1-13.5), when compared to women without prolapse [572].

In the cross-sectional Women’s Health Initiative (WHI), cystocele and rectocele were only weakly associated with constipation (OR 1.1 95% CI 1.0-1.2) [575]. Similar weak associations between prolapse and bowel dysfunction have been observed in other large cross-sectional studies [567,576-577]. Overall severity and prevalence of bowel dysfunction has shown poor correlation with findings of pelvic organ prolapse on radiological imaging [578-580]. Also at clinical examination, increasing vaginal descent and prolapse severity, show a generally weak (or absent) association with symptoms related to bowel dysfunction [566, 581-584]. In a substudy of the WHI, no specific bowel symptom was associated with increasing loss of pelvic organ support in any vaginal compartment [577]. When considering compartment-specific pelvic floor defects, most studies suggest that increasing posterior vaginal wall defects and perineal descent are correlated more to symptoms of obstructive defecation [567, 580, 582].

#### 2. PELVIC SURGERY AND POP

Even though the notion that hysterectomy increases the risk of pelvic organ prolapse has wide acceptance, longitudinal studies confirming a temporal association are few and previous studies often do not differentiate between various types of hysterectomy. A number of cross-sectional and retrospective studies implicate hysterectomy as an independent risk factor for pelvic organ prolapse. However, due to a delay of onset, large population samples and a sufficiently long duration of follow-up are required to determine an association with adequate statistical certainty.

In a nationwide prospective cohort study, Altman et al. [585] reported that 3.2% of women with hysterectomy had pelvic organ prolapse surgery, compared with 2.0% in non-hysterectomised controls, corresponding to a risk of 1.7 (95% CI, 1.6-1.7). In this study, vaginal hysterectomy had the highest risk for subsequent prolapse surgery (HR 3.8, 95% CI, 3.1 to 4.8) in comparison to non-hysterectomised controls. These data are largely in agreement with the longitudinal
Oxford Family Planning Association study by Mant et al. [586] reporting increased overall incidence rates for prolapse surgery following hysterectomy. Although not separating various hysterectomy techniques, Mant et al. determined that the risk of prolapse following hysterectomy was 5.5 times higher (95% CI 3.1-9.7) in women whose hysterectomy was performed for prolapse as opposed to other benign conditions. A history of hysterectomy has also been shown to increase the risk of prolapse in several cross-sectional and retrospective studies [587-588].

Specific risk factors for posthysterectomy prolapse have been assessed in two case-control studies. Both Dällenbach et al. [589] and Forsgren et al. [590] showed that pelvic floor surgery before hysterectomy was the strongest risk factor for developing posthysterectomy pelvic organ prolapse (OR 7.9, 95% CI 1.3-48.2 and OR 2.8, 95% CI 1.0-7.7 respectively). The risk of prolapse repair was 4.7 times higher in women whose initial hysterectomy was indicated for prolapse [589]. Vaginal vault prolapse involves the loss of vaginal apical support and can only occur after hysterectomy [591]. Marchionni et al. reported a 4.4% overall incidence of vaginal vault prolapse after hysterectomy but in women where uterine prolapse was the indication for hysterectomy the incidence was 11.6% [592].

It has also been suggested that other pelvic surgery may predispose women to subsequent genital prolapse including: rectopexy for rectal prolapse (OR 3.1; 95% CI 1.4-6.9) [593]; gynaecological surgery in general (OR = 3.9, 95% CI 1.8-8.8) [594], and retropubic colposuspension procedures are associated with a near 30% risk of subsequent vaginal vault and posterior vaginal prolapse at long-term evaluation [595-596]. In a prospective cohort study of 374 women, the 10-year re-operation rate was 17% after traditional prolapse or incontinence surgery [597]. Having undergone pelvic organ prolapse or incontinence surgery prior to the index operation increased the risk of re-operation to 17% compared with 12% for women who underwent a first procedure (p=0.04) [597].

3. GENETIC EPIDEMIOLOGY OF UI AND POP

The aetiology of female pelvic floor disorders is widely recognised to be multifactorial, yet the complex interaction between genetic predisposition and environmental influences is poorly understood. Evidence in support of a genetic influence on pelvic floor disorders derives from studies on familial transmission of disease, studies on ethnic group diversity and twin studies.

4. FAMILIAL TRANSMISSION

A large number of studies suggest that the risk for urinary incontinence “runs in the family” [598-603]. In the Norwegian Nord-Trendelag health survey (EPINCONT), daughters of mothers with urinary incontinence had an increased risk of stress incontinence (RR 1.5, 95% CI 1.3 to 1.8), mixed incontinence (RR 1.6, 95% CI 1.2-2.0), and urgency incontinence (RR 1.8 95% CI 0.8-3.9) [600]. Although study methodology and the magnitude of the risk estimates vary, studies on familial transmission of incontinence are in agreement: having a first degree female family member with stress urinary incontinence increases the risk for an individual becoming afflicted by the same disorder [604].

There is far less evidence to support the familial transmission of pelvic organ prolapse. In a case-control study, Chiaffarino et al. [605] showed that in comparison with women whose mother or sisters reported no prolapse, the risk for prolapse was higher in women with mothers (OR 3.2 95% CI 1.1-7.6) or sisters (OR 2.4 95% CI 1.0-5.6) reporting the condition. In young women (≤45 years of age) who had been operated on for prolapse, the familial incidence of genital prolapse was about 30% [606].

It is, however, a common misunderstanding that familial aggregation of any pelvic floor disorder invariably is a result of genetic factors. Risk estimates derived from family members in most cases cannot distinguish between heritability and non-inherited (environmental) factors in the family environment. Familial environmental influences which may have a direct effect on transmission of risk for stress urinary incontinence and pelvic organ prolapse includes smoking habits, socio-economic status, care seeking behaviour, attitudes towards physical exercise, dietary and drinking habits, and toilet training.

5. ETHNIC AND RACIAL INFLUENCES

The variation of disease occurrence in groups of different racial origin yet similar environmental exposures, lend support to the presumed genetic influence on the causation of benign pelvic floor disorders. This again provides circumstantial evidence for a genetic contribution to pelvic floor disorders since most of these studies have been unable to control for heritability in relation to the complex interaction of environmental factors.

There is consistent evidence to suggest that Caucasian women are at increased risk of stress urinary incontinence when compared to African-American women [607-610]. In a consecutive analysis of women referred for gynaecological care, Caucasian race increased the risk for stress urinary incontinence by two-fold (OR 2.2. 95% CI 1.3-3.7) when compared to African-Americans [611]. Three studies report higher risk of symptoms associated with overactive bladder in African-American women when compared to Caucasians [608-609, 611].

In cross-sectional studies from the US, African-American ethnicity conferred a significantly lower risk (OR 0.4 95% CI 0.2-0.8) [573] and Asian-Americans
had a higher risk of pelvic organ prolapse when compared to Caucasians (OR 1.4 95% CI 1.1-1.9 [612]). In women presenting for routine gynaecological examination 67% of Asian-American patients had stage 2 or greater prolapse as compared to 26% of African-American and 28% of Caucasian patients [612]. In the WHI, Hispanic women had the highest risk for uterine prolapse (OR 1.2 95% CI 1.0-1.5) and African-American (OR 0.6 95% CI 0.5-0.8) the lowest when compared to Caucasians [575]. Also within racial groups, the risk may differ as shown when comparing prevalence of pelvic organ prolapse between tribes in rural Gambia [613].

6. TWIN STUDIES

By comparing monozygotic female twins with identical genotype, and dizygotic female twins who on average share 50 percent of their segregating genes, the relative proportions of phenotypic variance resulting from genetic and environmental factors can be estimated. A genetic influence is suggested if monozygotic twins are more concordant for the disease than dizygotic twins whereas evidence for environmental effects comes from monozygotic twins who are discordant for the disease.

Recent studies in twins have indeed suggested a genetic influence on the phenotype for pelvic floor disorders [614-616]. However, studies based on volunteers are liable to bias since pairs who are concordant for the disease, are more likely to participate [617]. Only recently have large-scale population based genetic epidemiological studies in twins become available which clearly suggest a genetic contribution to pelvic floor disorders while controlling for both shared and non-shared environmental risk factors [618]. For both stress urinary incontinence and pelvic organ prolapse the genetic variation in liability to develop surgically managed disease after adjusting for age and parity was estimated to be about 40%. Recognising the considerable environmental effects and that heritability estimates in twins are likely to represent the upper limit of the genetic effects, [619-620] the influence of genetic factors should not be overstated. The role of gene-by-environment interactions, i.e. that certain genes may increase the risk for pelvic floor disorders only when the individual is exposed to a specific risk factor, remains to be decided and further complicates attempts to determine the genetic effects [621].

7. CANDIDATE GENES

A number of candidate genes which may be involved in the heritability of pelvic floor disorders have been investigated. Polymorphisms of the collagen type I gene have been shown to increase the risk of stress urinary incontinence, [622] and knock-out of the nitric-oxide-syntase gene in mice results in voiding disorders [623]. Mutations in lysyl-oxidase-like-1 gene is associated with pelvic organ prolapse [624]; ATP receptor P2X3-deletion in mice increases bladder capacity and reduces urinary frequency; and polymorphisms of the endothelin-1 gene may be involved in pelvic organ prolapse [625-626]. Polymorphisms in the promoter segment of laminin gamma 1 gene increases the susceptibility for early-onset pelvic organ prolapse [627]. Other candidate genes are almost certainly waiting to be discovered and results are so far of a preliminary nature.

8. OBSTETRICAL FACTORS AND POP

The debate on the importance of mode of delivery and obstetrical events to the development of pelvic floor disorders later in life is largely unresolved. For ethical and practical reasons, randomised controlled trials to study the causal effects of vaginal versus caesarean delivery will never be performed. Observational studies will therefore most likely remain the main source of knowledge on this subject. Nonetheless it is widely accepted that childbirth is a significant risk factor for pelvic organ prolapse, presumably due to overt or occult pelvic floor tissue trauma. Controversy does, however, remain with regard to the protective effects of Caesarean section and if specific obstetrical events should be considered as risk modifiers. Due to a delayed onset of pelvic organ prolapse in relation to giving birth, studies on the subject need a long duration of follow-up as well as large study populations to be able to elucidate the possible causative events. Therefore, the majority of studies on the subject are typically designed as cross-sectional surveys or retrospective cohort or case-control studies.

Pregnancy in itself has been identified as a risk factor for stress urinary incontinence. With regard to pelvic organ prolapse, the association is less well substantiated. In a clinical case-control study, all 21 nulliparous non-pregnant women had POP-Q stage 0 or 1, whereas 47.6% of 21 nulliparous pregnant women had pelvic organ descent corresponding to stage II (p<0.001) [628]. Overall POP-Q stage was higher in the third trimester than in the first (p=0.001). Also Sze et al. [629] found that in 94 nulliparous women evaluated at the 36 week antepartum visit and six weeks postpartum, POP-Q staging increased.

A large number of studies identify childbirth as one of the strongest predictors for developing pelvic organ prolapse later in life [573, 575, 586, 588 629-633]. It is also a recurrent observation that number of deliveries is associated with the risk for prolapse. In the prospective Oxford Family Planning Association study [586], childbirth was the single strongest risk factor for developing prolapse in women under 59 years of age and the risk increased by every delivery. Similar findings derived from the WHI [575], where a parity of one conveyed an overall two-fold risk increase for prolapse compared to having no children, after which
A wide variety of risk factors for pelvic organ prolapse, other than those addressed above, have been identified in the literature. Most of these have been investigated as part of larger multivariate analyses based on cross-sectional surveys or retrospective case-control studies. Overall, the evidence for these associations are largely of level III-IV and further research is needed to disentangle the effects and interactions of environmental risk factors for prolapse.

Several somatic risk factors for pelvic organ prolapse have been identified. Generalised connective tissue disorders such as Ehlers-Danlos disease and Marfans syndrome [636-637] have been linked to an increased risk of pelvic organ prolapse. In a community-based study of prolapse in rural West Africa, chronic anaemia was the strongest risk factor for prolapse after parity and age (OR 2.1 95% CI 1.1-3.4) [613] and chronic obstructive pulmonary disorders. Skeletal abnormalities such as thoracic kyphosis, lumbar lordosis and pelvic dimension changes have been associated with an increased risk for prolapse [638-639]. Women with joint hypermobility have a significantly higher prevalence of genital (and rectal) prolapse in comparison to women with normal mobility [640-641]. Weak associations have also been shown for osteoporosis and rheumatoid arthritis [634]. Variates that did not demonstrate any significant linkage to prolapse includes body mass index [642-643], the presence of chronic obstructive pulmonary disease and diabetes mellitus [587, 643]. Pulmonary impairment has been shown to be more common in women with loss of pelvic organ support compared to those without [644].

A low educational level (OR 2.16, 95% CI 1.10-4.24) [645] and low annual income [646], are socio-economic factors which have been associated with an increased risk for pelvic organ prolapse.

In 21,449 non-hysterectomised Italian women, higher education was associated with a protective factor for uterine prolapse [635]. However, despite significant differences in educational level, smoking habits, alcohol consumption, and socio-economic indices, the prevalence of pelvic organ prolapse did not differ between Croatian urban and rural women [647]. Physically strenuous occupation have also been shown to influence the risk for pelvic organ prolapse. In a register based study of 28,000 Danish assistant nurses exposed to repetitive heavy lifting, the risk for prolapse was higher among the nurses compared to controls (OR 1.6 95% CI 1.2-2.2) [648].

Women who were labourers/factory workers had significantly more severe prolapse than other job categories (p < 0.001) in a cross-sectional study of women presenting for routine gynaecological care [646]. Also, hard physical training may increase the risk for prolapse as women attending paratrooper training, were more likely to present stage II prolapse compared to controls (RR=2.7 95% CI 1.4-5.4) [649].
Most studies have used a cross-sectional design and there is limited longitudinal data to suggest a causal relationship between symptoms of obstructed defaecation and pelvic organ prolapse or vice versa.

Posterior vaginal wall prolapse and perineal descent are the compartment specific defects most clearly associated with symptoms of obstructive defaecation.

A number of studies suggest that hysterectomy and other pelvic surgery may increase the risk for pelvic organ prolapse (LE 2).

Hysterectomy due to pelvic organ prolapse and other pelvic floor surgery are the strongest predictors of secondary pelvic floor surgery (LE 2).

Stress urinary incontinence and pelvic organ prolapse have familial transmission patterns mediated by either genetic or environmental factors (LE 2).

Stress urinary incontinence is more common in Caucasian women, and pelvic organ prolapse in Caucasian and Hispanic women when compared to African American women (LE 2).

Twin studies suggest that heritability contributes to the liability of developing pelvic floor disorders but environmental effects are substantial.

Childbirth is associated with an increased risk for pelvic organ prolapse later in life. Current evidence also suggests that increasing number of childbirths increases the risk (LE 2).

It remains undecided if caesarean section prevents the development of pelvic organ prolapse but most studies indicate that caesarean is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth (LE 2).

There is a dearth in the understanding of how specific obstetrical events and the process of labour and delivery affects the risk for pelvic organ prolapse.

Life style factors and socio-economic indices appear to be associated with the risk for pelvic organ prolapse.

A number of somatic diseases and conditions have been linked to the occurrence of prolapse but the cause-effect relationship is undetermined.

The discussion here relates to UI only, as data and literature for FI and POP are very scarce. However, many of the principal arguments will be relevant to these conditions as well.

**I. GENERAL PROBLEMS IN SURVEY RESEARCH**

The well documented variation in prevalence estimates is thought to result at least in part from several confounders common to survey and epidemiological research. Herzog and Fultz[73] in a review of the prevalence and incidence of UI in community-dwelling populations, proposed that past investigations were plagued by sampling and non-response issues, by self selection and attrition, by definitional, conceptual, and measurement issues. Comprehensive reviews about measurements and methodological aspects of investigating UI are provided.[361] It is clear that there are large methodological challenges to rigorous research in this field. In general, quality of recent large studies has undoubtedly improved, but the scientific community must continue to deal with methodological challenges in order to achieve progress.

**II. DIFFERENT DEFINITIONS AND MEASUREMENT**

A major problem in research on UI has been the use of different definitions and measurements, and this might contribute to the wide range of reported prevalence estimates. The former ICS definition of UI – as a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable - included objective demonstration of urine loss as one critical component. This aspect limited the ICS definition for community based epidemiological investigations, because objective demonstration of UI is difficult to achieve outside of the clinical setting, and studies which were able to include this aspect in their assessment might have produced different prevalences. In addition, a social or hygienic aspect of the definition was problematic in epidemiologic studies because it added a subjective aspect to an objectively defined condition and therefore confounded the investigation of prevalence, incidence, and risk factors. In our previous report[2] we argued for reconsideration of the definition of UI, and we emphasized that the core of the definition should be "any involuntary loss of urine". In accordance with this view, ICS changed its definition in 2001 to UI being "the complaint of any involuntary leakage of urine"[1].
The new definition makes epidemiological research easier. But three consequences should be addressed:

1. Epidemiological studies should not be based on this definition alone, and all studies should include a minimal additional data set, standard confounders, and questions specific to the aim of the study. This is discussed in the Section on Recommendations for further research.

2. The number of persons fulfilling the definition will increase. This should not be interpreted as an increase in the number potential of patients.

3. Public awareness, case finding of health care personnel, and help seeking behaviour may be affected of a new and more extensive definition.

Studies have used different severity levels and time frames for defining UI. A factor further complicating the conceptualization and measurement of UI in epidemiologic studies lies in the nature of the condition. UI is a chronic condition (or set of conditions) that often starts slowly and comes and goes for a considerable time period before it become fully established.[361] If people get used to their UI or notice it less, this can interfere with valid assessment.

Ideally self-report measures are validated by clinical evaluations. However, clinical and even urodynamical investigations should be regarded as other measures, not necessarily as gold standards, because it is known to be difficult to demonstrate all urinary symptoms in the clinical setting.

Holteledahl[212] calculated prevalence estimates using different definitions of UI for the same sample of 50 to 70 year old women. The prevalence of any self-reported leakage was 47%. Self-reported regular UI with or without objective demonstration was found for 31% of women, regular incontinence according to the former full ICS definition for 19%. Another study found prevalences of 69% and 30% for any UI and the former ICS definition, respectively [33]. The results indicate that the former ICS definition was rather restrictive.

Low response rates may further bias prevalence estimates.[361] Known differences between responders and non-responders can be compensated during the analysis. The major problems is unknown differences in response rates and other characteristics. Incontinent women may not answer (or deny UI) because of embarrassment or related handicaps. But incontinent women may also find the subject particularly relevant and therefore respond to a greater extent than continent women. At present, we do not know much about how these factors may affect the comparison between incontinent and continent women.

One paper explored the problem of underreporting incontinence and how it can be altered with the use of an introduction to the incontinence questions and probing.[79] Another paper explored the issue of selection bias in mailed surveys. The first wave had higher prevalence of incontinence than follow-up mailings, and thus individuals with UI tended to respond on the first wave.[657] In an English mailed survey on incontinence and other urinary symptoms, a sample of non-responders were traced, and those eligible were asked questions from the survey.[658] Compared with the responders, the non-responders overall showed little differences in reporting of urinary symptoms. However, non-responders >70 tended to be of poorer general health, and they reported certain urinary symptoms more frequently.

### III. SUMMARY POINTS

- The lack of epidemiological data from populations underrepresented in research limits the world wide application of the present information.
- Many investigations are plagued by sampling and non response issues, by self selection and attrition. Many early studies were obtained from sampling patients seeking care.
- A major problem is the use of different definitions of incontinence. The new ICS definition makes epidemiological research easier.
- There are large methodological challenges to research in the field of UI. Unless the scientific community deals with these issues, progress will be difficult to make.

### J. HELP SEEKING BEHAVIOUR

A majority of people with UI have not sought help,[78, 81, 333, 340, 342] and this is confirmed also in recent publications.[322, 326, 327] Reasons given by people for not seeking help include: not regarding incontinence as abnormal or serious,[78, 330] considering incontinence to be a normal part of ageing,[335] having low expectations of treatment[78, 330] and thinking they should cope on their own.[501, 497] Some studies also confirm the notion that embarrassment may be an important reason for not seeking help.[332-334] There is an association between help seeking and condition-specific factors like duration, frequency and amount, and people's perceptions of the impact of incontinence,[78, 81, 358, 359, 322] but other more personal characteristics like individual health care behaviour and attitudes may also play a role.
In a Norwegian study 4.4% of all women >20 years old in a community consulted their general practitioner for UI during a 3 year period. But mentioning the symptoms to a physician may not be enough. There are reports of doctors not responding, either by ignoring the statement of symptoms or by providing a dismissive explanation, and people interpreting a lack of response from the doctor as an indication that no treatment is available. In a study of management of incontinence in general practice, 30% of the women who had told their doctor about their symptoms perceived that they were offered no help. It is probable that many primary health care providers lack confidence in managing UI, and that this contributes to under treatment in those seeking help.

Only a small proportion of incontinent community-residing women have had surgery, medication, or exercise regimens. In addition to seeking help from the formal health care system, common responses to symptoms of illness are self-management and self-treatment behaviour. The major method of actively managing UI among community residents is the use of absorbent products.

It is obvious that millions of men and women suffer from their UI, and that for many of them good treatment options are available. However, for many persons with very mild or occasional UI it is probably adequate not to seek help from the health care system. Others are satisfied with just information and understanding about the causes and in many cases self care may be quite appropriate. A Danish study has shown that simple information and advice was adequate “treatment” for 23% of the women attending an open access incontinence clinic. A Swedish study found that among 136 women with UI, 36% wanted clinical evaluation, and only 24% subsequently started treatment.

Both epidemiological and qualitative research in this field should be encouraged in order to understand cultural, religious, and personal factors for help seeking behaviour worldwide. Specifically, other than condition-specific factors should be further explored, e.g. persons’ health care behaviour, perceptions and attitudes.

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

There are indications of underreporting also of FI and patients’ reluctance to report symptoms or to seek treatment. It has been shown that women are more willing to report FI than men. For POP we have no information.

III. SUMMARY POINTS

- Recent publications confirm that a majority of people with FI, UI, and POP have not sought help.
- Only a small proportion of urinary incontinent community-residing people have had surgery, medication, or exercise regimens.
- Increasing severity, increasing duration, and urge/mixed type of UI are related to consulting a health care provider.
- Associations other than condition-specific factors should be further explored in future research, e.g. persons’ health care behaviour, perceptions and attitudes.
- Health care personnel should be encouraged to approach persons at risk for FI, UI and POP. People with such symptoms should be assessed so services and treatment can be offered and targeted. The patient’s view of management, even denial, should be respected.

K. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT

We have emphasised some major and important differences between epidemiology and clinical work. These differences may have several implications. A selection process is most often accomplished first by self-selection (help seeking), then a referral system, which provides specialist physicians to a patient population with higher prevalence of disease, more severe disease, and often skewed type distribution, thus obtaining test results with fewer false positives, better diagnostic accuracy, and more efficient use of resources. However, such intended and purposeful selection bias has its drawbacks. There is growing evidence that this selection process introduces bias into research and hampers our ability to generalize hospital based research back to general or primary care populations. Furthermore, it may result in recommendations and guidelines for diagnosis or therapy derived from tertiary care centres that are inappropriate at the primary care level. Often guidelines, review articles or teaching material do not take into account the varying prevalence and variation in clinical picture between community and hospital. They may also emphasise use of tests or equipment that are not appropriate or relevant for primary health care, thus leading to over utilisation of referrals. Data from hospitals or specialist level may also overestimate level of burden, costs and number of persons in need of treatment if such data are used for extrapolation.
back to community level. Therefore it is important that this Consultation uses different algorithms for initial and specialised care (see other relevant chapters).

One study provides substantial empirical evidence to support the existence of selection bias for UI.[322] The analyses were based on three populations of incontinent women: Community level (epidemiological survey), primary care level (prospective study), and secondary care level (university hospital, prospective study). The general practice patients were older and the hospital patients younger than those in the community. From community via general practice to hospital, there was an increase in duration, frequency of leakage, amount of leakage, severity and perceived impact of incontinence. Help-seeking at the primary care level was associated with increasing age and severity, and with urge symptoms and impact. Referral from general practice to hospital was only associated with (lower) age and urge symptoms.

Under the subtitle Severity and impact we have given examples of how the prevalence estimates for women change dramatically when bothersomeness and severity are considered. Taken together with selection bias, this emphasises caution when epidemiological data are used in a clinical context. It concerns “level of care” in several ways; there is a large transitional zone from healthy to diseased, there is a danger of medicalisation, and there is a danger of treating patients at a higher level than necessary. Risk factors, predictors and correlates discovered in epidemiological studies are probabilistic of nature and may not be decisive in the clinical assessment of an individual patient. In addition, the attributable risk due to some known risk factors may be statistically but not clinically significant.

The objective of the study was to estimate the current and future number of people with LUTS, including overactive bladder (OAB) and Urinary Incontinence (UI) utilising the current ICS definitions. Age- and gender-specific prevalence rates from the EPIC study[651] were applied to the worldwide over 20 year old population (4.2 billion) with males and females stratified into five-year age groups (20-24 to 80+). Projected population estimates for all worldwide regions were based on the United States Census Bureau International Database (IDB)[652].

Estimates were presented for 2008, 2013 and 2018 and are summarised in Tables 20 and 21. Table 21 summarises the estimated number of individuals with certain LUTS symptoms by year and sex in the world population and Table 22 describes the estimated number of individuals of LUTS and OAB over 10 years across the world regions.

Estimates and projections featured in this analysis were based on prevalence rates of LUTS described in the EPIC study – based primarily on a European population. The prevalence rates featured in the EPIC study are similar to other prevalence rates of LUTS that were found in others studies across other countries [653-654].

The projections in this report assume the prevalence rates of LUTS will remain throughout the year 2018 for all age and sex groups (Figure 9).

Prevalence of LUTS will also increase as other factors related to LUTS, such as obesity, increases. The estimated number for present and future years are not true numbers but are based on a projected population configured by the International Database (IDB). The IDB’s estimates and projections are drawn by Census Bureau demographers and are based on reviewed censuses, surveys, and vital statistics provided by National Statistics Offices [9]. Data on international migration and refugee movements, public health efforts, socio-political circumstances, and historical events such as natural disasters and conflict are all considered when the IDB calculates the estimates and projections (Figure 10).

It is anticipated that with the overall aging of the population the prevalence of LUTS will also increase. It has been shown that LUTS are burdensome to individuals [655-656] and the likely increase in the number of individuals experiencing. LUTS has implications on healthcare resources and overall health burden. This analysis is an estimate of the number of individuals with LUTS based on a conservative prevalence rate, and so the future number of those with certain LUTS may surpass those of this report (Table 22).

I. WORLDWIDE ESTIMATES OF CURRENT AND FUTURE INDIVIDUALS (≥20 YEARS) WITH LOWER URINARY TRACT SYMPTOMS INCLUDING URINARY INCONTINENCE AND OVERACTIVE BLADDER

In order to effectively plan health care resources it is necessary to estimate the prevalence and incidence of illnesses to know to what extent resources require to be allocated to a specific illness health care condition. This chapter has dealt with three major global problems, urinary and faecal incontinence as well as pelvic organ prolapse, that affect women and men throughout the world. At the ICI meeting in Paris data were presented regarding worldwide estimates of current and future individuals (≥20 years) with LUTS including urinary incontinence and overactive bladder [650].
<table>
<thead>
<tr>
<th>LUTS Symptoms</th>
<th>Male 2008</th>
<th>Male 2013</th>
<th>Male 2018</th>
<th>Female 2008</th>
<th>Female 2013</th>
<th>Female 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Incontinence</td>
<td>98</td>
<td>109</td>
<td>120</td>
<td>250</td>
<td>275</td>
<td>301</td>
</tr>
<tr>
<td>UUI</td>
<td>22</td>
<td>25</td>
<td>27</td>
<td>27</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>MUI</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>43</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>SUI</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>127</td>
<td>140</td>
<td>153</td>
</tr>
<tr>
<td>Other1</td>
<td>55</td>
<td>61</td>
<td>66</td>
<td>53</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Storage Symptom (Noct ≥1)</td>
<td>1,050</td>
<td>1,151</td>
<td>1,250</td>
<td>1,249</td>
<td>1,363</td>
<td>1,474</td>
</tr>
<tr>
<td>Any Storage Symptom (Noct ≥2)</td>
<td>597</td>
<td>655</td>
<td>713</td>
<td>760</td>
<td>831</td>
<td>901</td>
</tr>
<tr>
<td>Noct ≥1</td>
<td>942</td>
<td>1,035</td>
<td>1,127</td>
<td>1,098</td>
<td>1,200</td>
<td>1,301</td>
</tr>
<tr>
<td>Noct ≥2</td>
<td>388</td>
<td>427</td>
<td>467</td>
<td>464</td>
<td>509</td>
<td>555</td>
</tr>
<tr>
<td>Urgency</td>
<td>205</td>
<td>226</td>
<td>247</td>
<td>249</td>
<td>273</td>
<td>297</td>
</tr>
<tr>
<td>Frequency</td>
<td>127</td>
<td>139</td>
<td>152</td>
<td>161</td>
<td>174</td>
<td>186</td>
</tr>
<tr>
<td>Voiding Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voiding Symptoms</td>
<td>515</td>
<td>563</td>
<td>610</td>
<td>402</td>
<td>511</td>
<td>473</td>
</tr>
<tr>
<td>Intermittency</td>
<td>164</td>
<td>181</td>
<td>198</td>
<td>148</td>
<td>176</td>
<td>175</td>
</tr>
<tr>
<td>Slow Stream</td>
<td>156</td>
<td>173</td>
<td>193</td>
<td>122</td>
<td>161</td>
<td>146</td>
</tr>
<tr>
<td>Straining</td>
<td>132</td>
<td>145</td>
<td>157</td>
<td>83</td>
<td>120</td>
<td>98</td>
</tr>
<tr>
<td>Term Dribble</td>
<td>289</td>
<td>315</td>
<td>340</td>
<td>210</td>
<td>276</td>
<td>245</td>
</tr>
<tr>
<td>Post Micturition Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Mic3 Symptoms</td>
<td>332</td>
<td>365</td>
<td>396</td>
<td>297</td>
<td>350</td>
<td>348</td>
</tr>
<tr>
<td>Incomplete Emptying</td>
<td>263</td>
<td>288</td>
<td>314</td>
<td>257</td>
<td>290</td>
<td>302</td>
</tr>
<tr>
<td>Other Post Mic Incontinence</td>
<td>108</td>
<td>118</td>
<td>129</td>
<td>64</td>
<td>96</td>
<td>76</td>
</tr>
<tr>
<td>Any LUTS (Noct ≥1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any LUTS (Noct ≥1)</td>
<td>1,260</td>
<td>1,377</td>
<td>1,490</td>
<td>1,379</td>
<td>1,460</td>
<td>1,623</td>
</tr>
<tr>
<td>Storage + Voiding Symptoms</td>
<td>350</td>
<td>386</td>
<td>422</td>
<td>309</td>
<td>373</td>
<td>367</td>
</tr>
<tr>
<td>Storage + Post Mic Symptoms</td>
<td>247</td>
<td>273</td>
<td>299</td>
<td>238</td>
<td>274</td>
<td>282</td>
</tr>
<tr>
<td>Voiding + Post Mic Symptoms</td>
<td>205</td>
<td>226</td>
<td>247</td>
<td>158</td>
<td>205</td>
<td>187</td>
</tr>
<tr>
<td>Storage + Voiding + Post Mic</td>
<td>166</td>
<td>183</td>
<td>202</td>
<td>137</td>
<td>173</td>
<td>163</td>
</tr>
<tr>
<td>Any LUTS (Noct ≥2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any LUTS (Noct ≥2)</td>
<td>933</td>
<td>1,020</td>
<td>1,104</td>
<td>994</td>
<td>1,068</td>
<td>1,170</td>
</tr>
<tr>
<td>Storage + Voiding Symptoms</td>
<td>247</td>
<td>273</td>
<td>299</td>
<td>237</td>
<td>275</td>
<td>283</td>
</tr>
<tr>
<td>Storage + Post Mic Symptoms</td>
<td>188</td>
<td>207</td>
<td>227</td>
<td>190</td>
<td>214</td>
<td>226</td>
</tr>
<tr>
<td>Voiding + Post Mic Symptoms</td>
<td>205</td>
<td>226</td>
<td>247</td>
<td>158</td>
<td>205</td>
<td>187</td>
</tr>
<tr>
<td>Storage + Voiding + Post Mic</td>
<td>130</td>
<td>144</td>
<td>158</td>
<td>119</td>
<td>142</td>
<td>142</td>
</tr>
</tbody>
</table>
Figure 9: Estimated number of individuals with UI 2008, 2013 and 2018 grouped according to gender [650].

Figure 10: Estimated number of individuals with LUTS 2008, 2013 and 2018 grouped according to gender [650].
Much biomedical research is observational and the reporting of such research is often inadequate which hampers the assessment of its strengths and weaknesses and of a study's generalisability. The STROBE (Strengthening of the Reporting of OBservational studies in Epidemiology) statement was introduced [661]. It is a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross sectional studies. The use of this checklist is highly recommended.

II. SUMMARY POINTS

- The spectrum of severity of anal and urinary incontinence, as well as pelvic organ prolapse, and the symptom profile of patients referred to specialist centres do not necessarily reflect the spectrum of disease seen in the community.
- The selection and referral process may introduce bias into research and hamper the ability to generalise hospital-based research back to primary care populations.
- One should be very careful with calculating numbers of patients in need of therapy based on epidemiological data.

I. RECOMMENDATIONS FOR FURTHER RESEARCH

Much biomedical research is observational and the reporting of such research is often inadequate which hampers the assessment of its strengths and weaknesses and of a study’s generalisability. The STROBE (Strengthening of the Reporting of OBservational studies in Epidemiology) statement was introduced [661]. It is a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross sectional studies. The use of this checklist is highly recommended.

I. URINARY INCONTINENCE

It is recommended that more sustained research on measurement of UI should be performed including, its
types and severity to move the research ahead. Longitudinal study designs are needed to estimate incidence of UI and describe the course of the condition and its different forms and to investigate its risk factors and possible protective factors.

There is still little knowledge with regard to prevalence, incidence, and other epidemiological data in developing countries. It is recommended that fundamental research regarding prevalence, incidence and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.

Crude prevalence studies (descriptive epidemiology) from USA and Europe are abundant, and further studies should be done only with recommended and validated questionnaires or in order to combine data from the prevalence study with studies of co-factors and predictors (analytical epidemiology). Control for confounders, stratification, and multivariate techniques should be increasingly used because of the need for more advanced epidemiological analyses of risk factors and comorbidity. Strength of associations should be determined by relative risks and odds ratios, and confidence limits should be given. We have still very little knowledge of the absolute and relative importance of several risk factors, and almost no information about the attributable risk of the factors in the society.

Some potential risk and protective factors deserve more attention. For example, the role of pregnancy and childbirth in the development of UI must be studied in a fashion that links population-based methods to clinical assessment of pregnancy, delivery and the birth trauma and follows women over many years. Such a design is necessary because the effect of pregnancy and childbirth may become clear only years later when the woman is older and because the woman will not be able to report the exact nature of the tear or episiotomy, etc. There should be more emphasis on the associations between UI and specific diseases like stroke, diabetes, psychiatric disease and genital prolapse. Genetic components should be investigated.

Primary prevention is the main goal in the management of human disease. An important strategy would thus be to identify the individuals at risk, and then take measures to reduce the risk among those individuals or in certain risk groups. Based on current knowledge there are no well documented efforts that can be done in order to avoid the occurrence of UI in large populations. Primary prevention studies should be encouraged, but the epidemiological basis for choosing appropriate interventions is weak.

In surveys based on questionnaires or interviews symptoms can be registered. There are convincing data suggesting that the different types may reflect quite different pathologies and risk factors. Differentiating the types in future research might therefore prove very fruitful. Methodological work has still to be done in this area, but typical type descriptions should be included in new studies. Likewise, studies of risk factors should include important and known confounders such as age, parity, and weight.

Variations in definitions and measurement issues are fundamental and lead to problems with assessing the findings in epidemiological studies. We need to improve epidemiological studies by including variables that better characterise UI, so that more advanced and informative analyses may be conducted. It is therefore recommended that all epidemiological studies include a minimum data set (Table 23), including elements of screening question, frequency measure, quantity of urine loss, duration, type, and severity. In addition, it is recommended that validated measures of bother/quality of life and urinary symptoms other than UI should be included. We here also refer to the chapter from the committee on symptom and quality of life assessment.

In addition, it is recommended that validated measures of bother/quality of life and urinary symptoms other than UI should be included.

Table 23. Elements in a minimum data set recommended for all epidemiological studies

- Screening question for any involuntary urine loss
- Frequency measure. For example, classification into categories of none, less than once a month, one/several times a month, one/several times a week, every day/nigth, all the time
- Quantity of urine loss for a typical episode. For example, classification into categories of none, drops, small amounts, moderate amounts, much/a great deal
- Duration. For example months, years
- Type. Based on typical description; stress, urge, mixed and other
- Severity. Either by combining existing questions or by a validated index

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

In these areas there is a need for more epidemiological research in all areas; prevalence, incidence, and risk factors. Many of the fundamental methodological issues relevant to UI discussed above are highly relevant to the fields of FI and POP.

The committee emphasises that uniform definitions of
References


119. Jumadilova, Z., Zyczynski, T., Paul, B. et al.: Urinary incontinence in the nursing home: resident characteristics


389. Muscatello DJ, Rissel C, and Szonyi G. Urinary symptoms and incontinence in an urban community prevalence and


539. Fornell EU, Wingren G, Kjolhede P. Factors associated
543. Lukacz, E. S., Lawrence, J. M., Buckwalter, J. G. et al.: Epidemiology of prolapse and incontinence questionnaire: validation of a new epidemiologic survey. Int Urogynecol J Pelvic Floor Dysfunct, 16: 272, 2005


Committee 2

Cell Biology

Chairman
C.H Fry (U.K)

Members
A.J Kanai (USA),
A. Roosen (Germany),
M. Takeda (Japan),
D.N Wood (U.K)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABMA</td>
<td>α,β-methylene ATP</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>α, β-actin</td>
<td>isoforms of actin</td>
</tr>
<tr>
<td>AITC</td>
<td>allyl-isothiocyanate</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate</td>
</tr>
<tr>
<td>3-APMPA</td>
<td>3-amino-1-propylphosphonic acid</td>
</tr>
<tr>
<td>A- receptor</td>
<td>adenosine-receptor</td>
</tr>
<tr>
<td>α-receptor</td>
<td>alpha adrenoreceptor</td>
</tr>
<tr>
<td>AT</td>
<td>angiotensin</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BOO</td>
<td>bladder outlet obstruction</td>
</tr>
<tr>
<td>B-receptor</td>
<td>bradykinin receptor</td>
</tr>
<tr>
<td>β-receptor</td>
<td>beta adrenoreceptor</td>
</tr>
<tr>
<td>BKCa</td>
<td>large conductance K⁺ channel</td>
</tr>
<tr>
<td>BSMC</td>
<td>bladder-derived smooth muscle cell</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>calcium ion</td>
</tr>
<tr>
<td>CA trans</td>
<td>trans-cinnamaldehyde</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CaM kinase</td>
<td>Ca-mitogen kinase</td>
</tr>
<tr>
<td>cGK</td>
<td>cGMP-dependent protein kinase</td>
</tr>
<tr>
<td>cGMP</td>
<td>cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>CICR</td>
<td>Ca²⁺-induced Ca²⁺ release</td>
</tr>
<tr>
<td>c-kit</td>
<td>a protein-tyrosine kinase receptor</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>chloride ion</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>Cx</td>
<td>gap junction protein, connexin</td>
</tr>
<tr>
<td>CPI-17</td>
<td>an MLCP inhibitor</td>
</tr>
<tr>
<td>DAD</td>
<td>diacylglycerol</td>
</tr>
<tr>
<td>4-DAMP</td>
<td>N-2-chloroethyl-4-piperidinyl diphenylacetate</td>
</tr>
<tr>
<td>E</td>
<td>elastic (Young’s) modulus</td>
</tr>
<tr>
<td>EAG</td>
<td>ether-a-go-go-related gene</td>
</tr>
<tr>
<td>ENaC</td>
<td>epithelial Na⁺ channel</td>
</tr>
<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>EP receptor</td>
<td>prostaglandin E₂ (PGE₂) receptor</td>
</tr>
<tr>
<td>ER</td>
<td>endoplasmic reticulum</td>
</tr>
<tr>
<td>ET</td>
<td>endothelin</td>
</tr>
<tr>
<td>G-protein</td>
<td>guanosine phosphate binding protein</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminooxylic acid</td>
</tr>
<tr>
<td>G-I tract</td>
<td>gastrointestinal tract</td>
</tr>
<tr>
<td>GRK</td>
<td>G-protein-coupled receptor kinase</td>
</tr>
<tr>
<td>HK1077</td>
<td>a rho-kinase inhibitor</td>
</tr>
<tr>
<td>HERG</td>
<td>human ether-a-go-go related gene</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
<tr>
<td>ICC</td>
<td>interstitial cell of Cajal</td>
</tr>
<tr>
<td>IC-MY</td>
<td>ICC in longitudinal muscle layer</td>
</tr>
<tr>
<td>IC-SM</td>
<td>ICC in circular muscle layer</td>
</tr>
<tr>
<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
</tr>
<tr>
<td>IL-6</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>IMI</td>
<td>inter-micturition interval</td>
</tr>
<tr>
<td>IP₃</td>
<td>inositol triphosphate</td>
</tr>
<tr>
<td>IPSS</td>
<td>international prostate symptom score</td>
</tr>
<tr>
<td>k</td>
<td>stiffness</td>
</tr>
<tr>
<td>K⁺</td>
<td>potassium ion</td>
</tr>
<tr>
<td>KATP</td>
<td>intracellular ATP-gated K⁺ channel</td>
</tr>
<tr>
<td>KCl</td>
<td>potassium chloride</td>
</tr>
<tr>
<td>KCNQ</td>
<td>voltage-gated K⁺ channel, KQT-like superfamily</td>
</tr>
<tr>
<td>L₀</td>
<td>optimal resting length for a muscle</td>
</tr>
<tr>
<td>L₂</td>
<td>second lumbar spinal level</td>
</tr>
<tr>
<td>LUT</td>
<td>lower urinary tract</td>
</tr>
<tr>
<td>m receptor</td>
<td>muscarinic receptor (gene level)</td>
</tr>
<tr>
<td>M receptor</td>
<td>muscarinic receptor (protein level)</td>
</tr>
<tr>
<td>MLCK</td>
<td>myosin light chain kinase</td>
</tr>
<tr>
<td>MLCP</td>
<td>myosin light chain phosphatase</td>
</tr>
<tr>
<td>MPEP</td>
<td>6-methyl-2-(phenylethyl)pyridine</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribose nucleic acid</td>
</tr>
<tr>
<td>MS</td>
<td>mechanosensitive</td>
</tr>
<tr>
<td>mtNOS</td>
<td>mitochondrial nitric oxide synthase</td>
</tr>
<tr>
<td>Na⁺</td>
<td>sodium ion</td>
</tr>
<tr>
<td>NA</td>
<td>noradrenaline</td>
</tr>
<tr>
<td>NANC</td>
<td>non-adrenergic, non-cholinergic</td>
</tr>
<tr>
<td>NiCl₂</td>
<td>nickel chloride</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NK receptor</td>
<td>neurokinin receptor</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
</tr>
<tr>
<td>nNOS</td>
<td>neuronal nitric oxide synthase</td>
</tr>
<tr>
<td>OAB</td>
<td>overactive bladder</td>
</tr>
<tr>
<td>P</td>
<td>pressure</td>
</tr>
<tr>
<td>P2- receptor</td>
<td>receptors to ATP, subtype X/Y</td>
</tr>
<tr>
<td>pA₂</td>
<td>negative logarithm of dissociation constant</td>
</tr>
<tr>
<td>PAÇAP</td>
<td>pituitary adenylyl cyclase activating peptide</td>
</tr>
<tr>
<td>4-PBA</td>
<td>4-phenylbutyrate</td>
</tr>
<tr>
<td>PDE</td>
<td>phosphodiesterase</td>
</tr>
<tr>
<td>PE</td>
<td>phenylephrine</td>
</tr>
<tr>
<td>PG</td>
<td>proglandin</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase-A</td>
</tr>
<tr>
<td>PLC</td>
<td>phospholipase-C</td>
</tr>
<tr>
<td>PT</td>
<td>pressure threshold</td>
</tr>
<tr>
<td>RAR</td>
<td>recto-anal reflex</td>
</tr>
<tr>
<td>ROK/ROCK</td>
<td>rho-associated kinase</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcriptase polymerase chain reaction</td>
</tr>
<tr>
<td>S1</td>
<td>first sacral spinal level</td>
</tr>
<tr>
<td>SCI</td>
<td>spinal cord injury</td>
</tr>
<tr>
<td>SCL</td>
<td>spinal cord transection (transacted)</td>
</tr>
<tr>
<td>SERCA</td>
<td>sarcoplasmic reticulum Ca²⁺-pump</td>
</tr>
<tr>
<td>sGC</td>
<td>soluble guanylate cyclase</td>
</tr>
<tr>
<td>SHR</td>
<td>spontaneous hypertensive rat</td>
</tr>
<tr>
<td>SIS</td>
<td>small intestine submucosa</td>
</tr>
<tr>
<td>sG⁻-gene</td>
<td>encoding the BK channel α-subunit</td>
</tr>
<tr>
<td>SKCa</td>
<td>small conductance K⁺ channel</td>
</tr>
<tr>
<td>SM</td>
<td>smooth muscle myosin</td>
</tr>
<tr>
<td>SMPP-1M</td>
<td>a smooth muscle myosin phosphatase</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>T</td>
<td>wall tension</td>
</tr>
<tr>
<td>T10</td>
<td>tenth thoracic spinal level</td>
</tr>
<tr>
<td>7TM receptor</td>
<td>7-transmembrane helix receptor</td>
</tr>
<tr>
<td>TMB-8</td>
<td>an IP₃ receptor blocker</td>
</tr>
<tr>
<td>TREK channel</td>
<td>TRIP-related K⁺ channel</td>
</tr>
<tr>
<td>TRPA</td>
<td>transient receptor potential, ankyrin</td>
</tr>
<tr>
<td>TRPM</td>
<td>transient receptor potential, melastatin</td>
</tr>
<tr>
<td>TRPML</td>
<td>transient receptor potential, mucolipin</td>
</tr>
<tr>
<td>TRPP</td>
<td>transient receptor potential, polycystin</td>
</tr>
<tr>
<td>TRPV</td>
<td>transient receptor potential, vaniloid</td>
</tr>
<tr>
<td>TTFa</td>
<td>thymoquinone/urocanic acid</td>
</tr>
<tr>
<td>TX</td>
<td>tetrodotoxin</td>
</tr>
<tr>
<td>TUNEL</td>
<td>terminal deoxynucleotidyl transferase</td>
</tr>
</tbody>
</table>
# CONTENTS

## I. INTRODUCTION

## II. THE UROTHELIUM AND SUBUROTHELIUM
1. INTRODUCTION
2. THE UROTHELIUM: CHANGES IN DISEASE AND BACTERIAL INFECTIONS
3. SECRETORY AND SIGNALING PROPERTIES OF THE UROTHELIUM/ SUBUROTHELIUM
4. INTERACTIONS BETWEEN UROTHELIUM/ SUBUROTHELIUM AND DETRUSOR

## III. CELL PHYSIOLOGY OF MUSCLE CONTRACTION: DETRUSOR
1. CONTRACTILE MECHANISMS
2. ELECTRICAL ACTIVITY AND ION CHANNELS
3. DETRUSOR ACTIVATION AND RELAXATION
4. SPONTANEOUS ACTIVITY
5. TRIGONE

## IV. THE URETHRA
1. INTRODUCTION
2. URETHRAL SMOOTH MUSCLE
3. URETHRAL SKELETAL MUSCLE

## V. CELL PHYSIOLOGY OF NEUROACTIVE AGENTS IN THE LOWER URINARY TRACT
1. MUSCARINIC CHOLINERGIC TRANSMISSION
2. ADRENERGIC TRANSMISSION
3. PURINERGIC TRANSMISSION
4. NITRERGIC MECHANISMS
5. NICOTINE AND NICOTINIC RECEPTORS
6. ADENOSINE RECEPTORS
7. NEUROPEPTIDES

## VI. BIOMECHANICAL PROPERTIES OF THE BLADDER WALL
1. ACTIVE AND PASSIVE CONTRACTILE PROPERTIES OF THE BLADDER WALL
2. COMPLIANT PROPERTIES OF THE BLADDER AND BLADDER WALL
3. BIOMECHANICAL PROPERTIES OF LOWER URINARY TRACT TISSUES AND COLLAGEN SUBTYPES
4. PROPERTIES OF THE PELVIC FLOOR AND GENUINE STRESS INCONTINENCE
5. THE ACTIVE PROPERTIES OF MUSCLE IN THE LOWER URINARY TRACT
6. TENSION AND PRESSURE

## VII. THE LOWER GASTRO-INTESTINAL TRACT
1. THE NORMAL PHYSIOLOGY OF THE RECTUM AND ANUS
2. INNERVATION
3. SMOOTH MUSCLE TISSUES
4. INTERSTITIAL CELLS
5. FUTURE DIRECTIONS

## VIII. NOVEL MOLECULAR TARGETS

## IX. TISSUE REPLACEMENT AND TRANSLATIONAL RESEARCH
1. INTRODUCTION
2. INJECTABLE THERAPY
3. TISSUE REPLACEMENT
4. APPROACHES TO GRAFT GENERATION
5. CONCLUSION

## X. RECOMMENDATIONS FOR LOWER URINARY TRACT AND LOWER GASTRO-INTESTINAL TRACT RESEARCH

## REFERENCES
This aim of this report is to describe the cell and tissue physiology and biochemistry of the lower urinary tract that will help to understand the pathophysiology of the overactive bladder and lower gastrointestinal (G-I) tract and to highlight potential avenues whereby the conditions may be better managed. The report will attempt to explain the most important features of the lower urinary and G-I tracts, and describe important changes that are associated with functional disorders. It is not always possible to differentiate between primary and secondary changes to tissue that are associated with tract dysfunction but this is not necessarily important if potentially useful targeted models are identified that may be used to develop new therapeutic and other approaches to manage urinary and faecal incontinence.

Since the previous consultation [1] there has been considerable advance in our understanding of the lower urinary and G-I tract, particularly with respect to the bladder. In particular the urothelium has emerged as an important tissue in mediating lower urinary tract sensations, and the principles learnt may in the future be applied to the G-I tract. Equally, our understanding of the mode of action of some useful drugs and a greater understanding of their molecular targets has been radically altered, which should enable the development of better-targeted drugs. Figure 1 shows a diagrammatic representation of the bladder wall with some of the structures and receptors that will be described in the following sections.

Increased understanding of these tissues has also facilitated tissue-engineering approaches to develop functional implants and recent advances will be described. This report has attempted to reflect these advances. It will refer to the previous report when basic principles were described, and when some aspects were discussed in depth and re-examination might be repetitious. All referenced material is from peer-reviewed publications, most of which have appeared after the previous consultation [1].

II. THE UROTHELIUM AND SUBUROTHELIUM

1. INTRODUCTION

The previous report [1] concentrated on the structure

Figure 1: Schematic representation of the bladder wall and its principal nervous connections. The different layers are shown with some of the main pathways and receptors denoted. Positive (+) implies stimulatory and negative (−) implies inhibitory.
as well as the transport and barrier functions of the urothelium, and those factors that may alter the permeability of the membrane. In the intervening period the urothelium has been increasingly recognised also to have secretory functions that allow it to behave as a sensory and signaling structure, influencing the activity of both nerves and also underlying tissue layers. In this mode it interacts closely with the underlying suburothelial layer so that the whole structure can be regarded as a functional unit. Figure 2 shows the structure of the urothelium. Below the basal cells of the urothelium is a connective tissue layer, sometimes referred to as the lamina propria, in which is embedded a rich network of capillaries, unmyelinated and myelinated nerves and a functional syncitium of interstitial cells (myofibroblasts).

2. THE UROTHELIUM: CHANGES IN DISEASE AND BACTERIAL INFECTIONS

The urothelium consists of three layers: i) an apical (umbrella) cell layer with a very low permeability to urine and pathogens; ii) an intermediate layer; and iii) a basal layer that interacts with the extracellular matrix of the suburothelial region for structural support. The barrier is determined by: the low mobility of the aliphatic chains in phospholipid molecules (high degree of saturation, high concentrations of sphingomyelin and cholesterol) [2]; segregation of low mobility lipids into the outer leaflet of the apical membranes [3]; the presence of uroplakin proteins in the apical membrane and the presence of tight junctions between adjacent cells [4,5]. When the bladder is empty, large numbers of vesicles underlie the apical membrane. As the bladder fills, these vesicles are inserted into the apical membrane to maintain a constant relationship between the area of apical membrane and the volume of the bladder. The role of uroplakins and defects in their structure in relation to lower urinary tract anomalies remains unclear. Ablation of the uroplakin-II gene in mice [6] or loss of uroplakin expression in patients with myelomeningocele [7] led to hyperplastic growth of the urothelium and may interfere with the development of underlying smooth muscle. In addition, UPIII expression is a powerful prognostic factor in patients with upper urinary tract urothelial carcinoma [8].

Uropathogenic *Escherichia coli* (UPEC) is the main causative agent for urinary tract infections in women [9]. With animal models of cystitis UPEC have part of their pathogenic cycle as an intracellular phase within urothelial cells where replication and formation of bacterial communities occurs [10], before exiting the host cell. Invasion is facilitated by adhesive fibres - type-I pili [11]. Thus, UPEC can form hidden intracellular reservoirs of bacteria that can persist for several weeks that may be protected from antibiotics. Whilst much of the formative work has been carried out on animal models, recently intracellular bacterial communities from exfoliated urothelial cells have been detected in the urine of patients [12].

3. SECRETORY AND SIGNALING PROPERTIES OF THE UROTHELIUM/SUBUROTHELIUM

In recent years the ability of the urothelium to respond to stimuli such as stretch and osmolarity changes, and its release of various chemical factors including substance P [13], nitric oxide (NO) [14], ATP [15] and ACh [16], has been recognised. Histological studies have shown there are many sensory neurons located in the urothelial/suburothelial region that label for receptors to these factors, or contain sensory peptides. Moreover, the extent of labeling is altered in conditions that result in bladder overactivity, or in the presence of agents designed to attenuate the condition [17-20]. The proximity of these afferent nerves therefore implies that they could interact with the urothelium to detect changes in bladder fullness. Urothelial cells themselves also express sensory receptors typically found on primary afferent nerves; including P2XY receptors [21,22], TRPV1,2,4 [23,24], TRPA1 [25], TRPM8 [26], B1,2 bradykinin receptors [27], adrenergic
receptors [14,28], nerve growth factor receptors [29] and amiloride-sensitive Na⁺ channels [30-32].

One of the first stretch-released factors to be identified in the urothelium was ATP, which was released in response to stretch or hypotonic stimulation from various species [15] including humans [33]. Figure 3 shows that stretch-dependent ATP release from the bladder wall is dependent on an intact mucosa, and that release is attenuated by amiloride. The latter observation supports the hypothesis that epithelial Na⁺ channels regulate ATP release (see section VIII 2-b). It is hypothesized that purinergic receptors on sensory neurons and/or myofibroblasts are targets. P2X₃ receptors have been identified as the likely target for activation of suburothelial afferents. This suggests that P2X₃ receptors are involved in sensory activation during the filling phase, as inferred from observations of P2X₃ knockout mice, which exhibited a reduced afferent firing and micturition reflex [34,35]. The relevance of this mechanism is illustrated in figure 4, where it is observed that intravesical amiloride increases inter-micturition interval [446].

The intrinsic activity of suburothelial myofibroblasts was potentiated by P2Y receptor activation [36], most likely through the P2Y₆ subtype [37]. This suggests that there are multiple targets for urothelial-derived ATP. The release of ATP increases when damage occurs to the urothelial layer, for example, in interstitial cystitis [38] or spinal cord injury [39] and may be reduced by treatment with botulinum toxin, for example [40]. There is also a marked increase in the expression of the gap junction protein connexin26 in the urothelium [41]. The enhancement of cell-cell communication may lead to increased sensitivity and propagation of signals through the urothelium in response to stimuli. Therefore, it may be hypothesized that increased urothelial ATP is a contributing factor to afferent sensitization through enhanced activation of suburothelial nerves and/or myofibroblasts.

ACh also is released from the urothelium in response to stretch; the amount increases with age and oestrogen status [42-44]. Most likely this release is through a non-vesicular mechanism, mediated by organic cation transporter type-3 [45]. Urothelial-derived ACh, like ATP, may also have a role in promoting sensory activation. This arises from the fact that anticholinergic drugs reduce detrusor overactivity and urge during the filling phase of the bladder, when efferent nerves are not activated [46].

Hence, it can be hypothesized that anticholinergics are not acting on the muscle but elsewhere, possibly muscarinic receptors in the urothelium. Recent studies investigated the localization of muscarinic and nicotinic receptors in the human [47] and mouse [48] urothelium. All five muscarinic subtypes were expressed throughout the urothelial layers. There was specific localization of the M₂-subtype to the umbrella cells and M₁ to the basal layer, and M₃ receptors more generally distributed. M₃, but not M₂, receptor expression was reduced in human tissue from patients with idiopathic detrusor overactivity. However, it is not known if this was evident throughout the urothelium/suburothelium or confined to a specific region [49]. The mechanism by which ACh modulates these activities is still unclear. However, blockade of urothelial muscarinic receptors with atropine inhibits stretch-induced ATP release [50]. Stretch-released ACh may therefore act in a feedback mechanism to induce basolateral ATP release. Thus, the urothelium is clearly more than a barrier, demonstrating a role in modulating bladder contractile and sensory activities. The cellular transduction mechanism from the urothelium is still unclear, but elucidation of how the urothelium communicates with the detrusor and the sensory nerves could uncover potential therapeutic targets.

A network of interstitial cell-like myofibroblasts have been identified in the suburothelium that label for vimentin, are connected by gap junctions containing Cx43 (Figure 5) and are closely apposed to unmyelinated nerve endings [51,52] and label with c-kit [53]. Isolated myofibroblasts respond to exogenous ATP (via P2Y receptors) by generating nifedipine-resistant intracellular Ca²⁺ transients and a subsequent Ca²⁺-activated Cl⁻ current [36,54]. At the prevailing negative resting potential, this current generates a transient depolarization. These responses mirror spontaneous Ca²⁺ transients and inward current [36]. Thus, local release of ATP from the urothelium may be postulated to generate depolarizing Ca²⁺ waves that spread across the myofibroblasts network and thus amplify and modulate local responses to endogenous ATP. The ability of myofibroblasts to form functional networks can involve mechanisms other than via gap junctions: if two isolated cells are pushed together, each cell demonstrates enhanced responses to ATP without the obvious formation of gap junctions. Cadherin-11 has been demonstrated on myofibroblast membranes [55] and their activation by intercellular adhesion may offer a mechanism. This enhancement of response is abolished by the c-kit receptor tyrosine kinase inhibitor, glivec.

These purinergic responses are mimicked by extracellular acidosis and attenuated by capsaicin and NO donors. The latter effect is in keeping with the demonstration of NOS/guanylate cyclase activity in these cells [56]. The effect of extracellular acidosis and capsaicin is of significance as it proposes a mechanism whereby the bladder wall may respond to local ischemia – a feature of bladder filling – especially in the presence of outflow obstruction or reduced compliance [57-59].
Figure 3: ATP release from the bladder during lateral stretch. A: ATP release from a section of the bladder wall, with the mucosa removed (left-bar of pair) or retained (right-bar of pair). Wall segments were held at slack length, or stretched by 30 and 50% of the slack length. Values normalised to release at slack length with mucosa, *p<0.05. B: The effect of 1 mM amiloride on ATP release from the bladder wall – mucosa intact – under different degrees of stretch, *p<0.01.

Figure 4: The effect of intravesical amiloride on the micturition reflex in urethane-anesthetized rats. A: Typical tracings of continuous cystometry (CMG) during filling: before, during and after washout of amiloride. B: the effect of amiloride on intercontraction interval (ICI) in normal rats. C: the effect of amiloride on intercontraction interval (ICI) in rats with outflow tract obstruction, * p=0.01; ** p<0.01. From [446]
Muscarinic M<sub>2</sub> and M<sub>3</sub> receptor labeling has also been localized to suburothelial myofibroblasts and is increased in samples from idiopathic overactive bladders; an increase in M<sub>2</sub> receptor labeling was also seen in samples from patients with painful bladder syndrome [60]. Isolated myofibroblasts do not respond to exogenous muscarinic receptor agonists by a rise of intracellular [Ca<sup>2+</sup>], so the intracellular signaling mechanisms remain unknown [36].

However, these observations may be of significance as it has been demonstrated that C-fibre and Aδ-fibre afferent firing in response to bladder filling was reduced by relatively M<sub>3</sub>-selective antimuscarinics [61], or less-selective agents such as oxybutynin [62] or tolterodine [63]. The latter study was of additional interest as it demonstrated that the decrease of afferent activity persisted after desensitization of a proportion of the afferents with resiniferatoxin.

4. INTERACTIONS BETWEEN UROTHELIUM/ SUBUROTHELIUM AND DETRUSOR

Several lines of evidence indicate that the urothelium/suburothelium directly modulates detrusor function, through inhibitory and excitatory mechanisms. Using in vitro detrusor preparations the potency and the maximum contractile response to acetylcholine, but not KCl, are reduced if the urothelium is intact. The substance is unknown at present, it is diffusible but is not NO, adenosine, GABA, a cyclo-oxygenase product or mediated by the small conductance Ca<sup>2+</sup>-sensitive K<sup>+</sup>-channel [64-67]. However, whether it involves activation of a beta-adrenoreceptor or the release of a beta-agonist is controversial [65,68].

Of interest is that a similar phenomenon is present in preparations from ureter, but in this case may involve a cyclo-oxygenase product [69].

Optical imaging of transverse sections of the bladder wall shows propagating Ca<sup>2+</sup> and membrane potential waves in the suburothelial layer in response to physical stretch or very low concentrations of carbachol. After a delay these responses spread to the detrusor layer initiating activity there [70], figure 6. Optical imaging of bladder sheets, with the urothelial surface uppermost showed similar propagating waves elicited by UTP in the presence of a urothelial/suburothelium, but absent if it was removed [71]. UTP was chosen as this purine elicits excitatory responses from sub-u-rothelial myofibroblasts, but not directly from detrusor itself. Isolated strips of detrusor generate spontaneous activity, especially if the urothelium/suburothelium is intact, and such activity is also up-regulated by exogenous UTP [71].

Thus, there is evidence that a suburothelial population of myofibroblasts is an intermediate stage in the sensory response to bladder wall stimuli. It acts as a variable amplifier of the sensory response mediating signals between the urothelium and sensory afferents or the detrusor smooth muscle layer, either directly or via the activation of afferent nerve fibres [72].

Moreover, the increase of myofibroblast numbers in conditions associated with bladder overactivity [41,73] suggests it is a mechanism that may be targeted to alleviate this condition. Agents that modulate myofibroblast activity, such as glivec, also reduce spontaneous activity in the bladder [74,75].
1. CONTRACTILE MECHANISMS

Smooth muscle cells of the bladder are spindle shaped single nucleated cells organized into bundles separated by connective tissue. The thin filaments are composed of α- and β-actin, that are attached to dense bodies on the cell membrane. The thin filaments provide the binding sites for the myosin thick filaments. There are four myosin isoforms that exhibit different contractile properties—smooth muscle myosin (SM) 1A, 1B, 2A and 2B. Adult bladders are composed of approximately equal amount of SM1B and SM2B (the SM1B:SM2B ratio is ~1) [76]. SM1 produces more force than SM2; SM-A types are more slowly contracting than SM-B. In obstruction, there is a shift to more SM1A, which therefore results in slower and more forceful contractions to overcome increased resistance. A detailed description of the contractile proteins and associated intermediate filaments has been recently published [77].

An increase of the sarcoplasmic [Ca^{2+}] from a basal level of 50-100 nM is required to initiate detrusor contraction, half maximal activation is achieved at about 1 μM [78]. The source of Ca^{2+} can be extracellular, via L- and T-type Ca^{2+} channels [79,80] or from intracellular stores [81]. Release from intracellular stores may be separately mediated by activation of IP3 receptors, as it can be blocked by receptor inhibitors, or via ryanodine receptors [82]. The increase of the sarcoplasmic [Ca^{2+}] is transient and Ca^{2+} are either removed from the cell via Na+/Ca^{2+} exchange [83], or re-accumulated in the intracellular stores via a SERCA pump; the activity of the latter is modulated by intracellular proteins, such as phospholamban [84]. As with other smooth muscles, the contractile proteins are activated by phosphorylation of myosin by a myosin light chain kinase (MLCK), which in turn is activated by a Ca^{2+}-calmodulin complex. Relaxation will occur if the myosin light chain is dephosphorylated, by a myosin light chain phosphatase (MLCP), which in the pig bladder is SMPP-1M phosphatase [85]. The sensitivity of the contractile system can therefore be altered by altering the activities of MLCK or MLCP. A schematic diagram of contractile activation is shown in figure 7.

MLCK activity is decreased by itself being phosphorylated which could be achieved via a number of kinases including: CaM kinase II, mitogen-activated protein (MAP) kinase, cAMP-dependent kinase (PKA) and p21-activated kinase [86,87], although details of the pathways that modulate MLCK activity in detrusor are unclear. MLCP activity can also be reduced by phosphorylation, which would increase the Ca^{2+}-sensitivity of the contractile system. Of significance is inhibition of MLCP activity by rho-associated kinase (ROK/ROCK) [88], which in turn is activated by small G-proteins of the rho-family. In detrusor the two isoforms of ROCK (I and II) have been identified [88]. Inhibitors of ROCK activity, such as Y-27632 and HA-
1077, attenuate nerve-mediated and carbachol-activated contractions, as well as contractures in cell permeabilised preparations, but do not affect depolarization-mediated (with high [KCl]) contractures other modifying agents. The most significant K⁺ channel in detrusor is the Ca²⁺ activated large conductance K⁺ channel (BKCa). This channel has a physiological role in determining membrane potential, action potential repolarisation [107,108] and regulating contractile events [109,110]; channel opening is coupled to intracellular Ca²⁺ sparks emanating from ryanodine receptors [108]. Outward current is also modulated by Ca²⁺-current influx through L-type and T-type Ca²⁺ channels. In the former case this has been proposed as a mechanism to regulate Ca²⁺ influx into the myocyte [111], and in the latter case as a basis for spontaneous fluctuations of membrane potential [100]. Reduction of BK channel activity may contribute to myogenic bladder overactivity, as deletion of the slo-gene that encodes for the channel protein enhances muscle sensitivity to cholinergic and purinergic agonists [112], conversely injection of slo-cDNA reduced overactivity [113]. BK channel activity is regulated by phosphorylation of the pore-forming α-subunit, or associated proteins [114], and affords a mechanism whereby cAMP and cGMP, through PKC, can regulate channel function [115,116]. Conversely, the Ca²⁺-dependent phosphatase, calcineurin, decreases BKCa conductance [117] so that overall Ca²⁺ exerts a complex control of channel function – the ability to identify molecular targets for this in channel is considered in section VIII 3-c.

2. ELECTRICAL ACTIVITY AND ION CHANNELS

Detrusor smooth muscle is an electrically excitable tissue capable of generating evoked and spontaneous action potentials [86]. The upstroke phase is carried by Ca²⁺ ions, predominantly through L-type Ca²⁺ channels, and repolarisation is mediated by K⁺ efflux through several K⁺ channels [79,97]. Ca²⁺ influx through Ca²⁺ channels is sufficient to elicit further release from intracellular stores [98] and sustain contractions. T-type Ca²⁺ channels have also been described in detrusor muscle and the proportion of total inward Ca²⁺ current is increased in cells from overactive bladders [99]. Because T-type channels are activated at more negative membrane potentials it was proposed that they could contribute to increased spontaneous activity in the overactive bladder [100]. Exposure of detrusor muscle strips to low NiCl₂ concentrations, when a selective T-type channels inhibition is achieved, indeed attenuated spontaneous contractile activity [101].

A number of receptor modulators that alter detrusor contractility affect also the L-type Ca²⁺ current. Antimuscarinic agents such as propiverine, attenuate L-type Ca²⁺ current [102-104]. The effect is probably mediated via M₃ receptors as the action is blocked by 4-DAMP [104]. β-agonists also attenuate Ca²⁺ current by a cAMP/protein kinase A-dependent mechanism [105], whilst the antispasmodic agents alverine citrate reduced action potential repolarisation rate, which was interpreted as an inhibition of Ca²⁺ current inactivation, thus increasing Ca²⁺ influx [106].

Intracellular ATP-gated K⁺ channels (KATP) have also been described in detrusor smooth muscle, and channel openers hyperpolarise the cell and reduce spontaneous activity. A problem with the use of these channel modulators is that of tissue specificity, as many are as potent, if not more, in generating similar responses in vascular smooth muscle. Agents with greater uro-selectivity have been developed [118] but there has been little progress with the use of such agents to attenuate bladder overactivity.

Stretch-activated channels could serve a dual purpose in the detrusor myocyte: to permit cation influx to depolarize the cells and thus cause contraction to counter the initial stretch, and to initiate intracellular signaling cascades that may initiate cellular reconfiguration or growth [119,120]. Physical stretch of detrusor myocytes opens non-selective cation channels, depolarizes the cell and augments Ca²⁺ influx through Ca²⁺ channels [121]. Stretch also increases K⁺ conductance either through increasing BK channel activity [122] or by opening a separate TREK channel [123,124]. In view of the complex effects of mechanical stretch on channel gating the overall significance of these responses remains unclear.
3. DETRUSOR ACTIVATION AND RELAXATION

In the normal human bladder acetylcholine is the sole neurotransmitter eliciting contraction, i.e. there are no atropine resistant contractions, whilst in many pathologies associated with bladder overactivity ATP is an additional activator [125-128]. Moreover age is also associated with atropine-resistant contractions [128]. With animal bladders, except for old-world monkeys, a dual muscarinic-purinergic activation is present. When muscarinic and purinergic receptors are inactivated there is generally no recorded neurotoxin (TTX)-dependent contraction, indicating that acetylcholine and ATP are the two major neuroactivators.

Despite the fact that M2 receptors predominate over the M3 subtype, most studies conclude that the latter mediates at least 95% of contractile activation [see 129,130]. More recently, the role of M2 receptors has been re-evaluated. It has been advocated that M2 receptors exert a more significant role in certain pathological conditions (eg, denervated or hypertrophied bladders), or when the M3 receptor is desensitized [131-133], although this conclusion is not reached by all [134]. One possibility for this discrepancy is that M2-dependent actions may derive from the urothelium [136], and that this pathway becomes more significant in these pathological conditions. The question arises as to what are the functions of M2-receptors in the normal bladder and several studies indicate that they facilitate the function of other receptors, such as M3 receptors [136], or counteract the relaxant effect of β-adrenoceptor agonists [137]. However, there is little difference on overactive bladder function between the effect of more selective M1/M3-selective blockers and those with a less specific action (balanced receptor blockers), although the side-effect profiles are different [138].

The major effect of ATP on detrusor smooth muscle is through ionotropic P2X receptors, generating depolarizing non-specific cation influx, which opens L-type Ca2+ channels to permit further Ca2+ influx [139]. The potency of the non-hydrolysable ATP analogue α,β-methylene ATP (ABMA) to elicit increases of intracellular [Ca2+] was not different in nerves isolated from the urothelium [140]. Non-neuronal tetrodotoxin (TTX)-resistant contractions that occur in the detrusor have several aliases including: autonomous; intrinsic; micromotion; microtransient; non-micturition; phasic; rhythmic; spontaneous or transient activity. This activity was first reported by Sherrington in cats, as transient rises in bladder pressure seen during the filling phase [148]. Spontaneous smooth muscle contractions can also stimulate afferent fibres and generate centrally-mediated ‘reflex’ bladder contractions. These contractions, which are also referred to as non-micturition or phasic contractions, can be abolished with intravesical capsaicin without affecting smooth muscle-mediated spontaneous activity [149].

In neonatal rats, spontaneous activity, resistant to TTX, is absent at birth, increases in amplitude by week two, then changes from high-amplitude low-frequency to adult-like low-amplitude high-frequency activity by week six [70,150,151], figure 9. Micturition in neonatal rats is mediated by a somato-bladder spinal reflex pathway that is activated by the mother licking the perineum of the pup. During postnatal development, this primitive reflex is replaced by supraspinal mechanisms that control mature brain-to-bladder reflexes and voluntary voiding [152]. This developmental change in the central control of voiding occurs in concert with changes in peripheral neurotransmission and the spontaneous properties of the bladder smooth muscle [153-155]. Neurotically-evoked bladder contractions are mediated entirely by cholinergic mechanisms in bladders from one-week-old rats, but become primarily purinergic in bladders from two-week-old animals. In bladders from spinal cord transected (SCT) rats [41] and outlet-obstructed
124 bladders, there is a reemergence of high-amplitude low-frequency spontaneous activity similar to that observed in neonatal bladders.

1. The neurogenic hypothesis: reduced peripheral or central inhibition increases activation of the micturition reflex and contractions associated with detrusor overactivity [156].

2. The myogenic hypothesis: changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells leads to the generation of uninhibited contractions [157].

3. The urotheliogenic hypothesis: changes in the sensitivity and coupling of the suburothelial myofibroblast network leads to an enhancement of spontaneous detrusor activity [158].

4. The autonomous hypothesis: structures within the bladder wall coordinate to drive spontaneous contractions, which become enhanced in pathology [159].

5. A small leak of transmitter from motor fibres sufficient to cause small local contractions or increase tone [160].

The neurogenic hypothesis can account for neurogenic detrusor overactivity, but does not fully account for so-called sensory overactivity. However, it may well form a distinct subset of patients with detrusor overactivity because muscle samples taken from such bladder are no different from stable bladders and different from other non-neurogenic (idiopathic) overactive bladder samples [e.g. 127].

Spontaneous activity can be recorded from isolated muscle strips and several reports record an increase in samples from overactive bladders. Contractions are resistant to neurotoxins but generally labile to Ca²⁺-channel blockers or K⁺ channel openers [77]. Such activity can be recorded in isolated cells, as spontaneous changes to membrane potential and intracellular Ca²⁺. Moreover the incidence of such activity is enhanced in cells isolated from overactive bladders. The origin of such activity is not known at present. Whilst up-regulated activity in isolated cells may be present, this will not alone explain spontaneous activity in multicellular preparations. Two possibilities have been proposed for increased intercellular communication. One is that there is an increase of intercellular coupling through gap junctions. Gap junctions are composed of the connexin (Cx) family of proteins. In human detrusor, expression of the main intermuscular connexin, Cx45, is actually less in samples from idiopathically overactive bladders and this correlated with a higher gap junction resistance in such samples [161]. Other groups however, suggest that another connexin isoform, Cx43, forms gap junctions between muscle cells and expression is upregulated in overactive bladders [162,163]. However, Cx43 labels interstitial cells in the detrusor layer although their number has not been reported to increase in overactive bladder models [77]. These cells are characterized by their labelling for the tyrosine-kinase receptor protein c-kit [160] – as are the suburothelial equivalents – close apposition to muscle cells and nerves [53], and the generation of spontaneous and carbachol evoked Ca²⁺ and electrical activity [164-166]. It is postulated that rather initiate spontaneous activity in the detrusor syncitium, interstitial cells modulate its activity [167], possibly by co-ordinating activity in different muscle bundles. However, these cells could form a control point for regulation of spontaneous activity, as they are innervated by nerves that label for nitric oxide synthase [55], and also express cGMP activity [168].

The urotheliogenic hypothesis is premised on a urothelial-myofibroblast network connected by gap junctions supporting pacemaker-driven spontaneous activity where bladder pathology, due to spinal cord transection for example, leads to an upregulation of gap junctions in the urothelium and myofibroblast network. This, in turn, leads to the formation of an increasingly functional myofibroblast syncytium with focal pacemaker activity that drives spontaneous contractions. The mechanism whereby this may drive

**Figure 9: Spontaneous and evoked activity in isolated rat bladders.** A: a neonatal rat bladder showing large spontaneous contractions (arrowed) and larger contractions evoked by electrical field stimulation (EFS, 10 Hz) during the red bars. The EFS contraction, but not the spontaneous activity, was abolished by the neurotoxin, tetrodotoxin (TTX, 1 µM). B: a similar experiment in an adult rat bladder. The spontaneous activity is now of small amplitude, randomly fluctuating events. Modified from [70].
activity in the detrusor layer has been considered above (section II.3). Figure 10 shows an experiment consistent with this hypothesis. Isometric tension recorded from detrusor strips, with the urothelium removed (top) or left intact (bottom). Both respond similarly to a maximum concentration of the cholinergic agonist carbachol, but in the bottom trace not only is there significant spontaneous activity but it is up-regulated by the purine UTP, that excites suburothelial myofibroblasts, but not directly detrusor smooth muscle.

![Figure 10](image)

**Figure 10:** The influence of an intact mucosa on spontaneous activity in isolated bladder wall strips from guinea-pig bladders. A: a strip with mucosa removed; UTP and carbachol were applied as indicated by the horizontal lines. B: a similar experiment with a strip with an intact mucosa. Modified from [71]

The autonomous hypothesis takes into account the potential role of interstitial cells within the bladder wall but does not clearly indicate a specific mechanism by which spontaneous activity is driven. It most likely represents a qualitative description of a combined myogenic/urotheliogenic hypothesis. As with the urotheliogenic hypothesis spontaneous bladder contractions are enhanced by low-dose muscarinic stimulation, via M3-receptors on suburothelial myofibroblasts. Activity is modulated by ATP, substance P, nicotinic receptor agonists, noradrenaline and nitric oxide, by unspecified mechanisms [169-171].

5. TRIGONE

The bladder base consists of the trigone, the urethrovesical junction, deep detrusor, and the anterior bladder wall. The outstanding developmental and functional position of the bladder trigone has been confirmed in decades of urological research and is defined as the triangular region situated between the ureteral orifices and the bladder outlet. It has always been considered to play a crucial role in ureterovesical function, continence and micturition.

Histologically, the trigone is characterised by smaller myocytes in smaller muscle bundles than in detrusor which exhibit extensive electrical coupling via gap junctions [172,173]; it also contains a greater amount of connective tissue than detrusor.

The original, and still prevailing, concept of a functional entity of bladder base, trigone, and ureterovesical junction, was first been developed by Waldeyer [174] in the late 19th century and later refined by Tanagho [175-177]. According to this concept, the spirally-oriented ureteral muscle fibres become longitudinal, as the ureter pierces the bladder wall obliquely, travels 15-20 mm, and terminates at the ureteral orifice. Fibres from each ureter fan out over the base of the bladder to form a superficial triangular sheet of muscle that extends from the two ureteral orifices to the internal urethral meatus and, from there, further down the urethra to insert at the verumontanum. The edges of this muscular sheet, the so-called superficial trigone, are thickened between the ureteral orifices (the interureteric crest or Mercier’s bar) and between the ureters and the internal urethral meatus (Bell’s muscle). A few centimetres from the bladder, the fibromuscular sheath of Waldeyer departs from the outer muscular layers, surrounds the prevesical ureter longitudinally, and continues in the bladder as the so-called deep trigone, which is fixed at the bladder neck. The trigone is backed by outer, longitudinal and middle, circular smooth muscle layers of the detrusor. In the space between Waldeyer’s sheath and the ureter, only loose fibrous and muscular connections in the sense of a gliding plane are found. As the bladder fills, the bladder wall telescopes outward on the ureter, thereby increasing intravesical ureteral length. This facilitates passive occlusion of the ureter by the urine and warrants, like a flap valve, the basis for a reliable antireflux mechanism. This concept requires a competent vesico-ureteric anchoring, mainly provided by a strong contralateral ureteral smooth muscles blending in the shape of the interureteral ridge. Periodic contraction of this interureteric crest is thought to support the occlusive mechanism by further elongating the intravesical part of the distal ureter.

In fact, trigonal myocytes in the bladder base have recently been shown to exhibit marked spontaneous activity, which is mainly carried by Ca\(^{2+}\)-influx via membrane L-type Ca\(^{2+}\)-channels. Similar to interstitial cells, Ca\(^{2+}\)-activated Cl—channels rather than K\(^{+}\)-channels contribute to the generation of spontaneity. Extensive gap junction coupling ensures electrical propagation and provides sustained spontaneous contraction of the interureteric crest [173].
Accordingly, the trigone is thought to develop, with the ureter, from an outgrowth of the mesonephric duct, and the common mesodermal origin of the vesical neck musculature, the trigone, and the ureterovesical junction is emphasised [175]. However, recent studies challenge this concept of a common developmental origin and suggest rather that the trigone is formed predominantly from bladder muscle; and the contribution from ureteral longitudinal fibers at the lateral edges that is much more limited than previously thought [178,179].

Within the lower urinary tract, the bladder base and trigone represent an area of dual parasympathetic-muscarinic and sympathetic-adrenergic innervation. Whilst mRNA measurements, western blotting, radioligand binding assay and receptor autoradiography studies have detected only low densities of \( \alpha_1 \)-adrenoceptors in the detrusor of several species, including humans, a more consistent, and in some comparative studies, greater \( \alpha_1 \)-adrenoceptor expression was observed in the trigone and bladder neck region. The \( \alpha_1 \)-adrenoceptor seems to be the most abundant subtype in humans [180]. Reports about the proportion of adrenergic, muscarinic and other transmitter systems in the trigone are variable. Speakman et al. [181] found the maximum contraction to carbachol was no more than 50% of that elicited by phenylephrine (PE) in human tissue, but detected comparable reduction (40%) of electrically-evoked contractions by either muscarinic or \( \alpha \)-adrenergic antagonists. Templeman et al. [182] showed a maximal responsiveness to PE of only 68.7% compared to carbachol in longitudinal strips of the pig trigone, when the urothelium had been removed. Roosen et al. [183,184] found a predominant muscarinic innervation and agonist responsiveness of the superficial guinea-pig trigone, with a reduction of electrically-evoked contractions by prazosin of 41.0% compared to atropine and mean maximal contractions to PE of 67.6% relative to those of carbachol. However, the functional significance of this dual innervation is much less clear. Whilst it is widely agreed in animal experiments that adrenergic stimulation via sympathetic nerves is active during the storage phase and induces contraction of the bladder base and internal urethral smooth muscle sphincter, the role of the parasympathetic innervation is much more controversial. Some propose that cholinergic axons exert a relaxing effect on urethral and bladder neck smooth muscle via generation of nitric oxide during micturition [185]. However, strip preparations from the bladder base have been shown to contract not only to carbachol superfusion, but also to the muscarinic component of electrically-released endogenous neurotransmitters. Moreover, there is a significant adreno-muscarinic synergism in the guinea-pig bladder trigone – figure 11 - where the adrenergic pathway primarily operates through \( \text{Ca}^{2+} \)-sensitisation of the contractile machinery [183,184]. This is capable of a more than four-fold potentiation of muscarinic force activation which, in turn, seems to be a basically \( \text{Ca}^{2+} \)-dependent event. This synergistic mechanism might cause an even stronger contraction of the interureteric muscle in cases of involuntary detrusor contractions (induced by increased parasympathetic tone) and thereby prevent urinary reflux into the ureter.

If, as some suggest, the trigone takes part also in urinary outflow control, this synergy might lead to a higher closure pressure in cases of involuntary detrusor contractions and thereby prevent urinary leakage.

In general, the bladder base is thought to provide a rather stable structure against which the bladder dome can contract and relax during the micturition cycle. This might be the reason for the relatively high amount of connective tissue and the high spontaneous activity within individual myocytes. However, it is believed that during micturition the trigone may relax and cause a “funneling” effect to facilitate voiding. As in the urethra, animal experiments have shown that NO is the key relaxing factor in the bladder base [185-187]. NO effectively relaxes isolated smooth muscle preparations from the outflow region, suggesting that it may be involved in the decrease in intraurethral pressure observed at the start of normal micturition. This NO-based relaxation provides an effective mechanism to allow the bladder base and trigone to switch from a closed to open state, especially in combination with the adrenergic control of the \( \text{Ca}^{2+} \)-sensitisation of the contractile machinery.

Figure 11: Effects of muscarinic and adrenergic agonists on the guinea-pig trigone. A: isometric tension from an isolated strip exposed to carbachol (1 \( \mu \text{M} \)). During the shaded region the strip was also exposed to phenylephrine (10 \( \mu \text{M} \)). B: a similar experiment from an isolated cell loaded with the \text{Ca}^{2+} \text{ indicator Fura-2. Modified from [180].}
IV. THE URETHRA

1. INTRODUCTION

During voiding, relaxation of the bladder outlet precedes detrusor contraction and during filling the outlet is contracted. Several mechanisms contribute to these functions, mediated through urethral smooth and skeletal muscle as well as the mechanical properties of the lamina propria. Inadequate closure of the urethra during filling could contribute to stress urinary incontinence. Smooth muscle is arranged as an outer circular layer and an inner longitudinal component, contraction of the circular should maintain continence, and longitudinal muscle may shorten during micturition. In women it has been suggested that there is greater dependence on surrounding support from the pelvic organs for the intra-abdominal portion of the urethra, resulting in the maintenance of an intra-abdominal portion of the urethra and buttressing against the fixed proximal portion of urethra, in combination with pressure generated by the urethral musculature. Therefore, the smooth muscle component may be more for maintaining a continence mechanism. It has been estimated that as much as 50% of total urethral pressure in women is due to smooth muscle tone [188,189]. The urethra is innervated by both the sympathetic and parasympathetic systems. Activity in pelvic nerve parasympathetic fibres relaxes urethral smooth muscle, especially in the proximal portion, and therefore the outflow region; sympathetic fibres (T10-L2) generate contraction.

2. URETHRAL SMOOTH MUSCLE

Sympathetic control is mediated by α1 receptors, mainly the α1A/L subtype in both human and animal models [190,191]. Partial α1A/L agonists, such as Ro 115-1240, have been proposed as agents that may be used to manage stress urinary incontinence in women without significant cardiovascular side-effects [192,193], although their effectiveness remains to be demonstrated. α2 receptor agonists induce contraction in several animal models but this has not been reproduced in human preparations [180]. Urethral relaxation can be mediated via β-receptor activation, predominantly the β3 subtype. However, this mechanism is probably less important than in detrusor [180,194]. Of interest however is the observation that the β2-agonist clenbuterol also increased urethral skeletal muscle contraction raising the possibility that it may have a role in the treatment of urinary incontinence by inhibiting the detrusor contraction and augmenting external urethral sphincter activity [195,196]. Urethral relaxation during voiding is mediated by release of NO. Furthermore, prejunctional muscarinic receptors may limit noradrenaline release from sympathetic fibres, thus contributing to relaxation [197]. Muscarinic agonists generate urethral contraction, although receptor density is lower than in detrusor and clinical studies show little effect on urethral pressure [185].

NO-mediated relaxation is due to production of cGMP and activation of cGMP-dependent protein kinase, cGK. Electrical field stimulation generates relaxations that are abolished by inhibitors of NO production and are absent in mice lacking cGK [198]. The mechanism for relaxation does not seem to involve myocyte hyperpolarisation and awaits definitive evaluation [199]. CO can also exert relaxation through a rise of cGMP, which may be equivalent in magnitude to the effect of NO [200]. Derangements of the NO system have been demonstrated in several disorders associated with lower urinary tract function, such as diabetes, bladder outlet obstruction or bladder inflammation [201,202].

Sex hormones play an important role in modulating urinary tract smooth muscle function, including that from the urethra. Lack of oestrogen following menopause may contribute to decreased urethral tone, urethral integrity and incontinence, and the older literature suggested that estrogen supplementation may be beneficial [203]. However, several recent clinical studies indicate that supplemental oestrogen lowers collagen content in the periurethral connective tissue and decreases urethral closure pressure [204-206] thereby worsening the symptoms of incontinence [207-209]. Similarly, recent studies in rabbits indicate that the response of urethral pressure to α-adrenergic agonists is equivalent between control, ovariectomized and ovariectomized rabbits with oestrogen replacement [210].

Urethral smooth muscle exhibits spontaneous electrical and mechanical activity that will contribute to the overall tone exhibited by the tissue. Electrical activity occurs as bursts of spikes superimposed on a slower more rhythmic activity, and could be initiated by autonomic transmitters [211]. Two types of Ca2+- currents – L-type and T-type - have been recorded in isolated myocytes. Blockade of the former type reduced the number of spikes in each burst; the frequency within bursts was attenuated by blockade of T-type current [212]. However, both channels represent targets that may modulate spontaneous activity. The muscle cells are closely associated with interstitial cells that may be responsible for such activity, or at least modify it [165,213]. Activity in these cells results from intracellular Ca2+ release, itself triggered by Ca2+ influx, and the generation of Ca2+-activated depolarising current that generates the electrical activity. The observation that interstitial cells are closely associated with NOS-synthase containing nerves suggests that they may be intermediaries between nerves and urethral smooth muscle [214].
3. URETHRAL SKELETAL MUSCLE

The skeletal muscle of the urethra wall (rhabdosphincter) forms an incomplete ring of skeletal muscle around the urethra [215]. In human tissue three fibre types have been described; fast-twitch fatigue-sensitive, fast-twitch fatigue-resistant and slow-twitch, with the majority fatigue-resistant [216, 217]. Muscle bulk decreases with age and also with parity in women [218, 219], figure 12. Stress urinary incontinence (SUI) may be associated with a loss of muscle mass in the urethra [218, 220], due to increased apoptosis and/or denervation [221]. Alternatively, a decrease in motor nerve function may also contribute to SUI as shown in a mouse model where vaginal distension with a balloon reduced leak point pressures and the number of nerves in the urethra, without affecting muscle mass [222].

Selective inhibitors of serotonin (5-HT) and noradrenaline (NA) uptake, such as duloxetine, have been developed as potential agents for the therapeutic management of SUI [227], because 5-HT and NA terminals are present in Onuf’s nucleus that supplies the rhabdosphincter with motor nerves [228]. Analyses of current data suggest that the effect of duloxetine on alleviating USI is small, but significant [229], thus accounting for its limited use.

The striated muscle of the urethral sphincter may undergo abnormal activity resulting in urinary retention, Fowler’s syndrome [230,231]. The origin of the condition is unknown but one hypothesis is that it is due to ephaptic (i.e. direct cross-talk) electrical transmission between cells, much as can occur between nerve axons under certain conditions [232]. Neuromodulation may be effective in restoring voiding activity but there remain significant complication rates [233,234].

V. CELL PHYSIOLOGY OF NEUROACTIVE AGENTS IN THE LOWER URINARY TRACT

1. MUSCARINIC CHOLINERGIC TRANSMISSION

Acetylcholine is released not just from parasympathetic and somatic motor nerves to smooth and skeletal muscle targets respectively, but also from non-neuronal sources such as the urothelium. Muscarinic receptors are one of the main targets and are expressed throughout the lower urinary tract, nicotinic receptors are considered below. The muscarinic receptor family is divided into five subtypes based on molecular (m1-5) and pharmacological (M1-5) characteristics. Currently, the M1-4 receptors have been pharmacologically characterized, while an M5-specific compound has yet to be developed [235]. In detrusor, immunoprecipitation analyses show m2 and m3 subtypes are expressed, with m2 receptors in three- to nine-fold excess [236]. In normal human detrusor the minor M3 fraction is responsible for contractile activation, although the M2 component may modulate the overall response and become prominent in pathological bladders (see section III 3). M3 receptors are coupled to Gq/11-proteins, which importantly activate the enzyme phospholipase-C (PLC) to convert membrane phosphoinositides to the second messengers inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 in turn releases Ca2+ from intracellular stores, after binding to an IP3-receptor, to activate the contractile proteins. There is a body of experimental evidence to support the relevance of this pathway in detrusor: muscarinic agonists generate a rise of [Ca2+] independent of membrane potential and release is blocked by the IP3-receptor blockers TMB-8 [111]; and carbachol-potency is reduced by other IP3-receptor blockers such as heparin and PLC.
inhibitors [237,238]. Moreover inositol phosphate production mirrors tension generation in detrusor strips exposed to muscarinic agonists [239]. However other work casts doubt on the exclusiveness of this pathway, in part due to the relative ineffectiveness of other PLC inhibitors reducing carbachol-induced tension. It has been suggested that activation of the rho-kinase pathway by G-protein activation and of protein kinase C by DAG reduces the activity of myosin light chain phosphatase as so increases the Ca2⁺ sensitivity of the contractile proteins (see section III 1); the rise of intracellular Ca2⁺ was explained by activation of non-specific cation channels coupled to L-type Ca2⁺ channel activation [90,240-242]. Several attempts to reconcile the controversy have been attempted. Frazier et al [243] reasoned that different experimental protocols and PLC inhibitors used by different groups might partly be responsible and concluded that PLC activation was not important, whilst other have found considerable species differences in the relative importance of inositol phosphate and other pathways [244]. In addition, it must be cautioned that some of the data for these experiments rely on the use of compounds such ryanodine and cyclopiazonic acid (both Ca2⁺-store inhibitors) that have poor penetration into muscle preparations, so that a lack of effect cannot always be taken as a lack of importance for a particular pathway. M2 receptors are coupled to Gι-protein that reduces cAMP production by its influence on adenylyl cyclase activity. It has been proposed that M2 receptor activation inhibits the effect of other agonists that increase cAMP production, such as β-receptor stimulation. Recent reviews summarise the role of muscarinic-dependent pathways in the bladder and their relevance to contractile activation [130,245], and are summarized in figures 13 and 14. Muscarinic receptors are also localized on urothelial cells and myofibroblasts in the suburothelial and muscle layers (Section II.3) but where there role is less certain.

Presynaptic muscarinic receptors have also been described where it is proposed that they modulate transmitter release in either a negative (M2/4) or positive (M1 [246]) feedback mode. Knockout experiments indicate that M4, rather than M2 receptors inhibit transmitter release [247].

2. ADRENERGIC TRANSMISSION

Adrenergic receptors are predominantly found in the bladder neck and trigone regions and are activated by release of noradrenaline from sympathetic innervations to induce contraction of the smooth muscle in these regions. In the detrusor adrenergic receptors are also present that induce relaxation. There are five distinct adrenergic receptor types: α1, α2, β1, β2 and β3, with each being further divided into subtypes. The α1 subtype predominantly induces the closure of the bladder outlet through contraction of the urethral smooth muscle, while presynjucional α2-receptors modulate the release of neurotransmitters from sympathetic nerves There are also α1-receptors (α1A and α1D subtypes) expressed on the detrusor smooth muscle, but they do not appear to mediate contractile activity [185]. However, noradrenaline can affect autonomous contractions of an isolated whole bladder preparation [171]. There is also evidence that α1D receptors are present on the urothelium and may play a role in modulating reflex voiding [248].

All three β-subtypes are expressed in the detrusor smooth muscle with the β3-receptor being most highly expressed [249]. The β2 and β3-receptors can cause significant relaxation of trigonal and detrusor smooth muscle with apparent differences between species [250]. Furthermore, the effect is slightly smaller in hypertensive compared to normotensive rats [251]. There is much interest in specifically targeting β3-receptors for treatment of detrusor overactivity as it has a significant effect on reducing spontaneous detrusor contractions [252]. The β-receptor mediated relaxatory mechanism is thought to involve the rise of cAMP and modulation of large conductance Ca2⁺-activated K⁺ (BKCa) channels [253] – see figure 14. β-receptors are also found on the urothelium where their stimulation can induce release of NO and may also be involved in the release of the urothelial-derived inhibitory factor [67]. A comprehensive survey of the in vitro and in vivo actions of β-receptor modulators has been provided [180].
3. PURINERGIC TRANSMISSION

The role of ATP as an extracellular signaling molecule is now well accepted. In most mammalian species ATP is co-released with ACh from parasympathetic nerves and activates purinergic receptors to initiate detrusor contraction. This is in contrast to healthy human bladders where contraction is predominately mediated by ACh. However purinergic nerve mediated contraction is increased in a number of bladder pathologies including hypertrophy, idiopathic overactivity, interstitial cystitis, neurogenic damage and aging (Section III.3). The increase of atropine resistance in bladder disorders may be due to: increased sensitivity of detrusor cells to ATP, increased release from motor nerves, or reduced ATP hydrolysis within the neuromuscular junction. The three possibilities have been investigated using human detrusor samples from stable and overactive bladders. Only the last hypothesis was considered a possibility as ectonucleotidase activity in overactive human bladder samples was significantly reduced [254]. The purinergic P2 receptors are divided into P2X and P2Y families based on pharmacological and molecular studies [255,256]. P2X receptors are ionotropic ligand-gated non-specific cation channels while P2Y receptors are metabotropic G-protein coupled. Currently seven P2X receptors subtypes have been cloned and characterized (P2X1-7). P2X1 receptors are the predominant subtype throughout the detrusor smooth muscle (figure 14) and activation generates an inward, depolarizing current sufficient to activate L-type Ca2+ channels to generate an action potential and Ca2+ influx to initiate contraction [139].

All P2X receptors are present in cat bladder urothelium in the basal and apical layers [22]. Although the precise functional role of P2X receptors within the urothelium is still to be established, P2X2 and P2X3 may be involved in nociceptive signaling [257] and their expression has been shown to be up-regulated in painful bladder disorders including interstitial cystitis [258].

ATP released from the urothelium in response to hydrostatic pressure changes is believed to be important in bladder sensation and the initiation of micturition (section II.3).

There are eight subtypes of P2Y receptors (P2Y1,2,4,6,11-14) linked either to Gq/11 (P2Y1,2,6), Gi (P2Y12-14) or several proteins: Gq/11/Gi (P2Y4); Gq/11/Gs (P2Y11) [259,260]. P2Y receptors, although not a specific subtype, have been implicated in relaxation of smooth muscle, possibly via cAMP-dependent PKA activity [86]. P2Y1,2,4 have been identified on the urothelium [261]. Activation of P2Y receptors on urothelial cells from the rat evokes ATP release which may play a role in autocrine or paracrine signaling to modulate micturition [262]. P2Y6 receptors have also been located on sub-urothelial myofibroblasts and respond to UTP with inward currents and large, transient increases in intracellular Ca2+ [36,54]. In the cat P2Y4 receptors were detected in nerve bundles close to the urothelium and detrusor smooth muscle, however their role remains to be established although activation of P2Y receptors could alter the release of neuropeptides through increases in intracellular Ca2+ [256].

4. NITRERGIC MECHANISMS

There are three nitric oxide synthase (NOS) isoforms, encoded by separate genes, named for the tissue that they were first isolated from or the order in which the genes were cloned: neuronal NOS (nNOS) or NOS 1; inducible NOS from macrophage (iNOS) or NOS 2; and endothelial NOS (eNOS) or NOS 3. There is also a form of nNOS that has a unique leader sequence that localizes the enzyme within mitochondria.

Figure 14: A; Muscarinic, M2 and adrenergic β3 signalling pathways. These pathways influence the intracellular cAMP levels, either increasing (β3) or decreasing (M2) levels, through their influence on adenylate cyclase activity. cAMP, through a protein kinase-A (PKA) pathway, will promote relaxation by attenuating phosphorylation of the myosin light chain. B: Major ion channels in detrusor smooth muscle and their interaction. Two channels, the ionotropic P2X1 receptor and the L-type Ca2+ channel will conduct cation inward current thus depolarising the cell. The Ca2+ activated K+ channel (BKCa) will conduct outward current.
(mtNOS). Each of these enzymes can be found in every cell type of the LUT. The expression of several factors determine if there is a relaxatory effect to nitric oxide: NOS; the NO receptor, soluble guanylate cyclase (sGC); and phosphodiesterase (PDE), the enzyme that degrades cGMP, the product of sGC activity. There are eleven PDE isoforms so far identified, PDE1-5 are described in the bladder [263-265]. PDE5-selective inhibitors such as sildenafil (Viagra) and vardenafil are structural analogs of cGMP and competitively inhibit PDE. NO-donors have a rather small relaxatory effect on detrusor [266], but PDE inhibitors, such as vardenafil, relaxed pre-contracted detrusor [265], suggesting a relatively high endogenous PDE activity. These findings are corroborated by the beneficial effects of PDE5 inhibitors with LUTS, when used to treat erectile dysfunction [267]. The importance of NO-mediated mechanisms in urethral relaxation has already been highlighted (section IV.2) [268]. The cellular pathways in contraction that are mediated by NO as shown in figure 15.

Capsaicin releases nitric oxide from the urothelium [28] and therefore may have effects on nearby cells in the suburothelial region including afferent nerves and myofibroblasts [168]. Nitric oxide has also been shown to free up tight junctions and disrupt the urothelial umbrella cell permeability barrier [269]. Accordingly, upregulation of iNOS during inflammation could compromise barrier function and exacerbate the pathology.

5. NICOTINE AND NICOTINIC RECEPTORS

Transmission at parasympathetic pelvic ganglia is mediated largely by nicotinic receptors [270], but there is also evidence for the involvement of nicotinic receptors at other sites in the lower urinary tract. Nicotine may evoke release of acetylcholine from motor nerves, which itself may be upregulated by tachykinins acting via NK2 receptors [271,272]. This contractile effect of nicotine is blocked by the nicotine receptor antagonist hexamethonium. The nicotinic receptor is a pentamer of subunits and to date 17 different subunits have been identified (α1-10, β1-4, γ, δ, ε) so that there is a large variety of potential receptors. Mutation studies suggest that the α3 and β4 subunits are required for bladder function [273], which is in keeping with the pentamer structure in autonomic ganglia – (α3)2(β4)3.

Nicotinic receptor subtypes have also been localized to the urothelium, specifically for the α3, α5, α7, β3, and β4 subunits [274]. Based on experiments infusing agonists and antagonists into the bladder lumen it was proposed that these subunits form two types of nicotinic receptor, one that increases and one that decreases bladder activity. Later studies have detected a wider range of subtypes with differential distribution to various layers of the urothelium [48]. Nicotinic pathways may also have a role in alleviating the effects of bladder inflammation. With artificial models of inflammation blockade of nicotinic receptors exacerbated the effect whilst activating the receptors produced the opposite effects, possible through an involvement of the cytokine IL-6 [275,276].

6. ADENOSINE RECEPTORS

Whilst purinergic, P2, receptors have been the subject of considerable scrutiny the pyrimidine P1 receptor family has received less attention. Four subtypes have been cloned, A1, A2A, A2B and A3 and all are G protein-coupled receptors. A 1/3 receptors are negatively coupled to adenylyl cyclase activity, whilst A2 receptors are positively coupled. Adenosine relaxes bladder preparations pre-contracted by carbachol through an A2 (possibly A2B) receptor mechanism [277]. A1 receptor binding was evident in a number of smooth muscle organs except bladder [278]. However, another study using the A1 receptor agonist 2-chloroadenosine generated contractions linked to a PLC mechanism [279]. Using guinea-pig bladder preparations it has been proposed that A2-receptor

Figure 15: Nitric oxide (NO)-dependent pathways. Shown here is a scheme for a urethral smooth muscle cell where NO-dependent pathways are particularly important. NO is produced by activation of nitric oxide synthase and diffuses to a target cell, whereupon it increases cGMP production from GTP, by activation of guanylate cyclase (GC). cGMP, through a PKC pathway promotes relaxation. Muscarinic and adrenergic pathways are shown for completeness. Shown also are the sites of action of phosphodiesterase (PDE) inhibitors, sildenafil and tolafentrine.
relaxation is mediated by K<sub>ATP</sub> channel activation, through increased adenylate cyclase activity, principally involving the A<sub>2A</sub> receptor [280]. Adenosine also relaxes urethral smooth muscle, but the receptor subtype is unclear [281]. The confusion regarding the involvement of particular receptor subtypes may in part be due to the evolving knowledge regarding the specificity of different receptor subtype modulators. All four subtypes are also localized to the urothelium with some differential distribution to the different layers. Adenosine is released from the urothelium, especially when mechanically stretched and it was hypothesized that adenosine receptors may mediate increase of umbrella cell surface area under bladder stretch [282].

7. NEUROPEPTIDES

Various neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, neurokinin A, vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP), are released in the bladder from efferent and afferent [283] nerves and urothelial cells [284]. These peptides may also be released by noxious stimulus and promote inflammation. CGRP is an alternative product of the calcitonin gene expressed preferentially in nerve tissue. CGRP inhibits spontaneous activity and relaxes ACh-induced tension. Tachykinins (Substance P and neurokinin A) are prototypic of endogenous agonists of specific G-protein coupled receptors, termed tachykinin NK<sub>1</sub> and NK<sub>2</sub>. NK<sub>1</sub> receptors have been found in blood vessels and the urothelium of all species thus far examined, whereas their expression in muscle cells seems restricted to rats and guinea-pigs [285]. The stimulation of NK<sub>1</sub> receptors activates phospholipase C leading to inositol phosphate accumulation and is linked to smooth muscle contraction. Substance P has stimulatory effects on detrusor smooth muscle and urothelium. NK<sub>2</sub> receptors are localized on detrusor muscle of all mammalian species studied, including humans [286,287], and in the suburothelial layer in rats. The stimulation of NK<sub>2</sub> receptors is coupled to inositol phosphate accumulation and is excitatory in the bladder. In the human bladder, tachykinin receptor type NK<sub>2</sub> predominates. VIP and PACAP receptors (VPAC<sub>1/2</sub> and PAC<sub>1</sub>) are G-protein coupled receptors located on neurons and smooth muscle. They are coupled to several signal transduction pathways, including activation of adenylate cyclase and elevation of cyclic guanylate monophosphate levels in tissues [77, 288]. VIP release evokes relaxation of detrusor and urethra smooth muscle. There is indirect evidence to suggest that these various peptides can be released antidromically from afferent nerves in the bladder through different stimuli [289]. Potential stimuli for ‘efferent-release from afferents’ may be the intrinsic contractions associated with detrusor overactivity. However, whether this contributes to the enhanced spontaneous activity seen in pathology would depend on the peptide(s) released.

VI. BIOMECHANICAL PROPERTIES OF THE BLADDER WALL

1. ACTIVE AND PASSIVE CONTRACTILE PROPERTIES OF THE BLADDER WALL

The lower urinary tract is a hollow, neuromuscular system composed of four major layers: urothelium which lines the lumen; lamina propria; muscular detrusor and an outer serosal layer. The biomechanical properties of the bladder wall are principally dictated by the connective tissues of the lamina propria and the smooth muscle cells and connective tissues of the detrusor layer.

The detrusor, which comprises 60% to 70% of the thickness of the normal bladder wall, is composed of smooth muscle cells aligned in longitudinal and circumferential layers but are highly variable in cross-section, length and orientation; this orientation also changes during contraction [290]. Accordingly, the rise in luminal pressure during bladder contraction is not directly proportional to the sum of the muscle tension generated by cross-bridge formation in the myocytes. Some of the generated tension is absorbed by the connective tissues and only cells tangential to the radius of curvature of the wall contribute to force generation [291].

In principle, the different portions of the lower urinary tract need to exist between two physical states: high compliance, low wall stress, as exists in the bladder during filling; and high wall stress as exists during voiding in the bladder and in during storage in the urethra to maintain continence.

Overall wall tension results from the passive and active properties of the tissue; the former result from the viscoelastic properties of the collagen and elastin fibers in the extracellular matrices of the lamina propria and detrusor as well as the detrusor smooth muscle cells themselves. The active properties result from contraction of the component muscular structures within and surrounding the lower urinary tract and transmission of the resultant force through the extracellular and intracellular tissues. Whether the high compliance state is merely an absence of contraction of the muscular components or is contributed by active relaxation is a subject of increasing debate.

The translation of changes in wall tension to an increase or decrease of intraluminal pressure will also depend on the geometry of the system, i.e. the shape, intravesical volume and wall thickness. It is important to remember that whilst intraluminal pressure changes are the driving force for fluid movements in the lower urinary tract, the relationship with wall tension is highly dependent on geometrical factors.
2. COMPLIANT PROPERTIES OF THE BLADDER AND BLADDER WALL

There exists some inconsistency regarding the use of various terms to describe the relationship between distending or compressive forces and the resulting deformation. The stiffness, $k$, of a body is the ratio of an applied force to the resulting change of dimension; the inverse parameter is compliance and is a measure of the ‘distensibility’ of a system. In three dimensional terms pressures and volumes are substituted for force and distension, e.g. bladder compliance ($C$) is the ratio of change to bladder volume, $V$, per change to unit intravesical pressure, $P$, i.e. $C = \Delta V / \Delta P$. Generally, the elastic (Young’s) modulus, $E$, is not the same as stiffness; $E$ is a property of the constituent material, stiffness is an extensive property, i.e. a property dependent on the material and the geometrical shape of the body. Here compliance and stiffness will be used.

In principle, it is difficult to state a standard value for compliance for several reasons: bladder capacity increases with age whereas intravesical pressures do not vary as much; intravesical pressure itself is a function of bladder volume (see below) and thus compliance would vary as the bladder fills. Furthermore, it must be emphasised that compliance is a steady-state property so that measurements should only be made when any stress-relaxation has fully subsided. Several approaches have been attempted to account for these confounding factors. A normalization factor has been introduced in urodynamic studies to correct for values calculated in different size bladders [292,293]. Ex vivo, non-linear pressure-volume relationships have been transformed into linear stress-strain relationships to correct for different initial bladder volumes [294], when more direct comparisons can be made with data from tissue strips [294,295], figure 16.

Outflow tract obstruction in human and animal models has variable effects on bladder and isolated strip compliance. With shorter periods of obstruction compliance does not seem to alter [296], whilst after more extensive periods compliance may either decrease [297-300] or increase [294,295,301]. Most likely the different effects result from the severity and duration of the obstruction, with the bladder progressing from a hypertrophied low compliance state to a high compliance state that may mark end-stage failure [302]. The physiological consequences of this progression of function need to be considered. A decreased compliance will mean that intravesical pressures should rise more for a given amount of filling and if maintained can contribute to upper tract damage [303]. One consequence of a greater compliance will be that detrusor contractions will be less effective in raising pressure and thus make voiding more difficult [289]. It is thus important to determine which physical properties of the bladder wall determine changes to the compliance of the bladder.

3. BIOMECHANICAL PROPERTIES OF LOWER URINARY TRACT TISSUES AND COLLAGEN SUBTYPES

The passive properties of LUT tissues will depend on the respective properties of the muscular and extracellular components and the respective proportions of each [291,304]. The most significant extracellular components in this context are collagen and elastin; of the former collagen types I and III have the most influence on mechanical properties [305].

In obstructed bladders collagen type-I and type-III content rises in the lamina propria, but particularly in the detrusor muscle layer, with an increased ratio of type-III to type-I reported in some [306-309]. Such increases of collagen may be accompanied by reduction of elastin gene expression [310]. Collagen

*Figure 16: Bladder pressure-volume and derived tension-length relationships. A: ex vivo pressure-volume relationships for three different bladders from fetal sheep: red and blue symbols, obstructed bladders; black symbols, unobstructed control. B: derived tension-circumference plots from the data in part A. Tension was calculated according to Laplace’s Law (see text for details) and circumference was calculated from bladder volume assuming a spherical shape. MK Farrugia, M Godley, P Cuckow and CH Fry, unpublished data.*
forms large fibers and predominates in tissues with high tensile strength, whilst collagen III, forming smaller fibers, imparts increased flexibility to tissues and an ability to rearrange during bladder filling [311]. This may be of particular importance to bladders undergoing hypertrophy with a large increase of muscle mass. Collagen synthesis by cells is upregulated by physical stretch, which may provide the basic stimulus in bladder outflow obstruction [312] and may be determined by an increased release of basic fibroblast growth factor from the urothelium [313]. During bladder development the collagen III:I ratio shows an inverse relation to compliance [314]; however other geometrical factors, as mentioned above, will also determine compliance so that changing collagen ratio per se is only one factor among many. The biomechanical properties of the bladder wall will depend not just on the quantity and type of collagen, but also on its packing arrangement, and much work is required to determine the inter-relationship of these factors in determining overall tissue compliance. Figure 17 illustrates information that may be obtained by X-ray analysis on collagen packing arrangement.

**Figure 17**: Collagen visualisation in whole tissue and formation of glycation end-products. A: wide angle X-ray diffraction pattern of hydrated rat tendon. Meridional reflections are from helical layers in the longitudinal axis of the collagen molecules; equatorial reflections from lateral packing of collagen molecules. B: the reactions of non-reducing sugars, such as glucose (shown here in open-chain configuration as in aqueous solution), with amine groups, such as lysine, on protein molecules (R). The initial steps involve production of a Schiff base (a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group) and an Amadori rearrangement product. Such products can then combine causing cross-linking between protein molecules leading to disorganization of protein structure. Environmental and other factors can have significant effects on the passive properties of the bladder. For example oestrogen deprivation reduced the smooth muscle, and increased the collagen content of the bladder wall [210]. The aduction (combination) of sugar to protein without the action of an enzyme (glycation or non-enzymic glycosylation) is associated with diabetes and ageing and a significant factor in damage to extracellular and cellular proteins by promoting cross-linking and aggregation. Figure 17 shows the first steps whereby a reducing sugar, such as glucose, reacts with a basic residue on a protein to form a Schiff base and Amadori product. The subsequent interactions of these products generates cross-linking between adjacent protein chains and a loss of integrity and function. This formation of advanced glycation end-products increases the stiffness of tissues [315]. However several studies have shown that bladder compliance actually increases in animal models of diabetes [316,317] so that the exact relation of this condition and the formation of advanced glycation products remains unclear.

Stress-relaxation is a feature of the whole bladder and isolated muscle strips. It is a visco-elastic phenomenon that manifests itself as a partial reduction of stress (pressure or tension) after a rapid change of strain (volume or length). Physiologically this is advantageous to the filling bladder as it enables steady-state changes of pressure to be minimized during filling. Practically it means that if a bladder is rapidly filled then changes to intravesical pressure may be greater than during slow-fill and give the impression that compliance is less than it actually is. Compliance is a steady-state measurement and changes to pressure or tension should only be made when any stress-relaxation has finished. Stress-relaxation may reside from a rearrangement of the cellular and extracellular elements in a muscle component, although isolated cells also show the same phenomenon indicating that internal rearrangement of cytoskeletal elements must also occur [318]. In the over-compliant obstructed bladder the extent of stress-relaxation diminishes in the same proportion as steady-state stiffness [295]. Because the proportion of extracellular material increases in these bladders this suggests that the phenomenon may reside in both the cellular and extracellular components.

Detrusor muscle also undergoes a phenomenon of strain-softening: this is a reduction of steady-state stiffness on stretch to a new length, distinct from viscoelastic behavior [319,320]. Different stress-strain relationships are illustrated in figure 18. When the muscle is relaxed the process is irreversible, possibly due to cross-link breakages and can take many minutes, even hours, to develop. However, when active force is generated the process is reversible as new cross-bridges are made. Thus the passive
4. PROPERTIES OF THE PELVIC FLOOR AND APPARATUS.

Some studies have indicated down-regulation of oestrogen receptors in tissue samples of women with stress urinary incontinence (SUI) [330]. However, greater cross-linking of fibres was observed in these SI women, which would decrease the Ca²⁺-sensitivity of the contractile apparatus.

5. THE ACTIVE PROPERTIES OF MUSCLE IN THE LOWER URINARY TRACT

The role that intracellular Ca²⁺ plays in activating the contractile machinery was also considered previously and is up-dated in the section on the cell physiology of detrusor smooth muscle (III.3; V.I).

a) Length-tension relationships

All smooth muscles exhibit a bell-shaped dependence for active force on its initial resting length, i.e. there is an optimum resting length, L₀, at which active force is maximal. However, this length-tension curve extends over a greater range of initial lengths than does striated muscle. This is particularly true of detrusor where passive extension much beyond L₀ does not greatly reduce force [333]; human detrusor exhibits similar curves to those from animal preparations [334]. This has obvious physiological advantage whereby large changes in bladder circumference will still permit adequate force development by individual myocytes. Changes to tissue length are reflected in changes to cell length, so that these curves reflect accurately the length-dependence of contractions from individual myocytes [335,336]. There is evidence that length-tension relations are shifted rightwards, i.e. to longer lengths, in samples from some overactive bladders [337], but when normalized to L₀ curves do not vary much between control and pathological organs [338].

b) The contractile state

There is divergence of opinion whether absolute force (normalized to cross-section area) varies in samples from normal and pathological bladders. This is an important issue as it is important to know if conditions such as detrusor underactivity or overactivity are mirrored by changes to the contractile state of detrusor muscle. Alternatively they may be due to others causes such as alteration (total or proportional) to the amount of muscle in a bladder sample, the extent of functional innervation, or the physical properties of the extracellular matrix. Therefore, in this respect care must be exercised in the interpretation of experimental data, as contractile responses evoked agents such as muscarinic receptor agonists may give different responses compared to nerve-mediated responses. In the latter, a reduction of force may be due to denervation rather than muscle failure. To measure the relative extent of denervation compared to contractile
failure one method is to calculate the ratio of tension evoked by nerve-mediated stimulation and an agonist such as carbachol. A reduction of the ratio would imply denervation [339]. Animal models of bladder hypertrophy due to obstruction suggest some contractile failure [295,340,341], but not in all cases [294] and it may be hypothesised that failure is a feature of later growth when a decompensated, more compliant bladder is generated by obstruction. With human detrusor there is little evidence that agonist-induced force is different in detrusor from normal and overactive bladders [127]. There have not been systematic studies of the contractile state of detrusor samples from underactive human bladders. Perhaps the most interesting task in this context is to determine the basis of the condition described as detrusor hyperactivity with impaired contractile function – a symptomatic condition [342] that describes bladder overactivity with incomplete emptying. It is ascribed to a reduction of detrusor contractility [342,343] although this is a description based on urodynamic measurements rather than one derived from principles of muscle mechanics.

6. TENSION AND PRESSURE

Contraction of the muscle component of a hollow system such as the lower urinary tract generates a wall tension (stress) that manifests itself as a change of internal pressure, i.e. energy per unit volume, and by Pascal’s principle is everywhere the same in a static system. The quantitative relationship between pressure, \( P \), and wall tension, \( T \), is not linear but governed by Laplace’s Law, which for a uniform cylinder or radius, \( r \), and wall thickness, \( d \), is given by:

\[
P = \frac{2Td}{r}
\]

Thus a large radius sphere generating the same unit wall tension as a smaller sphere will undergo a smaller pressure change. This can lead to confusion when changes of pressure, regardless of the size of the vessel, are equated linearly to changes of wall tension and muscle performance. Two situations exemplify the need to understand the inter-relationship between pressure and wall tension: i) changes to internal pressure by passively filling the bladder; ii) calculation of active wall tension from internal pressure changes. The first situation [294] shows that when pressure-volume relationships are generated during bladder filling the plots are non-linear and are crucially dependent on the volumes used to fill the bladder. When normalised to wall tension versus changes to bladder radius the plots are linearised, enabling the compliance or stiffness to be calculated (compliance here is change of radius required to generate a unit change of wall tension). The second approach, to estimate active contractile properties of the bladder from pressure changes has been attempted from urodynamic measurements [344] and has been used to compare contractile properties of the bladder in patients with different pathologies [345]. However, this approach is really only useful when the pressure changes manifest wall tension changes alone and not when the energy in the fluid volume is being used to move fluid – i.e. when the pressure is generated isovolumically [346]. Furthermore, changes to contractility can then only be evaluated when muscle length (approximated by bladder radius) is constant, otherwise changes to the length-tension relationship will have occurred to confound the active tension estimations. Figure 19 shows calculations of pressure - left - for a bladder contracting isometrically (constant volume) at two different volumes during development of wall tension. The larger volume bladder develops pressure. Shown also is the change of pressure during the development of wall tension when a bladder is emptying, or remaining at constant volume. In the

![Figure 19: Contraction and pressure changes in a hollow organ. A: tension is developed in a unit element of the wall of a spherical organ as a function of time (dotted line). The solid lines show that consequent change of isovolumic pressure at two volumes, 200 and 400 ml. For the same amount of tension developed, the internal pressures are different. B: Pressures developed in a spherical organ due to the same change to tension as in part A. For the brown curves, volume (dotted line) remains constant; for the green curves volume reduces as the organ empties. Note again the different pressure profiles.](image-url)
latter case more pressure develops as the bladder empties, because the radius is reducing as a function of time. The other extrapolation drawn from muscle mechanics is to estimate changes to the force-velocity relationship from pressure-flow studies. Again a superficial resemblance exists between the two relationships but often calculations fail to recognize the non-linear relationship between force and pressure, and also between velocity and flow, is the cross-sectional area through which the flow occurs is not constant. Attempts to review the various paradigms that relate urodynamic to muscle dynamical properties have been made [347-350], and further hydrodynamic analyses of the lower urinary tract are awaited.


text

VII. THE LOWER GASTRO-INTESTINAL TRACT

1. THE NORMAL PHYSIOLOGY OF THE RECTUM AND ANUS

The ano-rectum is a functional structure that maintains faecal continence and also facilitates defaecation, when appropriate. The structure is shown in figure 20. Continence is maintained by maintaining an adequate rectal capacity at pressures less than that required to overcome the resistance offered by a competent anal sphincter, analogous to the condition in the lower urinary tract. Anal sphincter competence is due to a combination of internal sphincter tonic contraction, augmented by voluntary control via the external sphincter [351]. The anal sphincter mechanism may be helped by a sling effect of the puborectalis muscle around the anal canal, and the magnitude of the anorectal angle correlates with the severity of incontinence [352]. Faecal incontinence is increased in patients where the muscle has been divided; however, results from procedures that generate an acute anorectal angle are inconclusive [353]. Rectal compliance is maintained on filling by a reflex decrease of tone. The ano-rectum contains the necessary systems of receptors, neural networks and pacemaker cells to maintain the filling and emptying functions, assisted with external autonomic and somatic control.

The rectum is normally empty, but fills as faecal material accumulates in the descending and sigmoid colon, and is pushed forward through occasional peristaltic waves (mass movements). Volume of first sensation is up to 70-90 ml, urgency develops above about 200 ml [354,355]. A recto-anal sampling reflex [356] occurs on rectal distension that lowers pressures [357-359] in the anal canal allowing the contents to approach the mucosa, whilst the external sphincter remains contracted. The considerable sensory innervation of this region can distinguish between the gaseous (flatus) or solid state of the material. If defaecation is inappropriate contents are returned to the rectum, assisted by an increase of rectal compliance and inhibition of descending pathways. Such a sampling reflex can normally occur four to ten times per hour [360]. With larger volumes in the rectum, defaecation can be voluntarily deferred by contraction of the external sphincter and puborectalis (Figure 21).

If defaecation is appropriate intra-abdominal and intra-rectal pressures are raised to overcome sphincter resistance; the process is assisted by reflex relaxations of the internal and external sphincters, as well as the puborectalis. An increase of the anorectal angle also facilitates the process; brought about by taking up a sitting or squatting position and puborectalis relaxation. Upon completion, the internal sphincter and puborectalis transiently contract and restore the anorectal angle.

Continence is therefore maintained by a number of factors:

- effective anal sphincters and an acute anorectal angle to provide a proper barrier
- a suitably large, compliant and evacuable reservoir
- intact sensation in the ano-rectum
- proper consistency of the faeces

The most common cause of incontinence is damage to, or dysfunction of, the external and internal anal sphincters or their nerve supply. In addition, damage to sensory nerves that detect stools in the rectum will derange the reflexes that maintain continence. Damage may occur during childbirth, pelvic tumours, haemorrhoid surgery or neurodegenerative conditions. A decrease of rectal compliance can occur following radiation treatment or inflammatory bowel disease. Other manifestations of pelvic floor dysfunction such as rectal prolapse, rectocoele or weakness of pelvic floor muscles will all increase the likelihood of faecal incontinence.

2. INNERVATION

Parasympathetic innervation to the rectum and anal canal, via the pelvic plexus, originates mainly from sacral segments S1-S4 (pelvic splanchnic nerves).
the sympathetic supply is from T11,12 and L1,2. These fibres have the usual antagonistic effect on function with parasympathetic fibres increasing peristalsis and secretions. Somatic fibres to the external sphincter and pelvic floor muscles originate from Onuf's nucleus in S2-S4 and run in the pudendal nerve. Somatic and visceral afferents also arise from the ano-rectum: somatic fibres accompany the pudendal nerves and visceral afferents the parasympathetic and sympathetic efferents. The target for the postganglionic fibres can be the enteric nerve plexi that lie between the smooth muscle layers or the smooth muscle cells. Moreover there is increasing evidence that interstitial cells of Cajal (ICC – see below) are the main target for excitatory and inhibitory motor neurones that modulate smooth muscle contractility. The density of neurones in the myenteric and submucosal plexi declines towards the distal rectum and into the anus, but do not disappear together [362,363]. However, the variability of neuronal ganglia is variable along the ano-rectum and between patients and thus renders difficult the generation of criteria to neuronal deficits akin to intestinal neuronal dysplasia [364]. The use of botulinum toxin A is increasing advocated to manage various spastic conditions in the gastrointestinal tract [365,366], but as with its use in the lower urinary tract, its mode of action is unclear, although it has been postulated to diminish sympathetic activity [367]

Hirschsprung's disease is a developmental disorder of the enteric nervous system, characterised by an absence of ganglion cells resulting in functional obstruction. The aganglisation begins at the anus and continues proximally. The absence of ganglion cells results in an increase of extrinsic innervation, in particular adrenergic innervation, resulting in an increase of muscle tone and a functional obstruction. This pathology may be exacerbated by increased myogenic tone and loss of inhibitory control mediated through ICC [368,369]. The genetic basis of the disease has been investigated, and one hypothesis is that it is a failure of neural crest cells to migrate. A number of mutations have been identified including the proto-oncogene RET, an associated protein EDNRB, as well as various endothelin-receptor genes [370-372].

3. SMOOTH MUSCLE TISSUES

The rectum. The rectum is composed of outer, longitudinal and inner, circular layers of smooth muscle, as in proximal regions of the G-I tract, and generate phasic rhythms at 10-20 per hour [373]. The circular muscle develops little intrinsic tone, in contrast to that developed by the longitudinal muscle layer. Relaxation is induced by both alpha- and beta-receptor agonists with the latter generating more long-lasting responses [374]. Experiments with isolated strips show that nerve-mediated contractions are mediated by cholinergic (M3) and non-cholinergic components, with little sympathetic, adrenergic activation [375]. The non-cholinergic fraction is importantly mediated by tachykinins acting on NK2 receptors. The sympathetic supply to the rectum exerts an inhibitory influence, as cutting the thoraco-lumbar supply reduces motility of the rectum [376,377], which may by a presynaptic effect on excitatory nerves analogous to their action in lower urinary tract. In addition, the rectum receives a nitricergic innervation that relaxes the smooth muscle, as evidenced in preparations from human and animal sources [378,379]. 5-HT receptors

Figure 21: Components of faecal continence and defaecation. A: the conditions required for faecal continence. These include: appropriate muscle function in the anus and rectum to maintain a closed outlet and compliant reservoir; appropriate structural features; and proper consistency of the faeces. B: The stages in (deferred) defaecation.
also mediate smooth muscle tone and peristalsis throughout the gastrointestinal tract. In human and canine rectum preparations relaxation is also mediated via 5HT4 receptors [380-382]. This is of interest because 5HT4 receptor-agonists might be used as modulators of rectal tone as they have uses in the management of gastro-intestinal disorders [383], although reported cardiac side-effects have resulted in agents such as cisapride being withdrawn from the North American market [384]. More recent prokinetic receptor agonists (eg ATI-7505) may have fewer cardiac side-effects and so may prove safer alternatives [385].

The anal canal. The longitudinal smooth muscle layer of the rectum extends into the anal canal, to form a conjoint longitudinal coat, whilst the circular layer forms the internal anal sphincter. The responses to autonomic transmitters differ from the rectum whereby the anal sphincter muscle is relaxed by muscarinic and β-adrenoceptor agonists and contracts to α-adrenoceptor agonists. The longitudinal muscle contacts to both α- and β-adrenoceptor agonists [386]. The response to adrenoceptor agonists reflects the predominant effect of extrinsic sympathetic fibres in maintaining control of the anal sphincter [387]. Parasympathetic fibres have been suggested to modulate sympathetic nervous activity [388]. Nitric fibres offer the predominant relaxatory tone and may exert their effect via the enteric nerve system (below) [389]. Oral intake of the NO precursor L-arginine had no effect on anal pressures [390], but topical application of L-arginine paste to anal fissure did ameliorate the condition [391]. The different responses along the anorectum may in part be due to the variation of receptor populations in this region [392]. Angiotensin II (AT) has been proposed as an important mediator of tone in the anal sphincter and ACE-inhibitors as well as AT1 receptor antagonists reduce internal anal sphincter pressures [393-395].

The distribution of receptor subtypes in the anorectum is of interest because of the desirability of developing more tissue selective agents to modulate muscle function. β3-receptor subtypes have been demonstrated throughout the gastrointestinal tract in both human and animal preparations [396,397], and this may provide a role for receptor modulators as is being advocated in the lower urinary tract. Muscarinic responses are predominantly mediated by M3 subtype receptors.

There has been considerable interest in the role of the rho-kinase system in maintaining and modulating tone in the anal sphincter [398], and has been proposed as a potential therapeutic target [399]. This pathway may be involved in the relaxatory effect of the PDE5 inhibitor, sildenafil on precontracted anal smooth muscle [400,401]. Such pathways may be useful in the management of anal fissure, but an understanding of this mechanism will also be valuable in the investigation of the basis of faecal incontinence.

4. INTERSTITIAL CELLS

Interstitial cells of Cajal (ICC) accompany the enteric nerve plexuses that run between the successive smooth muscle layers of the gastrointestinal tract: IC- MY in the longitudinal layer as they are associated with the myenteric plexus; and IC-SM in the circular muscle layer. They form an extensive network through connections via gap junctions, and also form similar junctions with adjacent smooth muscle cells. ICC are believed to be pacemaker cells in the gastrointestinal tract as evidenced by spontaneous electrical signals arising from ICC and propagating to smooth muscle cells [402-405]. ICCs are probably the target for neuroeffector nerves from the autonomic and enteric systems supplying the gastrointestinal tract, rather than the smooth muscle cells themselves [406]. Rhythmic electrical activities in ICCs varies in cells from different sites in the gastrointestinal tract; however most are mediated by transient increases of the intracellular [Ca2+] arising from intracellular stores that subsequently open Ca2+-dependent ion channels to generate transient depolarisations [407]. The particular roles of intracellular Ca-stores, including the endoplasmic reticulum and mitochondria, vary in cells from different sites. ICCs express a surface marker to a receptor tyrosine kinase, kit, that not only acts as a characterising feature of the cell but is also vital for cell function.

Within the anorectum ICCs have been identified but their distribution is heterogeneous. In the rectum there were dense networks in the myenteric and submucosal layers, whereas in the anal sphincter they were confined to regions around the muscle bundles [408]. In the rectum ICCs have been shown to be the target of relaxatory nitric fibres, as heterozygous kit knock-out mice, as well as those deficient in nitric oxide synthase demonstrate impaired relaxation [409]. Others have suggested that ICC may not be responsible for all aspects of anal tone, rather that they determine intrinsic tone of the tissue. However, more complex reflexes, such as the recto-anal reflex (RAR; i.e. relaxation of the internal anal sphincter in response to anal stretch) may be more independent of ICC [410]. Furthermore, the latter study showed that different sources of NO mediated different functions – endothelial NOS regulated basal tone and neuronal NOS mediated the RAR and relaxation mediated by electrical stimulation of nitric fibres. Thus the precise inter-relationship between ICCs, smooth muscle cells and NOS-dependent muscular tone in the ano-rectum remains to be clarified.

5. FUTURE DIRECTIONS

There is still an incomplete knowledge of the factors
that regulate the contractile state of the smooth and skeletal muscles of the ano-rectum, as well as the role of the enteric and extrinsic nerve supplies, along with the interstitial cells that seem to mediate between nerves and smooth muscle. Much data obtained from studies of obstructive conditions can shed light on these control system and be used to understand better failure of continence mechanisms. Furthermore, the cellular biology that underlies sensation in the ano-rectum, as a basis of sampling reflexes for example, is little understood. However, several studies have shown that a subset of patients with faecal incontinence demonstrates an increase of urgency that may underlie the condition [411-413]. An interesting aspect is whether the emerging field of lower urinary tract sensation may be applied to the analogous situation in the ano-rectum.

VIII. NOVEL MOLECULAR TARGETS

1. INTRODUCTION

The previous sections have described recent advances in the multiplicity of mechanisms that regulate lower urinary tract function, and that may undergo changes associated with pathological changes to function. Various signal transduction mechanisms have been implicated in these controls that may make suitable targets for manipulation of function. According to the most recent classification [414], signal transduction mechanisms have been sub-classified into seven categories, namely.

- 7TM (seven-transmembrane helix) metabotropic receptors of the G protein-coupled superfamily;
- Transmitter-gated channels;
- Ion channels;
- Catalytic receptors;
- Nuclear receptors;
- Transporters;
- Enzymes.

This report will highlight several examples from the first and third categories as sources of novel targets for the treatments of urinary incontinence. The following terminology and definitions are derived from the most recent classification, “Guide to Receptors and Channels, 3rd Edition [414]. Emphasis in this section will be on targets covered less comprehensively above.

2. METABOTROPIC RECEPTORS

a) Acetylcholine-Muscarinic receptors

Among the many 7TM (metabotropic) receptors, muscarinic receptors are the most important for urinary bladder contraction, and currently for treatment of the overactive bladder.

The urinary bladder is profusely supplied with autonomic nerve fibers, which form a dense plexus among the detrusor smooth muscle cells. The majority of these nerves are excitatory cholinergic and contain acetyl cholinesterase [415]. Whilst they occur in profusion throughout the muscle coat of the bladder, some muscle bundles are more richly innervated than others. Thus, normal human detrusor contraction is mediated almost exclusively through muscarinic receptor stimulation by released acetylcholine, and responses are completely abolished by atropine [416]. Detrusor strips from normal human bladders produce little response to single stimuli and require repetitive activation of the intrinsic nerves to induce a response.

Molecular cloning studies have revealed five distinct genes for muscarinic ACh receptors in rats and humans, and five receptor subtypes (m1-5) correspond to these gene products [416] – see also section V.1. Muscarinic receptors are coupled to G-proteins; M1, M3 and M5 preferentially couple by Gq to phosphoinositide hydrolysis and diacylglycerol production, and M2 and M4 couple to Gi and inhibit adenylate cyclase activity. The abundance and roles of the various receptors have been considered above (Sections III and V).

Desensitization of muscarinic acetylcholine receptors is one mechanism that may cause detrusor smooth muscle to become less sensitive to incoming stimuli. This is mediated by phosphorylation of the muscarinic acetylcholine receptor by guanosine phosphate binding G-protein coupled receptor kinase (GRK) [417-419], and m2 and m3 GRK2 mRNAs have been described. Protein expression of GRK2 in normal bladder detrusor is significantly higher in obstructed bladder detrusor in patients with benign prostatic hyperplasia [419]. Failure of the desensitizing mechanism may therefore contribute to detrusor overactivity with bladder outlet obstruction.

Non-neuronal acetylcholine release is also described, from the bladder urothelium, or the suburothelial space, although its function in unknown (see also section II). The non-neuronal acetylcholine release is increased by stretch, is increased with age [420] and may contribute to pathogenesis of overactive bladder.

b) Adrenergic beta-receptors

During urine storage, sympathetic nerve activity to the lower urinary tract is important: with both relaxation of bladder smooth muscle, via adrenergic ß-receptors, and contraction of urethral smooth muscle via adrenergic ß1-receptors [421] - (see also section V.2). There are three ß-receptor subtypes, ß1, ß2, and ß3, and gene expression of ß3 receptors and relaxation of human detrusor via the same receptors has been recently reported [249,422-424]. Several ß3-agonists (KUC-7483, YM-178, FK-175) have been developed, and are undergoing clinical trials.
The beta-adrenoceptor is a Gs-protein-coupled receptor and activation elevates smooth muscle camp, which may trigger relaxation of smooth muscle. Downstream effectors activated via a cAMP-dependent mechanism(s) include plasma membrane K+ channels, such as the large-conductance, Ca2+-activated K+ (BKCa) channel. ß-adrenoceptor-mediated relaxant mechanisms also include cAMP-independent signaling pathways, suggested by several pharmacological and electrophysiological studies. In airway smooth muscle, direct activation of the BKCa channel by Gs-α is a mechanism by which stimulation of β2-adrenoceptors elicits muscle relaxation independently of the elevation of cAMP [425]. The α3 adrenoceptor is recognized as an attractive target for drug discovery, as activation of β1 or β2-receptors can have undesirable side effects such as tachycardia or muscle tremors. Consequently, recent efforts have been directed toward the design of selective β3 agonists [145]. GW427353, a novel agonist, evokes bladder relaxation and facilitates bladder storage mechanisms in the dog [146]. The β3 agonist CL-316243 increases urine storage in SHRs [147].

**c) Endothelin**

The three isoforms of the 21-amino-acid peptide endothelin (ET-1, ENSG00000078401, ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205) mediate their actions via the 7TM receptors ETA and ETB [426]. Non-selective peptide (e.g. TAK044, pA2 8.4) and non-peptide (e.g. bosentan, pA2 6.0–7.2; SB209670, pA2 9.4) antagonists can block both ETA and ETB receptors. The predominant role of ETA receptors in the contractile effects of ETs in the detrusor has been confirmed by several other investigators in animal, as well as in human bladders [427,428]. Features of ETA and ETB receptors are summarised in Table 1.

In human detrusor, ET-1-induced contractions are mediated mainly by the ETA receptor and not by the ETB receptor. RT-PCR revealed positive amplification of the ETA, but not ETB, receptor mRNA fragments [429]. This is in contrast to findings in guinea pig bladder, where both ETA and ETB receptors contributed to ET-induced contraction [430]. The functional role of ETs in the detrusor has not been established. The slow onset of the contractile effects seems to preclude direct participation in bladder emptying. It has been suggested that ETs may be involved in regulation of detrusor muscle tone by a direct effect [430]. However in the rat bladder ET-1 potentiates the contractions evoked by both transmural nerve stimulation and applications of ATP at peptide concentrations 10-fold below those needed to produce an increase in bladder tone [427]. This suggests a modulatory effect on detrusor neurotransmission. The selective ET-A antagonist LU 302146 acts on the atropine-resistant component of efferent detrusor activation since additional administration of atropine almost completely abolished detrusor contraction. This observation raises the possibility that ET-receptor antagonists might be beneficial in patients with neurogenic bladder dysfunction or in patients with functional or anatomical BOO [431].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>ETA</th>
<th>ETB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensembl ID</td>
<td>ENSG00000151617</td>
<td>ENSG00000136160</td>
</tr>
<tr>
<td>Principal transduction</td>
<td>Gq/11, Gs</td>
<td>Gq/11, Gi/o</td>
</tr>
<tr>
<td>Potency order</td>
<td>ET-1, ET-2&gt;ET-3</td>
<td>ET-1, ET-2, ET-3</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>—</td>
<td>[Ala1,3,11,15]ET-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sarafotoxin S6c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IRL1620</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BQ3020</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>A127722 (9.2–10.5)</td>
<td>A192621 (8.1)</td>
</tr>
<tr>
<td></td>
<td>LU135252 (8.9)</td>
<td>IRL2500 (7.2)</td>
</tr>
<tr>
<td></td>
<td>SB234551 (8.7–9.0)</td>
<td>Ro468443 (7.1)</td>
</tr>
<tr>
<td></td>
<td>PD156707 (8.2–8.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FR139317 (7.3–7.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BQ123 (6.9–7.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BQ788 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Probes</td>
<td>[3H]-S0139 (0.6 nM)</td>
<td>[125I]-IRL1620 (20 pM)</td>
</tr>
<tr>
<td></td>
<td>[3H]-BOQ123 (3.2 nM)</td>
<td>[125I]-BQ3020 (0.1 nM)</td>
</tr>
<tr>
<td></td>
<td>[125I]-PD164333 (0.2 nM)</td>
<td>[125I]-[Ala1,3,11,15]ET-1 (0.2 nM)</td>
</tr>
<tr>
<td></td>
<td>[125I]-PD151242 (0.5 nM)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Endothelin receptors. The values in parentheses for the selective antagonists are pKi values**
ET-1 and ET<sub>A</sub> receptors might be involved in the generation of premicturition contractions in BOO rats, and endothelin ET<sub>A</sub> receptor antagonists, such as YM598, may have ameliorating effects in patients with bladder overactivity associated with BOO [432]. ET<sub>A</sub> receptor inhibition could be an effective treatment for neurogenic bladder overactivity in pathological conditions such as SCI [433]. ET<sub>A</sub> receptors play an important role in the lower urinary tract contraction, and that the selective endothelin ET<sub>A</sub> receptor antagonist YM598 has ameliorating effects on various urinary dysfunctions, including benign prostatic hyperplasia [434].

d) GABA<sub>B</sub>

Functional GABA<sub>B</sub> receptors are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> ENSG00000168760: GABA<sub>B2</sub> ENSG00000136928. Principal transduction is via G<sub>i/o</sub>. Selective agonists are 3-APPA, 3-APMPA (CGP 35024,), (R)-(−)-baclofen, and CGP44532, and selective antagonists are CGP62349, CGP55845, SCH50911, 2-hydroxy-s-(−)-saclofen and CGP35348.

Detrusor overactivity may be controlled by modulating the afferent input from the bladder and the excitability of the sacral reflex centre and suggests a novel method to treat obstructive bladder patients with oral gabapentin [435]. Fourteen of 31 patients with refractory OAB and nocturia improved with oral gabapentin. Gabapentin was generally well tolerated and can be considered in selective patients when conventional modalities have failed [436].

e) Glutamate metabotropic receptors

There are two major classes of glutamate receptors, the ionotropic receptors which form ligand-gated cation channels [437] and the metabotropic receptors (mGluRs) which are a family of G-protein coupled receptors activating distinct signal transduction pathways in neurons [438]. The former includes n-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-l-isoxazole-4-propionic acid (AMPA), and kainite receptors, which have been revealed to play essential roles in the control of micturition reflexes [439,440]. The latter, mGluRs are constituted of eight groups on the basis of sequence homology, transduction mechanism and agonist pharmacology, and less is yet known about the functional roles in the lower urinary tract. These studies examined whether the group I mGluRs (ie, mGluR1 and mGluR5) participated in the micturition reflex of decerebrate, unanesthetised mice. Glutamate is involved in many CNS functions, and drugs acting on the different glutamate receptors may affect not only micturition [441, 442].

Female wild-type C57BL/6 mice and mGluR1 knockout mice under decerebrate, unanesthetised conditions were used for in vivo cystometry with 6-methyl-2-(phenylethynyl)pyridine (MPEP, 0.3-30 mg/kg i.p.), a selective mGluR5 antagonist. Inter-micturition interval (IMI) was measured during continuous infusion cystometrograms. Blocking mGluR1, mGluR5 or both increased bladder capacity and mGluR1 and mGluR5 additively interacted to transmit afferent signals from the bladder (figure 22). Thus, a group I mGluR antagonist, which blocks both mGluR1 and mGluR5, would exert a beneficial effect more potently than a drug targeted at either mGluR1 or mGluR5 alone. Therefore, these may be promising drugs to treat storage dysfunctions, including detrusor overactivity and urgency urinary incontinence [443].

f) Prostanoid receptors

Prostanoid receptors are activated by the endogenous ligands prostaglandin (PG) D<sub>2</sub> (D), PGE<sub>2</sub> (E), PGF<sub>2α</sub> (F), PGH<sub>2</sub> (H), prostacyclin [PGI2 (l)] and thromboxane A<sub>2</sub> (TX). Measurement of the potency of PGI<sub>2</sub> and TXA<sub>2</sub> is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies. Prostanoid actions are mediated by specific receptors on cell membranes, including DP, EP, IP, and TP receptors that preferentially respond to PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2</sub>, PGI<sub>2</sub>, and TXA<sub>2</sub>, respectively. The EP receptor itself is subdivided into four subtypes: EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub> (table 2) [444, 445].

The signaling pathways vary. For example, TP receptors signal via G<sub>q</sub> protein, activating IP<sub>3</sub>/diacylglycerol pathways, but also other G-proteins may be involved. EP<sub>1</sub> receptors signal via IP<sub>3</sub> generation and increased cell Ca<sup>2+</sup>; activation of EP<sub>2</sub> and EP<sub>4</sub> leads to an increase in cAMP; and EP<sub>3</sub> activation inhibits cAMP generation via a pertussis toxin-sensitive G<sub>i</sub>-coupled mechanism and may also signal via the small G-protein, rho. Prostanoids may affect excitation-contraction coupling in the detrusor in two ways, directly by effects on the smooth muscle, and/or indirectly via effects on neurotransmission.

The prostanoid receptor most important for detrusor function has not been established. Mice lacking EP<sub>1</sub> receptors had normal cystometry, but did not react to intravesical PGE<sub>2</sub> instillation, which caused detrusor overactivity in wild-type controls. Obstruction of EP<sub>1</sub> receptor-knockout mice did not prevent the resulting increase in bladder weight but prevented the increase in spontaneous contractile activity (non-voiding contractions) seen in wild-type controls [231]. Prostaglandin E<sub>2</sub> enhances the micturition reflex through C-fiber afferents via EP<sub>1</sub>. Therefore, EP<sub>1</sub> selective antagonists may improve bladder storage function [446]. However, EP receptor distribution and the implications for bladder mucosa function are not fully understood. EP<sub>2</sub> and EP<sub>4</sub> mRNA are over-expressed in the urothelium of obstructed human urinary bladder compared to non-obstructed bladder.
Figure 22: Modulation of mGlu receptor activity and continuous infusion cystometry. A: effect of 6-methyl-2-(phenylethynyl)pyridine (MPEP, 30 mg/kg i.p.), a selective mGluR5 antagonist, on bladder activity during continuous infusion (30 µl/min) in a decerebrate, unanesthetized mouse. The dose increased the inter-micturition interval approximately 26% of the baseline value in this animal without a suppression of micturition pressure. B: the time-course of the effect of MPEP (0.3, 3 and 30 mg/kg i.p.) or vehicle on inter-micturition interval (IMI) in decerebrate, unanesthetized wild type mice. C: the time-course of the effect of MPEP (30 mg/kg i.p.) or vehicle on IMI in decerebrate, unanesthetized mGluR1 knockout mice. The peak increase of IMI was similar to that in wild-types. M Takeda, unpublished data

Table 2. Prostanoid receptors. The values in parenthesis for the selective antagonists are pKi values.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensembl ID</td>
<td>ENSG00000 160951</td>
<td>ENSG00000 125384</td>
<td>ENSG00000 050628</td>
<td>ENSG00000 171522</td>
</tr>
<tr>
<td>Principal transduction</td>
<td>Gq/11</td>
<td>Gs</td>
<td>Gi/o</td>
<td>Gs</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>E&gt;F,I&gt;D,T</td>
<td>E&gt;F,I&gt;D,T</td>
<td>E&gt;F,I&gt;D,T</td>
<td>E&gt;F,I&gt;D,T</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>ONO8711 (9.2), SC51322 (8.8)</td>
<td>-</td>
<td>L798106 (7.7)</td>
<td>GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (7.6)</td>
</tr>
<tr>
<td>Probes</td>
<td>[3H]-PGE2 (1–25 nM)</td>
<td>[3H]-PGE2 (5–22 nM)</td>
<td>[3H]-PGE2 (0.3–7 nM)</td>
<td>[3H]-PGE2 (0.6–24 nM)</td>
</tr>
</tbody>
</table>
This overexpression significantly correlated with International Prostate Symptom Scores (IPSS), especially the storage IPSS component [447]. Hence, in contrast to the previous mouse data, EP2 and EP4 could be promising receptor subtypes for the treatment of overactive bladder [446].

3. ION-CHANNELS

a) Calcium (voltage-gated)-channels

Calcium (Ca\(^{2+}\)) channels are voltage-gated ion channels present in the membrane of most excitable cells and form hetero-oligomeric complexes. The \(\alpha_1\) subunit is pore-forming and provides the extracellular binding sites for practically all agonists and antagonists. The ten cloned \(\alpha\)-subunits can be grouped into three families:

- a) the high-voltage activated dihydropyridine-sensitive (L-type, CaV1.x) channels;
- b) the high-voltage activated dihydropyridine-insensitive (CaV2.x) channels and
- c) the low-voltage-activated (T-type, CaV3.x) channels.

Each \(\alpha_1\) subunit has four homologous repeats (I–IV), each repeat having six transmembrane domains and a pore-forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane-spanning S4 segment, which contains highly conserved positive charges. Many of the \(\alpha_1\)-subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of \(\alpha_1\), \(\beta\) and \(\gamma_2\)-\(\delta\) subunits. The \(\gamma\) subunits have not been proven to associate with channels other than \(\alpha_1S\). The \(\alpha_2\)-\(\gamma_1\) and \(\alpha_2\)-\(\gamma_2\) subunits bind gabapentin and pregabalin.

Activation of detrusor muscle, both through muscarinic receptor and NANC pathways, seems to require both influx of extracellular Ca\(^{2+}\) through Ca\(^{2+}\) channels and mobilization of intracellular Ca\(^{2+}\) [448,449]. The importance of each mechanism may vary between species and also with respect to the transmitter studied.

b) Epithelial Na\(^{+}\) channels (ENaC)

Epithelial Na\(^{+}\) channels (ENaC) are responsible for sodium reabsorption by the epithelium lining the distal part of the kidney tubule, and fulfill similar functional roles in some other tissues such as the alveolar epithelium and the distal colon. This reabsorption of Na\(^{+}\) is regulated by aldosterone, vasopressin and glucocorticoids, and is one of the essential mechanisms in the regulation of sodium balance, blood volume and blood pressure.

The degenerin epithelial Na\(^{+}\) channel (ENaC) family has been proposed as a transducer of sensory stimuli in several species [450-453]. These ENaCs seem to be mechanosensitive (MS) according to many findings. In the rabbit urinary bladder, ENaC changes its Na\(^{+}\) transporter properties after changes of hydrostatic pressure [451]. ENaC in the renal pelvic epithelium of rats participates in the activation of afferent renal MS neurons by increased renal pelvic pressure [31]. Thus, ENaCs are likely to be involved in MS transduction in the bladder, and may be related to the pathophysiology of changes in sensory nerve function by upregulation of ENaCs in the bladder epithelial cells or afferent nerve terminal. ENaC is expressed in the mammalian urinary bladder and it has been proposed that amiloride-sensitive Na\(^{+}\) transport across the apical membrane of the mammalian urinary bladder epithelium is mediated primarily by ENaC [454].

1. ENaC in human urinary bladder:

The \(\alpha\)-, \(\beta\)-, and \(\gamma\)-subunit ENaC proteins and mRNA are clearly expressed in human bladder epithelium with and without BOO. The quantified ENaC mRNA expression correlates significantly with the storage symptom score (figure 4).

2. ENaC in rat and rabbit urinary bladder:

Intravesical infusion of amiloride (1 mM) significantly reduces the frequency of reflex voiding during bladder filling, increases bladder capacity, with no effect on the amplitude of micturition pressure. Stretch (50%) induced significant increase in ATP release from whole layer bladder strips, but only a slight increase in muscular layer strips without epithelium. Amiloride (1 mM) significantly suppressed stretch-evoked ATP release from bladder epithelium [455,456]. cAMP stimulates the insertion of new Na\(^{+}\) channels into the apical membrane of the rabbit bladder epithelium [457].

c) Potassium channels: The 6TM family: Maxi-K channel

Potassium channels are fundamental regulators of excitability. They control the cell membrane potential, the frequency and the shape of the action potential, and the secretion of hormones and neurotransmitters. Their activity may be regulated by transmembrane voltage, Ca\(^{2+}\) and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming \(\alpha\)-subunit often associated with auxiliary regulatory subunits. The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families.

The 6TM family of K channels comprises the voltage-gated Kv subfamilies, the KCNQ subfamily, the EAG subfamily (which includes HERG channels), the Ca\(^{2+}\)-activated s/o subfamily (actually with 7TM) and the Ca\(^{2+}\)-activated SK subfamily. As for the 2TM family, the pore-forming \(\alpha\)-subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. Kv1.1 with Kv1.2; KCNQ2 with KCNQ3).
Large-conductance, voltage- and Ca$^{2+}$-activated K$^+$ (Maxi K, or BK$_{Ca}$) channels regulate the resting potential and repolarization of the action potential, and play a critical role in modulating contractile tone of smooth muscle, including the detrusor [107,458], and neuronal processes. Not only BK$_{Ca}$ channels, but also small-conductance (SK$_{Ca}$) channels, are regulators of excitability in detrusor smooth muscle. Ca$^{2+}$ entry through voltage-dependent Ca$^{2+}$ channels activates both BK$_{Ca}$ and SK$_{Ca}$ channels, but Ca$^{2+}$ release (Ca$^{2+}$ sparks) through ryanodine receptors activates only BK$_{Ca}$ channels [459, 460]. Thus, BK$_{Ca}$ channels are more important in counteracting enhanced spontaneous mechanical activity with urinary bladder smooth muscle stretch. Phasic contractions of human detrusor, due to transmitter release, are dependent on calcium entry through L-type Ca$^{2+}$ channels and BK$_{Ca}$ channels have a very significant role in reducing both cholinergic- and purinergic-induced contractility [112]. Thus, Ca$^{2+}$-dependent K$^+$ channels could contribute to pathologies such as overactive detrusor and represent attractive pharmacological targets for decreasing phasic contractions of detrusor smooth muscle in OAB [461]. The selective antagonist for BK$_{Ca}$ channels, NS-8, decreased the discharge rate of the afferent pelvic nerve on bladder filling in rats [122]. Thus, NS-8 might have the potential for treating patients with urinary frequency and incontinence.

The importance of the BK$_{Ca}$ channel is also demonstrated by the observation that local h-slo cDNA (i.e., the BK$_{Ca}$ channel) injection ameliorated detrusor overactivity in a rat model of partial urinary outlet obstruction [113]. It was proposed that expression of h-slo in rat bladder functionally antagonized the increased contractility normally observed in obstructed animals, and thereby improved detrusor overactivity and also indicated a potential utility of gene therapy for urinary incontinence. Consistent with increased urinary bladder contractility caused by the absence of BK$_{Ca}$ currents, slo(-/-) mice demonstrate a marked elevation in urinary frequency [462]. BK$_{Ca}$ channels consist of distinct α and β-subunits. Whereas only one α-subunit has been identified until now, four putative β-subunit types have been cloned. The existence of BK$_{Ca}$ α- and β-1-subunits in human urinary bladder (both in the mucosal layer and the detrusor) have been demonstrated with a combination of genetic and immunohistochemical methods. The expression level of BK$_{Ca}$ channels in the detrusor muscle and the mucosal layer decreased in BOO bladders compared with controls, consistent with the possibility that they have a pivotal role in the generation of OAB induced by bladder outlet obstruction [463] (figure 23).
A novel BKCa channel blocker, A-272651, represents one of the first small molecules that could be used to characterise BKCa channels in physiological and pathological states [464]. No other K+ channel opener seems to have passed the proof of concept stage, and there is at present no convincing evidence showing that K+ channel opening is a useful principle for treatment of detrusor overactivity [465]. The safety and tolerability of escalating doses of hMaxi-K, a gene transfer product of the human Maxi-K (BKCa) channel, were confirmed by clinical and laboratory tests in 11 patients with moderate to severe erectile dysfunction. hMaxi-K gene transfer is potentially a viable approach to the treatment of erectile dysfunction and other smooth muscle diseases with targeted access [466].

d) Transient receptor potential (TRP) cation channels

The TRP superfamily of cation channels, whose founder member is the Drosophila Trp channel, can be divided, in mammals, into six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with varied permeation properties. The TRPC ('Canonical') and TRPM ('Melastatin') subfamilies consist of seven and eight different channels, respectively (i.e., TRPC1-7 and TRPM1-8). The TRPV ('Vanilloid') subfamily comprises six members (TRPV1-6) whereas the TRPA (Ankyrin) subfamily has only one mammalian member (TRPA1). The TRPP ('Polycystin') and TRPML ('Mucolipin') families are not fully characterised. Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and are only briefly mentioned here [467,468].

The importance of stretch-evoked ATP release from urothelium, and the subsequent activation of afferents has been described above (section II). The nature of the mechnosensitive (MS) processes responsible for ATP release is unclear but ENaCs and TRP ion channels are candidates [469]. With respect to TRP channels several have been identified, and many also have thermosensing properties [470].

Among several thermosensing TRP channels, TRPA1, TRPM8, TRPV1, and TRPV4 are candidates of molecular targets of the novel treatments for urinary incontinence (table 3) [471]. TRPA1 may be a candidate for an MS channel, with cold-sensing capability [472,473]. In addition to activation by mechanical stimuli, TRPA1 is also a cold receptor: activation is initiated when the temperature is decreased to 17°C [474]. Intravesical infusion of ice water elicits uninhibited contraction of bladder in infants and patients with neurogenic bladder and it is reasonable to assume that TRPA1 is involved in the bladder-cooling reflex and should provide a further treatment target [475].

• TRPA1 and TRPM8 in the rat and the human urinary bladder:

Whole mount double-staining demonstrates expression of TRPA1 on the CGRP-reactive sensory nerve termini, but not on mucosa of the bladder (figure 24) and is much greater in the obstructed bladder. Expression of mRNA and protein of TRPA1 and TRPM8 were confirmed by quantitative RT-PCR and immunohistochemistry. During cystometry, 0.6 mM trans-cinnamaldehyde (CA; an agonist of TRPA1) decreased the pressure threshold (PT), inter-micturition interval (IMI) and micturition pressure (figure 25) – similar results were obtained with AITC: allyl-isothiocyanate. The effects on PT and IMI were completely reversible. Desensitization of C-fibres by capsaicin significantly attenuated the effects of 0.6 mM CA on PT and IMI (p=0.022, 0.002). These results, couple to the fact that TRPA1 expression is increased in the obstructed bladder, suggest that both TRPA1 and TRPM8 may contribute to the pathophysiology of OAB [476,477].

e) ER stress

In bladder outlet obstruction (BOO), mechanical stress and ischemia/hypoxia are implicated in structural and functional alterations to the urinary bladder. In other organs, mechanical stress and hypoxia trigger a

Table 3. Possible implication between TRP ion channels and lower urinary tract function

<table>
<thead>
<tr>
<th>Channels</th>
<th>Agonist</th>
<th>Thermo-threshold</th>
<th>Sense</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPA1</td>
<td>Isothio-cyanate (Mustard)</td>
<td>&lt;17°C</td>
<td>Pain, Hot Cold ?</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>TRPM8</td>
<td>Menthol</td>
<td>&lt;28°C</td>
<td>Cool, Menthol</td>
<td>Urinary bladder, Prostate</td>
</tr>
<tr>
<td>TRPV1 (vanilloid receptor)</td>
<td>Capsaicin (hot pepper)</td>
<td>&gt;43°C</td>
<td>Pain, Hot, Burning</td>
<td>Urinary bladder, Prostate</td>
</tr>
<tr>
<td>TRPV4</td>
<td></td>
<td>&gt;28°C</td>
<td>Warm ?</td>
<td>Urinary bladder</td>
</tr>
</tbody>
</table>
Figure 24: Expression and localization of TRPA1 protein in L6-S2 dorsal root ganglia (DRG) and smooth muscle of the rat urinary bladder. A,B: TRPA1 immunoreactivity at small to medium sized neurons of L6-S2 DRG. C: TRPA1 immunoreactivity in the detrusor smooth muscle layer. D-F: The DRG neurons innervating the bladder were labelled retrogradely by injecting SP-DiIC<sub>18</sub>(3) into the urinary bladder wall two weeks earlier. Some SP-DiIC<sub>18</sub> positive neurons expressed TRPA1 (arrow) while some others not (arrow head). This is most clearly seen in the merged picture (yellow). G-I: TRPA1 also co-localizes with CGRP at the nerve termini in the lamina propria of urinary bladder (arrow). Scale bar: 50 μm. M Takeda, unpublished data

Figure 25: TRPA1 and TRPM8 function and expression. A,B: in vivo rat cystometry using physiological saline solution or TRPA1 agonist (CA: trans-cinnamaldehyde) under urethane anesthesia. A: the effect of 0.6 mM cinnamaldehyde (CA) on inter-contraction interval (ICI), *p=0.05. B: the effect of 0.6 mM cinnamaldehyde (CA) on pressure threshold (PT). C: the expression of TRPA1 and TRPM8 mRNA in the human bladder mucosa (muc), detrusor muscle (musc) and prostate (pros). D: the expression of TRPA1 mRNA was significantly higher in the mucosa of BOO (bladder outlet obstruction) than non-obstructed human bladder, but not in the muscle layer, nor in the prostate, p<0.01. M Takeda, unpublished data
particular response, the endoplasmic reticulum (ER) stress response. ER stress is defined as accumulation of unfolded or misfolded proteins in the ER, which induces a coordinated adaptive program called unfolded protein response (UPR). UPR alleviates ER stress by suppression of protein synthesis, facilitation of protein folding via induction of ER chaperones, including a 78 kDa glucose-regulated protein (GRP78) and reinforced degradation of unfolded proteins. If the stress is beyond capacity of the adaptive machinery, however, cells undergo apoptosis via several mechanisms including induction of CCAAT/enhancer-binding protein-homologous protein (CHOP) [478].

Hence, the involvement of ER stress in the damage of the bladder caused by BOO has been examined. An experimental model of BOO was established in rats by complete ligature of the urethra for 24 h, and bladders were subjected to Northern blot analysis and assessment of apoptosis. Isolated urinary bladders and bladder-derived smooth muscle cells (BSMCs) were also exposed to mechanical strain and hypoxia and used for analyses. To examine the involvement of ER stress in bladder damage, effects of a chemical chaperone, 4-phenylbutyrate (4-PBA), were evaluated in vitro and in vivo. Outlet obstruction for 24 hours induced expression of ER stress markers, GRP78 and CHOP, in the bladder, and was associated with induction of markers for mechanical stress (cyclooxygenases 2) and hypoxia (vascular endothelial growth factor and glyceraldehyde-3-phosphate dehydrogenase). When isolated bladders and BSMCs were subjected to mechanical strain, induction of GRP78 and CHOP was not observed. In contrast, when BSMCs were exposed to hypoxic stress caused by CoCl₂ or thenoyltrifluoroacetone (TTFA), substantial up-regulation of GRP78 and CHOP was observed, suggesting involvement of hypoxia in the induction of ER stress (figure 26). In bladders subjected to BOO, the number of TUNEL-positive cells increased in the epithelial cells and BSMCs. Similarly, treatment with TTFA or CoCl₂ induced apoptosis of BSMCs, and 4-PBA significantly attenuated ER stress and apoptosis triggered by these agents. Furthermore, in vivo administration with 4-PBA significantly reduced apoptosis in the bladder subjected to BOO [479].

Figure 26: Induction of apoptosis in cultured detrusor smooth muscle cells (DSMCs) by hypoxic stress and BOO and attenuation by molecular chaperones. A: Upper panels. DSMCs were exposed to 500 mM TTFA (thenoyltrifluoroacetone) for eight-hours and observed by phase-contrast microscopy. Lower panels. Induction of apoptosis in the bladder by BOO. Control bladders and bladders subjected to BOO for 24 hours were examined by DAPI staining (4',6-diamidino-2-phenylindole staining) and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling assay (TUNEL), to count apoptotic cells. B: Induction of apoptosis in the bladder by BOO. Control bladders and bladders subjected to BOO for 24 h were examined histologically by 4',6-diamidino-2-phenylindole staining (DAPI) and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling assay (TUNEL). C. The effect of 4-phenylbutyrate (4-PBA) on the apoptosis of the urinary bladder induced by BOO. Rats were administered daily with either ethanol vehicle or 4-PBA (120 mg/kg, i.p.) for three-days and subjected to BOO. Histological analyses were performed using hematoxylineosin (HE) and DAPI staining, and TUNEL assay. All data are means±SE (n=4). The values represent the percentage of cells undergoing apoptosis. M Takeda, unpublished data.
These results suggest that outlet obstruction caused ER stress via hypoxic stress in the bladder and that hypoxia-triggered ER stress may be involved in the induction of apoptosis. ER stress may therefore trigger BOO-induced detrusor overactivity, or OAB. Hence, chemical chaperons such as 4-PBA might be a novel pharmacotherapy for prevention of BOO-induced bladder dysfunction, or urinary incontinence (figure 27).

![Figure 27: Hypothesis of the possible implication of BOO, hypoxia-induced ER stress and urinary bladder injury. The possibility of novel pharmacotherapy for BOO-induced bladder injury or dysfunction by attenuation of BOO-induced apoptosis in the bladder by chemical chaperones such as 4-PBA.]

1. INTRODUCTION

Translational research must maintain two key components:

- A direct pathway to impacting on patient care
- An ethical responsibility to improve on current treatment

Tissue engineering is now at a stage where research is moving out of the laboratory and into the clinical arena and now demands that financial and well as scientific imperatives must be considered. A recent estimate for the development of a new tissue engineered device is in excess of €10MM, with a time span of not less than five years [480]; the NIH spent $643 million on stem cell research in 2006. The evolution of organ replacement therapy through cell culture and implantation has attracted considerable attention from both the medical profession and the media. Progress must be closely monitored to ensure that the driving forces of the commercial requirements of stakeholders balance the necessary clinical objectives.

Several groups have produced innovative and progressive work and in the last twenty years there has been a move from predictions of success to a more considered approach. The progression has been evident with an increasing understanding of the complexity of the problem. Technology has developed to allow various means of producing a pure cell culture – including better understanding of selective media, and fluorescent-activated cell sorting. An increasing number of abstracts at major urological conferences in recent years further testifies to the proximity of clinical application.

2. INJECTABLE THERAPY

This work is a step away from the production of a functional and implantable graft. Its strengths include no requirement for the use of a scaffold and the final functional outcome is largely dependant on the host's regenerative abilities.

Animal model work suggests that in the case of stem cell therapy there is cellular differentiation, and in the example of sphincteric replacement this may lead to cells with characteristics of smooth and skeletal muscle. Some data claim a clinical cure rate approaching 90% with these therapies [481], and in addition measurable parameters such as maximum urethral closing pressure can be improved with injection of stem cells [482]. Histological evidence for the generation of muscle fibres is also evident [483]. In a randomized control trial comparing the treatment against conventional injectables the use of stem cells fared far better. But there is a need for multicentre trials before such a treatment could become accepted as a standard [484].

3. TISSUE REPLACEMENT

a) Urethra

There have been attempts at urethral regeneration – most commonly by implantation of a matrix to stimulate regeneration. Acellular bladder collagen has been used to replace tissue in an animal model [485]. Success was improved by initial epidermal seeding – the cells of which disappeared six months after grafting. Growth and subsequent blood supply may be improved by adding growth factors, such as VEGF, and cell selection [486]. It appears that ex vivo urethral regeneration has, hitherto been unsuccessful. However, a clinical trial using tissue engineered buccal mucosa demonstrates that in a near three-year follow up series there is promise: there is a 100% initial graft
take, with two out of five patients requiring either
partial or total graft excision; the remainder having
patent urethras but have required instrumentation
[487]. Bigger groups of patients have had small
intestine submucosa (SIS) implanted as a graft for
the treatment of urethral stricture disease and
demonstrate a success rate of up to 85% with this
technique – the poorest outcomes with reconstruction
of the penile urethra [488,489]. Seeded tubular
constructs have been used with success in preclinical
studies and this is an area that awaits further
development. However, one must compare the
potential success, against conventional treatment, or
even the culture of single layer grafts, and consider
the resource implications of such a treatment strategy.
Recent data suggest that there may be a less invasive
approach to establishing urothelial cultures. Multi-
layered cultures of urothelial cells were established
from bladder washings from 29 patients [490]. Using
careful cell selection and culture techniques it is
possible that grafts could be created in this way.

b) Bladder

The complexities of generating a tissue-engineered
urothelium have been widely acknowledged. In order
to survive, imbibition and inosculation will not be
sufficient – the graft must have an adequate vascular
supply. Furthermore, for functional success the smooth
muscle must be controlled i.e. with a functional
innervation. The generation of a seeded co-cultured
cellular construct continues to be a major research
directive. Alternatives have been trialled, such as the
urothelial-lined uterus [491], but have not yet reached
a stage of clinical application. The issue of graft
nutrition appears to be helped considerably by
wrapping the graft in omentum. Such grafts appear
to show reasonable in vitro characteristics [492], as
well as improvement in some clinical parameters such
as compliance and capacity [493]. The questions
relating to the sensory status of the construct and the
voiding function remain open. Data have shown the
phenotypic similarities of cultured cells to their native
counterparts [494], although this has not yet translated
into in vivo success. However, a recent improvement
appears with the use of dynamic cell culture [495].
Other components may be developed with the use of
further stem cell technology, in conjunction with
stromal cells. The scaffold in turn can be considered
as 3 components:

- Support mechanism for cells
- Nutrient supply for cells
- Functional control of cells

a) Support mechanism for cells

Many potential scaffolds have been trialled. Options
include the creation of a layer of urothelium; which is
then seeded as a new lining and incorporated as part
of another organ in augmentation. Examples have
included bowel and uterine covered segments used
to expand bladders [490]. It is likely that different
organs and, perhaps different disease states, will
require different scaffolds. With developing technology
and understanding of the interaction of the scaffold and
cells there is a necessity to explore this area. Improved
biocompatible (CO alkene) polymers have increased
cellular activity [500]. Mechanical properties have not
been widely investigated. However, the growth of cells
may be influenced by the physical properties of a
scaffold, more than previously realised, and factors
such as the elastic modulus may be important in
generating optimal cell growth [501]. Cells cultured on
a dynamic bioreactor, that stretched and relaxed the
culture plate, improved the contractility of the resultant
cells. Those cultured on a static plate showed no
measurable contractility whilst preconditioned cells
showed tetanic and twitch responses between 1 and
4 weeks of culture [495]. In addition work is constantly
aiming to find alternative scaffolds including the amnion
(although this has not been tested for urological
application) as alternatives to decellularised bladder
matrix and SIS [502].

b) Nutrient supply for cells

The culture of cells ex vivo has led to a number of
solutions for providing cell nutrition. Bioreactor
technology has become an area of subspecialist
development in its own right. It appears that problems
arise with removal from the bioreactor and
implantation, and the difficulties in establishing and in
vivo nutrient supply. Baumert et al have pursued the
possibility of early transition of the construct to an
‘omental bioreactor’ for neo-ureters – with seeded
constructs being placed intra-abdominally and wrapped in omentum. Animal data suggest that this may be a successful strategy for final culturing - with the generation of a vascularised multilayered, terminally differentiated graft [492,503]. Other factors, such as pretreatment of scaffolds with growth factors, may also have both a direct effect on nutrient availability and utilisation leading to enhanced cell growth [486,504]. The possibility of growth factors stimulating specific co-culture of a capillary network have also to be considered [505].

c) Functional control of cells

There are two aspects to this: firstly, the differentiation of cells. Factors that may influence this have been mentioned but included either stimulation of cells (such as stretch for muscle cells [495]), or the use of selective media. The generation of the correct cell line is vital and forms part of the functional control. Secondly, the generation of a mechanism that will allow functional control of the final graft. The ideal will be to include sensory responses from the graft – a tissue engineered substitution cystoplasty would be completely insensate, making control difficult except by timed voiding. The motor control of an implant is also important. This does not appear to be an issue for the injectable therapies discussed earlier but may be for free grafts. Histology from animal work with such implants suggests that there is a degree of neural ingrowth at the periphery of grafts when harvested [506], however there is no specific reference to the voiding function of these grafts. Indeed the continuation of this work suggests that contractile function may only be seen in cells that have been cultured in a dynamic environment [494] – with very poor contraction seen in cells not treated in this way.

5. CONCLUSION

Current work in this field is impressive and fast moving. It is now evident that with the involvement of commercial interest the huge financial investment will be expected to generate return. The focus of this work must remain our consumer – the patient. Outcomes must be at least as good as currently available treatments in order to gain recognition and credibility and no commercial pressure should be allowed to compromise this. The complexities and interaction of different graft components have highlighted many difficulties to progress. The increased application of stem cell work and an understanding of host-regenerative strategies may overcome some of these obstacles. Dynamic culture and the further development of bioreactor technology also hold hope for further development.

It is clear that none of these therapies could be advocated outside a trial setting and that data regarding each patient needs to be carefully followed up and preserved in the interests of long term results.

X. RECOMMENDATIONS FOR LOWER URINARY TRACT AND LOWER GASTRO-INTESTINAL TRACT RESEARCH

1. Integrate data from reductionist experiments to formulate better systems-based approaches in the investigation of the pathology of the LUT and LGIT.

2. Generate improved experimental approaches to investigate the pathophysiology of the LUT and LGIT by:
   • the development of characterised animals models
   • use of human tissue from well-characterised patient groups.

3. Encourage greater emphasis on basic research into our understanding of tissues receiving relatively little attention: i.e. the lower gastrointestinal tract; the bladder neck and urethra.

4. Generate a more multidisciplinary approach to investigate the function of the lower urinary tract through collaborations between biological, physical and mathematical sciences.

5. Increase interaction between higher education institutions (HEIs), industry and medical centres to encourage translational approaches to research.

6. Bring about a greater emphasis on the importance of research to medical trainees through:
   • establishing research training as a core component of medical training
   • increased access to support funds, especially scholarships and personal awards
   • organisation of focussed multidisciplinary research meetings, either stand-alone or as part of larger conferences
   • greater interaction between medical centres and HEIs

7. Increase emphasis on research into lower urinary tract and gastro-intestinal tract in HEIs through:
   • greater representation on grant-funding agencies
   • encouragement of submission to high impact-factor journals and recognition of research published in specialty journals
   • more integrated teaching and training opportunities
REFERENCES


82. Wuy C, Sui GP, Fry CH. The role of the L-type Ca2+ channel in refilling functional intracellular Ca2+ stores in guinea-pig detrusor smooth muscle. J Physiol 2002; 538: 357-369.


104. Zhu HL, Brain KL, Aishima M, Shibata A, Young JS, Sueishi K, Teramoto N. Actions of two main metabolites of propiverine (M-1 and M-2) on voltage-dependent L-type Ca2+ currents


Wahl EF, Lerman SE, Lahdes-Vasama TT, Churchill BM. Measurement of bladder compliance can be standardized by a dimensionless number: theoretical perspective. BJU Int 2004; 94: 895-897.


Committee 3

Neural Control

Chair

L. BIRDER (USA)

Co-Chairman

M. DRAKE (UK)

Members

W. DE GROAT (USA),
C. FOWLER (U.K),
E. MAYER (USA),
J. MORRISON (UAE),
J. PATON (U.K)

Consultants

D. GRIFFITHS (Canada),
I. MILLS (U.K),
K. THOR (USA)
# CONTENTS

<table>
<thead>
<tr>
<th>OVERVIEW</th>
<th>V. MIDBRAIN-BRAINSTEM CONTROL OF BLADDER FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVELS OF EVIDENCE</td>
<td>1. AFFERENT PATHWAYS TO THE BRAINSTEM</td>
</tr>
<tr>
<td>I. THE UROTHELIUM</td>
<td>2. DEFINING BRAINSTEM CIRCUITRY REGULATING BLADDER FUNCTION</td>
</tr>
<tr>
<td>1. INTRODUCTION TO THE ANATOMY AND BARRIER FUNCTION OF THE UROTHELIUM</td>
<td>3. THE PONTINE MICTURITION CENTER (PMC)</td>
</tr>
<tr>
<td>2. RESPONSE TO THE UROTHELIUM TO INJURY</td>
<td>4. BLADDER ‘FILLING’ NEURONES IN THE PMC AND MEDIAL RETICULAR FORMATION: WHAT’S THEIR ROLE?</td>
</tr>
<tr>
<td>3. UROTHELIAL HETEROGENEITY</td>
<td>5. OFF-SWITCHING MICTURITION – THE PONTINE CONTINENCE CENTRE (PCC)</td>
</tr>
<tr>
<td>4. ROLES FOR UROTHELIAL CELLS IN VISCERAL SENSATION</td>
<td>6. THE PERIAQUEDUCTAL GREY (PAG): IS THIS AN ESSENTIAL REGION FOR SUPPRESSING THE MICTURITION REFLEX?</td>
</tr>
<tr>
<td>5. CLINICAL SIGNIFICANCE OF THE SENSORY WEB</td>
<td>7. NEUROTRANSMITTERS &amp; MODULATORS WITHIN BRAINSTEM NETWORKS CONTROLLING BLADDER FUNCTION</td>
</tr>
<tr>
<td>II. AFFERENT NEURONES</td>
<td>VI. CORTEX AND BRAINSTEM CONTROL OF BLADDER FUNCTION</td>
</tr>
<tr>
<td>1. PROPERTIES OF BLADDER AFFERENT NEURONS</td>
<td>1. BACKGROUND</td>
</tr>
<tr>
<td>2. UROTHELIAL AFFERENTS</td>
<td>2. ROLE AND IMPORTANCE OF CEREBRAL CONTROL OF VOIDING</td>
</tr>
<tr>
<td>3. SENSITIVITY OF AFFERENT ENDINGS</td>
<td>3. CORTICAL AND SUBCORTICAL CENTRES INVOLVED IN BLADDER CONTROL. EVIDENCE FROM OBSERVATIONS OF LESIONS AND FROM FUNCTIONAL BRAIN IMAGING IN HUMANS</td>
</tr>
<tr>
<td>4. SPINAL CORD</td>
<td>4. WORKING MODEL OF BRAIN/BLADDER CONTROL</td>
</tr>
<tr>
<td>5. SPINAL CORD GLIAL CELLS AND MODULATION OF PELVIC AFFERENTS</td>
<td>VII. ABNORMAL LOWER URINARY TRACT FUNCTION</td>
</tr>
<tr>
<td>III. NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLES AND RHABDOSPINCTERS</td>
<td>1. ABNORMALITIES INVOLVING INFLAMMATION</td>
</tr>
<tr>
<td>1. STRUCTURAL ELEMENTS OF THE PELVIC FLOOR</td>
<td>2. INVOLVING ABNORMAL URINE STORAGE</td>
</tr>
<tr>
<td>2. INNERVATION OF THE FEMALE LEVATOR ANI MUSCLES</td>
<td>3. INVOLVING ABNORMAL VOIDING</td>
</tr>
<tr>
<td>3. INNERVATION OF URETHRAL AND ANAL RHABDOSPINCTERS</td>
<td>4. CO-MORBID DISORDERS</td>
</tr>
<tr>
<td>4. SPINAL URINE-STORAGE-REFLEX INHIBITORY CENTER (SUSRIC)</td>
<td>VIII. BRAIN-GUT INTERACTIONS</td>
</tr>
<tr>
<td>5. PHARMACOLOGY OF URETHRAL AND ANAL RHABDOSPINCTERS</td>
<td>1. BACKGROUND</td>
</tr>
<tr>
<td>IV. EFFERENT PATHWAYS TO THE BLADDER</td>
<td>2. ORGANIZATION OF HOMEOSTATIC REFLEXES: PROCESSING OF PELVIC VISCERAL INFORMATION WITHIN HIERARCHICAL ORGANIZED HOMEOSTATIC REFLEXES</td>
</tr>
<tr>
<td>1. PREGANGLIONIC NEURONS</td>
<td>3. CONSCIOUS PERCEPTION OF INPUT FROM THE BODY AS ASPECTS OF HOMEOSTASIS</td>
</tr>
<tr>
<td>2. GANGLIA</td>
<td>4. DESCENDING MODULATION OF HOMEOSTATIC REFLEXES AND FEELINGS</td>
</tr>
<tr>
<td>3. TERMINAL NERVE FIBRES</td>
<td>5. BRAIN CIRCUITS ACTIVATED BY ACUTE VISCERAL STIMULI: EVIDENCE FROM FUNCTIONAL BRAIN IMAGING STUDIES IN HUMANS</td>
</tr>
<tr>
<td>4. DESCENDING AND SPINAL SEGMENTAL INFLUENCES ON SPINAL AUTONOMIC CENTRES</td>
<td></td>
</tr>
</tbody>
</table>
This chapter deals with individual components regulating the neural control of the urinary bladder. This chapter has been completely remodeled and updated with the focus on factors and processes involved in the two models of operation of the bladder: storage and elimination. There has been significant new information since the last consultation in a number of fields:

- The urothelium and its roles in sensor and transducer functions including interactions with other cell types within the bladder wall ('sensory web')
- The location and properties of bladder afferents including factors involved in regulating afferent sensitization
- The neural control of the pelvic floor muscle and pharmacology of urethral and anal sphincters (focusing on monoamine pathways)
- Efferent pathways to the urinary bladder
- Abnormalities in bladder function including mechanisms underlying co-morbid disorders associated with bladder pain syndrome and incontinence

The next sections deal with the current understanding of brainstem neuronal networks, which regulate lower urinary tract function (1-4). The importance is reflected in the current advances in functional brain imaging (both positron emission topography or PET and functional magnetic resonance imaging or fMRI). These advances have had a major impact on understanding CNS control of the human bladder. This section has been completely revised to also include the recent advances in understanding of bidirectional brain-gut interactions in addition to discussion of homeostatic function and neural mechanisms underlying fecal and anal continence.

This book attempts to use Levels of Evidence throughout. The Oxford Centre for Evidence Based Medicine has laid down guidelines that apply to Levels of Therapeutic Interventions and Grades of Recommendations to Patients; the existence of dispute regarding each major conclusion should be documented. However this advice does not really apply to the basic sciences, where randomized controlled trials are not a common format of investigation, and acute studies with internal controls are more common.

Within this chapter we intend to be selective and report scientific evidence that has appropriate controls and achieves statistical significance. Other categories of evidence, e.g. uncontrolled studies, anecdotal information, hypothesis or speculation will be referred to as such.

Of some importance in this field are species differences, and efforts have been made to make it very clear when each new topic is introduced in which species the observation was made with special emphasis as to the extent comparable data exists for humans.

In this report, we intend to indicate whether the conclusions are based on (A) peer-reviewed papers in reputable journals (B) evidence in book chapters or reviews, and (C) Abstracts: abstracts will only be mentioned if they refer to a systematic study with good statistical methodology.
There is evidence that a number of functional pain syndromes are associated with changes in the epithelial layer. Alterations of bladder urothelium at the molecular and structural levels have been reported in both patients and animals modeled for various bladder disorders. It is likely that many therapies currently used in the treatment of bladder disease may target urothelial receptors and/or their release mechanisms.

1. INTRODUCTION TO THE ANATOMY AND BARRIER FUNCTION OF THE UROTHELIUM

The urothelium is the epithelial lining of the lower urinary tract between the renal pelvis and the urinary bladder. Urothelium is composed of at least three layers: a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells (diameters of 25-250 µm) known as ‘umbrella cells’ [5, 6] (Figure 1). The umbrella cells are interconnected by tight junctions (which are composed of multiple proteins such as the claudins) and are covered on their apical surface (nearly 70-80%) by crystalline proteins called uroplakins that assemble into hexagonal plaques [7-10]. Uroplakins and other urothelial cellular differentiation markers, such as cytokeratin 20, are not expressed in the stratified epithelium of the urethra. In some species, the umbrella cells and perhaps also the intermediate cells have projections to the basement membrane [5].

The ability of the bladder to maintain the barrier function, despite large alterations in urine volume and increases in pressure during bladder filling and emptying, is dependent on several features of the umbrella cell layer. These features include tight-junction complexes that reduce the movement of ions and solutes between cells and specialized lipid molecules and uroplakin proteins in the apical membrane, which reduce the permeability of the cells to small molecules (water, urea, protons) [5,11]. The apical surface of the urothelium is also covered with a sulfated polysaccharide glycosaminoglycan (GAG) or mucin layer that is thought to act as a nonspecific anti-adherence factor and as a defense mechanism against infection [12-14]. In addition, during bladder filling the umbrella cells become flat and squamous and this shape change is accompanied by vesicular traffic (i.e. exocytosis/endocytosis), adding membrane to the apical surface thereby increasing overall urinary bladder surface area [7,15,16]. There is evidence that this stretch-induced exocytosis is dependent on activation of epidermal growth factor receptor (EGFR) [17,18]. These processes allow the bladder to accommodate increasing volumes of urine during filling without compromising the barrier function. Exocytosis/endocytosis (vesicular recycling) may also play an important role in modulating the release of a number of neurotransmitters/mediators as well as regulation of the function of many receptors and ion channels in urothelial cells [19,20].

2. RESPONSE OF THE UROTHELIUM TO INJURY

Basal cells, which are thought to be precursors for other cell types, normally exhibit a low (3-6 month) turnover rate, in fact the slowest turnover of any mammalian epithelial cells [7,21]. It has been shown that neither urine-derived factors nor cyclic mechanical changes contribute to urothelial proliferation and differentiation; however accelerated proliferation can occur in pathology. For example, using a model (protamine sulfate) that selectively damages the umbrella cell layer, it has been shown that the urothelium rapidly undergoes both functional and structural changes in order to restore the barrier in response to injury [22]. The initiation of urothelial proliferation is thought to involve up-regulation of growth factors such as fibroblast growth factor and nerve growth factor (NGF) [23,24].

Figure 1: Ultrastructural features of umbrella cell apical membrane. Left panel: Scanning electron micrograph (high magnification) of apical surface of rabbit umbrella cell layer (hinges “H” marked with arrows). Right panel, high power view of tight junctions. (from Apodaca, 2004; Truschel et al., 1999).
Though the urothelium maintains a tight barrier to ion and solute flux, a number of local factors such as tissue pH, mechanical or chemical trauma, or bacterial infection can modulate the barrier function of the urothelium [7,25]. Other conditions such as bladder pain syndrome/interstitial cystitis (BPS/IC) or spinal cord injury are also associated with changes in urothelial barrier [26,27]. When the barrier is compromised, water, urea and toxic substances can pass into the underlying tissue (neural/muscle layers) resulting in urgency, frequency and pain during bladder filling and voiding. In some pathological conditions the disruption of the urothelial barrier is associated with ultrastructural changes and alterations in the levels of chemical mediators such as nitric oxide (NO) and adenosine triphosphate (ATP) that may alter epithelial function and/or integrity. Disruption of urothelial barrier integrity has also been linked to the expression of substances such as antiproliferative factor (APF), which also slows urothelial cell growth [28-30]. APF, a frizzled 8 protein detected in the urine of patients with BPS/IC, is secreted by bladder epithelial cells obtained from these patients. Treatment of urothelial cells from normal patients with purified APF decreases the expression of adhesion and tight junction proteins.

Urinary tract infections produced by uropathogenic Escherichia coli (UPEC) are initiated by bacterial adherence to uroplakin proteins on the apical surface of umbrella cells [25,31] (Figure 2). The UPEC express filamentous adhesive organelles (type 1 pili) that mediate both bacterial attachment and invasion of the urothelial cells. Internalization of UPEC in the umbrella cells and formation of intracellular colonies (biofilm-like pods) of UPEC in umbrella cells has been implicated in the mechanism of chronic urinary tract infections.

Disruption of urothelial function can also be induced by more remote pathological conditions that influence neural or hormonal mechanisms. For example, spinal cord transection in rats leads to a rapid alteration in the urothelial barrier including ultrastructural changes and increased permeability [26]. The changes are blocked by pretreatment with a ganglionic blocking agent, suggesting an involvement of efferent autonomic pathways in the acute effects of spinal cord injury on bladder urothelium. Other types of urothelial-neural interactions are also likely, based on the recent reports that various stimuli induce urothelial cells to release chemical mediators that can in turn modulate the activity of afferent nerves [5,20]. This has raised the possibility that the urothelium may have a role in sensory mechanisms in the urinary tract.

In summary, modification of the urothelium and/or loss of epithelial integrity in a number of pathological conditions can result in passage of toxic/irritating urinary constituents through the urothelium or release of neuroactive substances from the urothelium leading to changes in the properties of sensory nerves and in turn sensory symptoms such as urinary frequency and urgency. Thus chemical communication between the nervous system and the urothelial cells may play an important role in the generation of urinary bladder dysfunction.

3. UROTHELIAL HETEROGENEITY

Studies (comparing a number of species) have shown that the major part of the urinary tract is lined with a fully differentiated urothelium [9]. Findings in cultured cells reveal a distinct difference in morphology of ureteral and bladder urothelial cells, supporting a difference in cell lineage. There seems to be no apparent difference between the urothelium of the trigone compared to the detrusor, in contrast to cells from the proximal urethra [9,32]. In this region, there is a transition from urothelium to a stratified or columnar epithelium accompanied by a lack of urothelial-specific differentiation markers. Taken together, present evidence suggests at least 3 urothelial lineages: 1) those of the ureter/renal pelvis, 2) detrusor/trigone and 3) bladder neck/proximal urethra [33]. The functional significance of these findings has yet to be determined.

4. ROLES FOR UROTHELIAL CELLS IN VISCERAL SENSATION

While urothelial cells are often viewed as bystanders in the process of visceral sensation, recent evidence has supported the view that these cells function as primary transducers of some physical and chemical stimuli and are able to communicate with underlying cells including bladder nerves, smooth muscle and inflammatory cells (Figure 3).

There are at least 3 lines of evidence that suggest that
Figure 3: Hypothetical model depicting possible interactions between bladder afferent and efferent nerves, urothelial cells, smooth muscle and myofibroblasts. Stimulation of urothelial receptors and channels can release mediators that target bladder nerves and other cell types; urothelial cells can also be targets for neurotransmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e. autoregulation) or paracrine (release from nearby nerves or other cells) mechanisms. Abbreviations: ACh, acetylcholine; AdR, adrenergic receptor; BR, bradykinin receptor; H+, proton, MR, muscarinic receptor; NE, norepinephrine; NGF, nerve growth factor; NR, neurokinin receptor; NicR, nicotinic receptor; NO, nitric oxide; P2R, purinergic 2 receptor unidentified subtype; P2X and P2Y, purinergic receptors; PG, prostaglandin; SP, substance P; Trk-A, receptor tyrosine kinase A, high affinity receptor for nerve growth factor; TRPs, transient potential channels.
urothelial cells participate in the detection of both physical and chemical stimuli. First, bladder nerves (afferent and efferent) are localized in close proximity, and some within, the urothelium [20, 34-36]. A second line of evidence suggesting that urothelial cells play a role in sensory function is the expression of numerous receptors/ion channels similar to that found in both nociceptors and mechanoreceptors. And finally, these cells secrete a number of transmitters or mediators capable of modulating, activating or inhibiting sensory neurons.

**a) Urothelial-Neuronal Signaling**

Recent studies have shown that both afferent and autonomic efferent nerves are located in close proximity to the urothelium. Peptidergic, P2X- and TRPV1- immunoreactive nerve fibers presumed to arise from afferent neurons in the lumbosacral dorsal root ganglia are distributed throughout the urinary bladder musculature as well as in a plexus beneath and extending into the urothelium [20,34]. (Figure 4) In humans with neurogenetic detrusor overactivity intavesical administration of resiniferatoxin, a C-fiber afferent neurotoxin, reduces the density of TRPV1 and P2X3 immunoreactive suburothelial nerves, indicating that these are sensory nerves [37,36]. In addition, immunohistochemical studies have also revealed both adrenergic (tyrosine hydroxylase) positive as well as cholinergic (choline acetyltransferase, ChAT) positive nerves in close proximity to the urothelium [35].

A network of cells with morphologic characteristics similar to those of myofibroblasts or interstitial cells is also detected in the suburothelial space of the bladder in both humans and animals [39-41]. These cells, which are extensively linked by gap junctions and have close contacts with nerves, can respond to neurotransmitters, such as ATP released from nerves or urothelial cells, suggesting that they could act as intermediaries in urothelial-nerve interactions [40-42]. Thus the anatomic substrates for bidirectional urothelial-neural communication exist within the urinary bladder.

**b) Involvement of the Urothelium in “Sensing” Chemical and Mechanical Stimuli**

The involvement of urothelial function in sensory signaling is suggested by the finding that urothelial cells express various receptors that are linked to mechanor or nociceptive sensations. Examples of neuronal “sensor molecules” (receptors / ion channels) that have been identified in urothelium include receptors for purines (P2X1-7 and P2Y1,2,4) adenosine (A1, A2a, A2b and A3), norepinephrine (α and β), acetylcholine (muscarinic and nicotinic), protease-activated receptors (PARs), amiloride- and mechanosensitive epithelial sodium channels (ENaC), bradykinin (B1 and B2), neurotrophins (p75, trkA, EGF family ErbB1-3), corticotropin releasing factor (CRF1 and CRF2), estrogens (Erα and ERβ), endothelins and various TRP channels (TRPV1, TRPV2, TRPV4, TRPM8 and TRPA1) [34, 43-51]. The expression of these various receptors enable the urothelium to respond to a number of “sensory inputs" from a variety of sources. These inputs include increased stretch during bladder filling, soluble factors (many found in the urine) such as epidermal growth factor (EGF), or chemical mediators/ peptides/ transmitters such as substance P, calcitonin gene-related peptide (CGRP), corticotropin releasing factor (CRF), acetylcholine, adenosine or norepinephrine released from nerves, inflammatory cells and even blood vessels [5, 19, 20, 52, 53].

Various stimuli can lead to secretion of numerous chemical substances such as neurotrophins, peptides, ATP, acetylcholine, prostaglandins, prostacyclin, nitric oxide (NO) and cytokines that are capable of modulating, activating or inhibiting sensory neurons. [19, 20]. For example, urothelial-derived NO can be released in response to mechanical as well as chemical stimulation and may either facilitate or inhibit the activity of bladder afferent nerves [20, 54]. Release of various factors from the urothelium can also modulate the spontaneous activity of the underlying smooth muscle [42, 55].

The mechanism underlying release of chemical mediators from the urothelium, including whether all sensory “inputs” stimulate membrane turnover (i.e. vesicular exocytosis) is not well understood. What little is known about the roles and dynamics of membrane-bound cytoplasmic vesicles in urothelial cell physiology is derived from measurements of membrane capacitance and microscopy of fixed tissues and cells. For example, there is evidence that once released, ATP can act as an important autocrine mediator, which can induce membrane turnover as well as enhance both stretch induced exocytosis and

![Figure 4](image-url): Confocal image of the urothelium depicts afferent nerve fibers (red) located in close proximity to basal (green) urothelial cells.
endocytosis [56]. Alterations in membrane turnover can not only increase apical surface area (as described above) but also regulate the number and function of receptors and channels at the cell surface.

1. PURINERGIC RECEPTORS

Since the first report of distension-evoked ATP release from the urothelium there is now abundant evidence supporting a role for urothelially-derived release of ATP in autocrine and paracrine signaling within the lower urinary tract. ATP is released from both the apical and basolateral urothelial surfaces in response to bladder stretch and can act on P2X2 and P2X3 urothelial receptors to stimulate stretch-induced exocytosis [56]. (Figure 5) The expression of both P2X and P2Y receptors in nerve fibers and myofibroblasts in close proximity to the bladder lumen and the sensitivity of these cells to ATP suggests that basolateral ATP release from the urothelium may also influence function of myofibroblasts and bladder nerves [57, 58]; The amiloride-sensitive apical sodium channel, ENaC, may be involved in mechanotransduction by controlling basolateral release of ATP [59]. In addition, intercellular communication mediated by gap junctions in myofibroblasts could provide a mechanism for long-distance spread of signals from the urothelium to the detrusor muscle [42]. Adenosine is also produced and released by the urothelium, and may play important roles in modulating sensory afferent function and smooth muscle contraction [60].

2. TRP CHANNELS

The ability of capsaicin to evoke NO release from rat urothelium, reported in 1998, provided the first, albeit indirect, demonstration that TRPV1 channels are expressed in urothelial cells and that urothelial cells and afferent nerves, which also express these channels, share a number of common properties [61]. This ion-channel protein is activated by capsaicin, as well as to moderate heat, protons and lipid metabolites such as anandamide (an endogenous ligand of both cannabinoid and vanilloids receptors) [62, 63] TRPV1-positive nerves are in close contact with urothelial cells [64, 65]. Activation of urothelial cells with capsaicin or resiniferatoxin can increase intracellular calcium and evoke transmitter (nitric oxide, NO or ATP) release. Similar to that in sensory neurons, urothelial-response to vanilloids are enhanced by low pH, blocked by TRPV1 antagonists and eliminated in TRPV1 null mice [66]. In afferent neurons, TRPV1 is thought to integrate/amplify the response to various stimuli and to play an essential role in the development of inflammation-induced hyperalgesia. It seems likely that urothelial-TRPV1 might participate in a similar manner, in the detection of irritant stimuli following bladder inflammation or infection.

Though TRPV1-null mice are anatomically normal, they exhibit a number of alterations in bladder function, including a reduction in stretch-evoked and hypotonic-evoked ATP release and stretch-evoked increase in membrane capacitance [66]. In addition, TRPV1 knockout mice have a higher frequency of low-amplitude, non-voiding bladder contractions suggesting the possibility of a small but ongoing role for TRPV1 in normal urine storage function. These relatively benign changes may result from TRPV1 expression not only in afferent nerves that form close contacts with bladder epithelial (urothelial) cells but also in urothelial cells themselves. (Figure 6) These findings demonstrate that the functional significance of TRPV1 in the bladder extends beyond pain sensation to include participation in normal voiding function, and is essential for mechanically evoked purinergic signaling by the urothelium.

3. ADDITIONAL TRP CHANNELS

Much less is known about the involvement of other TRPs in bladder function or disease. TRPV4 which is a nonselective cation channel activated by a number of stimuli including heat, shear stress, changes in osmolarity and lipid ligands is expressed mainly within the epithelium of the urinary bladder [67]. While a definitive role for TRPV4 in bladder function has not been established, there is evidence that null mice exhibit impaired voiding responses and, intravesical instillation of a TRPV4 agonist in the rat triggers a novel voiding reflex which could regulate the late phase of micturition [68, 69]. In addition, in the awake ewe, TRPV4 may also be involved in a urethra to bladder reflex, proposed to facilitate bladder emptying [70]. Another member of the TRP family, TRPA1 (characterized as a thermoreceptor activated by noxious cold), is expressed in C-fiber afferents as well as urothelium and agonists to this channel induce bladder hyperreflexia [71]. Of interest is the finding that hydrogen sulfide, which may be formed during infection/inflammation, is an activator of TRPA1 [72].
4. ACETYLCHOLINE AND THE UROTHELIUM

There is evidence that the urothelium expresses the full complement of muscarinic receptors as well as enzymes necessary for the synthesis and release (except vesicular choline transporter) of acetylcholine. [53, 74]. Further, the urothelium is able to release acetylcholine following both chemical and mechanical stimulation [53]. Once released, urothelial-derived acetylcholine is likely to exert effects via a number of sites including smooth muscle, nerves as well as urothelial associated-muscarinic or nicotinic receptors, the latter that could contribute to feedback mechanisms modifying urothelial function. In addition, stimulation of urothelial-cholinergic receptors elicits release of mediators such as nitric oxide as well as ATP, which could alter bladder sensation by stimulating nearby sensory afferent nerves [73, 75, 76].

Thus, targeting muscarinic receptors and/or urothelial release mechanisms may play an important role in the treatment for a number of bladder disorders. In this regard, recent evidence suggests that botulinum toxins prevent the release of transmitters from the urothelium, which may suggest urothelial-released mediators contribute to sensory urgency [77].

5. CLINICAL SIGNIFICANCE OF THE SENSORY WEB

Defects in urothelial sensor molecules and urothelial-cell signaling are likely to contribute to the pathophysiology of bladder diseases. For example, a number of bladder conditions (BPS/IC, spinal cord injury (SCI), chemically-induced cystitis) are associated with augmented release of urothelial-derived ATP, which is likely to result in altered sensations or changes in bladder reflexes induced by excitation of purinergic receptors on nearby sensory fibers [9, 10, 47, 73].

ATP can also act in an autocrine manner that would act to facilitate its own release from urothelial cells [10]. Once released, ATP can alter the threshold for activation of ion channels such as TRPV1. This novel mechanism, which likely reflects activation of intracellular protein kinases and phosphorylation of the TRPV1 channel, represents a means by which large amounts of ATP released from damaged or sensitized cells, in response to injury or inflammation, could trigger the sensation of pain. Changes in epithelial signaling/barrier function would not be unique to the urinary bladder. For example, airway epithelia in asthmatic patients as well as keratinocytes in certain types of skin diseases also exhibit a number of similar abnormalities and compromised repair processes [78-80]. This is particularly relevant given the high incidence of associated diseases that can include both visceral and somatic conditions, many of which exhibit a shared loss of epithelial barrier function. Taken together, epithelial cells can respond to a number of challenges (including environmental pollutants and mediators released from nerves or nearby inflammatory cells) resulting in altered expression and/or sensitivity of various receptor/channels as well as changes in release of mediators, all of which could impact function.

II. AFFERENT NEURONES

There have been a number of new developments in this area since the last consultation as a result of the introduction of in vitro preparations, knockout animals and an increasing influence of molecular techniques. Up until recently most experiments have taken place on cats and rats, but several studies have been reported in mice and guinea-pigs, mainly using in vitro preparations. These involve recordings from the pelvic or hypogastric (lumbar splanchnic) nerves at peripheral sites near the bladder; hence the conduction velocities of the single units, which provided information relevant to the degree of myelination, have not been measured. These preparations have however been able to increase the knowledge of the location of afferent endings within the bladder wall and some of the physiological/pharmacological properties in relation to synaptic transmission at these nerve endings. Drugs that are toxic in the whole animal have also been used in isolated preparations, and some authors have used drugs to minimise the smooth muscle movements and the generation of inflammatory mediators; the latter are useful in the analysis, but may give rise to differences in the properties studied either in vivo or in vitro in the absence of such agents.

1. PROPERTIES OF BLADDER AFFERENT NEURONS

Afferent axons in the pelvic, hypogastric (lumbar splanchnic) and pudendal nerves transmit information...
from the lower urinary tract to the lumbosacral spinal cord [81-83] and studies in several species including cats, rats and mice have shown some similarities in properties.

The most sensitive afferents are excited by a physiological increase in volume and by detrusor contractions: it is believed that these low threshold afferents have small myelinated axons, are A-delta fibres (which are larger in diameter and conduct action potentials more rapidly than C-fibres) and that their endings are located in the detrusor smooth muscle. They have been called ‘in series tension receptors’ (84) because they are excited by bladder wall tension caused either by distension or by contraction, and neurons with this range of conduction velocities are less likely to contain peptides.

There have been a number of systematic studies recently in mice and guinea pigs that have provided detailed information about the classes of receptors in the pelvic and hypogastric nerves (Figure 7). In the mouse, it seems there may be at least four classes of mechanosensitive afferents, which include myelinated and unmyelinated fibres, and distributed in the serosa, muscle and urothelial layers of the organ; one class has mechanosensitive endings in both the muscle and urothelial layers. The lumbar splanchnic nerves contain principally serosal and muscular afferents whereas all four classes of afferents are present in the pelvic nerve (63% of which are muscular afferents) [85]. Another study found endings in the urothelium and in the muscle layers, as well as stretch-insensitive afferents and chemosensitive afferents [86]. The small myelinated afferents are involved in two processes: (a) sensing bladder volume, and (b) reinforcing reflex function by monitoring the contractile state of the detrusor. In particular these afferents, which form the most sensitive distension receptors, are most probably responsible for the sensation of fullness, and mediate the normal micturition reflex that involves a spinobulbospinal pathway that passes through the brainstem.

The unmyelinated afferents contain peptides and most appear to terminate within the lamina propria and within the transitional epithelium itself. Many of these afferents discharge within the higher range of physiological bladder volumes, and are not usually sensitive to detrusor contraction, possibly because only the former causes stretch of the urinary epithelium. The C-fibres in the urothelium and lamina propria contain peptides such as substance P and CGRP, which is a characteristic of one subgroup of afferent C-fibres. These and other C-fibre afferents may mediate the spinal C-fibre micturition reflex seen following cord transection in the cat [87]. It is not

---

Figure 7: Tension-mucosal mechanoreceptors. (A) Response of tension-mucosal mechanoreceptors to fast 3 mm stretch at 1000 µm’s, held for 10s. (B) Response of the same unit to mucosal stroking with a 0.1 mN von Frey hair (five strokes, indicated by asterisks). (C) Activation of the same tension-mucosal unit by mannitol (1 M) applied to its receptor field in the mucosa.
clear whether they also contribute to normal voiding in this species, but there is increasing evidence that they may be involved in normal bladder control in rats and mice. In rats and mice, these high threshold units respond to a range of intravesical pressures that overlap with the sensitivity of the low threshold units, so that these together cover the spectrum of pressures and volumes seen physiologically, and these may contribute to spinal automatic micturition mediated by the sacral cord.

A third group of unmyelinated bladder afferent axons does not respond to normal distending volumes but only become active during chemical irritation of the bladder, including high osmolality and high potassium solutions and during inflammation, when they behave like the high volume sensing C-fibres. These have been demonstrated in cats and rats, and are usually called ‘silent afferents’ (meaning that the last group do not respond to normal distensions, but can become mechanosensitive in inflamed or over-distended tissues). Thus it would be unwise to infer function simply on the basis of conduction velocity. This group of afferents also appears to be sensitive to ATP.

Ultrastructural studies of nerves in the human bladder have found only unmyelinated nerves in the urothelial and immediate suburothelial layer, the first small myelinated nerves appearing only close to the smooth muscle layers [88]. Whether or not the suburothelial nerves become myelinated as they pass towards the serosal surface cannot be ascertained from this study but it would be inadvisable to make deductions about the relative number of C and A-delta fibres in the human based on these observations. Table 1 shows the properties of afferent fibres, classified according to their volume thresholds.

2. UROTHELIAL AFFERENTS

Reference has already been made to the presence of CGRP-containing afferent endings that branch beneath and within the lamina propria, and within the urothelium itself. These axon collaterals can release neurotransmitters on to the various tissues in the lining of the bladder, including blood vessels, smooth muscle, urothelium, connective tissue cells, mast cells and other neurones. In addition there is evidence in the human bladder that intramural neurones receive axonal contacts from axon collaterals that contain the peptides characteristic of primary afferents (see the section on ganglia, and on integrative physiology).

The plexus of afferent nerves is thickest in the neck of the bladder and in the initial portion of the urethra, and it becomes progressively less dense in the adjacent regions. It does not extend beyond the equatorial region, and therefore the lamina propria of the cranial region of the bladder has no afferent axons. In contrast, the afferent innervation of the musculature is more diffuse, and appears uniform throughout the bladder. CGRP-immunofluorescence in urothelial afferent axons is enhanced in the surviving axons 5 days after contralateral denervation, a change which may be an early sign of regeneration of these axons [89]. In the human bladder, CGRP together with Substance P and NKA occur only infrequently in nerves in the muscle but are moderately frequent in the suburothelial layer. Also in the human there appears to be another population of CGRP-containing fibres that co-localize with NPY and galanin and some of these synapse on intramural ganglia within the bladder [90-93]. There is also recent evidence that nerves cross the basal lamina and enter the basal layers of the human urothelium [89]. Table 2 shows the properties of afferent nerve endings in different locations.

3. SENSITIVITY OF AFFERENT ENDINGS

The term afferent sensitivity refers to the gain of the afferent signal, i.e. the number of impulses that are fired by an afferent ending at any level of distension. Sensitizing mediators are able to increase the size of

Table 1. Properties of low and high threshold afferents from the bladder in cat, rat, mouse and guinea pig
the sensory signal (the frequency of impulse traffic) at a given level of distension, so the sensations that occur at a particular rate of firing in an afferent occur at lower bladder volumes if the afferent endings have been sensitized. (Figure 8).

The sensitivity of afferent endings may be influenced by the release of mediators from different cell types, including possibly the urothelium, myofibroblasts, nerve endings, smooth muscle, mast cells and other connective tissue cells. It is likely that many or all of these can release ATP, and some may release other mediators including nitric oxide, tachykinins (Substance P, Neurokinin A, Neurokinin B), growth factors (Nerve Growth Factor [NGF], Brain Derived Neurotrophic Factor [BDNF] and others) and other endogenous mediators such as nociceptin.

The similarity of the properties of the urothelial cells and the C-fibre afferents suggests that the most likely contender for a sensory cell may be a urothelial cell, but it is clear that the afferent endings themselves respond to a variety of stimuli, and that surrounding cells may simply enhance the gain of the transducer. The following paragraphs refer to some of the mediators that can sensitize bladder afferents.

a) ATP and P2X3 Receptors

Recent studies of mice have shown the P2X2/3 receptor, is present in small sensory neurones innervating the bladder, and that the effects of bladder distension on these sensory endings is markedly attenuated if the gene for the P2X3 receptor is deleted. Knockout mice that do not express this receptor exhibit
a marked urinary bladder hyporeflexia, characterized by decreased voiding frequency and increased bladder capacity, but normal bladder pressures [94, 95]. In addition, they have reduced pain-related behaviour in response to injection of ATP or formalin, and lose the rapidly desensitizing ATP-induced currents in their dorsal root ganglion neurons; they also have a reduction in the sustained ATP-induced currents in nodose ganglion neurons. Immunohistochemical studies localize P2X3 to nerve fibres innervating the urinary bladder of wild-type mice, and show that loss of P2X3 does not alter sensory neuron innervation density. Thus, P2X3 is critical for peripheral afferent pathways controlling urinary bladder volume reflexes, which take place at physiological volumes and pressures. Antagonists to P2X3 may therefore have therapeutic potential in the treatment of disorders of urine storage and voiding such as overactive bladder. In one recent study it was observed that humans with detrusor overactivity treated with botulinum toxin showed decreased levels of P2X3 and TRPV1 receptors in the bladder biopsies [96].

Some groups of bladder afferents appear to be sensitive to the release of ATP from the urothelium or other cells. In the last few years, the sensitivity of bladder afferents to ATP and mechanical stimuli has been studied intensively in the rat and mouse using protocols designed to avoid sensitization of the afferents [97-99]. In the rat, 90% of bladder afferent neurons gave persistent electrical responses to the P2X agonist α-β-methylene ATP that were inhibited by the P2X antagonist 2',3'-O-trinitrophenyl-ATP (TNP-ATP) which suggests that pelvic nerve afferents from the rat bladder express predominantly P2X (2/3) heteromeric receptors. In the mouse, Rong et al [99] found that the majority of the low threshold and nearly all the high threshold receptors were sensitized by α-β-methylene ATP, i.e. there was a reduction in the threshold and an increased peak activity during distensions. In addition some of the 'silent' afferents became mechanosensitive. The absence of sensitization in P2X3 knockout mice indicated that the responses were mediated by the P2X3 receptor. However there is a recent in vitro study in the guinea-pig that suggests that one group of afferents, the low threshold 'in series' tension receptors in detrusor muscle, are not sensitive to ATP [86].

b) Nitric Oxide

Nitric oxide (NO) is an important mediator that can be released from urothelium and from adjacent neurones. The detrusor however is not very sensitive to ATP [86].

NO may be involved in the control of afferent sensitivity, and we now know that NO may increase the activity of capsaicin-sensitive nerves within the bladder wall after spinal cord injury [101]. Basal release of nitric oxide has not been detected in the urothelium of the normal cat; however it is released in cats with feline interstitial cystitis [102], and from normal cats after the addition of agonists. Nitric oxide release from neurones depends on the enzyme nitric oxide synthase (NOS) and increased expression of neuronal NOS in bladder afferent and spinal neurones occurs following cord injury [103], and in bladder afferents following chronic bladder irritation with cyclophosphamide. There is also evidence that nitric oxide can inhibit the function of primary afferent neurones [104, 105]. This inhibitory effect may occur in the normal bladder because intravesical administration of a solution of oxyhemoglobin, a nitric oxide scavenger, induced bladder overactivity in the conscious rat [106]. The effect of oxyhemoglobin was reduced by pretreatment with ZD6169, a drug that suppresses capsaicin-sensitive bladder afferents, suggesting that oxyhemoglobin enhances afferent excitability.

Knockout mice that do not have neuronal NOS appear to have normal function in the lower urinary tract [107], and knockout animals that do not have inducible NOS do not show major abnormalities. However, the latter appear to need iNOS in the response to urinary obstruction [108].

c) Tachykinins: Substance P, Neurokinin A and Neurokinin B

The tachykinins are a group of neuropeptides that includes substance P and neurokinin A (which are produced by the same gene), and neurokinin B. They are found in small diameter afferent neurones, particularly within the C-fibre population, and may be released, along with other peptides, by afferent endings when these become active, e.g. during the axon reflex in skin. A similar event occurs in the bladder and is associated with the phenomenon of neurogenic inflammation. These peptides cause vasodilatation and an increase in capillary permeability, and are algesic agents.

In addition some tachykinins can sensitize sensory nerve endings. This view is based on (a) autoradiographic studies that show the disappearance of NK-2 receptors in the lamina propria in capsaicin-treated rats that are deficient in sensory nerves [109], (b) on studies in which afferents or dorsal root ganglia can be made hypersensitive using a NKA-analogue and other intravesical chemical stimuli such as high [K+] and high osmolality [110-112], and (c) the demonstration that the development of hypersensitivity to a number of sensitizing agents including high [K+] can be blocked by an NK-2 receptor antagonist [113, 114]. More recently it has been shown that rat dorsal root ganglion neurones are excited by NK2 agonists, but are inhibited by NK-3 agonists [115]. This NK2 action...
is on L- and N-type Ca\(^{2+}\) channels, whereas the NK-3 action is only on the L-type channels. Both of these effects are blocked by inhibition of protein kinase C.

d) TRP (Transient Receptor Potential) Receptors

Ion channels that act as receptors because they are responsible for transient receptor potentials (TRP) generally work by opening non-specific ion channels. Some are sensitive to capsaicin and other vanilloids (TRPV), while others are associated with other mediators, including cinnamaldehyde (TRPA1) and Melastatin (TRPM). TRP channels are opened by a variety of physical and chemical stimuli including heat, cold, mechanical stress, voltage, hydrogen ion concentration and osmolality, as well as by specific ligands, such as capsaicin, melastatin and trans-cinnamaldehyde. The nerve endings that contain these channels are therefore often polymodal in their properties, one of the characteristics of non-myelinated sensory endings, and also in other cell types, including the urothelium. TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1 have been described in different parts of the urogenital tract, and TRPV1 (the vanilloid receptor) has received special attention, particularly in relation to its role in bladder sensation [116].

The TRPV1 receptor is a cation channel expressed by nociceptive neurones and can also [117, 118] be activated by protons or temperature greater than 43 degrees C [119, 120]. Within the bladder, it may be that it is activated naturally by low pH, but such changes (e.g. in metabolic acidosis) are not usually associated with bladder pain. The expression of the TRPV1 receptor in sensory neurones is regulated by Nerve Growth Factor (NGF), and stimulation of the TRPV1 receptor with capsaicin causes the release of CGRP [121]. Capsaicin and resiniferatoxin act on unmyelinated afferent fibres throughout the body, but it is also clear that capsaicin can act on the urothelium by binding to TRPV1 receptors. Capsazepine is a blocker of this receptor and it has been found that nitric oxide (NO) release and the increase in intracellular Ca\(^{2+}\) induced by capsaicin are blocked by this antagonist. In addition to capsaicin and resiniferatoxin, a new agonist, piperine, has been shown to activate TRPV1 receptors and produce bladder hyperactivity and activity of sensory nerves in this organ in the rat [117, 118]. Several groups have searched for endogenous ligands for the TRPV1 receptors, and anandamide, palmitoylethanolamide and nociceptin are three compounds that deserve a mention, although much more work needs to be done to elucidate their exact roles. Anandamide and palmitoylethanolamide (PEA) are endogenous cannabinoids (acting on CB-1 and CB-2 receptors respectively) that also are agonists of TRPV1 receptors [122, 123] and may act on peripheral perivascular sensory terminals in a manner that is antagonized by the capsaicin antagonist capsazepine. These agents can also cause the release of CGRP and Substance P by increasing intracellular Ca\(^{2+}\), and have other actions, such as activation of G-proteins [124]. Both anandamide and PEA have been found to attenuate bladder hyper-reflexia induced by intra-vesical NGF [125-127]. The TRPV1 receptor seems to be important for normal bladder function and for excitation of low threshold distension-sensitive afferents in mice [128, 129] (Figure 9).

• Other TRP Receptors

The bladder-cooling reflex (induced by instillation of intravesical cold saline and termed the ice water test) is believed to be triggered by menthol-sensitive cold receptors in the bladder wall. Recently, this test has been used to distinguish sensory symptoms in patients with bladder pain syndrome and overactive disorders [130]. Because pain elicited in BPS patients was not accompanied by reflex detrusor contractions, this test may be of particular interest since the response of afferent nerves to cold (and to menthol) depends on a particular TRP receptor subgroup, TRPM8. In experiments in the guinea-pig bladder, the afferent nerves innervating the organ have been shown to express TRPM8, and the bladder cooling reflex is enhanced in the presence of menthol [131].

The TRPA1 channel is also expressed in dorsal root ganglion cells that innervate the rat bladder. Trans-cinnamaldehyde or allyl isothiocyanate, agonists of this receptor, cause bladder hyperreflexia and appear to act through C fibres that might be mechanoreceptive or nociceptive [132].

e) ORL Receptors

Nociceptin/orphanin FQ, another endogenous ligand that binds with the opioid receptor-like 1 receptor (ORL1 receptor, now also known as the 4th category of opioid receptors, OP4) has been shown to have naloxone resistant inhibitory effects on the micturition reflex. These actions are mediated at several sites including the capsaicin sensitive nerves in the bladder, and a central supraspinal site [133]. Nociceptin produces a long-lasting protection against capsaicin-induced desensitization of TRPV1 in afferent nerves, such that a chemoceptive micturition reflex could be repeatedly evoked by topical capsaicin in nociceptin-pretreated rats. This is in sharp contrast to the effects of nociceptin on the local response to capsaicin, which corresponds to the release of peptides from capsaicin-sensitive afferent neurons. Topical application of nociceptin onto the bladder serosa evokes a tachykinin-mediated contraction [133]. These results suggest that the afferent and ‘effenter’ functions of capsaicin-sensitive primary afferent neurons in the rat bladder are differentiated by nociceptin, and that nociceptin has a significant action on afferent sensitivity.
In humans nociceptin elicits a strong acute inhibitory effect on the micturition reflex in patients with a neurogenic bladder [134]). This was in contrast to the placebo, and led to the conclusion that nociceptin and other orphan peptide receptor agonists may be useful in future as drugs for the treatment of neurogenic urinary incontinence.

Local administration of kappa-opioid receptor agonists by intra-arterial injection attenuated the responses of pelvic nerve afferents to high pressure distension of the urinary bladder [135]. These agonists had essentially the same effects whether the bladder was inflamed or not. The conclusion was that the ability of kappa opioid agonists to attenuate the responses of afferents to large bladder distensions indicated a potential use for peripherally acting kappa opioid receptor agonists in the control of urinary bladder pain.

f) Neurotrophins

1. NERVE GROWTH FACTOR

(NGF; neurotrophin-1), the first of a group of growth factors called neurotrophins, is produced in larger quantities in humans with detrusor overactivity [136], BPS/IC and bladder cancer [137], in rats with inflamed bladders [138], spinal cord injury or chemically induced cystitis [139] or bladder outlet obstruction [140], in diabetic rats [141] and a number of other states. This protein is known to sensitize myelinated and unmyelinated afferents from the bladder [142, 143] and it is involved in the production of referred pain in bladder inflammation [144]. It also appears to stimulate the expression of the vanilloid receptor TRPV1 [121], and there is a suggestion that increased NGF levels resulting from intrathecal injection of NGF can induce a decrease in A-type K⁺ current density in the afferent pathway that may influence the emergence of bladder overactivity [145].

Recent studies in an animal model for BPS/IC termed feline interstitial cystitis (FIC) in which TRPV1 responses to capsaicin were measured in lumbo-sacral dorsal root ganglion neurones have suggested that affected neurones are increased in size and exhibit exaggerated responses to capsaicin that may be associated with enhanced activity of endogenous protein kinase C [146]. A further study from the same group suggested that the abnormal activity of afferent neurones from cats with feline interstitial cystitis may be due to changes in the behavior of K⁺ currents which are restricted to capsaicin-sensitive neurones [147].

2. BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)

levels in the urinary bladder and some other epithelia are higher than those found in the brain or skin [148]. In situ hybridization experiments showed that BDNF mRNA was made by visceral epithelial cells, in several types of smooth muscle, and in neurons of the myenteric plexus. However the receptors from BDNF (trkB and p75[NTR]) are not present on the urothelium but are present in neurons of the peripheral nervous system. Hence it is thought that in the bladder this neurotrophin is produced by the urothelium and can act on the afferent nerves. The mRNAs for NGF, BDNF and neurotrophin-3 all increase within 2 hours of bladder inflammation in the rat, and this increases expression may contribute to sensory and reflex hyperactivity [138]. Inflammation of the colon also appears to induce up-regulation of CGRP and TrkB (suggesting an involvement of BDNF) in bladder afferent neurons, and suggests that there may be cross sensitization of bladder afferent pathways by colonic inflammation [149]. In spinal cord injury there is also an increase in BDNF and galanin in the dorsal root ganglia and spinal segments below the lesion; interestingly NGF expression was reduced below the level of the lesion [150].

Figure 9: Stimulus-response profile of low threshold, LT (A) and high threshold, HT (B) bladder afferents. Note that the LT afferents have a blunted response profile in the TRPV1 -/- mice compared to wildtype (P<0.001, 2-way ANOVA and Bonferroni test). The response profile of HT afferents is unchanged (from Daly et al., 2007).
**NGF and TTX-Resistant Na⁺ Channels**

Sensitization of afferents appears to be an important mechanism that leads to reflex hyperexcitability, and a number of studies have linked the tetrodotoxin (TTX)-resistant sodium channel, sometimes known as Nav1.8 to this process. A number of sensitizing agents including NGF are known to induce increased expression of this membrane channel; this appears to be sufficient to change the properties of afferents so as to lower the threshold for firing of bladder (lower volume threshold for voiding) and induce spontaneous and burst firing (overactive contractions, urgency) [142]. TTX-resistant Na channels (Nav1.8 and Nav1.9) have been found in SP/CGRP immunoreactive small DRG giving rise to C-fibers supplying the bladder [151, 152]; these also express the trkA receptor, which binds NGF and is necessary for its action. Plasticity of TTX-sensitive and TTX-resistant Na⁺ channels (Nav 1.8 and Nav 1.9) occurs in these neurones after spinal cord injury, and a decreased expression of Nav 1.8 channel immunoreactivity and a small increase in Nav 1.9 channel immunoreactivity in bladder DRG neurons can be observed [153, 154].

The dependence of the sensitization of these afferent neurones and the occurrence of overactivity on NGF and its actions on the Nav 1.8 channels has been shown in experiments using immunoneutralization of NGF or antisense oligonucleotide treatment to reduce the expression of these channels in sensory neurons [151, 155]. More recently studies on ralfinamide, a drug that interferes with TTX-resistant sodium channels, indicate that this drug reduces inflammatory and neuropathic pain as well as bladder overactivity in rats. The ability of ralfinamide to reduce capsaicin-induced hyperexcitability and tonic activity of rat afferent neurones appears to be due to its action as a sodium channel antagonist [156].

In clinical studies the local anaesthetic lidocaine and the oral Na⁺ channel blocker, mexiletine, which operate by reducing excitability in sensitized neurones have been used to treat urge incontinence and hyper-reflexic conditions [157-162] with variable degrees of success.

4. **SPINAL CORD**

This section is concerned with the central projections of the primary afferent neurons. Axonal tracing experiments have been performed in many animal species [163, 164] and have localized the segmental distribution and spinal termination of afferent pathways in the pelvic, hypogastric and pudendal nerves. The primary afferent cell bodies of the pelvic and pudendal nerves are contained in lower lumbar and sacral dorsal root ganglia depending on species; whereas afferent innervation in the hypogastric arises in the rostral lumbar dorsal root ganglia. The central axons of the dorsal root ganglion neurons carry the sensory information from the lower urinary tract to second order neurons in the spinal cord.

Trans-ganglionic transport of axonal tracers has identified the spinal projections and terminal fields of visceral and somatic primary afferent neurones. The dorsal commissure (DCM), superficial dorsal horn and sacral parasympathetic nucleus (SPN) all contain interneurons with rostral projections that are activated during noxious [165, 166] or non-noxious stimulation [167] of the rat bladder and the urethra. These neurones are the site of origin of ascending pathways that project to various structures in the brainstem via spinal pathways that include the dorso-lateral funiculus [168, 169]. In humans spinal tractotomies for intractable pelvic pain provide the only insight available as to the organization of spinal pathways involved in bladder control in man [170].

Visceral afferent fibers of the pelvic [171] and pudendal [163] nerves enter the cord and travel rostrocaudally within Lissauer’s tract, and transversely around the dorsal horn via the lateral (LCP) and medial collateral pathways (MCP) to reach the deeper layers of the spinal cord. Within the spinal gray matter, the LCP and MCP provide a dense innervation to laminae I, V, and VII and the dorsal commissure. Muscle and cutaneous afferents in the pudendal nerve terminate in different regions of the cord.

**Afferents from the Urethra, Bowel and Genital Organs**

Studies have demonstrated that electrical stimulation of urethral afferent fibers when the bladder is full can evoke strong detrusor contractions sufficient for voiding in intact cats [172, 173] as well as acute spinalized cats [174]. Similarly, using minimally invasive methods to apply electrical stimulation within the proximal urethra via a catheter-mounted electrode, it has been shown that reflex bladder contractions can be generated in humans with complete paraplegia but these do not seem to produce efficient voiding can be evoked in chronic SCI cats by stimulation of an excitatory pudendal to bladder spinal reflex [176].

The excitability of the micturition reflex can be influenced by other sacral afferent pathways [177], including facilitatory effects resulting from stimulation of urethral afferents, and inhibition of bladder activity by stimulation of the dorsal nerve of the clitoris in keeping with known interactions from the vagina and colon [178]. Stimulation of urethral afferents by fluid flowing through the urethra can facilitate the micturition reflex; however contraction of the urethral sphincter resulted in inhibition of bladder motility [179].

Excitability of spinal neurons receiving afferent input from the bladder can also be modulated by input from other pelvic structures such as the colon [175, 180, 181]. This convergence of sensory information from a number of pelvic organs can occur at the level of the
spinal cord. In addition, the expansion of primary axon terminals within the spinal cord can also play a role in altering bladder reflexes. For example, it has been shown that expression of a number of peptides including CGRP, VIP as well as PACAP is altered in primary afferent terminals and may correlate with changes in bladder function following SCI [182-184].

Glutamate is an important excitatory transmitter in the afferent limb of the micturition reflex and mediates its effects by means of both NMDA and nonNMDA receptors. This conclusion is based on studies of C-fos expression and the transmission of afferent activity rostrally, and the depressive effects of both NMDA and nonNMDA glutamatergic receptor antagonists [185, 186].

Bladder afferent neurons contain a number of peptidergic neurotransmitters, and the central distribution of bladder afferent terminals and peptidergic immunoreactive fibers is quite similar. There has been considerable interest in the role of tachykinins in the micturition reflex [187] and in nociception. Intrathecal treatment of adult rats with intrathecal capsicain can result in a reversible block of the micturition reflex [188]. Further, while normal micturition is not altered following ablation of NK1-R expressing SC neurons using SSP-saporin, the response to a noicceptive stimulus was significantly reduced. These and other studies [188, 189] suggest that substance P and its receptors may play a part in transmission of bladder nociceptive responses at the first synapse in the micturition reflex.

5. SPINAL CORD GLIAL CELLS AND MODULATION OF PELVIC AFFERENTS

a) Anatomy and Function of CNS Glia

The nervous systems of animals are generally composed of two cell types: neurons, which propagate electrical currents and function as the signaling moieties of the nervous system, and glia, the functions of which are far less understood [190]. Central nervous system (CNS) glia, (which greatly outnumber the neuronal component [191, 192]), comprise ependymal cells, oligodendrocytes, astrocytes and microglia.

Astrocytes, (similar to neurons and oligodendrocytes) are ectodermal in origin. Two distinct types are described based on their morphology: fibrous astrocytes, which have long thin processes and are commonly found in white matter, and protoplasmic astrocytes, which have short thick processes and are typically found in grey matter. In the reactive state, protoplasmic astrocytic processes become more pronounced [193].

Astrocytes contribute to the regulation of the microenvironment in which neurons develop and function, maintaining a tight control on local ion (notably K⁺) and pH homeostasis. In addition, they are involved in the clearance of synaptically-released neurotransmitters, such as glutamate and GABA [194]. These multifunctional cells are key players in the ‘tripartite synapse’, which is composed of pre- and post-synaptic membranes and extra-synaptic astrocytic contacts; they have the potential to modify synaptic transmission and plasticity [195].

Microglia are considered to have a mesodermal origin and to enter the brain during the neonatal period; they are commonly considered to function as the resident macrophages of the CNS and are more abundant in grey than white matter. In the normal brain and spinal cord, they have a ramified morphology; when activated, such as when there is damage to the CNS, they rapidly retract their processes and migrate toward the site of injury, where they turn into macrophages and remove the debris [193].

While astrocytes and microglia present as two very different types of glial cell, it is now becoming increasingly known that they have functional similarities. Recent evidence has shown that spinal cord activation of either of the two cell types may be involved in both the development and maintenance of central sensitization in various chronic pain conditions. Thus, both astrocytes and microglia are attracting wide interest in the pain field [196].

b) Modulation of Neuronal Signaling by Spinal Cord Glia

At the level of the spinal cord (the first relay site in the transmission of nociceptive information from the periphery to the brain [197], dorsal horn glia may be activated by chemicals released from primary afferent terminals such as the neurotransmitters: SP, CGRP, NO, purinergic agents, glutamate, opioid peptides, and the chemokines: fractalkine or neuractin. Activation may result in altered cell morphology, changes in receptor expression, or release of factors by astrocytes and microglia, which in turn can lead to changes in neuronal function and ultimately influence pain transmission [198]. There is evidence that microglia may mediate the activation of astrocytes seen in both somatic and visceral pain pathologies—the ‘neuropathic pain triad’ [199]. Generally, microglial activation is transient, while astrocytic activation is much longer-lasting. However, activation of either of the two cell types promotes pain [196, 200].

While most reports on the contribution of glia to pain, study somatic rather than visceral forms of chronic pain, there is now increasing evidence pointing to a role for glia as key modulators during inflammatory pain. Microglia probably play a pivotal role in the initiation phase, while astrocytes are likely to contribute to the maintenance of the persistent pain state. There are reports in non-acute [201, 202] and acute [202] models of colonic irritation of altered glial cell morphology, in segments L6-S1 of the spinal cord.
In addition, in the naturally occurring chronic model of bladder pain syndrome/interstitial cystitis (BPS/IC) seen in the cat, a pronounced upregulation in immunointensity of astrocytic intermediate filament glial fibrillary acidic protein (GFAP) in dorsal horn regions which receive pelvic afferent input [202], has been reported. Preliminary findings from functional studies using primary cultures of astrocytes (Figure 10) isolated from lumbo-sacral region of cats with BPS/IC and normal cats (Hanna-Mitchell, Buffingtonm and Birder; unpublished data), point to significant differences in the physiology of astrocytes in regions of the spinal cord receiving pelvic afferent input following this pathology.

Together these findings indicate a pronounced activation of spinal cord astrocytes in animal models for BPS, which may plan an important role in the pain syndrome and open up new potential approaches for drug intervention.

**III. NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLES AND RHABDOSPHINCTERS**

1. STRUCTURAL ELEMENTS OF THE PELVIC FLOOR

The pelvic floor [203] in women is a bowl-shaped structure comprised of bone, muscle, and connective tissue. The rim of the bowl is formed by the bones of the pelvic girdle (sacrum, ileum, ischium, and pubis). The “inside and bottom” of the bowl is lined with striated muscle: the iliococcygeus and pubococcygeus (which together comprise the levator ani) as well as the coccygeus, and puborectalis muscles. The muscles are attached to the bone and to each other with various connective tissue supports. These 3 components, bone, muscle, and connective tissue provide support of the pelvic viscera (i.e. rectum, vagina, and bladder) but also allow for excretory and sexual function.

The viscera, as well as striated muscles that serve as true sphincters - urethral and anal rhabdosphincters - are attached to the pelvic floor muscles and each other by connective tissue but do not attach directly to bone. In addition to the urethral and anal rhabdosphincters, striated perineal muscles associated with the viscera include the urethrovaginal sphincter, the compressor urethrae muscle, the ischiocavernosus, and bulbospongiosus muscles [203-205]. In contrast to the levator ani muscles described above, the rhabdospincter and perineal muscles embryologically develop from the cloaca with a 2 week delay in striated muscular differentiation compared to the levator ani and other skeletal muscles [206, 207] and are completely separated from the levator ani muscles by connective tissue [204].

2. INNERVATION OF THE FEMALE LEVATOR ANI MUSCLES

The levator ani muscle of the pelvic floor is innervated by the levator ani nerve in human (Figure 11) [208], squirrel monkey [209-211], dog [212], cat (Karicheti and Thor, unpublished observations), and rat [213]. The levator ani nerve primarily arises from sacral spinal roots (e.g. S3-S5 in humans) and travels along the intrapelvic face of the levator ani muscle with a high degree of variability in branching patterns [208]. In humans, there is some controversy whether or not the pudendal nerve also innervates the levator ani muscle [214, 215]. This is not the case in other species (rat, cat, dog, squirrel monkey) where hodological studies show a marked loss of levator ani muscle mass and a decrease in levator ani myocyte diameter following transection of the levator ani nerve [211, 213] but no change in levator ani muscle mass or myocyte diameter following pudendal neurectomy [211, 213], 2) the existence of only a single motor endplate zone at the point of levator ani nerve insertion into the levator ani muscles [211, 213], 3) absence of contractions of levator ani muscles upon electrical stimulation of pudendal nerve efferent fibers (Thor and Karicheti, unpublished observations) and 4) phenotypically distinctive motor neuron labeling following application of nerve tracers to the pudendal and levator ani nerves [212, 216-221], respectively. All of these divergent techniques support the conclusion that only the levator ani nerve innervates the levator ani muscles with no significant contribution from the pudendal nerve in non-human species.

In consideration of the vast phenotypic differences between rhabdospincter pudendal motor neurons in Onuf’s nucleus and levator ani motor neurons (Figure 11 and Table 3), the likelihood of pudendal
Figure 11: A) Illustration of the course of the levator ani nerve in a left hemipelvis, sagittal view (arrow points to levator ani nerve). Abbreviations: S, Sacrum; S1-S5, sacral foramina; Cm, coccygeal muscle; LAN, levator ani nerve; IS, ischial spine; ICm, iliococcygeal muscle; Olm, obturator internal muscle; PCm, pubococcygeal muscle; PRm, puborectal muscle; ATLA, arcus tendinous levator ani; C, coccyx; V, vagina; U, urethra; R, rectum (from Barber, 2002). B-E) Photomicrographs of a single transverse section of sacral spinal cord from a squirrel monkey with pubocaudalis muscle injected with cholera toxin B (CTB) and the anal rhabdosphincter injected with fast blue. B) Bright field illumination shows cytoarchitecture of gray and white matter; white box indicates area shown in high power in panels D and E. C) Epifluorescent illumination showing CTB-labeled (bright green) levator ani motor neurons; white box indicates area shown in high power in panels D and E. D) High power photomicrograph of boxed area in panels B and C using epifluorescent illumination to show CTB-labeled levator ani motor neurons. Note large α and small γ CTB-labeled motor neurons; also CTB-labeled processes extending from levator ani motor neurons into Onuf’s nucleus (dashed circle) and the ventrolateral funiculus. E) Same area and section as panel D viewed with epifluorescent illumination to show fast blue-labeled (bright blue) anal sphincter motor neurons in Onuf’s nucleus (dashed circle). Close apposition between CTB-labeled levator ani motor neuron processes and fast blue-labeled rhabdosphincter motor neurons were observed (from Pierce, 2005).
motor neurons innervating the levator ani muscle in humans seems very small. Similarly, the distinct embryological origins of levator ani muscles versus rhabdosphincter and perineal muscles (the latter originating from the cloaca [206, 207]), as well as a separate “compartmentalization” of the rhabdosphincter and perineal muscles by connective tissue [204], are parsimonious with distinctive “special somatic” motor innervation by the pudendal versus typical skeletal motor innervation by the levator ani nerve. Possibly, the confusing morass of small muscles (puborectalis, compressor urethrae, urethrovaginal sphincter, urethral and anal rhabdosphincter, ischiocavernosus, bulbocavernosus), blood vessels, connective tissues, and nerves in the perineal region makes dissection, identification, and nomenclature of specific nerve branches and muscles difficult in cadavers.

Indeed, this morass has led to confusion regarding even the nomenclature of the muscles themselves [204, 205] and, without extreme care, a contribution of the pudendal nerve to levator ani muscle innervation might be confused. Alternatively, there may be true species differences between humans and other mammals in regards to a minor pudendal nerve contribution to minor levator ani muscles (e.g. puborectalis). However, the ability to conduct precise experimental manipulations in animals provides a clear conclusion that the pudendal nerve does not innervate the major muscles of the pelvic floor, i.e. iliococcygeus, pubococcygeus, or coccygeus muscles to a significant degree.

The positioning of the levator ani nerve on the intrapelvic surface of the muscles may expose it to damage as the fetal head passes through the birth canal [208]. This positioning also puts it in a favorable position to be activated when current is applied with a St. Mark’s electrode placed in the rectum. The positioning of the levator ani nerve, close to the ischial spine, also risks entrapment by sutures used for various suspension surgeries for pelvic organ prolapse (POP) and may account for dyspareunia, pelvic pain, and/or recurrent prolapse [222] associated with such surgery. Finally, since the ischial spine is used as a landmark for needle placement when applying a transvaginal “pudendal nerve” block [223], the possibility that this procedure also anesthetizes the levator ani nerve and pelvic floor muscles must be considered. These complicating factors of historically-accepted clinical concepts may explain why a possible innervation of the levator ani muscle by the pudendal nerve in humans remains controversial.

a) Levator Ani Motor Neurons and Sensory Innervation

Retrograde tracing studies involving injection of cholera
toxin B (CTB) into the levator ani muscle and fast blue into the anal rhabdosphincter muscle of squirrel monkeys [217] show that levator ani motor neurons are located in the sacral ventral horn (Figure 11 B-E) in a longitudinal column. In contrast to the very dense packing of sphincter motor neurons in Onuf’s nucleus [216, 218-221], the levator ani motor neurons are more diffusely distributed. Furthermore in contrast to the uniform intermediate size of pudendal motor neurons, levator ani motor neurons (Figure 11D) show a bimodal distribution of large neurons (presumably α motor neurons) and small neurons (presumably γ motor neurons). These 2 sizes of motor neurons are in keeping with the presence of muscle spindles (whose intrafusal muscle fibers are innervated by γ motor neurons) in levator ani muscle [224, 225] and the absence of muscle spindles in rhabdosphincter muscle [224, 226-230]; consequently levator ani may exhibit la (muscle spindle) evoked monosynaptic stretch reflexes, whereas the EUS does not [231-234].

Levator ani motor neuron processes (dendrites or axon collaterals) project into two important areas in the sacral spinal cord [217]. The first, medial lamina VI, is a region where primary afferent fibers from muscle spindle and Golgi tendon organs terminate [235, 236]. This again suggests an important role for stretch-activated contraction of levator ani muscles. Importantly, the second projection of levator ani motor neurons is to Onuf’s nucleus (Figure 11D-E), which contains rhabdosphincter motor neurons. These levator ani motor neuron processes form close appositions with sphincter motor neurons in both monkey [217] and rat (Thor, unpublished observations).

Presumably, these appositions reflect a neuroanatomical substrate for coordination of the rhabdosphincter and the pelvic floor muscles during micturition and defecation. Whether these projections are dendrites designed to receive common afferent input to levator ani and rhabdosphincter motor neurons, or if they are axon collaterals transmitting information from levator ani motor neurons to rhabdosphincter motor neurons to coordinate contractions is not known and will require electron microscopic or electrophysiological analysis to be resolved.

Dual-labeling immunohistochemistry combined with cholera toxin-B (CTB) tracing studies of the levator ani muscles of squirrel monkeys has shown that there are approximately 4 times as many afferent neurons versus motor neurons labeled following injection of tracer into the levator ani muscle [210]. About 7 of the neurons were large, myelinated (i.e. RT-97 neurofilament positive) that did not contain the peptide transmitter CGRP, binding sites for isolectin-B4 (IB-4), or the growth factor receptor, TrkA, immunoreactivity. Of the remaining small RT97 negative neurons, approximately 50% contained CGRP, IB-4 binding sites, and TrkA. It is tempting to speculate that the large, myelinated afferent neurons signal proprioceptive information from muscle spindle and Golgi tendon organs, while the small peptidergic, IB-4, TrkA positive neurons signal nociceptive information. A possible role for the large sensory neurons, in addition to control of levator ani contractility, may involve regulation of bladder reflex pathways during on-going levator ani contractile activity; while the small peptidergic fibers may play a role in detrusor overactivity associated with pelvic floor trauma or nerve entrapment by sutures during suspension surgeries, in addition to classical sensation of muscle nociception.

Transganglionic transport of CTB from the primary afferent cell body to their synaptic terminals in the spinal cord was only seen in medial lamina VI of the lumbosacral spinal cord, an area of termination for large, myelinated proprioceptive terminals [235, 236]. Since many of the CTB-labeled primary afferent neurons were positive for CGRP, IB-4, and TrkA, the absence of transganglionic CTB labeling in the superficial dorsal horn is likely due to an inability of small primary afferent neurons to transport CTB rather than a true absence of levator ani nociceptive terminals in the region. Experiments with a tracer (e.g. horseradish Peroxidase, HRP) that is transported to nociceptive spinal terminals should be done to confirm this.

In contrast to the rhabdosphincters [224, 226-230], levator ani muscles have been shown to contain muscle spindles [224] and evidence has been presented that they contain Golgi tendon organs [225].

b) Role of the Levator Ani Innervation in Pelvic Organ Prolapse in Monkeys

Because the pelvic floor is responsible for providing support of the viscera, and because one might expect contraction of pelvic floor muscles to be necessary for adequate support, damage to the levator ani innervation and subsequent muscle flaccidity might be expected to promote pelvic organ prolapse (POP). To test this expectation, the levator ani muscles were bilaterally denervated in 7 squirrel monkeys [209], which is a species that shows age and parity correlated POP similar to humans [237]. Surprisingly, these monkeys showed no POP following this procedure for 2-3 years after surgery, despite showing statistically significant decreases in levator ani muscle mass and myocyte diameter. However, a slight increase in bladder and cervical descent with abdominal pressure was seen on MRI evaluation compared to nulliparous controls. Of possible significance was the finding that, after a single birth, 2 of 4 bilateral levator ani neurectomy animals showed POP, which is unusual. A larger study is needed to confirm whether levator ani nerve damage may accelerate parity-related POP. Thus, these experiments indicate that, in the absence
of childbirth, the pelvic floor muscle plays a minor role in providing visceral support and suggests that the connective tissue plays the major role. Possibly after stretching of the pelvic connective tissue accompanying childbirth, the muscle plays a compensatory role. In support of this possibility, it was shown that levator ani muscle mass and myocyte diameter in monkeys with naturally occurring POP was equal to or greater than measurements in age-, parity-, and weight-matched monkeys without POP [209, 238], suggesting that the levator ani muscle attempts to prevent visceral descent by working harder, which induces hypertrophy.

3. INNERVATION OF URETHRAL AND ANAL RHABDOSPINCTERS

At the level of the pelvic floor, the urethra and rectum are surrounded by intimately associated bands of striated muscle fibers; the urethral and anal rhabdosphincters, respectively. The muscles do not have “dedicated” attachments to skeletal structures and thus act as a true sphincters (i.e. contraction produces virtually no movement except constriction of the lumen). In addition, there are small, thin bands of striated muscle (compressor urethra, urethrovaginal sphincter, bulbocavernosus, and ischiocavernosus) that surround the urethra, vagina, and/or rectum and have connective tissue attachments to the perineal body [203].

Extensive studies of the urethral rhabdosphincter, anal rhabdosphincter, bulbocavernosus, and ischiocavernosus muscles have shown that these muscles are innervated by the pudendal nerve [208, 216, 218-221, 239, 240], which originates from the sacral roots and passes along the lateral surface of the internal obturator and coccygeus muscles, through Alcock’s canal, to eventually approach these muscles laterally from the extrapelvic surface of the pelvic floor. The specific innervation of the smaller bands of muscles attached to the perineal body has not been characterized.

The nerve fascicles [241], as well as the motor nerve terminals and end plates [242] of the urethral rhabdosphincter, are preferentially located along the lateral aspects of the urethra in rat. Overlap, or crossing of the midline, between the left and right pudendal nerve terminal fields has been described in monkeys [243]. The urethral rhabdosphincter of both men and women contain neuronal nitric oxide synthase (nNOS) which is contained in a subpopulation (43%) of the muscle fibers, as well as nerve fibers, with concentration at the neuromuscular junction [244-246]. Additionally, nNOS has been localized to pudendal motor neurons which innervate the rhabdosphincter [247, 248]. nNOS is responsible for producing the transmitter nitric oxide. While NO is known to increase cGMP levels in many types of smooth muscle; its role in control of striated muscle and neuromuscular junction function is not well established [249]. An NO donor has been shown to reduce urethral pressures at the level of the rhabdosphincter [250], but it is difficult to conclude if the effect is on smooth or striated muscle.

Some evidence suggesting that the rhabdosphincter receives a “triple innervation” from somatic, parasympathetic, and sympathetic nerves [251] was based on anatomical studies that showed these fibers within the portion of the urethra that contains striated muscle fibers. However, this suggestion has been disputed by subsequent studies [252] that showed no physiological effects of autonomic nerve stimulation on striated sphincter function and showed that the autonomic fibers are only “passing through” the outer layer of striated muscle to reach the inner layers of smooth muscle.

a) Urethral and Anal Rhabdosphincter Motor Neurons and Sensory Innervation

Extensive hodological studies locate pudendal motor neurons that innervate the urethral and anal rhabdosphincters (and bulbocavernousus and ischiocavernosus) muscles along the lateral border of the sacral ventral horn in Onuf’s nucleus (Figure 11E) in man [253] monkey [218, 254], dog [212], cat [219, 220], hamster [255] and guinea pig [256]. Studies in cats [219], monkey [218], and man [253] show that within Onuf’s nucleus, urethral rhabdosphinctor motor neurons occupy a ventrolateral position and anal rhabdosphinctor motor neurons occupy a dorsomedial position within the confines of Onuf’s nucleus.

However in other species, urethral and anal sphincter motor neurons are located in separate nuclei. In rat[216], anal sphincter (and bulbospongiosus) motor neurons are located medially in the ventral horn, just ventrolaterally to the central canal; while the urethral sphincter (and ischiocavernosus) motor neurons are located in the same region as others species, i.e. along the lateral edge of the ventral horn. In the domestic pig [257] and Mongolian gerbil [258], anal sphincter (and bulbospongiosus) motor neurons are located just dorsolateral to the central canal.

Sphincter motor neurons are exceptionally different from motor neurons that innervate other striated (i.e. skeletal) muscles. They are densely packed within the confines of Onuf’s nucleus and exhibit tightly-bundled dendrites that run rostrocaudally within the confines of the nucleus, and transversely into the lateral funiculus, dorsally towards the sacral parasympathetic nucleus, and dorsomedially towards the central canal [219, 259]. This is similar to dendritic projections of bladder preganglionic neurons [260] and very different from that of limb motor neurons, suggesting that EUS motor neurons and preganglionic neurons receive inputs from similar regions of the spinal cord. It has been suggested that the dense
packing and dendritic bundling of sphincter motor neurons may be related to their special sphencteric function and may facilitate simultaneous activation of all sphincter motor units. Recurrent axon collaterals [259] in the absence of recurrent inhibition [232, 261] suggests a recurrent facilitation that may also reinforce simultaneous activation. Because the rhabdosphincters are not attached to bone, efficient closure of the sphincter requires symmetrical contraction of all motor units simultaneously, i.e. partial contraction in one part of the “circle” would be defeated by relaxation in another region, like squeezing a balloon only on one side. It has been suggested that the arrangement of somatic motor nerve terminals bilaterally at dorsolateral and ventrolateral positions in the urethra provide symmetrical activation and force generation [242].

In addition to their unique morphology, rhabdosphincter motor neurons are also physiologically distinctive from skeletal muscle motor neurons in that they do not exhibit significant monosynaptic inputs [232], Renshaw cell inhibition [232], nor crossed disynaptic inhibition [261]. The passive membrane properties (e.g. high input resistance, low rheobase, short after-hyperpolarization, membrane bistability, non-linear responses to depolarizing current injection, which was recently reviewed [262]) are uniquely conducive to simultaneous, prolonged, tonic activity, in keeping with the anatomical and functional properties described above.

While various studies have characterized primary afferent neurons of the pudendal nerve [216, 219, 263], it is difficult to specifically characterize the sensory innervation of the sphincters per se since the pudendal nerve innervates many visceral structures (e.g. urethra, genitalia, rectum, vagina) in addition to rhabdosphincters. However, the absence of labeling of the largest sensory neurons in sacral dorsal root ganglia following application of tracers to the pudendal nerve suggests that the sensory innervation of the rhabdosphincters does not contain large fiber sensory endings such as muscle spindles, Golgi tendon organs, or Pacinian corpuscles. Furthermore, multiple investigators using various techniques have not found muscle spindles or Golgi tendon organs in the rhabdosphincters themselves, nor have they found evidence of the large myelinated nerve fibers (i.e. Type Ia and Ib) associated with muscle spindle and Golgi tendon organs in the pudendal nerve [224, 226-230]. This is consistent with the absence of small γ motor neuron axons (which innervate muscle spindles) in the pudendal nerve [228] and the absence of rhabdosphincter connections to bone by tendons.

Local injection of HRP targeted to the urethral and anal rhabdosphincters [219] produced labeling of the spinal terminals of primary afferent neurons in lateral and medial lamina I, the intermediate gray matter, and the dorsal commissure gray matter. Since the HRP likely spread beyond striated muscle fibers into other tissues of the urethra and rectum, it is possible that this afferent labeling is associated with the viscera and not necessarily the striated muscle fibers. However, since no labeling was seen in large diameter primary afferent neurons nor in terminals in medial lamina VI, an area where large diameter myelinated fibers of muscle spindle and Golgi tendon organs nerves terminate [235, 236] it is again reasonable to conclude that the rhabdosphincters are not significantly innervated by large myelinated nerve fibers typically associated with other striated muscle.

b) Segmental Activation of Urethral and Anal Rhabdosphincters

Rhabdosphincter motor neurons can be activated via segmental [231-233, 264, 265] and descending pathways [232, 264, 267]. The segmental inputs can be activated by stretch receptors and nociceptors in the bladder or urethra or genitalia [268-271]. Electrophysiological studies [231, 233, 234, 264, 265, 272] show that stimulation of either pelvic nerve or pudendal nerve afferent fibers can activate polysynaptic spinal segmental reflexes that can be recorded at a latency of about 10 msec from electrodes placed on pudendal nerve efferent fibers or inserted directly into the urethral or anal rhabdosphincter muscles.

Previously, the afferent inputs from the urinary bladder have been emphasized as being of primary importance for activation of the segmental reflex by pelvic nerve stimulation and is often referred to as the “guarding reflex” or “continence reflex”. However, recent studies are placing greater emphasis on urethral afferent fibers [269, 271, 273] mediating spinal reflex activation of the urethral rhabdosphincter. It is tempting to speculate that the guarding reflex is actually activated more vigorously by urethral afferent fibers if urine inadvertently begins to pass through the bladder neck and into the proximal urethra, with a requirement for a rapid closure of the more distal urethral sphincter (i.e. guarding against urine loss) compared to simple bladder distension or increases in intravesical pressure.

The greater importance of urethral afferent fibers is also suggested by experiments where bladder afferent fibers are electrically stimulated. For example, [233] were unable to evoke pudendal nerve firing with electrical stimulation of pelvic nerve fibers close to the bladder in a high number of cats but were able to evoke firing with placement of electrodes more centrally on the pelvic nerve. In our lab (Karicetti and Thor, unpublished observations), we have also found that stimulating nerve bundles close to the bladder is often ineffective in producing a spinal reflex to the urethral rhabdosphincter and/or pudendal nerve, while in the same animals it is possible to consistently evoke a reflex by moving centrally on the pelvic nerve, which would include fibers from the urethra. Since the more
Figure 12: Activation of a ‘Spinal, Urine-Storage-Reflex, Inhibitory Center’ (SUSRIC) and reduction of inhibition by 5-HT1A receptor stimulation. A-C) Averaged tracings (10 sweeps each) of evoked potentials recorded from the urethral rhabdosphincter (URS EMG, top traces) and the hypogastric nerve (HN, bottom traces) resulting from paired pulses of electrical stimulation (1 V, 0.05 msec, 0.5 Hz) of pelvic nerve (PN) afferent fibers (arrows) with a delay of 100 msec between first and second stimuli in each trace, in chloralose-anesthetized female cats. A) Control. Note that the evoked potentials elicited by the first stimulus (i.e. ‘condition’ stimulus) recorded at 10 msec on the URS and 60 msec on the HN are much larger than the evoked potentials elicited by the second stimulus (i.e. ‘test’ stimulus). (The evoked potentials resulting from the test stimulus are denoted by an *). B) After administration of the 5-HT1A receptor agonist, 8-OH-DPAT, note that there is a small increase in the condition URS EMG evoked potential but a remarkably larger increase in the test URS EMG evoked potential (*), indicating that the inhibition of the URS EMG test potential by the conditioning stimulus is reduced. Also note that 8-OH-DPAT had no influence on the inhibition of the HN evoked potential. C) Subsequent administration of WAY100635, a 5-HT1A receptor antagonist after 8-OH-DPAT restores the inhibition. Note that the inhibition of the test pulse by the conditioning pulse has been restored to control values. D) Graph showing the relationship between the amplitude of the URS EMG test evoked potential (expressed as a percentage of the amplitude of the conditioning evoked potential) versus the condition-test (C-T) interval (i.e. time between first and second of the paired pulse stimulations) during the control period (blue squares, n=12), following 8-OH-DPAT (red triangles, n=8), and subsequent WAY 100635 (green circles, n=8). Remarkably, 8-OH-DPAT produced no change in the paired pulse inhibition of the HN evoked potential.
Figure 12: (Ctd) Importantly, acute spinal transection at the T10 level produced only a small decrease in the paired pulse inhibition, indicating that inhibition is mediated by a spinal network. No effects of 8-OH-DPAT on the paired pulse inhibition were seen in animals following acute T10 spinalization, indicating that the 5HT1A receptors responsible for diminishing the paired pulse inhibition are located supraspinally. E-F) Tracings of URS EMG potentials evoked by repetitive stimulation of the pelvic nerve (PEL) at a frequency of 5-Hz for 10 sec. at 1 V, 0.05 msec pulse. E) Note that during the control period that the amplitude of the second and subsequent PEL-URS evoked potentials are considerably reduced compared to the first potential. F) Note that after 8-OH-DPAT that the amplitude of the second and subsequent potentials are much less reduced (from Thor, 2008).
central electrode placement would also activate colonic and genital afferent fibers, additional experiments are needed to specifically compare urethral versus bladder versus colonic pelvic afferent fibers in evoking the “guarding reflex”.

Electrical stimulation of pudendal afferent fibers also evokes a spinal reflex activation of the rhabdosphincter [233, 274]. Since some urethral afferent fibers (as well as rectal, genital, and cutaneous afferent fibers) also travel in the pudendal nerve, it is possible that the spinal urethral rhabdosphincter activation by pudendal afferent stimulation is also a manifestation of the “guarding reflex”.

4. SPINAL URINE-STORAGE-REFLEX INHIBITORY CENTER (SUSRIC)

While electrical stimulation of pelvic and pudendal afferent fibers can activate urethral sphincter motor neurons via a spinal reflex, these same stimuli also produce an inhibition of urethral sphincter motor neurons in cats. In early studies of McMahon et al., [233] an inhibition of pudendal nerve spontaneous activity occurred for a period of 50 - 1,000 msec following pelvic nerve stimulation.

Recently, this inhibitory effect has been characterized using electrical stimulation of pelvic (PEL) and pudendal (PUD) nerve afferent fibers and recording of evoked potentials with urethral rhabdosphincter (URS) EMG electrodes (i.e. PEL-URS and PUD-URS reflexes, respectively) in cats [275]. In addition to recording these somatic motor urine storage reflexes, electrodes were also placed on the hypogastric (HgN) nerve (i.e. PEL-HgN and PUD-HgN reflexes, respectively) to record sympathetic urine storage reflexes. Both the somatic and sympathetic urine storage reflexes are reliably evoked when the frequency of PEL or PUD stimulation is below 1 Hz (Figure 12A-C). However, when the frequency is raised to 5 Hz or higher, the amplitudes of the reflexes immediately drop (Figure 12E). This is not a “rundown” phenomenon because the reflex drop occurs immediately after the first stimulus (i.e. upon application of the second impulse in a given frequency’s series of pulses). This suggested that the first stimulus was activating an inhibitory circuit that blocked the second and subsequent stimuli’s ability to evoke the reflex (Figure 13).

The activation of an inhibitory circuit was shown in anesthetized cats [275] using a paired-pulse or condition-test paradigm, where the first stimulus of a pair (i.e. the condition pulse) precedes the second stimulus of the pair (i.e. the test pulse) by incremental times (i.e. 10, 20, 50, 100, 200, 500, 1,000 msec). This paradigm showed that when a second (i.e. paired or test stimuli) stimulus was applied to the PEL and/or PUD nerve 50 - 500 msec after the first stimulus, the reflexes evoked by the second stimulus were reliably inhibited (Figure 12A,D). The paired pulse inhibition was maximal (2nd stimulus evoked potential was < 20% of the 1st stimulus evoked potential) at paired intervals of 50 - 100 msec and gradually disappeared at paired intervals of 1,000 msec or more (Figure 12B,D). A possible clinical correlation of SUSRIC...
activation may be the elegant demonstration that conditioning stimuli applied to the dorsal nerve of the penis (i.e. pudendal nerve afferent fibers) inhibited urethral rhabdosphincter contractions reflexively evoked by magnetic stimulation of the spinal cord at intervals of 20 - 100 msec [276].

The threshold stimulus intensity for evoking inhibition in cats was the same as the threshold stimulus intensity for evoking the reflex, suggesting the same, or similar sized, fibers activate both the reflex and SUSRIC. Inhibition of both the PEL - URS EMG and PEL - HgN evoked potentials showed similar intensity-response characteristics. The inhibition could be evoked by homologous (PEL after PEL and PUD after PUD) or heterologous (PUD after PEL or vice-versa) pulse pairing. Furthermore, stimulation of PEL afferent fibers close to the bladder, which did not evoke a URS reflex, also produced inhibition of the PEL - URS reflex evoked by an electrode placed more centrally on the PEL nerve that did evoke a PEL - URS reflex. This indicates that the inhibition is not due to refractoriness of the rhabdosphincter motor neurons.

The paired pulse inhibition was slightly reduced (10-15%) but otherwise similar after acute spinal transection at T10, indicating that the inhibitory circuit is located within the same segment as the PEL - URS reflex pathway (i.e. sacral cord). (Since L5 spinalization interrupts the PEL - HgN reflex, which precludes testing for its inhibition, we cannot speculate on the location of the inhibitory circuit for the PEL - HgN reflex except that it is caudal to T10.) Since this inhibitory center is located in the spinal cord, and inhibits both the somatic and sympathetic storage reflexes evoked by either PEL or PUD stimulation, the name, "spinal, urine-storage-reflex, inhibitory center" (SUSRIC), is suggested.

The two nerves that are effective for activating the SUSRIC, the pelvic and pudendal nerves, have spinal terminals that densely project to the dorsal gray commissure region of the sacral spinal cord [219, 277]. This is also an area that contains inhibitory GABAergic and glycnergic neurons that are thought to mediate urethral rhabdosphincter inhibition during micturition [278, 279]. Because pelvic and pudendal nerves densely innervate this same region of the spinal cord, it is tempting to speculate that these GABAergic and glycnergic neurons are also the inhibitory cellular substrate of SUSRIC. Requirement of multiple, parallel inputs to SUSRIC from pelvic nerve axons (e.g. bladder afferent fibers), pudendal nerve axons (urethral afferent neurons), and descending axons from the pontine micturition center might be valuable to prevent sphincter relaxation unless all 3 systems "agreed" that micturition should proceed. On the other hand, redundant inputs might also be valuable to ensure initiation and maintenance urethral sphincter inhibition until micturition is complete and all urine has flowed out of the bladder and completely through the urethra prior to urethral closure. Experiments to test this model are needed.

In addition to its physiological role, overactivity of SUSRIC may be involved in the pathology of stress urinary incontinence, while under activity may be involved in bladder-sphincter dyssynergia or retentive urinary dysfunction such as Fowler's syndrome [280].

• 5-HT1A Receptor Regulation of SUSRIC

Administration of the 5-HT1A receptor agonist, 8-hydroxy-dipropylaminotetraline, 8-OH-DPAT, significantly reduced the paired pulse inhibition of the SUSRIC to 20% of control in spinal intact animals (Figure 12A-D) [275]. The 8-OH-DPAT-induced reduction in paired pulse inhibition was reversed by WAY100,635, a highly selective 5-HT1A receptor antagonist, which confirms the role of 5-HT1A receptors in suppressing SUSRIC. 8-OH-DPAT also enhanced the ability of the PEL - URS reflex to follow high frequency (i.e. 2 - 10 Hz) stimulation (Figure 12E-F). Importantly, 8-OH-DPAT reduced the inhibition in spinal cord intact cats but not in animals with an acute T10 spinal transection, indicating that 5-HT1A receptors are working supraspinally, probably to inhibit a descending excitatory input to SUSRIC (i.e. disfacilitation of the inhibitory center).

Previous urodynamic studies in anesthetized cats [281-283] support the supraspinal location of 5-HT1A receptors that facilitate urethral rhabdosphincter activity. This support stems from urodynamic studies that showed a remarkable enhancement of spontaneous urethral rhabdosphincter EMG activity in the chloralose-anesthetized cat irritated bladder model when the spinal cord is intact [283] but not when the spinal cord is transected, even after spinal bladder reflexes have emerged following spinal shock [281, 282]. In other words, it is proposed that 8-OH-DPAT's enhancement of urethral rhabdosphincter activity results from stimulation of supraspinal 5-HT1A receptors, which subsequently results in a reduction of SUSRIC-mediated inhibition of rhabdosphincter motor neurons, i.e. excitation results from disinhibition (Figure 13).

a) Supraspinal Activation of Rhabdosphincters and Pelvic Floor Muscles

Supraspinal activation of urethral and anal rhabdosphincter motor neurons includes voluntary inputs (i.e. corticospinal [254]), as well as involuntary reflexic inputs (e.g. during coughing, sneezing, vomiting) presumably from nucleus retroambiguus in the caudal medulla [267, 284-286]. Nucleus retroambiguus also innervates the pelvic floor muscle [285, 286], as well as the abdominal muscles; consist
with a role in raising intra-abdominal pressure during Valsalva maneuvers. Generally, the pelvic floor and rhabdosphincter muscles are activated as a functional unit when voluntarily contracted. However, differences in activation between the rhabdosphincter and the pelvic floor muscles have been documented [287], indicating distinct CNS control systems and innervation. Clinical EMG recordings show that even during sleep, activity can be recorded from specific rhabdosphincter motor units [288].

Rhabdosphincter motor neurons are unique among somatic motor neurons in receiving input from the paraventricular hypothalamus [286], although the function of this input has not been determined. In addition, their input from brainstem serotonergic and noradrenergic neurons is among the most dense in the spinal cord [289-292]. Finally, rhabdosphincter motor neurons also receive input from the “L region” of the pons that might be important for maintaining continence, since a lesion in this area produced continuous incontinence in a cat [293].

1. **Relative Contribution from Levator Ani Nerve, Pudendal Nerve, and Hypogastric Nerve in Continence Mechanisms During Sneezing in Rats and Cats**

Analysis of the urethral closure mechanisms during sneeze-induced stress conditions in anesthetized female rats and cats has revealed that pressure increases in the middle portion of the urethra are mediated by reflex contractions of the rhabdosphincter as well as the pelvic floor muscles [294, 295]. Transection of the pudendal nerves reduced sneeze-induced urethral reflex responses by 67% and transecting the nerves to the ilioococygeus and pubococcygeus muscles reduced urethral reflex responses by an additional 25%.

Transecting the hypogastric nerves and visceral branches of the pelvic nerves did not affect the urethral reflexes indicating that sneeze-evoked urethral reflexes in normal rats were not mediated by these autonomic pathways. However, hypogastric nerve transection in conscious, chronic spinal cord injured, female rats reduced urethral baseline pressure, reduced postvoid residual urine volumes, reduced maximal voiding pressure, and increased voiding efficiency. This indicates that sympathetic pathways to the bladder neck and proximal urethra contribute to urethral pressure and functional outlet obstruction and voiding dysfunction after spinal cord injury in unanesthetized animals [296].

2. **Neurochemical Anatomy of Urethral Rhabdosphincter Motor Neurons**

In addition to their unique morphology, neurophysiology, and supraspinal inputs, rhabdosphincter motor neurons in Onuf’s nucleus also exhibit a plethora of unique and highly diverse neurotransmitter inputs, receptors, ion channels, and growth factors (Table 3). While many of the markers listed in Table 3 are likely involved in rhabdosphincter control, it is dangerous to assume a role in rhabdosphincter control based strictly on anatomical association with Onuf’s nucleus, since some motor neurons in Onuf’s nucleus innervate the ischiocavernous and bulbospongiosus muscles and thus may be involved in control of sexual function. The following section will offer some guidance regarding which transmitter and receptor systems are involved in control of rhabdosphincter function.

### 5. Pharmacology of Urethral and Anal Rhabdosphincters

The excitatory amino acid neurotransmitter, glutamate, mediates initiation of action potentials in rhabdosphincter motor neurons (and subsequent rapid contraction of the muscle) by binding to NMDA and AMPA receptors. Both spinal reflex activation and supraspinal activation of the rhabdosphincter are sensitive to NMDA and AMPA receptor antagonists [297-299]. Thus it is useful to think of these transmitters as part of the “hardwired” reflex circuitry that is involved in all or none activation of consistent and reliable storage reflexes, as compared to monoamines and peptide transmitters (see below), that play a role as modulators of the reflexes, increasing or decreasing the gain of the reflexes transmitted by the excitatory amino acids.

The inhibitory amino acids glycine, acting through strychnine-sensitive ionotropic receptors [279, 300], and GABA, acting through both GABA-A (ionotropic) and GABA-B receptors (metabotropic) [257, 301, 302] are thought to be major inhibitory transmitters regulating rhabdosphincter activity. Clinical studies have indicated that systemic [303] and intrathecal [304, 305] administration of the GABA-B agonist, baclofen, may reduce bladder-sphincter dyssynergia in some neurogenic bladder patients. However, because of the ubiquity of glycine and GABA in mediating inhibition of multiple systems, pharmacological studies linking either of these transmitters (or any other inhibitory transmitter) to the inhibition of rhabdosphincter activity during voiding are not definitive.

In addition to amino acid transmitters, the monoamine transmitters (serotonin and norepinephrine) are also important in modulating rhabdosphincter motor neuron activity [306]. It was the preferential association of norepinephrine and serotonin terminals [289-292] that led to extensive studies of noradrenergic and serotonergic control of rhabdosphincter function and eventual clinical studies of duloxetine, a norepinephrine and serotonin reuptake inhibitor, as a treatment for stress urinary incontinence [270, 307-311]. Elegant studies in humans using magnetic stimulation of brain and sacral nerve roots [312] have indicated that duloxetine increases the excitability of rhabdosphincter
motor neurons to both supraspinal and segmental inputs and to double urethral pressure responses to sacral nerve root magnetic stimulation. Importantly, duloxetine’s ability to increase urethral rhabdosphincter activity did not interfere with the inhibition of sphincter activity during voiding (i.e. bladder-sphincter synergy was well-maintained). Similar clinical results have been seen with S,S-reboxetine, a selective norepinephrine reuptake inhibitor [313, 314]. This approach of increasing synaptic levels of serotonin and/or norepinephrine is logical since, it has been shown that noradrenergic and serotonergic terminals associated with rhabdosphincter motor neurons show an age-dependent decrease in density in rats [315] that might explain the increased incidence of stress incontinence with aging.

Multiple adrenergic receptor subtypes play a role in control of the rhabdosphincter, and the results with norepinephrine reuptake inhibitors indicate that these receptors can be activated by endogenous norepinephrine in anesthetized cats [272]. Strong evidence exists that α1 adrenoceptors excite rhabdosphincter motor neurons [272, 316, 317]. Patch clamp studies [318] have shown a direct depolarizing effect of norepinephrine on rhabdosphincter motor neurons (Figure 14D) that can be blocked by the α1 adrenoceptor antagonist, prazosin. Similar conclusions regarding the excitatory effects of α1 adrenoceptors on rhabdosphincter neurons have been reached in clinical studies [317] where decreases in rhabdosphincter activity were seen after administration of prazosin to human subjects. On the other hand, strong evidence exists that α2 adrenoceptor stimulation has the opposite effect, i.e. inhibition, of rhabdosphincter activity [272, 319]. Importantly, the innervation of the urethral and anal smooth muscle (i.e. the hypogastric nerve) shows similar adrenergic pharmacology - an enhancement of activity by α1 adrenoceptors [272, 316, 320] and inhibition of activity by α2 adrenoceptors [272, 316, 321].

Multiple subtypes of serotonin (5-hydroxytryptamine, 5-HT) receptors are also involved in modulating rhabdosphincter motor neuron excitability. Strong evidence exists that 5-HT2 receptors can excite sphincter motor neurons [274]. Indeed duloxetine’s facilitatory effects on rhabdosphincter activity in anesthetized cats are mediated in part through activation of 5-HT2 receptors [270]. Both 5-HT2A and 5-HT2C receptor agonists increase rhabdosphincter EMG activity in dogs, guinea pigs, and rats [322, 323]. Recent in vitro rat spinal cord slice patch clamp studies show that part of this effect may be directly on rhabdosphincter motor neurons, as opposed to interneurons [318], since 5-HT induces a direct depolarization of rhabdosphincter motor neurons (Figure 14E). Interestingly, substance P, a peptide transmitter that is co-localized with 5-HT in raphe spinal nerve terminals, also produces direct depolarization of rhabdosphincter motor neurons in rat spinal cord slices [324], and thyrotropin releasing hormone (TRH), another peptide transmitter co-localized with 5-HT in nerve terminals, induces excitation of rat sphincter activity [325, 326] in vivo.

A peculiar finding regarding 5-HT2 receptor-induced activity of pelvic nerve-evoked rhabdosphincter reflexes in chloralose-anesthetized cats is that the effect is highly reproducible when the spinal cord is isolated (i.e. acute T11 transection), but it is highly variable and statistically insignificant when the spinal cord is intact [274]. This suggests that supraspinal 5-HT2 receptors have an opposing, inhibitory, effect that counteracts their spinal, excitatory, effect. Whether this phenomenon is an artifact of anesthesia and/or is specific to cats is important to determine.

Immunohistochemical and molecular studies in humans and dogs [322] have shown that 5-HT2A, 5-HT2B, and 5-HT2C receptor subtypes are associated with Onuf’s nucleus motor neurons. In addition, 5-HT2C receptor mRNA has been localized to anal sphincter motor neurons in the rat [327]. On the other hand, another immunohistochemistry study with retrograde labeling of urethral rhabdosphincter motor neurons and ischiocavernous motor neurons in rats indicates that the 5-HT5A receptor is associated with the former, while the 5-HT2A receptor is preferentially associated with the latter [328].

As described in the previous section on the SUSNRC, supraspinal 5-HT1A receptor stimulation enhances rhabdosphincter activity in cats [275, 281-283]. Importantly, the excitatory effects of 5-HT1A receptor agonists on the rhabdosphincter can still be “over ridden” by inhibitory mechanisms during voiding, i.e. bladder-sphincter synergy remains despite 8-OH- DPAT-induced enhancement of rhabdosphincter activity [275, 281-283].

The effect of 5-HT1A receptors on rhabdosphincter activity in rats is more complicated. Firstly, rats do not show an inhibition of rhabdosphincter activity during voiding like cats and humans but, instead, show a high frequency bursting (or “phasic firing”) of rhabdosphincter EMG activity during micturition [329]. This bursting is actually necessary for efficient voiding in rats presumably by creating a “pumping” action through the urethra. When the spinal cord is transected, this bursting disappears and rats present with urinary retention. Although the bursting is not seen in anesthetized spinal rats at any time [329], in conscious spinal rats, the rhabdosphincter EMG bursting gradually returns in some animals across a period of 6 weeks [330]. Interestingly, 5-HT1A receptor stimulation can unmask the bursting rhabdosphincter EMG activity in the anesthetized spinal rat [282, 331]. Chang et al [331] further showed that the center responsible for bursting activity in spinal rats was located between the T11 and L4 spinal segments. In
Figure 14: Monoaminergic modulation of sphincter motor neurons recorded using patch clamp electrophysiology. A-C) Visual identification of rat urethral sphincter motor neurons. A. Retrograde labeling of dorsolateral nucleus (DLN) motor neurons was accomplished by fluorescent dye injections into the urethral sphincter (adult), or the ischiorectal fossa (neonate). Dye was transported through the motor branch of the pudendal nerve to the lumbar spinal cord. B. Composite fluorescence and low-light image showing DiI-labeled DLN neurons in the ventral horn of an adult rat lumbar spinal cord section. The dotted line denotes the grey/white matter boundary, and the dorsal surface is oriented toward the top of the page. C. Enlarged neurons from B with a patch-clamp electrode schematic to demonstrate electrophysiological recordings from DLN neurons. Calibration bars are 80 µm (B) and 20 µm (C). D-E) Either norepinephrine (NE) or serotonin (5-HT) was bath applied to rat lumbar spinal cord slices containing DiI-labeled dorsolateral nucleus neurons. D. NE (1 µM) produced a reversible depolarization and action potential firing. E. 5-HT (10 µM) also produced a reversible depolarization and action potential firing (from Burgard, 2008).
the studies of Gu et al [282], 5-HT1A receptor stimulation had no influence on the asynchronous rhabdosphincter activity that precedes, and follows, micturition-associated bursting, it only re-organized the activity into the bursting or phasic characteristics that accompany micturition.

Another aspect of 5-HT1A receptor function in rats can be seen from studies of pelvic nerve-to-rhabdosphincter reflex potentiation. Early studies showed that this reflex can be potentiated by prolonged, low frequency electrical stimulation of the pelvic nerve and by bladder distention [332-334]. Subsequent studies showed that the potentiation involved a 5-HT1A receptor-based link [335].

An interesting and possibly important comparison between drug effects on rhabdosphincter activity in cats and rats is also shown with κ2 opioid receptors. In cats, the κ opioid receptor agonist, ethylketocyclazocine, selectively inhibits spinal rhabdosphincter reflexes [234]. In rats, it was found that a κ2 opioid receptor agonist inhibits the rhabdosphincter bursting pattern associated with micturition, leading to decreased voiding efficiency [336]. In these studies, κ opioid receptor stimulation had no influence on the asynchronous rhabdosphincter activity that precedes and follows micturition-associated bursting.

Thus there may be parallels between excitation of rhabdosphincter reflexes in cats with enhancement of rhabdosphincter bursting activity in rats on one hand (5-HT1A receptor-mediated), and inhibition of rhabdosphincter motor neurons in cats and suppression of bursting activity in rats on the other hand (κ opioid receptor-mediated). The fact that asynchronous rhabdosphincter activity in rat was not affected by either 5-HT1A or κ opioid receptor stimulation highlights differences in the organization of the asynchronous (spinal) and micturition associated-bursting (supraspinal) reflex control in rats.

Another possible parallel for exploration of rhabdosphincter function in rats might lie in comparing the above spinal micturition-associated rhabdosphincter bursting center with the spinal ejaculation center in rats: both centers are located in the mid-lumbar spinal cord [331, 337, 338], both centers exhibit “bursting” [329, 339]; 5-HT1A receptor agonists can facilitate both activities [340-342], κ opioid receptor agonists inhibit both activities [336, 343]. Of course it must be appreciated that differences between the two “bursting centers” exist (i.e. the former activates rhabdosphincter motor neurons while the latter activates bulbospongious motor neurons, the former has a period of 6 Hz while the latter has a period of 0.5 Hz).

Future Pelvic Floor Research Needs

The controversy regarding a contribution of the pudendal nerve to the innervation of the levator ani muscles should be addressed. As a first step, agreements regarding nomenclature should be established in regards to which muscles actually comprise the levator ani (i.e. should the definition include only the pubococcygeus, iliococcygeus, and coccygeus muscles or should it include the puborectalis, urethralis, urethrovaginal sphincter, the compressor urethrae; etc.). Careful characterization of these various muscles based on physiological criteria such as embryological origin, skeletal sites of origin and insertion, compartmentalization imposed by connective tissue boundaries, myofiber phenotype, and sensory structures (e.g. Golgi tendon organs and muscle spindles) is likely to provide insight into which types of motor neurons (i.e. alpha, gamma, or “special somatic”) innervate each muscle and which nerve carries their motor axons. Resolving this controversy is important for a number of reasons: surgical guidance, understanding iatrogenic pathologies, and understanding physiological and pharmacological control of the individual muscles.

A second important area regards the reflex control of the levator ani muscles and viscerosomatic interactions between pelvic floor muscles and pelvic viscera. While visceral and somatic reflex control of the rhabdosphincters has been extensively studied, studies of levator ani muscle reflexes are few. Understanding whether there are spinal reflex connections between, for example, bladder afferent fibers and levator ani motor neurons would further our understanding of contience control. Similarly, understanding anatomical connections between rhabdosphincter and levator ani muscles are important. Determining whether the cholera toxin B-labeled processes of levator ani motor neurons located in Onuf's nucleus (Figure 11 D-E) are dendrites or axonal collaterals may provide important insight into understanding physiological coordination between the pelvic floor and rhabdosphincters. Finally, understanding the role of levator ani primary afferent fibers in controlling lower urinary tract and bowel function might explain indirect bladder symptoms that might be induced by pelvic floor injury or suspension surgeries, as well as physiological controls of levator ani muscles over excretory function and vice-versa. The abundant small diameter peptidergic afferent fibers innervating pelvic floor muscle might also play a role in the etiology of chronic pelvic pain syndrome or interstitial cystitis; two conditions for which a frank pathological cause has not been determined.

A third important area for study is the relative importance of bladder afferent fibers versus urethral / bladder neck afferent fibers in eliciting the “guarding” or “continence” reflex. This is important since there are phenotypic differences between these two groups of afferent neurons in regards to neurotransmitter and ion channel phenotypes [344] that might be exploited to independently control urine storage and voiding dysfunction.
IV. EFFERENT PATHWAYS TO THE BLADDER

The motor arm of the lower urinary tract drives bladder contraction during voiding and the outlet contraction required for urine storage. In this section, spinal and peripheral elements contributing to the motor activity of the bladder is described, while the equivalent structures for the bladder outlet are discussed in section III.

1. PREGANGLIONIC NEURONS

Parasympathetic preganglionic neurons are located in the lateral part of the sacral intermediolateral gray matter in a region termed the sacral parasympathetic nucleus (SPN) and are small, fusiform-shaped cells which send dendrites into lateral lamina I of the dorsal horn, the lateral funiculus and medially into the dorsal grey commissure (DGC). Bladder pre-ganglionic motor neurons are located in the S1-S3 in the cat [361], dog [362] and monkey [363]. In cat these motor neurons are located ventrolaterally in the intermediolateral column, with cells innervating the colon lying dorsomedial. The guinea pig is similar; retrograde labelling following bladder wall injections reveals neurons bilaterally in the ventrolateral part of the intermediolateral column at S1 [256]. The rat is different, as preganglionic motor neurons are located at L6-S1 [364]; unilateral ventral root rhizotomy at the L5 level in the rat decreases peak cystometric pressures [365].

The parasympathetic preganglionic neurones project through the ventral spinal roots to the major pelvic ganglion [366-368], releasing the excitatory transmitter, acetylcholine. They are divided functionally into tonic and phasic types. In some species they also release opioid peptide transmitters and express nitric oxide synthase [369]; there is also evidence of involvement of pituitary adenylate cyclase activating peptide (PACAP), a peptide present in visceral afferent neurones, and of prostaglandins within the spinal cord [370]. The DGC also contains a group of interneurones, which are likely to be active during micturition [371, 372]. These DGC interneurones may influence the function of the parasympathetic preganglionic neurons [279, 371, 372].

At spinal levels L1–L2, both the intermediolateral horn and the DGC contain sympathetic preganglionic neurones whose axons project to the major pelvic ganglion. With ageing, there is selective attrition of preganglionic sympathetic neurones in L1–L2, which project to the pelvic ganglion, with reductions in the extent of the dendritic arbor of remaining cells [366, 367].

In man the preganglionic parasympathetic motor nerves to the bladder (and other pelvic organs, the rectum and descending colon) course through the pelvic nerves from the sacral anterior roots S2-S4. Stimulating these roots with implanted electrodes designed principally for bladder emptying in spinal cord injury [373] elicits two principal responses at S3; at low levels of stimulation, the external urethral sphincter, external anal sphincter and pelvic floor muscles are contracted. At high levels of stimulation, parasympathetic activation contracts the detrusor muscle, leading to efficient emptying of the bladder when the sphincter muscle relaxes [374]. Attempts to use extracorporeal magnetic stimulation to achieve the same effect [375] have shown insufficient power to activate the small parasympathetic neurons at the level of the lumbar-sacral roots [376].

2. GANGLIA

The peripheral ganglia convey the autonomic innervation to the lower urinary tract and reproductive organs, along with a substantial part of the extrinsic motor innervation of the lower bowel. There are substantial species differences in organization and neurochemistry of pelvic ganglion cells and their spinal inputs. Large mammals have a plexus of pelvic and intramural ganglia, containing both sympathetic and parasympathetic neurons. The guinea pig is intermediate in complexity, with separate posterior and anterior plexuses innervating different pelvic organs. In the rat and mouse, the pelvic plexus consists of the major pelvic ganglia (MPG) and a number of small accessory ganglia. In the rat there are two major pelvic ganglia and small accessory ganglia, with less cytological complexity and almost no intramural ganglia.

The preganglionic input releases acetylcholine, which acts on nicotinic receptors. Patients with megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMHIS) [377] have reduced or no alpha-3 nicotinic receptor subunit [378]. Selective gene knockout mice lacking the alpha-3 nicotinic receptor subunit alone or the beta-2 and beta-4 subunits in combination [379], develop severe bladder distension soon after birth, and later overflow incontinence. The detrusor muscle in these animals contracts in response to field stimulation or muscarinic agonists, but not nicotinic agonists [380], indicating the potential importance of alpha-3, beta-2, and beta-4 nicotinic receptor components in control of voiding, but not their functional location.

Within the pelvic plexus there is topographical representation of the pelvic organs. In the female dog, neurons supplying different pelvic organs are located in separate ganglia, which possess a distinctive composition of neurone types and different preganglionic supply [381]. Neurons retrogradely labelled from the urinary bladder mainly occur in ganglia located at the vesico-ureteric junction. They comprise catecholaminergic calbindin neurons and noncatecholaminergic neurons containing calbindin or NOS, with relatively sparse pericellular varicose nerve fibres.
In male mice [382], the major pelvic ganglia are close to the dorsal surface of the prostate gland. Their main inputs are the pelvic nerves, and the hypogastric nerve from the inferior mesenteric ganglion. The major outputs are the penile (cavernous) nerve and the supply to the urogenital organs. Tyrosine hydroxylase (TH) is expressed by one-third of neurons, almost all co-expressing dopamine beta hydroxylase (DBH). Numerous TH axons are present in the hypogastric nerve, but very few in the pelvic nerve, supporting a primarily sympathetic origin. Non-neuronal cells containing TH are also present, resembling small, intensely fluorescent (SIF) cells observed in many other autonomic ganglia [382]. Neurons immunostained for choline acetyl transferase (ChAT) have a complementary distribution to noradrenergic neurons. About half of the cholinergic ganglion cells contain VIP, distributed throughout most of the ganglion, with a cluster near the origin of the penile nerve [382]. Neurones with NPY are numerous and apparently randomly distributed throughout the ganglion, with marked variation between mouse strains. All noradrenergic neurons contain NPY, but many NPY neurons are not noradrenergic. Many of the cholinergic NPY neurons also contain VIP. ChAT is seen in varicose axon terminals closely associated with ganglion neurons. Neither NPY nor VIP are present in preganglionic terminals, except for a small number of individual neurones. The latter may arise from viscerofugal neurones in the myenteric plexus of the lower bowel [383].

Autonomic ganglia are also found in the vicinity of the bladder neck, trigone, proximal urethra and prostate. They receive noradrenergic and cholinergic excitatory innervation and non-cholinergic, non-noradrenergic inhibitory innervation [384]. Knowledge of this distribution allows strategic planning for surgical dissection (Figure 15). In ureteric reimplantation, several branches of the pelvic plexus travel to the ureterovesical junction and surround the distal ureter as a fine network in the human. The main neural elements are located 1.5 to 2 cm. dorsal and cranial to the bladder trigone, and dorsal and medial to the ureter in both female and male cadavers [385]. In the context of hysterectomy, cadaveric dissections show pelvic autonomic nerves are at greatest risk during sacrouterine dissection [386], corresponding with observed innervation density [387]. In addition pathophysiological processes such as ageing can influence the pelvic ganglia, for example the postganglionic sympathetic neurones in the major pelvic ganglion of rats [388, 389]. In the proximal female urethra, virtually all of the NOS immunoreactive cells also contain the carbon monoxide-synthesising enzyme, haem-oxygenase- (HO-) 2, but of the HO-2 positive cells, 25% did not show NOS immunoreactivity [390].

The bladder wall itself contains intramural ganglia, and small clusters of autonomic ganglion cells are present in the adventitial connective tissue and among the detrusor muscle bundles. There is species variation in the extent of intramural innervation of the bladder; ganglia are present in many species such as the guinea pig [383], while the rat bladder contains the post-synaptic innervation alone [391]. The ganglia are found throughout the bladder wall and vary considerably in size [91, 392]. They show immunoreactivity to vasoactive intestinal polypeptide (VIP), nitric oxide synthase (NOS), neuropeptide Y (NPY) and galanin (Gal) in varying amounts. However, they do not contain enkephalin (ENK), substance P (SP), calcitonin gene-related peptide (CGRP) or soma-
tostatin (Som) [90], suggesting that cell bodies of sensory neurones are not located in the intramural ganglia. Postganglionic sympathetic nerves, identified with antibodies to TH and NPY, also synapse on these neurones. Nicotinic receptors have been identified on intramural nerve cell bodies within the bladder [380]. α1-adrenergic facilitatory receptors in bladder parasympathetic ganglia (393).

The endothelins (ET-1, ET-2 and ET-3) mediate various biological effects through two receptor subtypes ET-A and ET-B. Electrostimulation of the sacral roots responsible for bladder contraction in the pig leads to detrusor activation with consecutive rise in bladder pressure, which can be partly inhibited by an ET-A receptor antagonist, probably by influencing the atropine-resistant component of efferent detrusor contractions of detrusor muscle strips [394]. Both ET receptors are widely distributed in the urinary tract. ET-1 modulates bladder function [395], eliciting potent and long-lasting contractions. It is synthesized locally and may be a paracrine mediator of detrusor contraction [397]. The predominant receptor sub-type in the bladder dome is ET-A [398].

3. TERMINAL NERVE FIBRES

The majority of nerves running in the detrusor stain positively for acetylcholinesterase and for vesicular acetylcholine transferase (VACHt) [392, 399] and are thought to be parasympathetic. Putative postganglionic sympathetic fibres immunoreactive for TH or NPY are rare in the detrusor, although they are moderately frequent in the suburothelium [92]. Nonetheless, presynaptic α1-adrenergic facilitatory receptors are present on efferent parasympathetic nerve terminals in the bladder wall [400, 401]. The parasympathetic efferents release acetylcholine to stimulate muscarinic receptors. However, the presence of additional substances allows immunohistochemical subclassification of nerve fibres, and raises the question as to whether additional transmitters other than ACh have a role in normal micturition function or disease pathophysiology. Many nerve fibres contain NPY and VIP, while some contain NOS or Gal. In the human bladder, markers for sensory nerves (SP, CGRP and neurokinin A) occur infrequently in nerves running in the detrusor, in contrast to the suburothelial layer [90-93]. In the mouse bladder, noradrenergic axons form a sparse supply in the trigone muscle, are quite rare in the detrusor muscle and are absent from the mucosa [382]. Cholinergic axons are prevalent in muscle and mucosa, with similar relative prevalence of co-localised peptides in the two regions. In the muscle of the trigone, the most common axons also contain both VIP and NPY. In the detrusor muscle, the most common axon type varied for the two strains studied. Noradrenergic / NPY axons provide a dense supply to blood vessels, in common with the other pelvic organs. Many vessels also have a sparse supply of VIP axons [382]. Cholinergic nerves are also present in the suburothelium; most of them in addition contain NPY and some contain NOS [92].

Smooth muscle cells in the bladder are grouped into fascicles, several of which make up a muscle bundle. They receive a dense innervation, which runs in line with the axis of the fascicle and is derived from coarse nerve trunks in the connective tissue around the fascicles and bundles. This innervation mediates the widespread co-ordinated detrusor contraction accompanying voiding. The anatomical relationship between the preterminal innervation and the muscle fascicles has been described in a serial sectioning study in the human bladder [402]. The nerve supply is distributed by a series of dichotomous branchings, illustrated schematically in Figure 16. Adjacent to the muscle bundles, 1 or 2 primary nerve trunks run parallel to the long axis of the bundle. These give rise to circumferential peribundle branches. Both the longitudinal and circumferential trunks give off transverse interfascicular branches, entering the bundle perpendicular to its long axis, approximately at the midpoint of the bundle. Within the bundle they give axial interfascicular branches running along the long axis within and closely adjacent to individual fascicles, ending in the preterminal and terminal varicose intrafascicular axial innervation.

4. DESCENDING AND SPINAL SEGMENTAL INFLUENCES ON SPINAL AUTONOMIC CENTRES

In the spinal cord, several transmitters mediate the effects of modulatory pathways that influence the onward progression of efferent activity from the SPN. Ascending and descending connections contribute to micturition reflex control, in many cases involving excitatory and inhibitory spinal interneurones between sacral and lumbar spinal segments. In a rat model of neurogenic bladder dysfunction (autoimmune encephalomyelitis), an exaggerated descending excitatory control arises at the spinal segmental level, which gives rise to detrusor overactivity [403].

Some animals with autoimmune encephalomyelitis develop detrusor areflexia rather than overactivity; in these animals, the excitatory control is probably dominated by segmental inhibition, mediated primarily by glycine receptor activation. Spinal shock in rats induces an alteration of glycine/glutamate concentration ratio [404]. A change in the ratio of excitation and inhibition was also observed in humans suffering from spasticity and pain [405]. Ageing affects many synaptic inputs [368]. This balance of inputs, and the potential plasticity of neuronal circuits, is crucial in understanding pathophysiological processes; following injury to spinal roots, plasticity can create new reflex circuits, including a somatic–CNS–bladder reflex, whereby scratching the skin in specific dermatomes may elicit bladder contractions [406-408].
Glutamate  Glutamate is present in the terminals of primary afferent neurons in the spinal cord along with interneurons and fibres originating in the medulla oblongata. In general, glutamatergic neurons tend to be excitatory, contrasting with generally inhibitory effects of glycinergic neurons; however, excitatory/inhibitory effects of transmitters can be reversed by the nature of the post-synaptic neuron. Thus, glutamatergic neurons can indirectly have an inhibitory effect if an inhibitory neuron is interposed before the ultimate target [409]. With ageing, there is a decrease in the density of glutamatergic synaptic inputs, which may influence urinary tract function [368]. Glutamate acts on spinal neurons through a variety of receptor subtypes. These include NMDA receptors, which are important in controlling polysynaptic reflex pathways at the lumbosacral levels. The NMDAR1 glutamatergic receptor sub-unit is present in the spinal cord of male rats, and is expressed in the SPN. Glutamate is present in the dorsal root ganglion cells supplying the bladder [410], and the NMDAR1 sub-unit is also present in L6 dorsal root ganglion cells of the rat [411]. In female rats, intrathecal injection of an NMDA receptor antagonist decreases bladder contraction pressure [412]. NMDAR1 receptors may be activated by glutamate released by afferents from peripheral and supraspinal origins to elicit bladder contractions [413].

Glycine/ gamma amine butyric acid  Glycinergic and GABAAergic interneurones have a major role in neural control processes mediating LUT function [414]. Glycinergic/GABAAergic projections to the lumbosacral cord inhibit the micturition reflex and also inhibit glutamatergic neurons [404]. Rectal distention prolongs the interval, decreases the amplitude and shortens the duration of bladder contractions in rats; this effect is not seen after simultaneous intrathecal injection of low dose strychnine (a selective glycine-receptor antagonist) and bicuculline (GABA-A receptor antagonist), suggesting that the inhibitory rectovesical reflex involves glycinerigic and GABAergic mechanisms in the lumbosacral spinal cord, which may be synergistic [415].

Serotonin  Spinal reflex circuits involved in voiding function have a dense serotonergic innervation [416] (Figure 17). Immunocytochemical studies in rats, cats and primates show that lumbo-sacral sympathetic and parasympathetic autonomic nuclei receive serotonergic inputs from the raphe nuclei [291, 292, 417, 418]. Activation of the central serotonergic system can suppress voiding by inhibiting the parasympathetic excitatory input to the urinary bladder, and 5-HT elicits a prolonged activation of thoracic sympathetic preganglionic neurons. Stimulation of the raphe nuclei in the cat inhibits reflex bladder activity [419-421].

---

**Figure 16:** Top panel: Diagram of the pelvic autonomic nerves in radical hysterectomy. Transverse section through the pelvis showing the bladder, cervix and rectum. Left side represents the conventional technique, right side represents the nerve sparing technique. Scale bar 250 μm. A, Vesicouterine ligament, conventional; B, vesicouterine ligament, nerve sparing; C, Sacrouterine ligament, conventional; D, Sacrouterine ligament, nerve sparing. Lower panel: Diagram of the pelvic autonomic nerves in radical hysterectomy. Frontal sections through the uterus and cardinal ligament. LA, uterine artery, UV, uterine vein, SN, splanchnic nerves, HN, hypogastric nerve. Left side represents the conventional technique, right side represents the nerve sparing technique. Scale bar 250 μm. A, Posterior cardinal ligament, conventional; B, posterior cardinal ligament, nerve sparing. From Maas C.P., et al. 2005
HT₁A and 5-HT₂ receptors are present in the SPN. However, in different species serotonin (5-hydroxy tryptamine, 5-HT) may have varying functions in the central nervous control of bladder activity [416]. For example, activation of 5-HT₁A receptors mediates inhibitory effects on 1, parasympathetic preganglionic neurons (PGN), 2, spinal interneurons (INT) that provide an inhibitory input to sphincter multineurons (MN) and 3, raphe neurons in the brain stem. The transmitter released by inhibitory interneurons has not been identified. Activation of 5-HT₁A and 5-HT₃ receptors also inhibits afferent input passing from the bladder to the brain. Blockade of 5-HT₁A autoreceptors in raphe neurons would increase raphe neuron firing and enhance serotonergic control of spinal reflex mechanisms. This effect would promote urine storage by enhancing sphincter activity and depressing bladder activity. From de Groat W.C., 2002.

Adrenergic

Descending catecholaminergic neurones are primarily located in the upper medulla or pons [315] (Figure 18). In clinical use, non-selective α₁-adrenergic antagonists influence urine flow and storage phase lower urinary tract symptoms; the two effects probably occur by different mechanisms, and both central or peripheral locations may be responsible [400]. Reflex bladder activity is modulated by at least two spinal α₁-adrenergic mechanisms.

Firstly, there is inhibitory control of reflex bladder contractions, probably by modulation of afferent processing. Secondly, there is excitatory modulation of the amplitude of bladder contractions due to regulation of the descending glutamatergic limb of the spinobulbospinal bladder reflex pathway [427, 428]. α₁A- adrenoceptors comprise 70% and α₁B-adrenoceptors comprise 30% of the α₁-adrenergic receptors in the rat lumbar spinal cord [429], while α₁D-adrenoceptors do not appear to have a significant role [428].

Substance P

Substance P-containing terminals are closely apposed to both sympathetic and parasympathetic preganglionic neurones projecting to the major pelvic ganglion [430]. Substance P-containing afferents in the pelvic nerve terminate in the outer laminae of the dorsal horn and in the region of the SPN and DGC [364, 431]. Substance P is also located in intraspinal neurones located in the dorsal horn [432] or DGC [433]. In young adult rats, substance P in the ventral horn is almost exclusively co-localized with serotonin and derived from descending axons of medullary neurones [430, 434, 435].

Notably, substance P is often co-localized with 5-HT in axon terminals in the lumbosacral spinal cord [436]. Functionally, substance P affects micturition reflex activity [437]; intrathecal administration of Substance P at spinal levels L₅–S₁ induces bladder contraction [438]. Substance P also increases the firing rate of sympathetic preganglionic neurones [439]. Studies in the rat show that substance P levels decline with ageing in both the dorsal and ventral regions of the lumbosacral cord [440, 441]. Substance P-immunoreactive innervation of the dorsolateral nucleus (supplying the EUS) is not obviously altered with ageing [442].
5. NEURAL TRAFFIC

Low frequency (10 Hz) stimulation of the pudendal nerve elicits a continence-like response, by decreasing parasympathetic outflow in the pelvic nerve and increasing sympathetic outflow in the hypogastric nerve, thus inhibiting the bladder and activating the external urethral sphincter. Stimulation of both genital and anal sensory branches in the pudendal nerve results in bladder inhibition. If low frequency stimulation is applied during a bladder contraction the bladder pressure decreases and the activity of the external sphincter increases. When the pudendal nerve is stimulated at higher frequency in the cat (intact or after spinal transection), the response is fundamentally different [444]. Following spinal transection, pudendal nerve stimulation at 33 Hz elicits bladder contraction synergically with reduction in external urinary sphincter activity, provided the bladder contains more than a threshold volume. Indeed, efficient post stimulus voiding can be induced by intermittent high frequency pudendal nerve stimulation [425]. Such activity may be influenced by various peripheral receptors, exemplified by menthol (TRPM8) [445].

6. PELVIC ORGAN INTERACTIONS AT THE EFFERENT NEURAL LEVEL

a) Bladder and Outlet

Neural coordination of physiological and behavioral functions depends on convergence within the nervous system of information from relevant areas, and convergence could result in collateral effects of pathology in one organ affecting function elsewhere. There is extensive convergence of pelvic organ input [446, 447] at the levels of the spinal cord, dorsal column nuclei, solitary nucleus, medullary reticular formation, and thalamus [448]. Convergent processing underpins the coherent functioning of systems controlled by efferent outflows diverging from a common starting point, as exemplified by the synergic co-ordination of bladder and urethra required for normal voiding. The fundamental role of supraspinal mechanisms in lower urinary tract synergy is well recognized. However, synergic lower urinary tract function may also be a feature of the peripheral innervation, independent of CNS co-ordination. In the female minipig, pre-ganglionic pelvic nerve stimulation evokes a pressure increase in the bladder and a pressure decrease in the urethra [449]. It remains to be determined whether this observation reflects coherent activation of separate motorneurones (excitatory to the bladder, inhibitory to the outlet), or whether postganglionic motorneurones send branches which supply both bladder and urethra. In the latter arrangement, release of different neuromuscular transmitters from branches of the same motoneurone, or interposition of an additional intermediary cell would be required. The former is circumstantially supported by the observed co-localization of acetylcholine- and nitric oxide-related enzymes [450].

b) Bladder and Bowel / Uterus

Clinicians are familiar with the detrimental effect of bowel disorders on lower urinary tract activity. Physiologically, the efferent limb of the micturition reflex is inhibited by afferent input from the rectum [451]; thus, rectal distention inhibits bladder activity via glycinergic and GABAergic mechanisms in rats [415]. Dual labeling studies show that many neurones in Barrington’s nucleus supply both colon and bladder, with smaller populations supplying the two organs separately (Figure 19; 20). At the level of the major pelvic ganglion, double-labeled cells are relatively infrequent, but processes of colonic-retrograde-labeled cells often surround cell bodies of equivalent cells for the bladder. Dual-labeled cells in the spinal cord are rare [452].

The pelvic organs are supplied by sensory and autonomic fibers in the hypogastric nerve [453]. Inflammation of the uterine horn or colon gives rise to inflammation in the bladder, an effect that can be eliminated by sectioning the hypogastric nerve [454]. Bladder overactivity induced by inflammation is
Figure 19: A, Fluorescent micrographs of sections at the level of (A1) the major pelvic ganglion, (A2, B1, B2 and C1) the lumbosacral spinal cord and (C2) Barrington’s nucleus of rats injected with PRV-Beta-GAL in the bladder and PRV-GFP in the colon and having different survival times. The viscera, tracer and survival time are indicated in each photomicrograph. BD, bladder. CO, colon. A1. Separate labeling from both viruses is apparent in the MPG at 48 hours. A2. In the same case, only occasional cells are labeled in the spinal cord. B1. Substantial labeling from both organs is visible in the preganglionic parasympathetic column of the spinal cord and most cells are singly labeled from either the colon or the bladder. The arrow points to a rare double-labelled neuron. B2. Bladder- and colon-related neurons in close proximity. Processes from the colon-related neuron (arrow heads) are apposed to the bladder-related neuron. C1. Increasing survival time results in greater number of double-labelled cells (arrows). In most double labeled cells PRV-Beta-GAL label from the bladder is surrounded by PRV-GFP label from the colon. C2. Section from Barrington’s nucleus from the same case as C1 indicating that only a few cells are transsynaptically labeled from the bladder and none from the colon at the survival time. Arrow heads point to the surface of the fourth ventricle and stars indicate the location of trigeminal mesencephalic neurons. Calibration bars: 50 µm A1 and A2, 30 µm B2 and C1, 50 µm B2, 50 µm C2. From Rouzade-Dominguez, M., et al. 2003.

Figure 20: Fluorescent photomicrograph of 30 µm thick coronal sections through dorsal pons, proceeding caudal to rostral. A, Sections from rats injected with PRV in the distal colon. B, Rats injected with PRV in bladder. PRV-labelled neurons are green and TH immuno-labelled neurons are red. The arrows in A2 point to double-labelled neurons, which appear yellow. The arrows in B2 point to bladder-related neurons near the ventricular surface. Dorsal is at the top, medial is to the right. BD, bladder. CO, colon. Arrowheads show the ventricular surface. Calibration bar 60 µm. From Rouzade-Dominguez, M., et al. 2003.
influenced by estradiol, probably mediated through effects on the sympathetic nervous control of the bladder [455]. There are several potential mechanisms by which neural input could contribute to emergence of inflammation in neighbouring organs [454] (Figure 21):

1. Axon reflexes occurring in hypogastric sensory nerves that branch to supply more than one pelvic organ. Though such branching has not yet been specifically identified, a small proportion of single afferent fibres may branch to supply the colon and bladder [456].

2. A dorsal root reflex; hypogastric afferents from the inflamed organ could, via a spinal interneuron, sensitize and antidromically activate other hypogastric afferents from an uninfamed organ, exemplified by sensitization of a population of spinal neurons responding only to bladder input with chronic colonic inflammation [457].

3. Input from the inflamed organ (via the hypogastric nerve) activates neurons in the dorsal horn that activate postganglionic neurons in the pelvic ganglion via thoracolumbar preganglionic neurons.

4. A spinal mechanism could be mediated by intraspinal connections to lumbar sacral preganglionic neurons (as seen for gynaecological organs [458]).

5. A suprasacral mechanism could be mediated through the brain stem [452, 459, 460].

7. EFFERENT INHIBITION

The possibility of bladder inhibition by the CNS can be inferred from various experimental observations [461]. The sympathetic nervous system mediates inhibition of ganglionic transmission to the bladder. Isolated whole bladders manifest spontaneous contractile activity [118, 461-465], suggesting the possibility of active neural inhibition of the bladder during urine storage. In the decentralised bladder, following transection of sympathetic input, addition of the ganglion blocking agent hexamethonium leads to an increase in spontaneous bladder activity, likewise suggesting that a peripheral reflex inhibits the bladder during urine storage [461]. Rat brainstem/spinal cord/bladder preparations or neonatal spinal cord/bladder preparations show tonic inhibition, arising at L6-S1 and involving a peripheral ganglionic synapse [465-467]. Clearly, efferent inhibition of the bladder will facilitate urine storage.

In the neonatal rat, considerable activity arises in the bladder wall when inputs from the lumbar sacral spinal cord are disrupted [465]. Selective spinal cord and root lesions indicate that intrinsic bladder activity of the neonatal rat is tonically inhibited by parasympathetic efferent outflow [465]. This path is additional to the predominant cholinergic preganglionic efferents mediating the main voiding reflexes. The functional difference in the two sets of cholinergic ventral root efferents may result from differing synaptic targets, since both are blocked by the nicotinic antagonist hexamethonium [465]. Thus, inhibitory efferents must synapse with noncholinergic inhibitory neurons in the major pelvic ganglia, in contrast to excitatory efferents synapsing with the cholinergic detrusor innervation.

In addition to efferent input, local reflexes may contribute to the inhibition of detrusor activity, probably driven by interstitial cells [468], so that peripheral autonomous activity increases as a result of bladder distension [462, 469]. This has been proposed to signify the presence of a regional regulatory influence [470] and a peripheral “pacemaker” [471] and various mechanisms for the propagation of activity within the bladder wall [464]. In the clinical context, processes affecting peripheral innervation would then predispose to emergence of inappropriate detrusor activity during urine storage (through loss of inhibitory fibres), associated with inefficient bladder emptying (through loss of excitatory fibres).

8. PERIPHERAL EXCITATORY MECHANISMS

Agonist exposure appears to elicit contraction by two different mechanisms, comprising a component derived from direct stimulation of the muscle cell (‘classical’ efferent), and a separate component which is more phasic, responsible for the obvious pressure fluctuations. The latter ‘intrinsic’ mechanism may involve an intermediary cell type [472]. Optical imaging and calcium-/ voltage-sensitive dyes in whole rat bladder preparations have detected electrical activity moving in a co-ordinated manner from localized regions over the entire bladder [473, 474]. The isolated whole bladder shows regionalized responses when exposed to cholinergic/muscarinic agonists [463, 465, 472, 475, 476]. Dynamic migrating localities of contraction and elongation, give rise to a complex mix of micromotion phenomena, including micro-contractions, microstretches and propagating waves. Several species show differences in contractile activity according to the region of the bladder from which a muscle strip is taken. Different effects are seen according to stage of development- spontaneous activity is not apparent in bladder strips from neonatal rats [401], but subsequently emerges, so that at one month, high-frequency spontaneous contractions occur in conjunction with high-amplitude, low frequency contractions.

The likely functional significance of peripheral excitatory mechanisms is exemplified by the rodent neonate voiding reflex, which is induced by parental stimulation of the perineum, prior to establishment of mature control by the higher micturition centres [401, 465]. The physiological role of such activity in the adult is not known, but could include; 1. Optimization of the bladder wall configuration for volume contained,
Figure 21: Five compatible mechanisms by which hypogastric nerve fibres can contribute to the process of inflammatory induction between organs. A. Branching sensory afferents. B. Dorsal root reflex. C. Multisynaptic route involving sensory afferents from the inflamed organ to the T-13/L1 segment of the cord followed by output from preganglionic fibres in the T13/L1 segment to postganglionic in the pelvic ganglion that innervate the uninflamed organ. D. Multisynaptic route involving sensory afferents from the inflamed organ to the T13/L1 segment of the cord followed by output from preganglionic fibres in the L6-S2 segments to postganglionic fibres in the pelvic ganglion that innervate the uninflamed organ. E. Multisynaptic route involving sensory afferents from the inflamed organ to the T-13/L1 segment of the cord followed by output from preganglionic fibres in the L6-S2 segments to postganglionic fibres in the pelvic ganglion that innervate the uninflamed organ. In this case the multisynaptic route includes ascending connections from spinal cord to brain and descending connections from brain to L6-S2. From Winnard, K.P. et al. 2006.
to ensure efficient voiding regardless of volume [477].
2. Stimulation of ‘in series’ receptors for signaling bladder volume [476].
3. A mechanistic component of accommodation during filling, a counterintuitive suggestion supported by the observation that accommodation in the colon involves synchronous contraction and relaxation [478].
4. Servoassistance of voiding for maintenance of contraction [479].

The potential importance of peripheral functional structures may explain the recognition that nerve growth factor can contribute to overactive bladder problems [480].

V. MIDBRAIN-BRAINSTEM CONTROL OF BLADDER FUNCTION

With the direct role of both limbs of the autonomic nervous system in regulating filling and voiding of the bladder, the involvement of brainstem circuitry is paramount in normal bladder function. The brainstem is involved in reflexes controlling filling, storing and emptying of the bladder. Clinical cases of lesions within specific brainstem regions, most notably the pons, can result in either bladder continence or incontinence problems. This section will review the current understanding of brainstem neuronal networks that influence the parasympathetic and sympathetic motor outflows destined for the detrusor and smooth muscle of the urethral sphincter.

1. AFFERENT PATHWAYS TO THE BRAINSTEM

Sensations of bladder fullness are conveyed to the spinal cord by the pelvic and hypogastric nerves, while input from the bladder neck and urethra is carried in the pudendal and hypogastric nerves. Afferents arising from the bladder and urethra are mechanoreceptive (Aβ fibres) and nociceptive (C fibres). The most important afferents for initiating micturition are those passing in the pelvic nerves, whose fibres terminate in discrete regions of the lateral aspect of the dorsal horn of the lumbar and sacral spinal cord (see [481, 482, 483] for reviews). Many of these dorsal horn neurones make spinal connections that mediate segmentally organised reflex responses. However, a proportion of the spinal interneurones send ascending projections to the brain. These afferents are involved in transmitting sensory information to the cerebral cortex and can trigger micturition mediated by neural circuitry within the brainstem.

Ascending fibres from dorsal horn neurones receiving afferent input from the bladder terminate in the gracile nucleus and the central aspect of the periaqueductal grey (PAG; Figure 22); the latter has been described as a most dense spinal innervation [483, 484], perhaps emphasizing its essential role. The gracile nucleus relays information regarding nociception to the thalamus and cortex. Those PAG neurones receiving direct spinal inputs project to multiple sites including the pontine micturition centre (PMC) and the thalamus for onward relay to the cerebral cortex [483]. Although these data are based on animal species, the pivotal role of the PAG and PMC has been confirmed in man using positron emission tomography [485, 486] and functional magnetic imaging [487] with and without a full bladder (see Figure 23). Indeed, the PAG projections to the PMC originate from its lateral aspects [488]. Since the spinal projections relaying bladder distension target the central PAG there is the possibility of some integration prior to onward transmission to the PMC. This is likely to include integration of descending information from higher brain regions such as the limbic system and cerebral cortex [483], which provide contextual information concerning the appropriateness for micturition. Recently, the parabrachial nucleus appears activated during bladder contraction and may also receive afferent inputs directly from the spinal cord or via other central structures (Fig 23).

2. DEFINING BRAINSTEM CIRCUITRY REGULATING BLADDER FUNCTION

It is evident from recent reviews [481, 482] that most regions of the brainstem involved in controlling bladder function are known. However, as is evident in figure 4 of de Groat’s (2006) review, it remains unclear how these central nervous structure are connected up (see Figures 23 & 24). Are there, for example, brainstem pathways running in parallel and/or series that drive the preganglionic motoneurones? A method of revealing key brainstem regions regulating end organ function that has the ability to address this is transneuronal retrograde labelling using pseudorabies virus (PRV). Both the bladder wall and urethra of the rat have been injected with PRV. This has resulted in similar regions of the brainstem being labelled, which supports the close coordination of detrusor and urethral muscle function as suggested previously [481]. The brainstem regions labelled included Barrington’s nucleus (the pontine micturition centre), midline raphe (magnus and obscurus), locus coeruleus (A6), subcoeruleus, A5, reticularis gigantocellularis and nucleus paragigantocellularis [489, 490] but also in neonatal rats only the prepositus hypoglossal nucleus and lateral vestibular nucleus [489]. In addition, the PAG was labelled (Figure 22). Recent work has also indicated a role for the medial parabrachial nucleus (Figure 22). Whilst this provides information concerning the major players within the brainstem, the PRV technique does not imply precise information about connectivity. For example, are all these brainstem regions connected in parallel to the spinal interneurones and / or pre-ganglionic neurones or are some positioned in series? Are reciprocal connections between these nuclei present? Much of this information remains unknown but seems important if one is to understand the way in which the brain controls bladder storage and emptying and how one obtains reversible switching between these essential
Figure 22: Schematic representation of the described sensory and motor pathways regulating bladder function in animals. Of note are roles for gracile nuclei in transmitting afferent information from the spinal cord to the thalamus and cortex; the pontine storage centre activated during bladder filling, the lateral parabrachial nucleus (as a sensory integration centre) and the rostral ventromedial medulla as a centre important during voiding. For further details and all references see text.

Figure 23: Consistent with animal studies, regions of the human brain, imaged using positron emission tomography including aspects of the midbrain (periaqueductal gray, the dorsal mesencephalic reticular formation) and brainstem (dorsolateral pontine tegmentum-pontine micturition center and dorsolateral pontine reticular formation-pontine storage centre) are evident when the bladder is filled. (From Kavis et al., 2005).
functions. Most anatomical, electrophysiological and imaging studies to date have concentrated on the PMC as this appears pivotal regarding bladder function in both animals and man.

3. THE PONTINE MICTURITION CENTER (PMC)

In the rat, the PMC is just dorsomedial to A6 [293, 491] whereas in the cat it appears to be within A6 extending ventromedial into the mesencephalic tract of the trigeminal nerve [266]. It is these regions that are termed Barrington’s nucleus- a region named after Barrington, who in 1925 was the first to describe this pontine control centre for micturition in the cat (Figure 22). In man, comparable regions in the pons can be imaged and found activated when the bladder is full (see Figure 23; [486]).

a) Barrington’s nucleus: is it the master of ceremonies for bladder emptying

Based on the finding that its activation (electrical or chemical stimulation) in rats and cats relaxes urethral sphincters and initiates bladder contractions [293, 492, 493], it seems reasonable to propose a dominant role for the PMC in micturition. Moreover, lesions localised to this pontine region in animals abolish micturition and cause urine retention [293]. Similarly, a PMC lesion (on the right hand side) resulted in urinary retention in man [494]. Thus, the PMC would appear to play a major point of convergence of numerous pro- and anti micturition drivers. Thus, it may be a major integrating centre and, indeed, possible ‘command’ centre for initiating and orchestrating the act of bladder emptying.

b) How is the PMC connected up?

The inputs to, and outputs from, the PMC are considered below:

1. INPUTS: As described above, the lateral aspects of the PAG send information regarding the degree of bladder distension. These inputs are powerful and can trigger micturition as evidenced by the finding that chemical stimulation of ventrolateral PAG can cause voiding [488]. Recently, Kuipers et al. [495] have examined the afferent inputs to the PMC using conventional anterograde and retrograde tracing techniques. In addition to the PAG (ventrolateral and dorsomedial aspects) inputs arose from: ventromedial pontomesulcillary terminal field (Figure 22); medial preoptic area, posterior hypothalamus (perifornical region). It is unclear as to the exact function of the pontomesulcillary terminal field, although Holstege believes this is a diffuse input providing a ‘general level-setting’ of PMC neuronal activity [496]. This might be interpreted as a potential mechanism for establishing a neuronal set-point or threshold beyond which micturition occurs. The medial pre-optic region may well provide inhibition and this may be important during sleep and/or sexual activity to suppress micturition [266, 483, 497], although the previous work by Gjone demonstrated that micturition could be evoked following activation of this region [498], which is inconsistent with an exclusive inhibitory role. The posterior hypothalamic region is involved in fight or flight (defense response). Its connection to the PAG may account for the urination reported in conscious animals during a defense response, since regions of the PAG can also evoke the defense response [499] and, via PMC, could also initiate urination [500].

The study by Kuipers et al. [495] in the cat failed to confirm the numerous central nervous afferent inputs to the PMC described by Valentino et al. in the rat [501]; these included the Kolliker Fuse nucleus, raphe, nucleus tractus solitarius, parabrachial nucleus, nucleus paragigantocellularis and the cuneiform nucleus. Whether a species difference can explain this seems unlikely. Certainly the regions labelled by Valentino et al. [501] map more closely to data obtained using PRV injected into the bladder wall or urethra (see [489, 490, 502]) as described above. With this said, it is likely that many of the nuclei that project to the PMC also connect to each other but this needs confirming using localised injections of neuronal retrograde and anterograde tracers.

2. OUTPUTS: During micturition the PMC exerts simultaneous excitatory influences on parasympathetic outflows that cause bladder contraction and complete emptying but inhibition of sympathetic preganglionic to relax the urethral sphincter. It is, therefore, entirely appropriate that within the PMC there are bulbospinal neurones (Figure 24): PMC sends direct projections to parasympathetic preganglionic motoneurones innervating the bladder [503]. The latter authors provided ultrastructural evidence of asymmetric (excitatory) synaptic contacts on sacral parasympathetic preganglionic neurones originating from the PMC. Moreover, single neurones have been recorded extracellularly from Barrington’s nucleus in cats (i.e. medial to the mesencephalic tract of the trigeminal nerve) and found to have sparsely projecting axons based on antidromic invasion testing from the dorsolateral funiculus of the first sacral segment [504-506]. An involvement of glutamate as the main neurotransmitter in this pathway has been described [507]. Such a pathway would explain bladder contraction. Urethral relaxation requires an inhibition of somatic motoneurones and this appears to be mediated from PMC projections onto inhibitory interneurones located in the intermediolateral cell column at the sacral segmental level [278]. Both glycine and gamma amino butyric acid are thought to play a role here [279, 508].

c) On-switching micturition: a role for the PMC

With the PMC being essentially a pre-motor (parasympathetic/sympathetic) micturition nucleus, it should fulfil certain criteria if it is involved in the initiation
of bladder contraction and sphincter relaxation. For example, neurones should project to the spinal cord, fire ahead of a bladder contraction and fire continuously with each bladder contraction. Previous studies have found pontine units that fired in phase with bladder contraction [509, 510], but whether these connected to the spinal cord directly was not tested. However, subsequent single unit recordings by Sasaki [504, 505] and Sugaya et al. [506] provide convincing evidence that many PMC neurones do project to the spinal cord. Studies have shown that feline spinally projecting neurones (as demonstrated using the antidromic collision test) located in Barrington’s nucleus discharged in phase with bladder contractions (Figure 25). Many had firing patterns not different to those recorded from bladder afferents. But this is not always the case. Indeed, some of these units fired prior to the onset of bladder contraction consistent with a role in initiating bladder contractions (Figure 25). Whilst the proof of causality is always a difficult one, these neurones do make excellent candidates for driving/initiating bladder contraction. Indeed, many were also shown to be synaptically activated (orthodromically) following electrical stimulation of the spinal cord [506] raising the possibility of bladder afferent input, which may assist in providing positive-feedback and additional excitatory drive to both sustain and possibly amplify firing during micturition. The latter of course should be taken cautiously as it is not clear whether the spinal input demonstrated originated from bladder mecanoreceptors. Physiological stimulation of the bladder mecanoreceptors themselves, rather than electrical stimulation of the spinal descending afferents, would be necessary to confirm this.

The issue of whether the PMC is the only pre-motor micturition initiating region is addressed by Sugaya et al. [506]. From their recordings, units localised to the rostral medial medulla (reticularis gigantocellularis and magnocellularis) could also be activated antidromically from the spinal cord (L1) and also fired in or out of phase with bladder contractions (Figures 22, 23 & 25). These units included those that fired just before and/or with bladder contractions as well as firing in between bladder contractions. Interestingly, many of these rostral medial medullary units responded at short latency (2 to 3 ms) following stimulation of the PMC, supporting direct orthodromic activation. Thus, Sugaya et al. [506] proposed two descending pathways from the PMC for initiating micturition: one direct to the parasympathetic preganglionic neurones and the other via the medial reticular formation. Incidentally, the study also showed that these medullary units could be orthodromically activated from L1 indicating the potential for bladder mechanosensitive afferent drive to these neurones, although no direct proof for this was given that this spinal input originated from the bladder wall.

A question arises as to whether the spinally projecting PMC and rostral medial medullary neurones are actually defined pre-parasympathetic versus pre-sympathetic neurones? Said differently, does a single unit project to both autonomic preganglionic neuronal types in the spinal cord (see [508, 511]). This relates to the current understanding that during micturition the bladder contracts (parasympathetic activation) but relaxes the urethral sphincter (somatic inhibition). No data exist for this presently. However, in the nucleus tractus solitarius located in the dorsomedial medulla, a similar issue exists. Here, neurones receive mecanoreceptor sensory inputs from arterial baroreceptors activated by increases in blood pressure, which when activated mediate simultaneous excitation of cardiac parasympathetic motor outflow but inhibition of vasomotor sympathetic activity, thereby reducing cardiac output and peripheral resistance respectively that together lower arterial pressure to normal levels. Simms et al. [512] recently reported that the cardiac parasympathetic limb was activated at a
higher pressure threshold compared to the sympathoinhibition. It was surmised that output neurones within NTS are dedicated and already destined for either the parasympathetic or sympathetic networks [512]. Thus, a similar organization may exist within the PMC and could be teased apart by differences in the bladder pressures threshold necessary for bladder contraction versus urethral relaxation. Moreover, each autonomic limb of the baroreceptor reflex could be modulated differentially (e.g. [513-515]).

4. BLADDER ‘FILLING’ NEURONES IN THE PMC AND MEDIAL RETICULAR FORMATION: WHAT’S THEIR ROLE?

Within both the vicinity of the PMC and medial reticular formation, neurones were encountered that fired during the interval between bladder contractions but were silent during contractions. These were termed type 2 neurones by Sugaya et al. [506] and ‘inverse neurones’ by Sasaki et al. [516]. Many of these neuronal types had spinal projections (e.g. 26/35 type 2 neurones of Sugaya et al. [506]) but some could not be antidromically back fired. Although the latter is not definitive proof that these cells do not project spinaly, the data are suggestive that they form a group of interneurones.

So, what is the function of these spinally and non-spinally projecting inverse neurones? Considering those with spinal projections, these cells might provide excitatory drive to sympathetic pre-ganglionics destined for the detrusor muscle to bring about active relaxation, via \( \beta_2/3 \)-adrenoceptor stimulation. In regard to the non-spinally projecting neurones that fire out of phase with bladder contractions, these may be involved in ensuring that the neurones which are active during bladder contractions that project spinally to the parasympathetic preganglionic neurones remain silent during filling via local inhibitory connections. If so, one might predict that they contain GABA or glycine as an inhibitory neurotransmitter.

Future studies could consider difference in neuronal phenotype spinally and non-spinally projecting neurones by juxtacellular labelling and post-hoc immunocytochemistry or in situ hybridisation to identify their neurochemical content (glutamergic versus GABAergic, for example) as elegantly performed by others in the cardio respiratory regions of the medulla [517, 518]. Equally, the non-spinally projecting PMC neurones that fired in phase with bladder contractions could provide a source of synaptic inhibition to prevent neurones involved in bladder relaxation from firing prematurely.
5. OFF-SWITCHING MICTURITION – THE PONTINE CONTINENCE CENTRE (PCC)

As Sasaki (2004) points out [505], since the majority of units recorded from Barrington’s nucleus (60/76) continued to fire after the onset of bladder relaxation and that almost all inverse neurones do not start to fire until after relaxation is well underway (Fig 25), there must be a separate region for ‘off-switching’ bladder contractions and for relaxing the detrusor muscle. Simultaneously the urethral sphincter should constrict to allow filling and prevent incontinence. For these functions, the pontine continence centre or PCC is considered. This region was also termed the L region being distinct from the M region designated to be the PMC (see [519]).

**Where is the PCC, what types of neurones exist and what are their connections?**

The PCC is located in the dorsolateral pontine tegmentum (Figure 22). Neuroanatomical evidence indicates that PCC neurones do not project to spinal regions influencing detrusor muscle. Rather, projections appear to be limited to Onuf’s nucleus in the sacral cord. This nucleus contains the urethral sphincter motoneurones, suggesting that PCC drives their contraction. Perhaps some of the PCC neurones therefore have a defined pre-motor autonomic function as discussed above in the context of the arterial baroreceptor reflex. However, activation of PCC can stop micturition contractions [520]. Importantly, 78% of PCC neurones fire during the relaxation phase of bladder contractions (Figure 25) and the onset of their firing can be prior to the initiation of bladder relaxation [521].

Indeed, this would make sense if their prime function is to close the urethral sphincter. Another potential role is in off-switching micturition. One argument against this is that there appear to be no connections between the PCC and PMC, although a small number of PCC units could be either ortho- or anti-dromically activated from the PMC using electrical stimulation [506], which does not necessarily indicate the origin of the input or axon terminal. Others believe that the PMC and PCC act independently [520].

However, evidence supporting a role in off-switching micturition is that lesions within PCC cause incontinence, excessive detrusor activity, an inability to store urine and relaxation of the urethral sphincter. Further, activation of the PCC stops micturition, excites the pelvic floor musculature and contracts the urethral sphincter [278, 520]. Whether the PCC is actively involved in off-switching micturition to allow filling and storage and how it does this are questions requiring future experimental consideration. An area that may play a role in regulating micturition is the periaqueductal grey or PAG.

6. THE PERIAQUEDUCTAL GREY (PAG): IS THIS AN ESSENTIAL REGION FOR SUPPRESSING THE MICTURITION REFLEX?

The PAG is often referred to as a relay between ascending bladder afferent information and PMC activation of sacral parasympathetic preganglionic motoneurones. The present evidence suggests that the PAG is not just a simple ‘relay’. As mentioned above, afferents of sacral origin terminate in central regions of the PAG but that onward transmission to the PMC originates from more lateral aspects [484, 488, 490, 502]. Therefore, some form of ‘neural integration’ within the PAG is very likely. Chemical stimulation of the ventrolateral PAG can trigger micturition together with defensive behaviours (see [522]) but equally inhibition of micturition can be evoked by stimulation of rostral dorsal and caudal ventral PAG regions as well as areas ventral to the PAG (e.g. dorsal mesencephalic reticular formation and nucleus reticularis pontis oralis; [523]). Lesions within the PAG abolish the micturition reflex in the pre-collicular decerebrate cat [524] but studies in human also report bladder overactivity [525]. Matsuura, Downie et al. (2000) have shown that micturition evoked by chemical stimulation of the ventrolateral PAG is mediated by Barrington’s nucleus in the urethane anaesthetized rat. Moreover, these same authors were able to obtain coordinated sphincter activation from the PAG (with bladder contraction) as well as sphincter activation without bladder contraction at different sites within the PAG. This suggests the PAG is involved in both voiding and storage functions. This proposal is consistent with single unit recording from the PAG: Liu et al. [523] recorded from 84 micturition-related PAG neurones of which the majority were storage neurones (i.e. fired during bladder filling; 58%; Figure 25). Further, PET imaging revealed PAG regions becoming active during urinary retention in man [485]. However, close examination of the recording sites in Liu et al. study [523] reveals that the majority of neurones (68 of the 84) were located ventral to the lateral/ventrolateral PAG (in which 16 were recorded) in the dorsal mesencephalic reticular formation and nucleus reticularis pontis oralis. Nevertheless, based on the prominence of storage neurones in this region the idea that it plays a role in both urinary filling and suppression of the micturition reflex was advanced by Liu et al. [523]. They also proposed that micturition neurones may reciprocally depress the storage neurones. If true, this makes this part of the midbrain important in terms of providing a command locus for on- and off- switching micturition. In support of this was the observation of diverse firing patterns of the neurones including augmenting and decrementing [523]. Such firing patterns have been ascribed roles as ‘phase-switching neurones’ in the respiratory network [526], and could well play a role
in the transition between storage and voiding. Some of the midbrain cells recorded by Liu et al. [523] also fired across voiding/filling or filling/voiding transitions (Figure 25); this again supports the possible role in switching again akin to the brainstem respiratory network [526] between filling and emptying of the bladder. With the well established connections of the PAG that include orbital and pre-frontal cortex, amygdale, pre-optic region of the hypothalamus [500], it is proposed that the PAG may form a site for the integration of information from both higher centres, such as cortex, and bladder distension afferent inputs. With this said, the PAG is a clear contender for decision making about when to void or not, which it could execute via connections to PMC and PCC respectively.

7. NEUROTRANSMITTERS & MODULATORS WITHIN BRAINSTEM NETWORKS CONTROLLING BLADDER FUNCTION

There is not the scope in this review to provide a thorough detailed coverage of all transmitters and modulators affecting brainstem regulation of the urinary bladder. For recent reviews see: [481, 482]. These latter reviews highlight the importance of classical transmitters (glutamate, GABA and glycine) and non-NMDA, NMDA, GABA_A and glycine receptors within the brainstem (and PMC) for regulating bladder capacity and micturition (see also: [297, 492]). Important observations include that both NMDA and non-NMDA receptors within the brainstem are important for micturition [527] and that the PMC is under tonic inhibitory tone mediated by GABA_A receptors [492]. This prompts the question as to where and how this inhibitory tone is generated. Possibilities could be the PAG or higher centres, such as pre-optic hypothalamic structures, for example. Below is a brief account of two important and clinically relevant transmitter systems affecting bladder function via effects within the brainstem.

a) Serotonin

Many transmitter systems have been investigated by drug applications into the brain ventricles. Whilst this determines whether or not a modulating system has an effect on micturition it is difficult to assess where this might be exerted. In their review [528], Burgard et al. emphasise that serotonin appears to affect nervous control of bladder function at multiple levels including sensory processing of bladder wall afferents within the dorsal horn of the spinal cord and at the level of the spinal motoneurones. In all cases this appeared to be inhibitory on detrusor muscle activity but excitatory on urethral sphincter. A model proposed, was that 5-HT_1A receptors were located on the terminals of sensory afferent fibres to depress neurotransmitter release. Similarly, Ito et al. [529] have described a predominance of an inhibitory effect evoked from the midline raphe system extending from the pons to medulla on micturition in cats. Where this effect is mediated (i.e. supra-brainstem, pons or spinal cord) is unclear. Moreover, 79 raphe neurones were recorded in which their firing was related to bladder pressure with 66% related to storage [529]. These data support a role of the raphe system in suppressing micturition and facilitating external urethral sphincter activity in cats, which is consistent with earlier studies identifying a central inhibitory role for 5-HT_1A receptors [283]. In stark contrast, this does not seem to be the case in the rat where 5-HT_1A system facilitates micturition [530].

b) Dopamine

In Parkinson’s disease, where there is a reduction in dopamine availability, the bladder is hyperactive (409). Yoshimura et al. [531] discovered that D_1 and D_5 receptors acting within supraspinal sites are inhibitory to micturition whereas other dopamine receptor subtypes were facilitatory. This is an important finding given the major clinical and psychological problems of incontinence.

• Looking towards the horizon

A number of pertinent questions regarding brainstem mechanisms regulating detrusor and urethral muscle have evolved. First, the issue of the neuronal mechanisms underpinning the switching from storage to voiding but also off-switching detrusor activity at the end of voiding remain unclear. Most brainstem neurones relating to bladder voiding/filling appear to show firing that is either in or out of phase with bladder contractions (as indexed by increases in bladder pressure). Whether this neuronal firing is a cause or consequence of the bladder contractions is unclear. Therefore, future studies could address the issue of the origin of neuronal activity (whether coincident with bladder contraction or relaxation) in terms of that generated centrally versus that which is dependent on sensory afferent mechanoreceptor feedback for midbrain and brainstem regions. Second, and a related issue, is following the volitional command to void, which lower brain structures execute this demand? Is this in the brainstem or midbrain (PAG) or higher centres? Based on the evidence presented here, a most likely candidate appears to be the PAG/dorsal mesencephalic reticular formation. This structure appears to have the right neuronal connections in terms of both ascending spinal afferent inputs and outputs to pontine micturition centres. In addition, it receives inputs from higher centres. Third, switching between voiding-filling-voiding has to be coordinated with the corresponding control of the urethral sphincters. This means there has to be cross talk between detrusor and sphincter neural circuits. Whilst evidence was discussed for a spinal inhibitory mechanism within the sacral cord, no such cross connectivity was found between PMC and PCC regions but there remains a possibility that some cross talk may exist in the PAG/dorsal mesencephalic reticular formation. Fourth, is whether there are within
the PMC/PCC (or PAG) neurones that are dedicated
to the sympathetic or parasympathetic nervous system
that exist as pre-motor autonomic neurones. It was
discussed above that such organisation exists for
brainstem control of the baroreceptor reflex in
regulating arterial pressure. Finally, some technical
issues. Most studies inflate the bladder and work on
spontaneous isovolumetric contractions. This is clearly
not physiological as the bladder does not void. This
will affect detrusor muscle mechanoreceptor afferent
feedback as well as afferent feed back from the urinary
tract. The bladder volume/pressure always remains
above the micturition threshold, again non-physio-
logical. Many of the early experimental studies were
based on the cat. Typically this was decerebrate
raising the issue of how this relates to the conscious
intact animal where higher centres are intact and
known to regulate micturition. It is clear that more
recent studies have ventured to the rat and most
recently man. One wonders how compatible the
regions regulating bladder function is between species
and whether the connectivity and neuronal
mechanisms are preserved or different. A good
example is the opposing effects of 5-HT1a receptors
in cats (inhibit micturition) versus rat (pro-micturition;
for references see above). This is an important issue
in terms of translating work from cat/rat to man. Whilst
serotonin seems to be inhibitory to detrusor muscle
activity in cat this is not the case in rat. Thus, the idea
that modulation of the descending serotonergic system
as a potential treatment strategy for incontinence in
human [528] will need further validation. However, it
is notable that areas identified as key brainstem sites
for micturition in animal models do relate to regions
identified in man using fMRI [486]. Finally, a universally
agreed consensus needs to be defined as to how to
correlate symptoms with smaller, more discrete
lesions at particular brain sites. However this “lesion”
literature is really quite sparse, presumably mainly
because if bladder symptoms occurred as a result of
a cerebral lesion the clinical picture was usually
dominated by a variety of other neurological deficits
and furthermore such bladder symptoms that there
were would not have been of interest to the majority
of neurologists. Initially the lesion studies were based
on observations made in life correlated with post
mortem or pathological specimens, but with
increasingly better means of imaging it was possible
to correlate symptoms with smaller, more discrete
abnormalities.

From what was written, the importance of the frontal
cortex and pons was clearly recognized and there
are a number of case histories of patients reported with
lesions at either site. Subsequent functional brain
imaging studies confirmed the clinically based findings
and then greatly extended our understanding of the
complex cortical and subcortical networks involved
in sensing bladder filling and activating appropriate
voiding. In fact the few further cases of “cortical
bladders” described since the emergence of functional
imaging findings have reported lesions at sites that
previously would probably not have been recognized
as being important in “lesion” evidence presented
here and summarized in Table 4. In fact functional
imaging and lesion studies should be regarded as
complementary because, functional brain imaging
provides information about regional activation of grey
matter, whereas lesions may give information about
damage to white-matter connecting pathways. The
lesion literature also improves our understanding of
patients’ complaints. Most of the functional imaging
studies to be reviewed were carried out using either
positron emission tomography (PET) or functional
magnetic resonance imaging (fMRI). Both provide
indirect measures of regional blood flow, assumed to
be related to local neuronal activity, but their temporal
resolutions are quite different: several minutes for
PET versus a few seconds for fMRI. For this reason
PET is good for measuring long-lasting states of a
system, while fMRI is better for following relatively
fast events. Experimental paradigms are therefore
quite different for the 2 techniques.

2. ROLE AND IMPORTANCE OF CEREBRAL
CONTROL OF VOIDING

In order to understand the cerebral control of voiding
it is helpful first to examine what would happen if there
were no such control. Provided brainstem and midbrain
are intact, micturition is organized in 2 phases, storage

VI. CORTEX AND BRAINSTEM
CONTROL OF BLADDER FUNCTION

1. BACKGROUND

The aim of this section is to present a synthesis of the
human literature and review what this tells us about
brain regions mediating specific aspects of human
bladder behaviour.

Prior to the advent of functional brain imaging
techniques, our knowledge of the cerebral and
brainstem areas involved in the control of micturition
was based on a small number of carefully observed
clinical cases: patients presenting with specific bladder
symptoms who were found by investigation to have
lesions at particular brain sites. However this “lesion”
literature is really quite sparse, presumably mainly
because if bladder symptoms occurred as a result of
a cerebral lesion the clinical picture was usually
dominated by a variety of other neurological deficits
and furthermore such bladder symptoms that there
were would not have been of interest to the majority
of neurologists. Initially the lesion studies were based
on observations made in life correlated with post
mortem or pathological specimens, but with
increasingly better means of imaging it was possible
to correlate symptoms with smaller, more discrete
abnormalities.

From what was written, the importance of the frontal
cortex and pons was clearly recognized and there
are a number of case histories of patients reported with
lesions at either site. Subsequent functional brain
imaging studies confirmed the clinically based findings
and then greatly extended our understanding of the
complex cortical and subcortical networks involved
in sensing bladder filling and activating appropriate
voiding. In fact the few further cases of “cortical
bladders” described since the emergence of functional
imaging findings have reported lesions at sites that
previously would probably not have been recognized
as being important in “lesion” evidence presented
here and summarized in Table 4. In fact functional
imaging and lesion studies should be regarded as
complementary because, functional brain imaging
provides information about regional activation of grey
matter, whereas lesions may give information about
damage to white-matter connecting pathways. The
lesion literature also improves our understanding of
patients’ complaints. Most of the functional imaging
studies to be reviewed were carried out using either
positron emission tomography (PET) or functional
magnetic resonance imaging (fMRI). Both provide
indirect measures of regional blood flow, assumed to
be related to local neuronal activity, but their temporal
resolutions are quite different: several minutes for
PET versus a few seconds for fMRI. For this reason
PET is good for measuring long-lasting states of a
system, while fMRI is better for following relatively
fast events. Experimental paradigms are therefore
quite different for the 2 techniques.

2. ROLE AND IMPORTANCE OF CEREBRAL
CONTROL OF VOIDING

In order to understand the cerebral control of voiding
it is helpful first to examine what would happen if there
were no such control. Provided brainstem and midbrain
are intact, micturition is organized in 2 phases, storage
and voiding, governed by reflexes involving the brainstem and spinal cord. During storage the urethral sphincter mechanism contracts tonically, preventing urine leakage, while the detrusor remains relaxed, so as to avoid developing a pressure that would expel urine. Urethral contraction is maintained by sacral reflexes known collectively as the ‘guarding reflex’; detrusor relaxation is ensured by absence of excitatory parasympathetic input as well as active sympathetic inhibition provided by spinal reflexes (2).

During voiding the urethral sphincter relaxes, facilitating urine flow, and the detrusor contracts so as to expel urine. This coordinated relaxation and contraction of urethra and bladder respectively is driven by a long-loop spinobulbospinal reflex (2), shown schematically in Figure 26. As the bladder fills, increasingly strong bladder afferents travel via synapses in the sacral cord to the brainstem and midbrain, where they synapse in the central periaqueductal gray (PAG). If the afferent signals exceed a trigger level, efferent fibres in the more lateral PAG are excited and they in turn excite the pontine micturition centre (PMC). Efferent signals from the PMC descend to the sacral cord, where they excite an indirect inhibitory pathway via the nucleus of Onuf that leads to sphincter relaxation [535] and an excitatory pathway to the bladder that leads to detrusor contraction; thus voiding occurs. In the absence of higher control, the reflex system just described would lead to involuntary bladder emptying (i.e. incontinence) whenever the bladder volume reached a critical level. However human behaviour relating to bladder function is fundamentally different from that of other species because in modern-day society we void in a controlled fashion, preferably in privacy. Embarrassment with inappropriate voiding and feelings of shame about incontinence are deeply embedded in human behaviour. Voiding at a socially acceptable time and place is only achieved by maintaining strict voluntary control of the voiding reflex.

The decision to void is based on a combination of factors, including one’s emotional state, an appreciation of the social environment and the afferent (sensory)  

<table>
<thead>
<tr>
<th>Key brain regions</th>
<th>Pathology</th>
<th>Number of cases</th>
<th>Effect on bladder behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>Various causes of frontal lobe pathology (1)</td>
<td>38</td>
<td>Altered bladder sensation and incontinence in absence of intellectual deterioration or retention</td>
</tr>
<tr>
<td></td>
<td>Frontal lobe tumours (537)</td>
<td>7</td>
<td>Frequency, urgency incontinence</td>
</tr>
<tr>
<td></td>
<td>Frontal abscess (540)</td>
<td>1</td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td>Frontal atresia/saenmatoma (539)</td>
<td>2</td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td>Anterior cerebral vascular lesions (538)</td>
<td></td>
<td>Various bladder disorders and hemiparesis</td>
</tr>
<tr>
<td>ACG</td>
<td>Bilateral infarction of anterior cingulate gyril (553)</td>
<td>1</td>
<td>Complex behavioural changes and incontinence</td>
</tr>
<tr>
<td></td>
<td>Glioma of ACG and supplementary motor cortex (553)</td>
<td>1</td>
<td>Urgency incontinence with loss of sensation</td>
</tr>
<tr>
<td>Insula</td>
<td>Glioma of insula and inferior frontal gyril (533)</td>
<td>1</td>
<td>Incontinence without loss of bladder sensation</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Pluritary tumours extending into the hypothalamus (534)</td>
<td>3</td>
<td>Urgency incontinence, weight loss, psychiatric symptoms</td>
</tr>
<tr>
<td></td>
<td>Cystic lesion of hypothalamus (551)</td>
<td>1</td>
<td>Incontinence</td>
</tr>
<tr>
<td></td>
<td>Ruptured anterior cerebral aneurysm (556)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PAG</td>
<td>Presumed inflammatory lesion (532)</td>
<td>1</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Pons</td>
<td>Posterior fossa tumours (558)</td>
<td></td>
<td>Voiding difficulty</td>
</tr>
<tr>
<td></td>
<td>Brain stem tumours (Ueki, 1963 #2994)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brainstem vascular lesions (564)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brainstem gliomas in children (563)</td>
<td>24</td>
<td>Urinary retention and disordered eye movements</td>
</tr>
<tr>
<td></td>
<td>Developmental malformation (559)</td>
<td>1</td>
<td>Urinary retention and disordered eye movements</td>
</tr>
<tr>
<td></td>
<td>Low grade glioma (560)</td>
<td>1</td>
<td>Paraparesis, urinary retention and disordered eye movements</td>
</tr>
<tr>
<td></td>
<td>R pontine lesion, unknown (494)</td>
<td>1</td>
<td>Urinary retention and disordered eye movements</td>
</tr>
<tr>
<td></td>
<td>Herpes encephalitis (651)</td>
<td>1</td>
<td>Urinary retention and disordered eye movements</td>
</tr>
</tbody>
</table>

Table 4. Effect on bladder behavior of pathological changes in key brain regions.
signals arising from the bladder. Knowledge of the extent to which one’s bladder content is comfortable and ‘safe’ is central in this process. Thus, voluntary control of the bladder and urethra has two important aspects, namely registration of bladder filling sensations and manipulation of the firing of the voiding reflex. The PAG – the most rostral part of the reflex pathway shown in Figure 26 – appears to have a pivotal role in both aspects. On the one hand it receives bladder afferents [535] and transmits them to higher brain centres and into the realm of conscious sensation. On the other hand it receives projections from many higher centres and controls the primary input to the PMC [536]. During bladder filling, such higher brain centres can suppress any excitatory signal from the PAG to the PMC and prevent voiding or incontinence. Then, when voiding is consciously desired, they can allow the PAG, and thus the PMC, to be excited.

Thus, during the storage phase, the net effect of higher (voluntary) control is tonic suppression of the voiding reflex. This suppression can be interrupted to allow voiding to occur if appropriate: i.e. if it is necessary (bladder volume is adequate), socially acceptable, and judged to be safe.

3. CORTICAL AND SUBCORTICAL CENTRES INVOLVED IN BLADDER CONTROL. EVIDENCE FROM OBSERVATIONS OF LESIONS AND FROM FUNCTIONAL BRAIN IMAGING IN HUMANS

a) Frontal Lobes

Although Andrew and Nathan (1) were not the first to describe disturbances of micturition resulting from a variety of causes of frontal lobe pathology, their celebrated paper reporting the syndrome of frequency, urgency (and in some patients faecal) incontinence causing distress to the patient, is regarded as seminal in the field. Their description of these patients cannot be improved upon.

“The patients described here were not demented, indifferent or lacking in social awareness; they were much upset and embarrassed by these symptoms. The acts of micturition and defecation occur in a normal manner; what is disturbed by this frontal lesion is the higher control of these acts. The lesion causes frequency and extreme urgency of micturition when the patient is awake, incontinence when asleep. The sensation of gradual awareness of increasing fullness of the bladder and the sensation that micturition is imminent, are impaired. When the syndrome is less pronounced, the sensation underlying the desire to micturate is absent, whereas the sensation that micturition is imminent still occurs. Then the patient is waylaid by a sudden awareness that he is about to pass urine; when neither sensation is experienced, the patient is amazed to find that he has passed urine. The threshold of the micturition reflex is much lowered. In the most complete form of the syndrome, the patient cannot inhibit the detrusor contraction of the micturition reflex; he is thus forced to empty his bladder as soon as the reflex occurs. When the syndrome is less pronounced, the patient can make a conscious effort to stop the act of micturition, and he may or he may not succeed. The lowering of the micturition reflex threshold may account for the fact that the patient

![Figure 26: The voiding reflex. The lines on the right (green) show bladder afferent activity ascending to the PAG during storage. Note there is no direct afferent input into the PMC. On the left (blue), lines show activation of the PMC by the PAG, with descending activity to the sacral cord from where the parasympathetic innervation to the detrusor arises. An inhibitory synapse onto the motor innervation of the sphincter (Onuf’s nucleus) results in relaxation of the striated sphincter muscle and thus synergistic detrusor sphincter activity. Note that higher brain regions control the voiding reflex almost exclusively via the periaqueductal grey (PAG), apart from a connection via the hypothalamus.](image-url)
does not feel the normal gradual filling of the bladder that underlies the desire to micturate; but it cannot account for the unawareness of the sensations arising from the activity of pelvic and perineal muscles or of the sensation that urine is passing.*

The cases of leucotomy in Andrew and Nathan’s series were regarded as most useful for localizing the lesion causing the syndrome. The significant plane of the lesion was that lying immediately anterior to the tips of the ventricles and the genu of the corpus callosum. Such lesions involved grey matter, in particular the superomedial part of the frontal lobe (see Figure 27); but they caused a permanent disorder of the control of micturition and of defecation only when they involved some of the white matter lateral to the anterior horns of the lateral ventricle. Lesions that did not affect this white matter caused only transient disordered control of micturition. Correspondingly, Andrew and Nathan’s Figure 10A suggests that most of the critical lesion area was in this white matter (Figure 27).

Subsequently the same features were observed in 7 patients out of a series of 50 consecutive frontal tumours [537]. In an analysis of patients with acute hemispheric strokes the occurrence of disturbance of micturition was found to be more common in frontal than occipital lobe lesions and there was an association with hemiparesis [538]. In 3 cases, Andrew and Nathan observed that lesions in similar areas to those discussed above led to urinary retention rather than incontinence (Table 4). Three further cases of frontal lesions with urinary retention have been reported. Successful treatment brought recovery of bladder function [539, 540].

Imaging studies, both PET [485, 541-544], and fMRI [545-548], are in agreement that, during bladder filling, storage and withholding of urine, there is activity in the right inferior frontal or dorsolateral prefrontal cortex, perhaps extending into the lateral part of the superior frontal cortex (Figure 28A,B). There is some right-sided predominance. In contrast there is little evidence for activation of the medial parts of the frontal cortex during storage. One PET study showed medial frontal activity during sacral nerve stimulation [548], but this is difficult to interpret; another study that showed medial frontal activity during filling [549] employed SPECT imaging, which has poor spatial resolution. An fMRI study showed abnormally weak activation in medial prefrontal cortex in subjects with urge incontinence [547], and further analysis revealed that bladder filling tends to provoke deactivation in this region [550]. Regardless, there is little overlap with the superomedial frontal region described by Andrew and Nathan (1), except in part of the anterior cingulate gyrus (ACG; see Figure 29). These observations are consistent with the concept that functional imaging reveals grey-matter activation or deactivation, while lesions may damage critical links in white-matter connecting pathways as well as grey-matter regions.

Neuroanatomical observations indicate that there is a strong and direct connection from medial prefrontal cortex to PAG [536]. It is tempting to postulate that this pathway is responsible for tonic PAG suppression of the voiding reflex, thus maintaining the storage phase. White-matter lesions in this pathway would then allow involuntary excitation of the voiding reflex, with resulting incontinence. It would appear from this account that bilateral lesions would be required to cause incontinence, yet in practice a lesion on one side seems to be sufficient. Andrew and Nathan’s suggestion – that this is because a unilateral lesion is likely to involve the fibres connecting one side with the other [551] – is difficult to follow.

Voiding has not been studied directly by fMRI, but there are 3 PET studies of voiding [535, 542, 543] and one fMRI study of simulated voiding [552]. All identify activation of the right inferior frontal gyrus (dorsolateral prefrontal cortex) and in the medial prefrontal cortex or nearby ACG (see next section).

b) Anterior Cingulate Gyrus (ACG)

The anterior cingulate is an extensive area with parts serving varied functions. The cases of aneurysm in Andrew and Nathan’s series of frontal lobe pathologies were thought to have involved the anterior end of the cingulate gyrus (1) (Figure 29, cyan circle). Incontinence was observed as part of a complex behavioural disorder following bilateral infarction of the anterior cingulate gyri [553]. A recent report of a patient in whom a glioma in the right posterior ACG and supplementary motor area was resected described how she experienced urgency incontinence and loss of bladder sensation following surgery [533].

Many functional imaging studies have observed ACG responses – activation or occasionally deactivation – to bladder filling, storage or withholding [485, 541, 542, 544, 547, 549]. The reported locations form a trail extending from dorsal to ventral ACG, suggesting that different parts of the ACG respond to the very varied experimental paradigms that were used (Figure 29). There is a cluster of activations near the anterior area identified from lesion studies by Dr Nathan (personal communication), confirming that this part of the brain is indeed critical for control of micturition. Response of the dorsal ACG to bladder filling is abnormally pronounced in patients with urge incontinence, even in the absence of any detrusor contraction [547, 550], suggesting that it is involved both in recruitment of accessory pathways (to help avoid loss of control of the bladder) and in the sensation of urgency that accompanies this situation. Imaging studies of voiding [541-543] and simulated voiding [552] have all revealed ACG involvement.

c) Insula

Given what we now know from functional imaging
Figure 27 A, B and C: Location of white matter lesions causing persisting incontinence (red: based on Andrew and Nathan’s Figures 10 A, B and C (1)); and of grey matter lesions causing incontinence (cyan: personal communication to CJF from Dr Nathan).

Figure 28A: Locations of peaks of activation reported as right inferior frontal or lateral prefrontal cortex, during bladder filling, storage and withholding of urine. Locations of peaks more than 20 mm from the midline are projected onto right lateral surface of brain. Note some overlap with insula shown in Figure 30.

Figure 28B: Medial prefrontal area activated in a few studies during withholding of urine. Locations of peak activation less than 20 mm from the midline are projected onto the midline plane.

Figure 29: Cingulate gyrus areas activated on withholding of urine or full bladder, projected onto midline plane (dots). The larger cyan circle is the projection of the superomedial grey matter area shown in Fig 27 onto the midline plane.
experiments about the importance of the insula in processing afferent activity from the bladder (see Figure 30) it is remarkable that there have not been more reported cases of bladder dysfunction from lesions at that site. Possibly the bilateral nature of insular connections, even though there is some right-sided predominance, protects against a drastic effect of insular lesions. One patient in whom a glioma affecting the inferior frontal gyrus and the insula was excised experienced incontinence without loss of bladder sensation [533].

Imaging studies during storage or withholding of urine show that regions reported as insula form a cluster near the expected location of that structure (Figure 30) [541-544, 547, 549, 554]. There is some overlap with the lateral frontal activations reported above and shown in Figure 28A. In the figure right and left sides are projected on the same brain surface, masking any right-sided predominance, and the insula is about 20 mm deeper than the brain surface shown. In healthy subjects, insular activation becomes stronger with increasing filling of the bladder, consistent with its postulated role in bladder sensation [555]. In normal elderly, this insular response to bladder filling decreases with age, consistent with age-associated loss of sensation. However, insula activity cannot by itself be responsible for conscious desire to void or urgency, because these sensations are lost following extensive frontal lesions [551], suggesting that integrity of connecting pathways between insula and frontal cortex is essential for conscious sensation. The insula was activated in only one [543] out of four imaging studies of real or imagined voiding, suggesting that it is not strongly involved in this phase of micturition.

d) Periaqueductal Grey (PAG)

A single case history describes a young man presenting with urinary retention in whom the only abnormality found was a small, presumed inflammatory lesion in the PAG [532]. Presumably in other cases the clinical picture was dominated by other symptoms and deficits that were more striking to a neurologist.

Given the spatial resolution of PET and fMRI (a few mm), it might be expected to be difficult to distinguish small but functionally different areas in the brainstem and midbrain. In fact however the brainstem/midbrain activations reported during the storage and voiding phases seem to cluster in 3 distinct regions (Figure 31), one of them being the PAG. PAG response to bladder filling is reported in 3 studies [485, 544, 547]. This response may reflect increased afferent signals arriving at the PAG (Figure 26) or increased inhibitory activity from the medial prefrontal cortex (MPFC), needed to prevent triggering of the voiding reflex (see Figure 32). The PAG responded to imagined voiding in one fMRI study [552], but not to real voiding.

e) Hypothalamus

Lesions at this site as a cause of bladder symptoms are rare but 3 cases of pituitary tumours, extending upwards into the hypothalamus have been described with urgency incontinence or retention, weight loss, psychiatric disturbance and bitemporal field restriction [534]. Other instances include gliomas involving the hypothalamus [551] or vascular disturbances of the anterior hypothalamus. Andrew and Nathan also reported five patients with bladder symptoms appearing after a ruptured cerebral aneurysm and speculated that the site of lesion responsible was the anterior hypothalamus [556].

Animal observations suggest that the anterior and caudal hypothalamus have monosynaptic connections with the PAG and PMC [536]. Correspondingly, two human brain imaging reports suggest response to bladder filling in a region near the caudal hypothalamus [485, 555], and one near the preoptic area [547]. It has

Figure 30: Locations of activation peaks reported as insula, during bladder filling, storage and withholding of urine, projected onto right lateral surface of brain. Note overlap with areas shown in Fig 28A.

Figure 31: Brainstem areas activated during storage or voiding, projected onto the midline plane.
been suggested that these connections allow the hypothalamus to inhibit voiding unless the situation is judged to be safe.

f) Pons

The demonstration by Barrington [557] in the cat that a centre existed at the level of the pons necessary for activation of micturition, provided the background for recognizing a comparable centre in humans and the early report of the association of difficulty with micturition with posterior fossa tumours [558]. Later histories of individual cases of discrete pontine lesions [559, 560, 561], [494] and reports of difficulties with micturition or retention as a feature of brainstem gliomas in children [562, 563] or vascular lesions [564], confirmed the likely existence of a comparable centre in humans. Studies using MRI to visualize the precise location of the responsible lesions, sited this in the dorsolateral pons, including the pontine reticular nucleus and the reticular formation, adjacent to the medial parabrachial nucleus and locus coeruleus [564]. Lesions in this location are frequently associated with disturbances of consciousness and respiration and bladder symptoms may therefore be overlooked. The commonest clinical association of urinary retention arising from a pontine lesion is an internuclear ophthalmoplegia or disorder of eye movements.

Functional imaging experiments have shown a cluster of activations near the postulated location of this pontine micturition centre (PMC), Figure 31. There are 3 reports of PMC activation during voiding [541-543] and – surprisingly – one in response to bladder filling [555]. However, excitation during bladder filling might be inhibitory rather than excitatory, a distinction that cannot be made by functional imaging.

A few studies suggest activation of the postulated pontine L-region or continence centre (Figure 31), somewhat ventral, lateral and/or caudal to the PMC (Figure 26): during storage [485], during failed attempt to void [541, 542], during imagined voiding [554], and during imaginary inhibition of voiding [552]. However, not all these studies recognized the L-region as such.

g) Other Regions

The regions discussed in sections 3.1 to 3.6 are reasonably well established since they are observed in lesion, imaging and (in some cases) animal studies. In particular, the triad insula/ACG/prefrontal cortex is well known from studies of other aspects of brain function [565]. Other regions relevant to bladder control however have been revealed only by functional imaging. They include parts of parietal and frontoparietal cortices, posterior cortex (precuneus, posterior cingulate cortex), putamen, caudate, parts of the limbic system (hippocampal complex, amygdala), and various parts of the cerebellum. Rarely seen in functional imaging experiments is activity in the basal ganglia, yet dopamine pathways are thought to have a profound inhibitory effect on the PMC in health, which is lost in Parkinson’s Disease.

4. WORKING MODEL OF BRAIN/BLADDER CONTROL

The diagram in Figure 32 shows what are currently thought to be the principal areas and connections involved in bladder control, with the more important connections identified by thicker lines. This scheme is hypothetical but offers, at this point in time, a framework based on evidence from the clinical reports of the effects of “lesions”, the regions shown to be activated in the PET imaging experiments (Figure 33) and the results currently emerging from functional MRI and connectivity studies.

The PMC is the final efferent brain nucleus involved in bladder control – when activated there follows coordinated sphincter relaxation and detrusor contraction, resulting in voiding. However the PMC has been shown to have only a few central connections (Figures 26 and 32) namely, from the hypothalamus and from the PAG. The PAG is now recognized as having a central role in mediating the influences of higher function on the PMC and so achieving voiding at brain- rather than bladder-determined volumes. To perform this role the PAG receives afferent input via the sacral roots conveying “bladder fullness” information, as well multiple inputs from higher centres including the

Figure 32 A: preliminary conceptual framework, based on current evidence, suggesting a scheme for the connections between various forebrain and brainstem structures that are involved in the control of the bladder and the sphincter in humans. Arrows show probable directions of connectivity but do not preclude connections in the opposite direction. PAG = periaqueductal grey; PMC = pontine micturition centre. Reproduced, with permission (2), based on the work of (4).
prefrontal cortex, ACG, insula and hypothalamus and also probably the basal ganglia and cerebellum. The insula (the right in particular) has been shown to respond in a way that suggests it is responsible for mapping and processing bladder as well as other visceral sensations and is sometimes referred to as the “sensory cortex of the autonomic nervous system”.

The ACG monitors stress and conflict and generates appropriate autonomic arousal. It may also determine how much attention is paid to signals from the bladder and how one reacts to them. The medial prefrontal cortex (MPFC) has a role in response selection and so may be involved in evaluating afferent activity. The MPFC is crucial for decision-making in an emotional and social context and is thus evidentially important in controlling micturition. It is close to the anterior cingulate region revealed by lesion studies and functional imaging (Figure 29) and has strong and direct connections with the PAG, suggesting that it may be responsible for maintaining the tonic suppression of the voiding reflex during the storage phase, which normally is only relaxed when the decision to void has been made. This decision is conveyed back to the PAG, which correspondingly excites or inhibits the PMC (Figure 34).

Figure 33: Brain areas involved in the regulation of urine storage. A meta-analysis of positron-emission tomography and functional MRI studies that investigated which brain areas are involved in the regulation of micturition reveals that the thalamus, the insula, the prefrontal cortex, the anterior cingulate, the periaqueductal grey (PAG), the pons, the medulla and the supplementary motor area (SMA) are activated during the urinary storage. Reproduced with permission from (3).

Figure 34: A preliminary working model of lower urinary tract control by higher brain centres. A: During storage, ascending afferents (yellow) synapse on the midbrain periaqueductal grey (PAG); they are relayed via the thalamus (TH) to the dorsal anterior cingulate gyrus (ACG: responsible for monitoring and warning) and to the right insula (RI: responsible for sensations such as desire to void) and lateral prefrontal cortex (LPFC); in the storage phase they pass to the medial prefrontal cortex (MPFC, red arrow) where the decision to void or not is made; in this phase the decision is not to void, and this situation is maintained by chronic inhibition of the PAG via a long pathway (red arrows) from the MPFC; consequently the pontine micturition centre (PMC) is also suppressed, and voiding does not occur. B: When the decision to void is made, the MPFC relaxes its inhibition of the PAG (green arrow) and the hypothalamus (H) also provides a ‘safe’ signal; consequently the PAG excites the PMC which in turn sends descending motor output (green arrow) to the sacral spinal cord that ultimately relaxes the urethral sphincter and contracts the detrusor, so that voiding occurs.
VII. ABNORMAL LOWER URINARY TRACT FUNCTION

Dysfunction of neural control may underpin a wide range of clinical urinary tract problems. On the afferent side, neural dysfunction will alter reflex activity and influence sensation, which can either be enhanced, reduced or altered (e.g. with the emergence of pain instead of usual bladder filling sensations). On the efferent side, motor activity within the components of the lower urinary tract (bladder and outlet) can be increased, reduced or uncoordinated. The following is not a comprehensive description of the entire scope of this complex arena, but focuses on key issues relevant in the clinical context.

1. ABNORMALITIES INVOLVING INFLAMMATION

• Bladder Pain Syndrome / Interstitial Cystitis (BPS/IC)

Although no consensus has been reached on the fundamental causes of Bladder pain syndrome/Interstitial Cystitis (BPS/IC), existing data suggest 3 pathophysiological mechanisms: epithelial dysfunction, mast cell activation, and neurogenic inflammation [566].

1. MAST CELL ACTIVATION – Mast cells may be activated by a number of mechanisms within the bladder wall. Increased permeability with influx of potassium ions may lead to sensory nerve up-regulation resulting in mast cell activation. Vasoactive, nociceptive and pro-inflammatory molecules released from mast cells can produce neuronal sensitisation and secretion of neurotransmitters that further stimulate mast cells. Mast cell – neuronal interactions may therefore provoke a vicious cycle in BPS/IC, contributing to the painful symptoms of the disease [567].

2. NEUROGENIC INFLAMMATION – The close physical relationship between the C fibres and mast cells is of particular importance, as substance P (SP) released from the nerve fibres degranulates mast cells. During degranulation, the mast cells release a multitude of proinflammatory agents including nerve growth factor (NGF), tumour necrosis factor-α (TNF-α), histamine, heparin, proteases, interleukins, serotonin and others. This induces an inflammatory response in the form of vasodilatation (redness) and plasma protein extravasation (oedema). Additionally, newly released nerve growth factor (NGF) stimulates a further increase in the number of afferent fibres, thus increasing the potential for further releases of SP and the transmission of nociceptive impulses. Neuroinflammatory models of cystitis result in increased levels of TNF-alpha, SP and NGF production in the bladder, paralleling the hypothesized neuro-inflammatory etiology of IC [568].

During mammalian development, NGF is required for the survival and growth of several populations of neurons. There is evidence to suggest that it also plays a role in the ongoing regulation of neural function, as well as inflammation and pain [569].

In the urinary tract, NGF is produced by the bladder, smooth muscle and urothelium, and levels of NGF increase in response to interstitial cystitis. In one study, patients with BPS/IC were found to have elevated levels of neurotrophic factors in their urine, including neurotrophin-3, nerve growth factor and glial cell line-derived neurotrophic factor [570]. This finding is consistent with the observation of increased NGF mRNA and protein in bladder biopsies from patients with BPS/IC compared with controls [571].

Intravesical NGF is known to sensitize bladder afferent fibres [142], and sequestration of NGF can reduce inflammation associated with chemical cystitis in a rat model [572]. Blockade of NGF using either endogenous antibody or antibody against the NGF receptor, or a fusion protein that prevents interaction between NGF and its receptor, prevents neural plasticity and bladder overactivity in experimental models of these conditions [143, 573].

Other substances including neurotrophins, prostaglandins, and tachykinins may also contribute to altered afferent excitability [574]. The potential relevance of these changes has been demonstrated in cats diagnosed with feline interstitial cystitis (FIC) (which demonstrates nearly all the characteristics and symptoms of human BPS/IC), in which capsaicin sensitive neurons are larger, with dorsal root ganglia that exhibit increased excitability and slower desensitisation to capsaicin, suggesting changes in the properties of the primary afferent neurons [146, 147], a finding that may be associated with tendency of NGF to stimulate TRPV1 expression.

2. INVOLVING ABNORMAL URINE STORAGE

a) Overactive Bladder / Detrusor Overactivity

Detrusor overactivity can arise in neuropathic conditions, secondary to bladder outlet obstruction or idiopathically. Several observations on structural and functional properties of the bladder have been made in individuals with detrusor overactivity:

• Patchy denervation is present within the bladder wall, while sensory neurones and parasympathetic ganglion cells are enlarged

• Exaggerated spontaneous myogenic activity can be seen in isolated detrusor muscle strips, with increased incidence of fused tetanic contractions

• Muscle strips also show altered responsiveness to nervous and pharmacological stimuli
• Characteristic changes in smooth muscle ultrastructure have been described.

Smooth muscle strips dissected from the bladder in detrusor overactivity often show altered responses to nerve stimulation and to various agonists. For example, in obstructed overactive bladders there is reduced contractile response to intrinsic nerve stimulation, along with supersensitivity to muscarinic agonists and potassium solutions [575-578]. Among neuropathic conditions, spina bifida is associated with supersensitivity to cholinergic agonists and potassium solutions, but there is no change in the sensitivity to intrinsic nerve stimulation [579]. In spinal cord injury, there is no reduction in sensitivity to electrical field stimulation, but the maximum force generated by each milligram of bladder tissue is significantly reduced [92]. In idiopathic detrusor overactivity, bladder strips show supersensitivity to potassium, but not to muscarinic agonists, and there is a reduced contractile response to intrinsic nerve stimulation [580]. Where functional denervation is present, there appears to be an increase in spontaneous contractile activity and presence of fused tetanic contractions, a feature more typical of well-coupled smooth muscles [581, 582]. A common ultra-structural feature of the overactive detrusor is the emergence of protrusion junctions and ultra-close abutments between the smooth muscle cells [583]. Overall, the cells may be better coupled electrically in detrusor overactivity, perhaps allowing spontaneous activity to propagate over a wider area. Bladder biopsies from overactive detrusor show a patchy denervation; some muscle bundles may be completely denervated, whilst neighbouring ones appear normal and in other areas sparser innervation is also seen [92, 579, 580, 584]. A similar pattern is seen in animal models [576, 585]. Overall, these observations suggest that response to loss of local innervation by the smooth muscle cell may explain the altered behaviour of the bladder in detrusor overactivity [575, 586].

Preclinical studies in animal models of OAB / detrusor overactivity contribute further to our understanding of the importance of neural control in this condition. The main models relevant to OAB include (i) instillation of irritative agents into the bladder during cystometry, (ii) partial bladder outflow obstruction, (iii) the spontaneously hypertensive rat, (iv) spinal cord injury, and other CNS lesions similar to those responsible for bladder dysfunction in humans [587]. Irritative agents are employed in animals to evoke a painful or irritant response, in particular through C-fibres. Both acetic acid and citric acid have been used, although the latter probably represents a better model since it is less irritant and therefore less likely to invoke an acute inflammatory response. Both agents have been shown to increase bladder contractile activity, decrease bladder capacity and reduce bladder compliance, while micturition pressure remains normal or is increased, suggesting that this model may contribute to understanding of increased bladder sensory activity, as may occur during the symptom of urgency. These effects are due to stimulation of nociceptive afferent fibres, confirmed through demonstration of increased c-fos expression in rat spinal cord and in regions of the periaqueductal grey [372, 588], an effect that can be eradicated by desensitization of TRPV1 receptors on the sensory neurones following pre-treatment with resiniferatoxin [589].

Partial bladder outflow obstruction has been achieved through application of urethral ligatures or a constricting ring that results in partial urethral occlusion, mimicking the obstruction seen in men with BPH who often develop secondry OAB [577]. The animals develop cystometric features such as increased bladder capacity and non-voiding bladder contractions, with associated histological features (muscle hypertrophy, patchy denervation and enlarged sensory neurones and parasympathetic ganglia) and detrusor functional features (spontaneous myogenic activity and altered response to stimuli) reminiscent of the human condition [586]. Afferent plasticity in animals with bladder outflow obstruction involves NGF, the content of which is increased in obstructed bladders prior to the enlargement of bladder neurones and the development of urinary frequency [590]. The relevance of NGF in the response to obstruction in animals is suggested by the finding that rats immunized with mouse NGF in order to develop autoantibodies do not develop neural plasticity and urinary frequency in response to obstruction [591]. While neuronal changes are evident in the obstructed model, further observations appear to indicate that the overactive phenotype in obstructed rats derives from a combination of increased propensity to localized muscle contraction, together with a tendency towards wider propagation of this activity in an organ that may have developed greater autonomy from central control as a result of the neuronal changes [592]. In this context, the relevance of peripheral contractile modules appear to emerge as the functional units of detrusor activity [477].

The spontaneously hypertensive rat (SHR) is a genetic model of hypertension, which is also known to exhibit abnormal bladder function; in particular, SHRs have been shown to have reduced bladder capacity and voided volume, increased urinary frequency and increased occurrence of non-voiding contractions, associated with altered detrusor innervation and physiological response [450]. Again, increased bladder smooth muscle NGF levels appear to be associated with these changes [593]. The bladders of SHRs also show increased levels of calcitonin gene-related peptide immunoreactive fibres (presumably afferent) with increased size of neuronal cross-sectional area profiles for bladder afferents in the L6–S1 dorsal root.
ganglia as well as the major pelvic ganglia [594]. The potential importance of the afferent innervation in this model can be highlighted by the finding that intrathecal application of antisense oligonucleotide against the tetrodotoxin-resistant sodium channel (Nav1.8) reduces bladder hyperactivity [595].

Spinal cord injury (SCI) in animals has been shown to result in changes in lower urinary tract function similar to those seen in humans [596]. Recovery of bladder function from the initial areflexia after SCI in animal models is dependent in part on plasticity of bladder afferent pathways and the unmasking of reflexes triggered by the normally silent capsaicin-sensitive C-fibre bladder afferent neurons, resulting in cystometric changes akin to those seen in neurogenic detrusor overactivity [596]. Studies in rats indicate that the increased excitability in the C-fibres is associated with an increase in the expression of sodium channels from a high-threshold TTX-resistant type to a low-threshold TTX-sensitive type [597].

Other animal models of CNS lesions associated with bladder dysfunction have also been developed. For example, a model of Parkinsonism secondary to 6-hydroxydopamine injection into the substantia nigra pars compacta in rats has been developed, confirming the relevance of D1/D5 dopaminergic stimulation in improving bladder capacity [531]. Furthermore, a model of bladder overactivity associated with cerebral infarction due to occlusion of the middle cerebral artery in rats has been shown to lead to significant ischaemia within the putamen and cerebral cortex, confirming the importance of these areas in the control of micturition [598]. In this latter model, a role for glutamatergic and dopaminergic stimulation in the development of bladder dysfunction has been demonstrated [598, 599]. These findings are consistent with the observation that anterior brain lesions in humans are more likely to be associated with incontinence than posterior, occipital lesions [600].

Additional evidence for the importance of emergent C-fibre contribution to afferent signalling in OAB and detrusor overactivity can be found in experimental clinical studies. For example, patients with various idiopathic and neurogenic bladder dysfunctions have reduced current perception threshold to direct bladder stimulation [601] and urethral stimulation [602] at frequencies that selectively stimulate C-fibres, indicating increased excitability in the C-fibre afferents in these patients. Similarly, ice water instillation (which excites C-fibres) into the bladder can trigger involuntary detrusor contraction in patients with neurogenic detrusor overactivity [603]. In addition, the efficacy of capsaicin and resiniferatoxin in the treatment of patients with both idiopathic and neurogenic detrusor overactivity confirms the role of C-fibres and the afferent limb of the micturition reflex in bladder storage conditions [604]. While the hyper-excitable C-fibres appear to be the conduit for the abnormal sensory signals from the overactive bladder, the origin of the sensations probably lies in the bladder wall itself, either in uncoordinated asynchronous localized detrusor contractile activity [476, 605] which may lead to urgency with negligible associated pressure rise within the bladder, or in a more co-ordinated propagation of autonomous contractile activity via emergent gap junctions providing more syncytial characteristics to the overactive detrusor [583].

b) Stress Urinary Incontinence

Stress urinary incontinence (SUI) is characterized by reduced outflow resistance during urinary storage due to weakness in the urethral sphincter mechanism. It is often associated with weakness of the pelvic floor and urethral musculature, but peripheral nerve dysfunction is also implicated, in particular pudendal nerve damage following childbirth in women [606]. Animal models have contributed to understanding of the importance of the peripheral innervation of the urethra in SUI, with development of disease models association with pudendal nerve crush and vaginal distension initiating neuropraxic nerve injury in rats [607] and mice [608]. The role of pharmacological neuromodulation in the treatment of SUI has shown that urethral function and therefore incontinence can be improved by augmenting somatic neuronal discharge using the serotonergic (5HT) and noradrenergic (NE) reuptake inhibitor duloxetine, which is thought to act in the sacral spinal cord at Onuf’s nucleus, the pudendal somatic motor nucleus of the spinal cord which is densely innervated by SHT and NE terminals [307, 609]. More recent data on the effect of the selective noradrenergic reuptake inhibitor, [S,S]-reboxetine in the treatment of SUI, indicate that the serotonergic activity of duloxetine may be redundant and that effects are dependent solely on noradrenergic reuptake inhibition [610, 611].

3. INVOLVING ABNORMAL VOIDING

- Bladder Outflow Obstruction

Bladder outflow obstruction (BOO) is typically associated with prostatic enlargement in men, although it is also seen in women following surgery for stress urinary incontinence and in children secondary to proximal urethral valves. Bladder overactivity is seen in many patients with BOO, and this storage dysfunction together with the associated neuronal changes has been described above. The voiding dysfunction per se seen in patients with BOO is caused by a combination of both passive and dynamic obstruction of the proximal urethra and, in some patients, by detrusor decompensation resulting in a deterioration in the contractile function of the bladder during voiding.

During obstructed voiding, the bladder is subject to high pressures required to expel urine through a region of high resistance. These pressures compromise detrusor
blood flow during voiding leading to periods of ischaemia and hypoxia, followed by reperfusion [612]. Recurrent cycles of ischaemia and reperfusion result in progressive neuronal damage in the bladder wall, an effect that has been seen in animal models of obstruction and bladder distension, as well as in an in vitro model in which detrusor muscle is intermittently exposed to hypoxic glycopenic perfusate followed by oxygenated glucose-containing perfusate [384, 613]. This neuronal damage initially has a patchy appearance, when it seems to be related to the development of an overactive phenotype in pigs [586]. With time, however, bladder denervation with incomplete voiding and chronic retention can develop, and this is associated with a more generalized detrusor denervation and reduced contractile response to neuronal stimulation in organ bath studies [614].

4. CO-MORBID DISORDERS

The significance of neural control mechanism in lower urinary tract dysfunction is further implied by a number of comorbid conditions that have been associated with BPS/IC and incontinence.

Patients with BPS/IC and SUI are more likely to report depressive symptoms. Findings on two validated depression measures indicate that patients with interstitial cystitis report significantly greater depressive symptomatology than healthy controls, although less than 20% notice moderate or severe depressive symptoms. This finding is consistent with the observation that patients with chronic pain experience a higher level of depressive symptoms than healthy controls and other chronically ill populations. Patients report low mood (56%), fatigue (63%), difficulty concentrating (49%), insomnia or excessive daytime sleepiness (49%) and are 3 to 4 times more likely to report suicidal thoughts than the general population [615]. The association of IC/PBS [616] and incontinence [617] with depression has been corroborated in other studies, although a more recent study suggests that, after multivariate adjustment for the influence of other urogenital symptoms, only the symptom of nocturia remains significantly associated with depression [618].

BPS/IC has also been associated with other chronic pain conditions, especially fibromyalgia [616, 619-621]. An association has also been shown for child abuse [616, 622]. Based on recent improvements in understanding of pain processing pathways in the central nervous system, and in particular the role of limbic structures, especially the anterior cingulate cortex, hippocampus and amygdala, in chronic and affective pain perception, a condition termed limbic associated pelvic pain has been proposed to explain the concurrence of these various chronic pain conditions. This limbic dysfunction is manifest both as an increased sensitivity to nociceptive afferents from pelvic organs, and as an abnormal efferent innervation of pelvic musculature, which undergoes tonic contraction as a result of limbic efferent stimulation, generating a further sensation of pain. The nociceptive afferents from these pelvic organs then follow the medial pain pathway back to the sensitized, hypervigilant limbic system. Chronic stimulation of the limbic system by pelvic pain afferents again produces an efferent contraction of the pelvic muscles, thus perpetuating the cycle [622].

VIII. BRAIN-GUT INTERACTIONS

The bidirectional interactions between different hindgut organs (urinary bladder, rectum) show both similarities and differences. The primary function of both organs is to store waste products, and to empty them in accordance with a) the state of filling as well as b) the overall state of the organism, and environmental and social constraints. While the former is accomplished by a series of hierarchal reflexes, the latter is accomplished by modulatory input from the brain to change the gain of these reflexes. While spinal and supraspinal reflexes are involved in both the regulation of bladder and rectal emptying, peripheral reflexes contained within the enteric nervous system are unique to the colorectum, while supraspinal reflexes involving the periaqueductal grey and Barrington’s nucleus (or pontine micturition center) appear to play a more prominent role in bladder emptying. Conscious perception of the state of these organs is the end result of various afferent inputs to the insular cortex, including visceral afferents, and inputs from cognitive and emotional arousal circuits. Based on this model, modulation of both emptying and perception of peripheral events in both health and disease can occur at multiple levels, and by various mechanisms. It is proposed that while peripheral changes in the end organ by inflammatory processes may play the primary role in organic disorders, central changes in modulatory circuits may play the primary role in so called functional disorders, like irritable bowel syndrome and bladder pain syndrome/interstitial cystitis (BPS/IC).

1. BACKGROUND

Functions required for the elimination of waste products are coordinated with each other, with the body’s needs and with appropriate behaviors. This integration is accomplished at different levels of the neuroaxis, from the lumbar spinal cord (reflex functions; bladder – rectal integration) to pontine nuclei such as Barrington’s nucleus (integration of bladder and rectal function with other information about the state of the organism) to the periaqueductal grey (PAG) and to cortical regions (insula, anterior cingulate cortex, ACC). The PAG and BN receive inputs from cortical and emotional brain circuits, integrating pelvic visceral function with voluntary behavior and with the emotional state of
the organism. Symptoms affecting several pelvic viscera, such as incontinence and chronic pain and discomfort related to the distal colon/rectum (irritable bowel syndrome, IBS) and to the urinary bladder (BPS/IC) often co-exist.

This section on bidirectional brain distal gut interactions tries to put rectal sensations and continence mechanisms into the larger context of regulation of homeostatic function, and highlights the differences and similarities in neural mechanisms underlying fecal and urinary continence mechanisms. The approach of providing a general framework to understand how the nervous system, in particular the human brain, processes and modulates visceral afferent input arising from two viscera derived from the embryological hindgut is useful to understand the comorbidity of fecal and urinary incontinence, and of BPS/IC and IBS.

**a) The concept of homeostatic emotions**

We humans uniquely experience feelings from each of the tissues of our bodies, including the viscera concerned with storage and evacuation of bodily waste (anorectum and the urinary bladder), because evolution has produced brain mechanisms in humans for the conscious perception of an image of the physiological condition of our bodies.

The classical term *interoception*, formerly used only to refer to visceral sensation, has been re-defined, to refer to the sense of the physiological condition of the body. Recent neuroanatomical findings indicate that all of the feelings from our bodies reflect its physiological condition and can be viewed as *homeostatic emotions*.

This includes not only visceral sensations such as hunger and thirst, but also a range of other sensations including rectal or urinary fullness, urge and pain. Like all emotions, these comprise both a (conscious) feeling and a motivation and motor response. While the anterior insula has been identified as an important neurobiological substrate involved in the conscious perception of feelings and sensations from our viscera, a set of brain circuits referred to as the emotional motor system [623] is involved in the mediation of the motor response to such visceral input.

**b) Homeostatic emotions drive behavior**

Sensory inputs that relate the body’s physiological condition, or homeostatic afferents, drive the homeostatic mechanisms that promote survival. The primordial means of regulating the evacuation of stool and urine in all vertebrates is motivated behavior, so the pathways that guide homeostatic sensory input to motivational processes must be ancient. Such behavioral motivation (and the accompanying autonomic and somatic motor changes required for the evacuation of waste products) is generated in non-humanoid mammals by a signal to the forebrain from the main homeostatic afferent integration site in the brainstem, the parabrachial nucleus (PBN).

As proposed by Craig, [624] evolution produced a new direct (spino-thalamo cortical) pathway in humans to the forebrain that surmounts the primal pathway and which generates both an affective motivation and a sensation in the limbic motor and sensory cortices (Figure 35A). The basic homeostatic (interoceptive) feelings or modalities include abdominal fullness as well as fecal and urinary urge. These feelings are the human percepts of distinct “homeostatic emotions” that directly relate to the body’s needs.

---

**Figure 35A** : Ascending projections of homeostatic afferents: Organization of interoceptive pathways. Small diameter afferents that travel with sympathetic and with parasympathetic efferent’s provide input to lamina I and NTS, respectively. In mammals, the activity of both types of afferents is integrated in the PBN, which projects to insular cortex. In non-human and human primates, a direct projection from lamina I and from the NTS exist to ventromedial thalamic nuclei (Vmpo and VMb, respectively). Neurons in these nuclei project in a topographical fashion to the mid/posterior insula. In humans, this cortical image of the homeostatic state of the organism if re-represented in the anterior insula on the same side of the brain. These representations provide the substrate for a subjective evaluation of interoceptive state.
The concept of homeostatic emotions, regardless of the valence of the emotion, is consistent with the reported activation of similar brain regions (insula, dACC) by a variety of both pleasant and unpleasant stimuli (reviewed in Vogt, 2005 [625]).

2. ORGANIZATION OF HOMEOSTATIC REFLEXES: PROCESSING OF PELVIC VISCERAL INFORMATION WITHIN HIERARCHICAL ORGANIZED HOMEOSTATIC REFLEXES

a) Enteric reflexes within the Enteric Nervous System

The hierarchal organization of homeostatic reflexes within the central neuroaxis, and which are pertinent to both anorectum and urinary bladder is shown in Figure 35B. A fundamental difference in the regulation of the distal gut and the urinary bladder is the prominent role of the enteric nervous system (ENS) as the primary reflex circuit mediating both filling and emptying of the distal colon. The ENS, which is considered the third division of the ANS [626], is made up of two ganglionated plexus situated between the different muscle layers of the gut (myenteric plexus) and the mucosa (submucosal plexus). Even in the absence of any central input, these enteric (or intrinsic) reflexes can generate proximal to distal propulsion of colonic contents (peristaltic reflex), and relaxation of the internal anal sphincter [627]. While the enteric reflex circuitry within the anorectum is unique to fecal continence, the spinal and supraspinal reflexes mediated by extrinsic afferents overlap considerably for bladder and rectum.

b) Lamina I afferents provide input to spinal and supraspinal reflexes.

The small-diameter afferent fibers that innervate the pelvic viscera course peripherally with sympathetic and parasympathetic nerves (e.g. splanchnic, pelvic, vagus), and with somatic nerves (e.g. pudendal). Many innervate the mesenteric ganglia and play a role in the communication between the central nervous system and the ganglionated plexus of the ENS. Many of these extrinsic afferents respond to chemical and mechanical stimuli over a broad range of thresholds and response slopes, so that they might be considered to represent a broad continuum of response properties. However, they can also be regarded as separable into different classes, including low-threshold, high-threshold (nociceptive), “silent” (unresponsive unless inflamed), and thermosensitive (primarily warm) [628, 629]. These classes may correspond to different functional roles and different subjective feelings. Within the gut, there are also several distinct anatomical patterns of innervation, with some fibers ending within the longitudinal muscle sheets, others ending within the enteric ganglia (intraganglionic laminar endings, IGLEs), [630] and others in close proximity to enterochromaffin [631] or to mast cells [632].

c) Spinal and supraspinal reflexes

The lamina I neurons that receive the small-diameter fiber inputs have projections within the spinal cord and brainstem (Figure 36A). In the spinal cord, their only major projection is to the sympathetic cell column of the thoracolumbar spinal cord, where autonomic preganglionic output neurons are located. In the brainstem, they project exclusively to the recognized homeostatic integration sites (e.g. caudal and rostral ventrolateral medulla, catecholamine cell groups A1-2 and A5-7, Barrington’s nucleus (“pontine micturition center”, PMC), PBN, periaqueductal gray [PAG]), which also receive parasympathetic afferent activity by way of the NTS and which are heavily interconnected with the hypothalamus and the amygdala complex (including the bed nucleus stria terminalis, BNST). The NTS that receives small-diameter fibers from parasympathetic nerves similarly projects to all of these sites. These spinal and bulbar
projections from lamina I and from the NTS provide the substrate for the hierarchical, modality-selective somato-autonomic reflexes activated by spinal small-diameter afferents that are crucial for homeostatic control of all tissues of the body [633].

Traditionally, the pontine regulation of the pelvic viscera had been considered specific for the urinary bladder and was accordingly referred to as the pontine micturition center (PMC). However, more recent work in rodents has clearly established a role of this pontine nucleus (Barrington’s nucleus, BN) as the anatomical substrate for the co-regulation of both bladder and rectosigmoid with central arousal circuits (via projections to the locus coeruleus) and with forebrain function [634] (Figure 37). Efferent projections from BN to the dorsal motor nucleus of the vagus (DMV) and to the sacral parasymathetic nucleus give this nucleus a unique role in the regulation of both upper and lower GI function through the two divisions of the parasympathetic nervous system [634]. Efferent projections from BN to the noradrenergic locus coeruleus are an important pathway by which afferent signals from both pelvic viscera can activate central arousal mechanisms, and hyperresponsiveness of these arousal circuits have been implicated in central pain amplification in functional visceral disorders such as IBS and PBS/IC [635]. The forebrain connections from the BN make this brain region ideally positioned to coordinate the activity of both pelvic viscera with behaviors that are appropriate for evacuation. Valentino et al. demonstrated evidence for the existence of 3 types of neuronal populations in BN, one of which is synaptically linked to both the bladder and the colon, and the other two populations which are specifically linked to either viscera [460, 452]. The authors concluded that these neuroanatomical substrates may underlie the central coordination of bladder and colon function and, in pathological states, may play a role in disorders characterized by a co-existence of bladder and colon symptoms.
Figure 37: Role of Barrington’s nucleus in the co-regulation of pelvic viscera. A, Barrington’s nucleus (or “pontine micturition center”, PMC) is in a unique strategic position to co-regulate upper and lower gastrointestinal function via vagal and sacral parasympathetic projections, and to influence higher brain functions via projections to cortical and emotional circuits. Close interactions with the noradrenergic locus coeruleus mediate the effect of pelvic visceral afferent input on emotional arousal circuits (ascending noradrenergic projections) as well as on descending pain modulation (descending noradrenergic projections). B, Afferent projections to Barrington’s nucleus as identified by retrograde and anterograde tracing studies. Different cell groups within Barrington’s nucleus receive either converging input from both pelvic viscera, or selective input from either bladder or rectum. BN receives descending projections from the periaqueductal grey (PAG), the lateral hypothalamus (LH), the bed nucleus striae terminalis (BNST), the medial preoptic nucleus (MPO) and cortical regions, including the ACC. From Valentino et al. [634]
d) Spino-thalamic input to interoceptive cortex

In sub-primates, ascending lamina I homeostatic afferent activity is integrated mainly in several brainstem sites (A1, PBN, PAG), which then provide an integrated signal to behavioral control regions in the forebrain. In primates, however, there is a novel, additional lamina I STT projection to a specific thalamo-cortical relay nucleus (VMPo) in posterolateral thalamus, which in turn projects to a discrete portion of dorsal posterior insular cortex (Fig. 35) [636]. This interoceptive cortex contains modality-selective representations of all afferent activity from lamina I (i.e., sympathetic afferent input) and from the NTS (i.e., parasympathetic input). In monkeys, this pathway is just visible, but in humans, it is greatly enlarged. Many functional imaging studies in primates confirm role of the insular cortex in pain, hunger, thirst, temperature, itch, muscle sensation, sensual touch, and cardiorespiratory activity, (reviewed in Craig, 2002 [636]), and it can be regarded as primary sensory cortex for the physiological condition of the body in primates. By contrast, in sub-primates the insular cortex appears to have a primordial role in modulating brainstem homeostatic integration (in PBN and other sites) and shows convergent, non-selective responses to homeostatic afferent inputs. The differences in the neuroanatomy of the insular cortex and its subregions have potentially important implications for the pathophysiology of IBS and BPS/IC. The modulation of visceral afferent input reaching the posterior insula is modulated by emotional arousal circuits and by cognitive input at the levels of the mid and anterior insula, respectively [624].

e) Spino thalamic input to limbic behavioral motor cortex

The ascending homeostatic afferent lamina I pathway in primates and humans also provides a direct thalamo-cortical pathway (by way of MDvc in medial thalamus) that activates the dACC (Fig. 35). In sub-primates, the dACC receives only integrated homeostatic input from the brainstem [636, 637]. On the basis of functional imaging and lesion studies in humans, the dACC can be directly associated with the affective aspect of visceral and somatic pain (unpleasantness), and with volition, behavioral motivation, as well as autonomic and motor responses [636,637,638,639,640]. Its interconnections with PFC regions, insular, and ventral striatal regions, along with its strong descending projections to the brainstem, particularly the PAG and the BN, strongly support the idea that it can be regarded generally as the limbic behavioral motor cortex, just as the insula can be regarded as the limbic sensory cortex [625-641].

3. CONSCIOUS PERCEPTION OF INPUT FROM THE BODY AS ASPECTS OF HOMEOSTASIS

Pain or discomfort from the pelvic viscera is often regarded as a distinct feeling, but from the perspective laid out above, pain can be viewed as another homeostatic feeling. It has characteristics exactly comparable to other feelings from the body. Pain normally originates with a change in the condition of the tissues of the body, a physiological imbalance that automatic (subconscious) homeostatic systems alone cannot rectify. It comprises both a sensation and an affective behavioral drive with accompanying autonomic adjustments. Depending on conditions, pain can be unpleasant (as usual) or pleasant (such as when it relieves an intense itch). Pain also generates characteristic reflexive motor patterns as do experimental gut and bladder stimuli. The behavioral motivation of pain is normally correlated with the intensity of the sensory input, but this can vary under different behavioral, autonomic and emotional conditions, so that pain can become intolerable or it can disappear, similar to any other homeostatic emotion (e.g., hunger). The modulation of the motivational aspect of a homeostatic emotion like pain can occur via inhibitory or excitatory prefrontal influences on brain circuits involving the dACC [640-642,643].

Viewing rectal or urinary urge and pain as homeostatic emotions provides a ready explanation of the interactions of these feelings from the body, including “gut feelings,” with other homeostatic conditions (including blood pressure, level of arousal, mood and affect) because homeostasis is an integrated, dynamic process. This conceptual perspective also provides a firm basis for explaining the interactions of pain and non-painful visceral discomfort with emotional status, emotional arousal or attention (i.e., the psychological dimension of pain), and it unifies the different conditions that can cause different types of pain/discomfort from different tissues under a common homeostatic function – the maintenance of the integrity of the body. All animals respond with emotional behavior to stimuli that in humans cause a feeling of pain [644]. An example relevant to preclinical studies in visceral pain mechanisms is the so called visceromotor reflex seen in response to colorectal or urinary bladder distension in rodents [645]. In primates, novel thalamo-cortical projections have emerged from this basic homeostatic system that provides direct pathways to encephalized cortical mechanisms for highly resolved sensations and motivations. In humans, these novel pathways are further elaborated, re-represented, and integrated with other forebrain emotional components in the anterior insula and in the orbitofrontal cortex (the fronto-insular region) (Figures 35A, B).

The concept of homeostatic emotions has considerable implications for the study of mechanisms underlying visceral pain and autonomic dysregulation in patients with symptom based (or “functional”) disorders of the GI and urinary tract. In the majority of these patients, primary symptoms (urgency, sensation of fullness, pain) are directly related to the altered perception of homeostatic feelings associated with the intestine,
rectum or urinary bladder (visceral hypersensitivity). Since rodents, the animals most commonly used in experiments to model these disorders, do not have the forebrain structures to generate the same conscious emotional feelings of humans, findings obtained in such animals (using so-called pseudo-affective reflex responses) may reflect primarily the phylogenetically shared enteric, spinal and brainstem components of homeostatic pathways (e.g. reflexes), but may provide little or no insight into the uniquely human experience of abdominal pain and discomfort, nor to the modulatory cortical influences related to this experience.

The VMpo also has a collateral influence to a portion of sensorimotor cortex (area 3a) that is intercalated between the primary somatosensory area and the primary motor area. Similarly, vagal afferent activation occurs in the lateral portion of area 3a of the primary sensorimotor region by way of the NTS and VMb. These projections can be associated with cortical control of the reflex actions of skeletal muscle in response to homeostatic afferent inputs, a role subsumed under the term “viscero-somatic” integration.

The forebrain interoceptive representation of the body’s condition in the dorsal posterior insula is successively re-represented in the middle insula and then in the right (non-dominant) anterior insula (636). Functional imaging data show that the right anterior insula is associated with subjective awareness of homeostatic emotions (e.g. visceral and somatic painful and non-painful sensations, temperature, sexual arousal, hunger, and thirst) as well as all emotions (e.g. anger, fear, disgust). This region is intimately interconnected with the dACC, which is co-active in such studies. Thus, viewing feelings from the body as homeostatic emotions enables neuroanatomical explanations of interactions with other homeostatic functions and with emotions at the level of the forebrain. Finally, recent evidence showing asymmetry in the sympathetic and parasympathetic afferent re-representations and control mechanisms in the left and right insula/orbitofrontal cortex and ACC seems to accord with the psychophysiological evidence for the forebrain asymmetry of positive and negative emotions [646]. In this context, it is of considerable interest that studies of central representation of both bladder [482] and rectal distensions [635] have repeatedly shown activation of the right ventrolateral PFC.

4. DESCENDING MODULATION OF HOMEOSTATIC REFLEXES AND FEELINGS

Lamina I neurons not only receive input via somatic and visceral afferents, but also receive descending (facilitatory and inhibitory) modulation directly from brainstem pre-autonomic sources, including serotonergic nuclei within the rostral ventral medulla and the noradrenergic pontine locus coeruleus complex (Figure 36). Indeed, lamina I and the spinal autonomic columns are the only regions in the spinal cord that receive descending modulation from the hypothalamus. Thus, the activity of lamina I neurons that ultimately produces the various feelings from the body is modulated by various tonic and phasically active, descending inhibitory and facilitatory pathways [647,648,649], whose primary purpose is control of homeostatic integration [650,651]. As pointed out by Mason [651,652,653], these serotonergic descending pathways from the PAG and ventromedial medulla are not only involved in descending pain modulation, but play a prominent role in various homeostatic functions including micturition and continence.

Recent evidence (in mice) suggests that the gain of the spino-bulbo-spinal reflex loops originating from neurokinin 1-receptor-containing lamina I neurons is not constant but can be modulated by peripheral primary afferent inputs from inflamed tissue or damaged nerves, [654] adapting the homeostatic response to the overall state of the organism. Thus, since the descending forebrain control of these pre-autonomic brainstem regions originates in brain networks associated with attention, emotion generation (i.e. the limbic system) and emotion regulation (PFC), these anatomic connections provide the basis for corticolimbic modulation of the afferent activity associated with feelings from the body, including pain and discomfort, at the spinal level as well as at the brainstem and forebrain levels (Figure 36).

5. BRAIN CIRCUITS ACTIVATED BY ACUTE VISCERAL STIMULI: EVIDENCE FROM FUNCTIONAL BRAIN IMAGING STUDIES IN HUMANS

Visceral sensations, including discomfort, hunger, fullness, early satiety, nausea, bloating or abdominal pain in humans are a subjective, conscious experience, that result from the modulation of homeostatic feelings by cognitive (attention, expectation), emotional (arousal, anxiety) and motivational factors, as well as memories of past experiences. Thus, the conscious experience is an image of the homeostatic state of the body represented in the insular cortex (Figure 35) and is further modified by these cortical and limbic inputs. In principal, altered perception of visceral stimuli could result from activity changes in visceral afferent signal processing areas alone (reflecting increased visceral afferent input to the brain from the gut), from alterations in distinct but overlapping pain modulation circuits (“central pain amplification”), or from variable combinations of these two overlapping circuitries [655,656,657] (Figure 37).

a) Activation of Regions involved in Homeostatic Emotions in Studies of the Human Brain-Gut Axis

Studies published during the past 5 years using widely
different experimental paradigms have confirmed the consistent activation of the central homeostatic afferent network consistent with the robust activation of homeostatic afferent pathways despite varying experimental paradigms and analysis techniques [658,659,660,661,662,663]. On the other hand, the variable activations of PFC and limbic regions, and the seemingly contradictory results on sex differences in reported studies is reflective of the fact that experimental paradigms and analysis techniques varied, and that the majority of these studies did not take into account cognitive and emotional aspects of pain modulation.

b) Modulation of Homeostatic Afferent Network Matrix by Cognitive and Emotional Stimuli

The brain has multiple ways to modulate the perception of afferent information and this modulation is influenced by the environmental context, the emotional state of the individual (e.g. fear, anxiety, or anger), cognitive factors (e.g. expectation, attention), or memories of previous sensory events (conditioned responses) (Figure 37A). Considerable progress has been made both on a preclinical and, more recently, on a clinical level to identify brain regions, circuits and mechanisms which play a role in the facilitation and inhibition of the subjective pain experience [649-664]. Both clinical and preclinical studies support a role for right orbitofrontal and right ventrolateral PFC in mediating inhibition of emotional and pain responses (reviewed in Lieberman et al. 2004 [643]) and for dorsolateral PFC in pain modulation [642-665].

- Cognitive Modulation

Attention. Aziz’s group (666) examined the modulatory role of attention on the brain responses to non-painful visceral (esophageal) distension in 7 healthy volunteers (6 males). Brain responses to phasic visual and esophageal stimuli were presented simultaneously while subjects were asked to focus their attention on either the esophageal or the visual stimulus (selective attention) or both (divided attention). Selective attention on the esophageal stimulus was associated with activation of sensory (somatosensory cortex) and cognitive (dACC) networks, while selective attention on the visual stimulus activated the visual cortex. During the divided attention task, more brain regions in the sensory and cognitive domains were activated to process esophageal stimuli, in comparison to those processing visual stimuli. These findings emphasize the importance of attentional processes in the modulation of sensory information from the body and the relative biological importance placed on visceral sensation, compared to other sensory modalities.

Expectation. A variety of studies in the somatic pain literature have evaluated brain responses to the expectation of an aversive stimulus [662-667, 668, 669,670]. These studies suggest that the brain can either up- or down-regulate sensory and limbic brain regions based on previous experience, familiarity with the stimulus and expected intensity [668]. Several early studies have shown some evidence of activation of the homeostatic afferent network during conditioned anticipation of a visceral stimulus [662-667]. Berman et al. studied the brain fMRI BOLD response to anticipated (cue condition) and delivered mild and moderate rectal distension in 12 healthy women and 14 female IBS patients [671]. Distension increased activity in the homeostatic brain regions and decreased activity in the infragluteal cingulate. As in previous studies comparing IBS patients and control subjects, the increases were more extensive in the IBS patients, with significant differences in midcingulate and dorsal brainstem. During cued anticipation of distension, activity decreased in the insula, dACC, amygdala and dorsal brainstem in healthy women, but not in IBS patients, consistent with a top-down modulation of homeostatic afferent networks by cortical regions. Three self-rated measures of negative affect during scanning were higher in IBS patients than healthy women (P < 0.001), and the anticipatory BOLD decreases in bilateral dorsal brainstem, centered in the pontine LCC, were inversely correlated with all three measures. The amplitude of anticipatory decrease in the LCC was associated with greater activation by subsequent distension in right orbitofrontal cortex and bilateral supragenual ACC – regions previously implicated in corticolimbic inhibition. When the cue was followed by a sham distension (e.g. no change in distension pressure from the resting pressure of 5 mmHg occurred), only IBS patients showed activation of the insula cortex, and this activation was limited to the more anterior portions of the insula. These findings are consistent with top-down modulation of the anterior insula by PFC influences, and with an enhanced top-down facilitation in IBS patients. In summary, these findings suggest that in healthy women, the brain decreases activity within the homeostatic brain matrix in expectation of a certain, inescapable pelvic pain stimulus. A failure to generate this down-regulation in IBS patients, and an inappropriate activation of the anterior insula during a sham distension, may be related to differences in cortically-mediated coping styles, emotional factors and linked arousal systems.

Yaguez et al. [672] studied brain responses during different phases of visceral aversive conditioning in 8 healthy volunteers (5 males) using fMRI. The authors used a classical conditioning paradigm in which different colored circles were used as conditioned stimuli and were paired with painful esophageal distension (learning phase), airpuff to the wrist or nothing. Brain responses during the learning phase
In summary, numerous studies have supported the hypothesis of changes in brain network connectivity. An analysis examining the covariation of these brain regions, as well as preliminary results from an effective connectivity modeling approach to the data, revealed that components of this network can be modulated differentially by top-down corticolimbic influences. These findings emphasize the importance of cognitive influences, such as expectation and memory recall in top-down modulation of brain regions involved in the processing of homeostatic information from the body.

**Hypervigilance.** Several lines of evidence indicate that IBS patients and other functional disorders have hypervigilance for symptom-relevant sensations [673]. Repeated exposure to experimental visceral stimuli can lead to decreased hypervigilance and, therefore, discomfort. In a longitudinal study of IBS patients exposed to 6 sessions of rectal inflations over a 1-year period, we examined regional cerebral blood flow to the inflations and anticipation of inflations using H215O-PET at the first and last session [674]. Subjective ratings of the rectal inflations normalized over the 12 months of the study, while IBS symptom severity did not, indicating decreased vigilance independent of changes in perceived disease activity. In response to rectal distension, stable activation of regions of the homeostatic afferent network (including thalamus and anterior insula) was observed over the 12-month period, while activity in limbic, paralimbic and pontine regions decreased. During the anticipation condition, there were significant decreases in dACC, amygdala, and dorsal brainstem (perhaps involving the LCC) activation at 12 months. One way to interpret these findings is that brain regions processing the feeling and the motivational dimension of the homeostatic emotion were affected differentially by the habituation process: while insula activation remained constant, dACC activity progressively decreased.

An analysis examining the covariation of these brain regions, as well as preliminary results from an effective connectivity modeling approach to the data, supported the hypothesis of changes in a network including the hypothalamus, amygdala, and dorsal brainstem. The fact that components of this network can be modulated differentially by top-down corticolimbic influences has important implications for a better understanding of symptom generation/modulation in functional GI disorders.

**c) Modulation of Homeostatic Emotions by Descending Modulation**

Since the beginning of the 20th century it has been known that the brain can tonically inhibit spinal cord excitability, thereby regulating the amount of peripheral sensory information reaching the central nervous system. More recent evidence has demonstrated the activity of both pain inhibitory and facilitatory mechanisms which can tonically and phasically regulate spinal cord excitability [647,648,649]. While top-down tonic pain inhibition modulation appears to predominate in healthy individuals during basal conditions, an up-regulation of descending pain facilitatory systems has been demonstrated in the maintenance of hyperalgesia in animal models of peripheral nerve injury [654]. An alteration in the balance between inhibitory and facilitatory pain modulatory systems has been proposed as a possible mechanism underlying chronic pain syndromes such as fibromyalgia [676] and IBS [677,678].

Zambreanu and coworkers were the first to demonstrate the activation of brainstem regions in the context of central sensitization in healthy human volunteers [679]. Using 3T fMRI, they compared whole brain responses, including the brainstem, to punctuate mechanical stimulation in an area of secondary hyperalgesia (induced by heat/capsaicin sensitization model) or in a control area. They found greater activation during stimulation of the hyperalgesic region in several cortical regions, including posterior insula, ACC and posterior cingulate cortex, as well as thalamus and pons. The brainstem activation was localized to the NCF (possibly involving PBN) and the PAG, brain regions that receive input from corticolimbic networks (including the rostral ACC), send projections to the rostroventral medulla and are part of a cortico-limbic-pontine pain modulation circuit [680,681] (see also Figure 36). There is preliminary evidence to suggest that patients with IBS may also show abnormal activation of brain circuits involved in pain modulation [660-682,683]. Two studies were performed by Wilder-Smith and coworkers [660-683] to study the central correlates of heterotopic pain inhibition. In the first study, they performed an fMRI study in 10 female patients with IBS (5 constipated-, 5 diarrhea-predominant bowel habit) and 10 female healthy control subjects to test the hypothesis that IBS patients show abnormal activation of diffuse noxious inhibitory control (DNIC) systems in response to a noxious stimulus [660]. DNIC activation can be quantified by the perceptual modulation of a painful stimulus (in this case noxious rectal balloon distension) by a secondary heterotypically applied nociceptive stimulus (in this case ice water immersion of the foot). They found that subjective pain ratings of rectal volume distension by the heterotypic cold pain stimulus was reduced in healthy controls but not in the IBS patient group, suggesting an inadequate activation of DNICs in the IBS patients. Following the heterotypic cold stimulus, a complex set of differences in response to rectal pain were found among the controls and the two IBS bowel habit-based sub-groups. These included decreased activation in insula, thalamus and PAG in...
the control group (perhaps reflecting the DNIC process) that was absent in the IBS patients. In the second study, similar perceptual results were found and differences were also found between IBS and controls during expectation of rectal pain, without actual distension [683].

More recent brain imaging studies in patient populations provide more direct support for alterations in cortico-limbic-pontine pain modulation networks in IBS patients leading to visceral hypersensitivity. Mayer et al. [682] examined three groups of male subjects, ulcerative colitis patients with quiescent disease (n = 9), patients with IBS (n = 9), and healthy male controls (n = 9), during actual and expected but undelivered rectal distensions using H215O-PET. This study found similar responses in all three groups in the homeostatic afferent network (anterior insula and dACC). However, IBS patients compared to both the ulcerative colitis and control groups showed consistently greater activation of limbic/paralimbic brain regions (amygdala, hypothalamus, ventral/rostral ACC, dorsomedial PFC), suggestive of increased activation of pain facilitatory pathways. In addition, the results showed activation in the ulcerative colitis and control subjects, but not IBS patients, in the lateral frontal regions and a brain region including the PAG. A connectivity analysis using structural equation modeling supported these regions acting as part of a pain inhibition network that involves lateral and medial frontal influences on the PAG.

In summary, a small group of hypothesis-driven studies aimed at evaluating specific mechanisms of visceral pain modulation (e.g. descending modulation) are beginning to demonstrate the activation of cortico-limbic-pontine networks, which may be the biological substrate of such endogenous modulation. The concept emerging from these studies is the ability of brain regions and networks involved in emotional generation (limbic circuits) as well as in emotion regulation (orbitofrontal, ventrolateral PFC) to modulate activity within the homeostatic brain matrix [655, 656]. Observations obtained with rectal and with bladder stimuli show many similarities in these activations [482]. Differences in the activation of these networks by cognitive or somatic stimuli between IBS patients and control populations suggest a possible role of such differences in the pathophysiology of enhanced visceral perception in IBS.

The concept of homeostatic emotions with a sensory feeling dimension (processed in the anterior insula) and a motivational dimension (processed in the dACC) provides a general framework to understand the interactions between peripheral afferent signals arising from the pelvic viscera, and centrally-mediated influences (including psychological factors, cognitions and emotions) on the conscious perception and associated autonomic responses to such stimuli. The deconstruction of symptoms into distinct contributions of specific brain networks mediating a variety of cognitive, emotional and motivational influences on the basic homeostatic afferent processing network may help to understand the pathophysiology of a variety of chronic disorders, including IBS and PBS/IC. A whole range of chronic disorders characterized by physical or emotional discomfort and pain (including functional visceral and somatic disorders, as well as disorders of mood and affect) can be conceptualized as disorders of homeostatic emotions. The ability to study a neurobiological substrate (e.g. brain activity) rather than relying on highly variable subjective symptoms, may make it possible to obtain insights about the role of genetic factors, receptor physiology, and drug interventions from much smaller samples of subjects, compared to epidemiological or traditional pharmacological studies.

REFERENCES

6. Lewis SA. Everything you wanted to know about the bladder epithelium but were afraid to ask. Am J Physiol Renal Physiol. [Invited Review]. 2000;278:F867-F74.

234


233. Thor KB, Hisamitsu T, Ropper JR, Tuttle P, Nielson G, deGroot WC. Selective inhibitory effects of ethylketocyclazocine on...


371. Vera PL, Nadelhaft I. Anatomical evidence for two spinal...


416. Shefchyk SJ. Spinal cord neural organization controlling the urinary bladder and striated sphincter. Prog Brain Res. 2002;137:71-82.


453. Finney SM, Stewie LH, Gillespie JI. Cholinergic activation of phasic activity in the isolated bladder: possible evidence for M3- and M2-dependent components of a motor/sensory system. BJU Int. 2007 Sep;100(3):668-78.


548. Blok BFM, Groen J, Bosch JLHR, Veltman DJ, Lammersma AA. Different brain effects during chronic and acute sacral modulation in urge incontinent patients with implanted neurostimulators. BJU Int. 2006;08:1238-43.


580. Charlton RG, Morley AR, Chambers P, Gillespie JI. Focal changes in nerve, muscle and connective tissue in normal and unstable human bladder. BJU Int. 1999 Dec;84(9):75-60.


Committee 4

Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse

Chairman

H. KOELBL (Germany)
V. NITTI (USA)

Members

K. BAESSLER (Germany),
S. SALVATORE (Italy),
A. SULTAN (U.K),
O. YAMAGUCHI (Japan)
CONTENTS

PREFACE

A. THE OVERACTIVE BLADDER

B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR

C. PATHOPHYSIOLOGY OF STRESS INCONTINENCE IN WOMEN: URETHRAL STRUCTURE, SUPPORT AND FUNCTION

D. PELVIC ORGAN PROLAPSE

E. FAECAL INCONTINENCE: GASTROENTEROLOGICAL PERSPECTIVE

F. CHILDBIRTH AND FAECAL INCONTINENCE

G. PATHOPHYSIOLOGY OF INCONTINENCE IN MEN

H. CAUSES OF TRANSIENT INCONTINENCE IN OLDER ADULTS

REFERENCES

LIST OF ABBREVIATIONS

ACS  American College of Surgeons
ANS  Autonomic Nervous System
ACh  Acetylcholine
AChE  Acetylcholinesterase
ASR  Anal Sphincter Rupture
ATP  Adenosine Triphosphate
BPH  Benign Prostatic Hyperplasia
BPO  Benign Prostatic Obstruction
CNS  Central Nervous System
CI  Confidence Interval
cAMP  Cyclic Adenosine Monophosphate
DO  Detrusor Overactivity
DM  Diabetes Mellitus
DSD  Detrusor Sphincter Dyssynergia
EMG  Electromyography
EAS  External Anal Sphincter
IBD  Inflammatory Bowel Disease
IBS  Irritable Bowel Syndrome
IAS  Internal Anal Sphincter
ICI  International Consultation on Incontinence
IPSS  International Prostate Symptom Score
ISD  Intrinsic Sphincter Deficiency
LUTS  Lower Urinary Tract Symptoms
MRI  Magnetic Resonance Imaging
MS  Multiple Sclerosis
NO  Nitric Oxide
NOS  Nitric Oxide Synthase
NGF  Nerve Growth Factor
OAB  Overactive Bladder
PMC  Pontine Micturition Center
PFD  Pelvic Floor Dysfunction
POP  Pelvic Organ Prolapse
POPQ  Pelvic Organ Prolapse Quantitation
PNTML  Pudendal Nerve Motor Terminal Motor Latency
RRP  Radical Retropubic Prostatectomy
RCOG  Royal College of Obstetricians and Gynaecologists
SSRI  Selective Serotonin Re-uptake Inhibitor
STRESS URINARY INCONTINENCE
STRESS Urinary Incontinence
TURP  Transurethral Prostatectomy
TUIP  Transurethral Incision of the Prostate
TTX  Tetrodotoxin
VLPP  Valsalva Leak Point Pressure
USI  Urodynamic Stress Incontinence
For this fourth International Consultation on Incontinence, the Committee on Pathophysiology is organized to consider causes of pelvic prolapse and faecal, as well as urinary incontinence. For any woman, childbirth and pregnancy contribute to the development of urinary as well as faecal incontinence; therefore these two conditions have been naturally integrated into a single chapter. Special problems of the elderly have also been included for this ICI. We have also been asked to consider pathophysiological mechanisms underlying pelvic organ prolapse. These three areas urinary incontinence, pelvic organ prolapse and faecal incontinence, are closely interconnected by virtue of similar location within the body. In the case of women, childbirth and pregnancy may contribute to one or all of these conditions. Yet there are also neurological factors, and gender specific factors which must be considered in the evaluation of any given patient. Thus, we have tried to provide a balanced overview of the subject, keeping in mind both the common and the distinct qualities of the various conditions, while organizing them in a logical, narrative manner that make any one section of the chapter easy to read.

In the area of women's stress incontinence, intrinsic urethral function continues to receive increased attention. As newer pharmacological agents to provide neural stimulation of the striated sphincter appear, and the limits of vaginal suspensory operations for correction of urethral dysfunction are reported, considerations of pathophysiology have shifted from the 50 year old paradigm regarding urethral mobility associated with vaginal prolapse in the genesis of incontinence. However, these newer directions should be considered against the background of half a century of observation and practical clinical experience. We therefore continue to recommend a balanced approach.

In the area of men's incontinence, the greatest concern remains the problem of sphincter injury following radical pelvic surgery and brachytherapy. While many thousands of procedures are performed annually, our knowledge about sphincter anatomy and function has progressed little. Instead, empirical methods of treatment and hopefully prevention have been advanced to treat affected individuals, and insofar as prosthetic implants remain an effective method of treatment, enthusiasm for further basic research into male sphincter function remains limited. In contrast to this kind of sphincter injury, the causes of incontinence associated with bladder outlet obstruction and prostatic enlargement have been well characterized, and little new knowledge has appeared in recent years. Finally, with respect to faecal incontinence and pelvic organ prolapse, two areas for this Committee's concern, the sections addressing them may appear to provide some overlap and possible redundancy.
A. THE OVERACTIVE BLADDER

I. INTRODUCTION

The most common problem with urine storage arises when the bladder fails to remain relaxed until an appropriate time for micturition. The symptom syndrome is called “overactive bladder” (OAB), which refers to the symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia [1]. According to the ICS terminology of 2002 [1], OAB symptoms are suggestive, but not diagnostic, of urodynamically demonstrable detrusor overactivity (involuntary detrusor contraction) during the filling phase which may be spontaneous or provoked. This may be further characterized as neurogenic when there is a relevant neurological condition. Common neurogenic causes include stroke, Parkinson’s disease, multiple sclerosis and spinal injury. Non-neurogenic etiologies may be related to outflow obstruction, aging estrogen deficiency, female anatomical incontinence, but most cases are idiopathic. This section focuses on pathophysiology of the overactive bladder and reviews studies that have provided insight into the mechanisms underlying bladder overactivity and OAB symptoms.

II. NEUROGENIC DETRUSOR OVERACTIVITY

1. SUPRAPONTINE LESIONS (Figure 1)

It is generally accepted that suprapontine lesions such as cerebrovascular disease and Parkinson’s disease produce detrusor overactivity. The patient with a suprapontine lesion loses voluntary inhibition of micturition, which corresponds to uninhibited overactive bladder according to a classification by Fall et al [2, 3].

Brain transaction studies in animals with an intact neuroaxis showed that suprapontine areas generally exert a tonic inhibitory influence on the pontine micturition center (PMC) [4, 5]. In humans, the cerebral cortex (medial frontal lobes) and the basal ganglia are thought to suppress the micturition reflex. Thus, damage to the brain induces bladder overactivity by reducing suprapontine inhibition.

The mechanism of overactive bladder induced by cerebral infarction or Parkinson’s disease has been further studied using animal models [6-8]. In the central nervous system, a glutamatergic pathway is known to play a role in both excitatory and inhibitory regulation of micturition [6, 9, 10]. Central dopaminergic pathways also have dual excitatory and inhibitory influences on reflex bladder activity [11]. It has been demonstrated that in the rat cerebral infarction model, bladder overactivity is mediated by NMDA glutamatergic and D2 dopaminergic excitatory mechanisms [8], suggesting that cerebral infarction may alter a balance between the facilitatory and inhibitory mechanism that results in up regulation of an excitatory pathway and down regulation of a tonic inhibitory pathway. Similarly, neuropharmacological studies in a monkey model for Parkinson’s disease have shown that detrusor overactivity may result from a loss of dopaminergic inhibition mediated by D1 receptors [4, 7].

2. SPINAL CORD LESIONS (Figure 2)

A spinal cord lesion above the lumbosacral level eliminates voluntary and supraspinal control of micturition, leading to bladder overactivity mediated by spinal reflex pathways [4, 12]. Disruption below the level of the pons leads to unsustained and uncoordinated detrusor contractions often associated with uncoordinated sphincter overactivity (detrusor-sphincter dyssynergia, DSD). Impairment or loss of bladder sensation is a typical feature.

Electrophysiologic studies of the effect of capsaicin on voiding reflexes have shown that the afferent limb of the micturition reflex in chronic spinal cats, consists of unmyelinated C-fibre afferents, whereas in normal cats it consists of myelinated A-delta afferents [4, 9, 14]. Since C-fibre bladder afferents in the cat do not usually respond to bladder distension [15], a considerable reorganization of reflex connections takes place in the spinal cord following the interruption of descending pathways from the brain. In humans with spinal cord lesions, neurogenic detrusor overactivity
is likely to be mediated by capsaicin-sensitive C-fibre afferents. Clinical experience with capsaicin supports the role of these C-fibre afferents in the pathophysiology of neurogenic bladder overactivity. Capsaicin has been used for the treatment of neurogenic bladder overactivity in patients with spinal cord injury or multiple sclerosis. When administered intravesically, capsaicin increases bladder capacity, reduces micturition contraction pressure, decreases autonomic dysreflexia and reduces the frequency of incontinence [16-18]. More recently, resiniferatoxin, an ultra-potent analogue of capsaicin, has been also used [19, 20].

In addition to changes in reflex pathways (i.e., C-fibre afferent-mediated micturition reflex), it has been demonstrated that a functional outlet obstruction resulting from DSD may alter the properties of bladder afferent neurons. For example, in chronic spinal animals, afferent neurons innervating the bladder increase in size, a change prevented by urinary diversion [21]. These observations suggest that some factors released in the obstructed bladder may be responsible for the neural change. Subsequently, the factors have been identified as nerve growth factor (NGF) [22].

Another type of plasticity in C-fibre bladder afferent neurons is evident as a change in excitability. Whole cell-patch clamp recordings have shown that hypertrophied bladder afferent neurons exhibit increased excitability due to a shift in expression of sodium channels from high-threshold Tetrodotoxin (TTX) resistant to low-threshold TTX-sensitive channels [23, 24]. In normal animals, TTX-resistant sodium channels are mainly expressed in C-fibre afferent neurons [25, 26].

III. NON-NEUROGENIC DETRUSOR OVERACTIVITY

1. OUTFLOW OBSTRUCTION (Figure 3)

Detrusor overactivity associated with outflow obstruction has long been recognized [27]. A recent study shows that approximately 50% of patients with symptomatic benign prostatic enlargement exhibit bladder outlet obstruction [28]. However, detrusor overactivity and OAB symptoms often occur independently of bladder outlet obstruction. Thus, detrusor overactivity and OAB symptoms in the male patients may result from outflow obstruction or a primary bladder abnormality [29]. The following review focuses on studies supporting outflow obstruction as the causative factor for detrusor overactivity.

a) Partial denervation

The hypothesis that denervation underlies obstructed non-neurogenic detrusor overactivity comes from the morphological studies of Gosling et al [30]. They demonstrated a reduction in acetylcholine esterase (AChE) staining nerves in obstructed human bladder muscle. Pharmacological studies performed on detrusor biopsies from patients with bladder outlet obstruction [31] have shown that muscle strips from patients with detrusor overactivity exhibit denervation supersensitivity to acetylcholine (the main excitatory neurotransmitter to the human bladder) and a reduction in nerve-mediated responses, as compared with strips from normal, stable bladder. Similar pharmacological and morphological evidences of denervation have been shown in studies using animal models of detrusor overactivity caused by urethral obstruction [32-34], demonstrating that there were significant increases in sensitivity to acetylcholine and other agonists such as high potassium, and the response to intramural nerve stimulation was significantly reduced (despite increased responsiveness of the muscle to exogenous acetylcholine), with both cholinergic and non-cho-
linergic (purinergic) neurotransmission being affected. These changes suggest a post-functional supersensitivity secondary to partial denervation of the obstructed detrusor muscle, and may be the basis of unstable bladder behaviour.

However, it is not clear how denervation develops in outflow obstruction. One possibility is that there is a reduction of blood flow due to the effect of raised intravesical pressure during voiding or the increased tissue pressure of hypertrophied bladder wall during filling. Such haemodynamic change has been demonstrated in a canine model of outlet obstruction [35]. Greenland and Brading also showed that bladder-outflow obstruction is associated with repeated episodes of prolonged detrusor ischemia in pigs [36]. Thus, the role of ischemia in changes in bladder function and structure following outlet obstruction has been well characterized. A more recent study using iNOS knockout mice [37] suggests that generation of NO soon after obstruction is necessary to prevent detrusor dysfunction, since NO produces vasodilatation and decreases platelet aggregation.

b) Changes in detrusor muscle contractility

Obstruction can alter the properties of the detrusor muscle. In the obstructed guinea pig bladder, the detrusor muscle shows a decrease in force development, suggesting a deterioration in detrusor contractility [38]. The cable properties of detrusor cells are also changed [39]. The length constant is reduced, suggesting a decrease in cell to cell propagation of electrical activity. The time constant of the cell membrane is prolonged, leading to greater instability of membrane potential. This may facilitate depolarization of the cell and activate L-type calcium channels. Such a mechanism could be further amplified by depolarizing currents supplied by a purinergic system, which has been shown to emerge in human obstructed bladder [40]. These findings suggest that, in general, individual cells are more irritable while synchronous activation is damaged, findings that are consistent with the abnormal bladder behaviour of obstructed bladder, i.e., the decreased contractility coexisting with bladder overactivity. In this respect, the changes in intercellular communication through gap junction have been evaluated. Gap junction protein, connexin 43(C?43) was shown to decrease in rat detrusor muscle with chronic partial bladder outlet obstruction [41]. However, other studies indicate that connexin mRNA and C?43 protein are increased in a rat model of bladder overactivity induced by outflow obstruction [42, 43].

Recently, a role of Rho-kinase in obstruction-induced changes in detrusor muscle contractility has received attention. One main pathway for inhibition of myosin light chain phosphatase and indication of Ca2+ sensitization involves a specific kinase(Rho-kinase), which is activated by RhoA via G-protein coupled receptors [44-46]. Ca2+ sensitization, mediated by the RhoA/Rho-kinase pathway, enables the detrusor muscle to contract at low intracellular Ca2+ concentration. It has been demonstrated that partial bladder outlet obstruction increased the expression of RhoA and Rho-kinase in rabbits [47, 48]. This upregulation of Rho-kinase may contribute to increased detrusor muscle tone or sustained contraction induced by the different contractile transmitter/mediators in the obstructed bladder [47, 49, 50].

c) C-fibre-mediated micturition reflex

A different interpretation for the mechanism underlying the development of detrusor overactivity is a possible reorganization of spinal micturition reflexes following outlet obstruction. Partial urethral ligation in a rat model results in hypertrophy of bladder afferent as well as efferent neurons [22, 51]. This hypertrophy of bladder neurons is accompanied by increased expression of NGF in the bladder as well as in sacral autonomic centres [52], leading to facilitation of the spinal micturition reflex [22, 52]. Similarly, in patients with outflow obstruction, a spinal reflex may be responsible for the development of detrusor overactivity. This reflex is thought to be mediated by C-fibres and clinically detected as a positive response to the ice water test. C-fibre neurons are also known to contain tachykinin and other peptides as neurotransmitters. It has been suggested that in rats with bladder outlet obstruction, tachykinins can influence via NK receptors both the spinal and supraspinal control of the bladder [53, 54].

With regard to the possible mechanisms for activation of afferent C-fibre nerves, Araki et al suggest a role for the epithelial sodium channel(ENaC) expressed in human urinary bladder urothelium [55]. They found that the expression levels of alpha-ENaC, beta-ENaC and gamma-ENaC were significantly greater in the obstructed bladders than those in controls. In addition, the quantified ENaC expression was shown to correlate significantly with the storage symptom score. Thus, the ENaC expressed in the bladder urothelium might be implicated in the mechanosensory transduction in the bladder afferent pathway, thereby inducing detrusor overactivity by outflow obstruction [55].

2. AGING

Major epidemiologic studies [56-58] indicate that the prevalence of OAB in both men and women increases with age. A study of men and women without underlying disease causing micturition disorder shows that storage symptom scores also increase with age, suggesting that bladder function in both sexes is subject to common age related alterations [59]. However, in the elderly, the boundaries between neurogenic and non-neurogenic are uncertain, since age associated neurogenic diseases such as subclinical cerebrovascular disorders, autonomic neuropathy and chronic brain failure commonly occur.
Computerized tomography, magnetic resonance imaging or functional brain imaging sometimes can detect the presence of cerebral lesions in elderly patients with detrusor overactivity [60, 61]. This may distinguish neurogenic from idiopathic detrusor overactivity in a considerable number of older patients.

With regard to aging-related detrusor overactivity, Elbadawi et al. have proposed a possible explanation based on detailed ultrastructural study [62-64]. Electron microscopic findings of detrusor biopsies have revealed a characteristic structural pattern in specimens from the elderly with detrusor overactivity. The main ultrastructural features of this dysfunctional pattern were abundant distinctive protrusion junctions and abutments which it was proposed mediated electrical coupling between the muscle cells and were involved in generation of myogenic contraction in the overactive bladder. In addition, if the patients had impaired detrusor contractility, there was superimposed widespread degeneration of muscle cells and nerve axons, which matched the special group of elderly patients with DO (Detrusor Overactivity) [65].

Age-dependent alterations in detrusor function have also been evaluated. Cystometry in conscious rats shows that bladder compliance decreases with aging [66]. In the rat detrusor muscle, the relaxant response to noradrenaline or isoproterenol has been shown to decrease with age, a change which may be related to decreased density of beta-adrenoceptors and decreased cyclic adenosine Monophosphate (cAMP) production [67]. In addition, age-related changes in cholinergic and purinergic neurotransmission have been studied recently in human detrusor muscle, showing that during electrical nerve stimulation, acetylcholine (Ach) release is decreased while ATP release is increased with aging [68, 69]. These changes in neurotransmission may contribute to the changes in bladder function in the elderly.

3. ESTROGEN DEFICIENCY

Lower urinary tract symptoms (LUTS) are common in elderly women. Menopause and subsequent estrogen deficiency have been implicated in the etiology of LUTS such as OAB symptoms. There have been few controlled trials to confirm the impact of -estradiol estrogen therapy on OAB. However, in a placebo-controlled trial of 17 vaginal tablets, the LUTS of frequency, urgency and urge incontinence significantly improved in the estradiol-treated group [70]. A meta-analysis of the effects of estrogen therapy on symptoms suggestive of OAB in postmenopausal women also showed that estrogen therapy was associated with significant improvements in all symptoms of OAB [71]. These studies suggest that the menopause at least has a significant role in the development of bladder overactivity and OAB symptoms.

Estrogen receptors (ERs) have been identified in the bladder and urethra [72, 73]. The mechanisms producing the effects of estrogen on bladder function have yet to be elucidated, but estrogen can influence bladder contractility in animals [74]. Particularly, bladder compliance has been to decrease with estrogen deprivation [75-77]. The effects of oophorectomy and estrogen replacement on the function of Rho-kinase in rat bladder smooth muscle have been investigated, demonstrating that estrogen might inhibit the function of Rho-kinase in bladder smooth muscle [78]. Since Rho-kinase plays an important role in the regulation of detrusor muscle tone [49, 50], this finding suggests that if estrogen deficiency results in increased Rho-kinase activity, detrusor muscle tone increases, thereby decreasing bladder compliance: features suggestive of bladder overactivity. In addition, a recent study [79] of the female rat bladder showed that as a result of estrogen deficiency, stretch-induced acetylcholine(Ach) release possibly from the urothelium increased, which may be a contributing factor to the development of detrusor overactivity (described later). It was also demonstrated that Ach release from cholinergic nerves was decreased by ovariectomy [79], suggesting that reduced Ach release from cholinergic nerves may cause the decrease in detrusor contractility. This may explain an abnormal bladder behaviour in elderly women that shows a coexistence of detrusor overactivity and impaired contractility [65].

4. PELVIC FLOOR DISORDERS

Detrusor overactivity is known to be associated with female stress urinary incontinence as a result of pelvic floor relaxation. This condition is called “mixed incontinence” which is defined as the combination of stress and urgency incontinence. Mixed incontinence accounts for approximately 33% of all cases of incontinence in women [80]. Successful surgical repair of stress incontinence (Burch colposuspension, TVT, etc) is associated with the cure of the urgency incontinence in 50% to 85% of patients [80-84].

This clinical experience suggests a connection between urethral afferents and the micturition reflex. Barrington reported that running water through the urethra or distension of the proximal urethra caused contraction of the detrusor in the cat [85]. Jung et al. also showed that in the rats urethral perfusion facilitated detrusor activity, and that intraurethral lidocaine(1%) caused a significant decrease in bladder contraction frequency [86]. These studies suggest that mechanosensitive afferent nerves activated by fluid entering the urethra can increase the excitability of the micturition reflex. In patients with stress incontinence, urine easily enters the posterior urethra, which may induce involuntary detrusor contraction and urgency to void. This mechanism is assumed to involve the pathophysiology of mixed incontinence.
5. IDIOPATHIC DETRUSOR OVERACTIVITY (Figure 4)

The diagnosis of idiopathic detrusor overactivity requires the exclusion of all known causes, but this should include all situations where etiology is unknown. Thus, the term is used to apply to a wide range of different conditions that may have a common final pathophysiologic pathway [87]. The following mechanisms are considered to be involved in the pathophysiology of idiopathic detrusor overactivity.

a) Myogenic basis

Brading and Turner [88, 89] have emphasized that myogenic changes (regardless of etiology) may contribute to the pathophysiology of idiopathic detrusor overactivity. On the basis of observation that denervation is consistently found in detrusor biopsy specimen from patients with various forms of non-neurogenic detrusor overactivity [90], they have proposed that partial denervation of the detrusor may alter the properties of smooth muscle, leading to increased excitability and increased coupling between cells. Thus, local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. However, electrophysiological studies [91] have shown that gap junction coupling is reduced rather than increased in detrusor muscle from patients with detrusor overactivity, suggesting the opposite effect on intercellular communication. Thus, it remains to be elucidated whether local activity spreads throughout the bladder wall.

In addition, this local contraction in the bladder wall has been shown to generate afferent discharge [92]. Recently, localized bladder activity was assessed by the micromotion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group [93]. This observation suggests that localized distortion of the bladder wall simulates afferent activity, which would precipitate a feeling of urgency and detrusor overactivity [93-95].

Thus, as Brading has stated [88], the changes in smooth muscle properties seem to be a necessary prerequisite for the production of detrusor overactivity.

b) Urothelial afferent function

Recently, the roles of the urothelium and suburothelial myofibroblasts in afferent activation have become the focus of intense interest. The C-fibre afferents generally have endings in the suburothelial layer of the bladder wall, but in some cases, they also penetrate the urothelium [96, 97]. Ferguson et al [98] demonstrated that ATP was released from the urothelium by bladder distension. In addition, ATP receptors(P2X3) are expressed on sensory afferent nerves [99, 100]. Thus, bladder filling causes a release of ATP from the urothelium, and ATP, in turn, can activate P2X3 receptors on afferent nerve terminals to evoke a neural discharge. Supporting this view, P2X3-deficient mice exhibit marked bladder hyporeflexia, associated with decreased voiding frequency and increased bladder capacity [101, 102].

In addition to ATP, prostanoids and nitric oxide(NO) are synthesized locally in both mucosa and muscle, and they are also released by bladder distension [103-106]. It is most likely that a cascade of stimulatory (eg.ATP, prostanoids, tachykinins) and inhibitory (eg.NO) mediators are involved in the transduction mechanisms underlying the activation of sensory afferent fibres during bladder filling [107].
This urothelial afferent transduction process suggests that up-regulation of the afferent activation mechanisms (e.g., an increased generation/release of ATP, increased sensitivity of afferent nerves to mediators, increased number of afferent nerves) can induce detrusor overactivity, causing the symptoms of OAB. Smet et al [108] have shown that the density of nerve fibres immunoreactive for substance P and CGRP was significantly higher in women with idiopathic detrusor overactivity than in normal age-matched women.

Furthermore, intravesical vanilloids (capsaicin and resiniferatoxin) have been shown to improve OAB symptoms in patients with idiopathic detrusor overactivity as well as with hypersensitivity disorders [109-111]. These studies suggest that C-fibres play an important role in idiopathic detrusor overactivity.

This sensory process is more complex than originally thought. A suburothelial layer of myofibroblasts (interstitial cells) that from a functional syncitium through C?43 gap junction can be identified in the bladder wall [112, 113]. These myofibroblasts make close appositions to unmyelinated nerves (afferent C-fibre nerves) [112]. The studies investigating human myofibroblasts show that the cells can respond to ATP by generating an intracellular Ca\(^{2+}\) transient, which is mediated by a P2Y receptor, most likely including a P2Y6 [114, 115]. On the basis of these observations, it has been hypothesized that the close relation between nerves and myofibroblasts allows for an amplification of the afferent system in its response to stimulatory mediators such as ATP.

c) Muscarinic mechanisms

Recent evidence supports a role for muscarinic mechanisms in urothelial sensory function. As mentioned previously, the bladder urothelium releases signalling molecules (ATP, prostaglandin, etc) that are considered to act on underling afferent nerve fibres. Acetylcholine (Ach) is one of these urothelial signalling molecules [116, 117]. Recently, several studies [116-118] have shown the presence of Ach-synthesizing enzymes (ChAT, CarAT) in the bladder urothelium. Yoshida et al. [116] found by microdialysis technique that there is a basal Ach release in human bladder, and that the released Ach was of non-neuronal origin, at least partly, generated by the urothelium. This non-neuronal release of Ach was shown to increase when bladder strips with intact urothelium were stretched [116], implying that the shear stress of the urothelium during distension of the bladder may be one of the releasing mechanisms.

Muscarinic receptors (mRNA and protein levels) are found in the urothelium [119-122]. The receptor subtypes identified by radioligand binding have been demonstrated to be predominant M2 receptors with a minor population of M3 and M1 receptors [120]. Furthermore, one study [122] showed M2 and M3 receptor immunoreactivity on suburothelial myofibroblast-like cells in the human bladder.

Thus, Ach released from the urothelium can activate muscarinic receptors in the urothelium in an autocrine fashion. Activation of muscarinic receptors in the urothelium releases substances (e.g., ATP) that modulate afferent nerves [123].

Ach and ATP released from the urothelium can activate muscarinic receptors and P2Y receptors, respectively on myofibroblasts that may be involved in the transfer of information between the urothelium and suburothelial afferent nerves [115]. In addition, Ach could be expected to enhance the myogenic localized activity which may increase firing of afferent nerves [92].

Based on this evidence, it can be assumed that an increase in Ach release from the urothelium and/or upregulation of muscarinic receptors in the urothelium as well as in suburothelial myofibroblasts may increase afferent nerve activity and contribute to the development of detrusor overactivity.

Supporting this view, Yoshida et al [116] showed that in isolated human detrusor, the non-neuronal Ach release was age-dependent and significantly higher in bladders from old (>65 years) than from young (<65 years) patients. These age-related changes in Ach release may contribute to the increased prevalence of OAB in the elderly. Mukerji et al. [122] also showed a significantly increased M2 and M3 muscarinic receptor immunoreactivity in myofibroblasts-like cells in bladder specimens from patients with idiopathic detrusor overactivity as compared with that in controls. Furthermore, the increase in M2 and M3 immunostaining in myofibroblasts significantly correlated with the urgency score.

6. PATHOPHYSIOLOGY OF NOCTURIA

Nocturia is now recognised as a clinical entity in its own right [124], and is highly prevalent and bothersome condition [125]. Whilst it may often co-exist with other LUTS, its pathophysiology is complex and multifactorial. Patients may experience nocturia for a wide variety of reasons [124], and it is crucial that the physician accurately identify the pathophysiology of the condition in each individual. This may include such diverse causes as endocrine disorders, sleep problems, OAB, BPO and so on, However, there is an increasing body of literature indicating that the most prevalent cause of nocturia is nocturnal polyuria (overproduction of urine at night). Half of all adults experience nocturia [125], and studies show that as many as 84% of these have nocturnal polyuria, either alone or in combination with other conditions [126-129]. Amongst women with a diagnosis of OAB, around 62% have nocturnal polyuria [129] amongst men with a diagnosis of BPO, up to 95% have nocturnal polyuria [130]. However, if patients have a diagnosis of BPO...
or OAB, the additional – or in some cases, only – true causal factor, nocturnal polyuria, can be overlooked.

This lack of awareness amongst physicians of the need to check for, and treat, nocturnal polyuria, can mean that for many patients, prescribed therapies (eg α1-blockers and anticholinergics) do not meaningfully improve their nocturia. Brubaker & Fitzgerald (2007) [129] report that, in the 62% of their OAB patients who had a nocturnal polyuria, solifenacin monotherapy led to no significant improvement in nocturia compared with placebo. Furthermore, discontinuation and non-adherence rates on OAB therapy are notably high, with only 32% on oxybutinin IR therapy adhering past 30 days [131]. Whilst poor adherence is a challenge that exists throughout the medical field, 68% discontinuation within a month is an unacceptably high rate, and may reflect the fact that patients do not perceive their medication as useful. The case is similar in BPO, with failure of traditional therapies often being attributable to the presence of underlying nocturnal polyuria: Yoong et al (2005) [132] report that 85% of BPO patients with nocturia unresponsive to α1-blocker treatment have nocturnal polyuria. Surgery (TURP) and traditional pharmacological therapies for BPO therefore frequently fail to provide a significant reduction in night-time voiding [133, 134].

Since nocturia is reported to be one of the most bothersome of LUTS [135, 136], it is crucial that patients are adequately treated. However, confusion or lack of awareness amongst physicians regarding the likely pathophysiology of nocturia means that many patients are not prescribed therapy that can improve their condition, and that they continue to experience night-time voiding to the detriment of their daytime quality of life. Patients may then assume that their nocturia cannot be treated, rather than continuing to seek help by requesting that their doctor reassess their condition. Steps to raise physicians’ awareness of the pathophysiology of nocturia should therefore be taken in order to improve the standard of care provided to patients.

B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR

Reduction in both perinatal and maternal mortality rates in recent decades has focused increasing attention on maternal morbidity and the long-term sequelae of childbirth. Antenatal education encourages expectant mothers to anticipate normal vaginal delivery, leading to an early restoration of normal pelvic floor function after the performance of routine pelvic floor exercises. Not least because of improved investigative techniques available during the past decade, the incidence and mechanisms of obstetric injury to the pelvic floor have come under scrutiny. A survey of female British obstetricians [137] revealed that one third indicated a personal preference for elective caesarean delivery of their own hypothetical uncomplicated singleton pregnancy; a general fear of pelvic floor trauma was cited as the most common reason for this choice. Despite being based on incomplete prognostic data, this sentiment may be echoed increasingly among obstetric patients and may lead to an unselective, and even misguided, increase in caesarean delivery rates.

Epidemiological studies have reported prevalence of stress incontinence ranging from 23 to 67 percent during pregnancy and 6 to 29 percent after childbirth, but little is known about how the condition affects women at this time. However, the prevalence of urinary incontinence may be nearly the same 8 weeks postpartum as during pregnancy.

About half of all women develop transient urinary incontinence during pregnancy. Three months postpartum, the prevalence and incidence rates of urinary incontinence are 9% to 31% and 7% to 15%, respectively. Antenatal incontinence increases the risk of postpartum incontinence, which in turn increases the risk of long-term persistent incontinence. After the first delivery, women delivered vaginally have two-fold more incontinence than those delivered by caesarean. The protective effect of caesarean on urinary incontinence may dissipate after further deliveries, decreases with age, and is not present in older women. Data are mixed about whether caesarean done before labour confers greater protection than caesarean done after labour. To understand the true impact of caesarean delivery on urinary incontinence, future studies must compare incontinence by planned (not actual) delivery modes, consider a woman’s entire reproductive career, focus on leakage severe enough to be problematic, consider other bladder symptoms as well as incontinence, and take into account other risk factors, particularly ante partum urinary incontinence. [138]

Caesarean section rates are progressively rising in many parts of the world. One suggested reason is increasing requests by women for caesarean section in the absence of clear medical indications, such as placenta praevia, HIV infection, contracted pelvis and, arguably, breech presentation or previous caesarean section. The reported benefits of planned caesarean section include greater safety for the baby, less pelvic floor trauma for the mother, avoidance of labour pain and convenience. The potential disadvantages, from observational studies, include increased risk of major morbidity or mortality for the mother, adverse psychological sequelae, and problems in subsequent pregnancies, including uterine scar rupture and greater risk of stillbirth and neonatal morbidity. An unbiased assessment of advantages and disadvantages would assist discussion of what has become a contentious issue in modern obstetrics.
Lavender et al. assessed, from randomised trials, the effects on perinatal and maternal morbidity and mortality, and on maternal psychological morbidity, of planned caesarean delivery versus planned vaginal birth in women with no clear clinical indication for caesarean section. A search of the Cochrane Pregnancy and Childbirth Group’s Trials Register (December 2005), MEDLINE (1974 to April 2005), EMBASE (1974 to April 2005), CINAHL (1982 to April 2005) and PsycNFO (1887 to April 2005) was carried out. Studies were selected for comparisons of intention to perform caesarean section and intention for women to give birth vaginally; random allocation to treatment and control groups; adequate allocation concealment; women at term with single fetuses with cephalic presentations and no clear medical indication for caesarean section. No studies were identified that met the inclusion criteria. Thus, there is no evidence from randomised controlled trials, upon which to base any practice recommendations regarding planned caesarean section for non-medical reasons at term. In the absence of trial data, there is an urgent need for a systematic review of observational studies and a synthesis of qualitative data to better assess the short- and long-term effects of caesarean section and vaginal birth. [139]

Lal et al. compared the incidence and severity of anal incontinence in primiparas after caesarean delivery versus spontaneous vaginal delivery. The trial comprised 184 primiparas who delivered by caesarean (104 emergency, 80 elective) and 100 who delivered vaginally were interviewed 10 +/- 2 months postpartum. Anal incontinence assessed by a comprehensive bowel function questionnaire was first present in nine (5%) mothers after caesarean delivery and eight (8%) after vaginal delivery (relative risk 0.611, 95% confidence interval 0.25, 1.53). Severe symptoms necessitating pad use affected two (3%) mothers after elective caesarean and one (1%) after vaginal delivery. Two (3%) mothers after elective caesarean, one (1%) after emergency caesarean, and two (2%) after vaginal delivery had at least two symptoms. Anal incontinence followed prelabor emergency caesarean in two mothers. Of the 22 mothers who sustained a second-degree tear, five (23%) had new anal incontinence compared with only one (3%) of 40 mothers with an intact perineum (Fisher exact test value = 9.697, P = .014).

Because severe anal incontinence followed elective and prelabor emergency caesarean, it seems that pregnancy itself can lead to pelvic floor disorders. A high incidence of anal incontinence is associated with a second-degree tear. Measures to detect and reduce postpartum anal incontinence should target all pregnant women and mothers, even after prelabor caesarean delivery. [140]

It is important that contributory obstetric factors are identified and their occurrence minimized. Vaginal birth has been recognized as being potentially traumatic to the pelvic floor. Women who have sustained significant anal sphincter injury are at greater risk of further damage of faecal incontinence with subsequent deliveries.

I. EFFECTS OF PREGNANCY ON PELVIC FLOOR FUNCTION

In spite of the great advances that have been made in many areas of obstetric care, ignorance still persists regarding the fundamental physiological facts about the impact of pregnancy and delivery on lower urinary tract function. There is a striking dearth of prospective studies regarding the relationship of pregnancy and delivery to the problem of urinary incontinence among women. Further research may reveal that stress incontinence in women is related, at least in part, to the pregnant state itself, rather than to trauma sustained at delivery. If true, this has significant implications for subsequent research efforts investigating the etiology of female urinary incontinence. Cutner and Cardozo have summarized the few papers that do exist as follows [141]:

"Lower urinary tract symptoms are so common in early pregnancy that they are considered normal. Their progression throughout the ante partum period and their resolution postpartum has been documented by several authors. However, the data are confusing and the underlying causes remain uncertain. The effects of normal pregnancy on the physiology of the lower urinary tract remain largely uninvestigated, in spite of the common pronouncements on this subject in the obstetrical literature [142-145]".

"It is commonly assumed that stress incontinence develops (at least in part) as the result of delivery trauma to the pelvic floor. However, several researchers have documented that many young nulliparous women suffer from occasional stress incontinence which is a significant clinical problem in as many as 5 % [146-148]".

In a study of the relationship of pregnancy to stress incontinence, Francis [142] found that 40 % of primigravid women had a history of occasional stress incontinence before becoming pregnant, and that if such a history was present their stress incontinence invariably became worse during pregnancy. If incontinence developed during pregnancy, it tended to disappear after the puerperium, but recurred with subsequent pregnancies and became progressively worse, eventually becoming a clinical problem when these women were no longer pregnant. Francis concluded that in women who develop stress incontinence in middle life, pregnancy itself, rather than parturition, revealed the defect and made it worse. Similar conclusions have been reached by other researchers [149-151].
The prevalence of persistent stress urinary incontinence is reported to be significantly higher in grand multiparae compared with nulliparae [152].

Moreover, Buchsbaum et al. investigated the role of vaginal delivery and familial factors in the development of urinary incontinence by comparing the prevalence of this condition in nulliparous women and their parous sisters. Among this sample of biological sisters, urinary incontinence was reported by 47.6% of nulliparous women and by 49.7% of parous women (P = .782). Considering the high concordance in continence status between sister pairs, and considering that the majority of parous women are continent, an underlying familial predisposition toward the development of urinary incontinence may be present [153].

II. PATHOPHYSIOLOGIC MECHANISMS OF BIRTH INJURY TO THE PELVIC FLOOR

Vaginal delivery, notably the first, is strongly associated with later surgery for stress incontinence, but the association is modified by maternal conditions and interventions during delivery. Vaginal delivery may initiate damage to the continence mechanism by direct injury to the pelvic floor muscles, damage to their motor innervations, or both. Additional denervation may occur with aging, resulting in a functional disability many years after the initial trauma. Physical and emotional health problems are common after childbirth, and are in frequently reported to health professionals despite the fact that many women would like more advice and assistance in dealing with them. There would seem to exist four major mechanisms by which childbirth (vaginal delivery) might contribute to the increased risk of urinary incontinence among women:

1. Injury to connective tissue supports by the mechanical process of vaginal delivery, especially instrumental vaginal delivery (forceps > ventouse delivery)
2. Vascular damage to the pelvic structures as the result of compression by the presenting part of the fetus during labour
3. Damage to the pelvic nerves and/or muscles as the result of trauma during parturition
4. Direct injury to the urinary tract during labour and delivery. The physiologic changes produced by pregnancy may make pregnant women more susceptible to injury from these pathophysiological processes

In a three-dimensional computer model Lien et al. predicted levator ani muscle stretch during vaginal birth. Serial magnetic resonance images from a healthy nulliparous 34-year-old woman, published anatomic data, and engineering graphics software were used to construct a structural model of the levator ani muscles along with related passive tissues. The model was used to quantify pelvic floor muscle stretch induced during the second stage of labour as a model the fetal head progressively engaged and then stretched the iliococcygeus, pubococcygeus, and puborectalis muscles. The medial pubococcygeus muscles undergo the largest stretch of any levator ani muscles during vaginal birth. They are therefore at the greatest risk for stretch-related injury [154].

Furthermore, in a prospective observational study Dietz et al. investigated 61 nulliparous women at 36-40 weeks of gestation and 2-6 months post partum. The assessment included an interview and 3-dimensional translabial ultrasound and was repeated 2-6 months postpartum. Fifty women (82%) were seen postpartum. Of the 39 women delivered vaginally, levator avulsion was diagnosed in 14 (36%, 95% confidence interval 21-51%). Among those delivered vaginally, there were associations with higher maternal age (P = .10), vaginal operative delivery (P = .07), and worsened stress incontinence postpartum (P = .02). Avulsion of the inferomedial aspects of the levator ani from the pelvic sidewall occurred in approximately one third of all women delivered vaginally and was associated with stress incontinence 3 months after childbirth [155].

Boreham et al described levator ani (LA) anatomy in postterm nulliparas using 3-dimensional (3-D) magnetic resonance (MR). LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in 92% of the 84 women. The LA shape was characterized as “U” in 53% and “V” in 47%. Mean LA volume was 13.5 (3.7) cm³. There was a positive association between LA volume and higher fetal station (P = .02) and increasing BMI (P < .001). However, no relationship between LA volume and station was found after adjusting for BMI. BMI was correlated with LA volume in postterm nulliparas. LA insertion into the symphysis and the iliococcygeus arch were well-preserved overall and morphometry was variable [156].

Vaginal delivery causes partial denervation of the pelvic floor (with consequent re-innervations) in most women having their first baby. Pelvic floor muscle strength is impaired shortly after vaginal birth, but for most women returns within two months. In a few this condition is severe and is associated with urinary and faecal incontinence. For some it is likely to be the first step along a path leading to prolapse and/or stress incontinence [157].

There is a growing body of evidence that multiparity, forceps delivery, increased duration of the second stage of labour, partially due to epidural anaesthesia, third degree perineal tear and high birth weight (> 4000 g) are important factors leading to pudendal nerve damage [158-161].
To identify obstetric factors associated with clinical significance [164].

Marker for pelvic floor denervation makes it of uncertain value during the first pregnancy, the risk of stress incontinence occurring 15 years later is doubled. Squeeze pressure improved during the same period and to establish whether pelvic floor denervation after vaginal delivery in 80% of women who have a long active second stage of labour and heavier babies show the most EMG evidence of nerve damage. An elevation in perineal body position as well as a decrease in the area of the urogenital hiatus and of the levator hiatus at two weeks postpartum suggests a return of normal levator ani geometry after vaginal delivery in most patients [163].

In a longitudinal study of a cohort of 96 primigravidae followed up 7 and 15 years pelvic floor neurophysiology was performed and questionnaires were administered to determine the natural history of stress incontinence and to establish whether pelvic floor denervation after the first delivery is associated with symptoms of stress urinary incontinence in the future. Urinary incontinence symptoms were recorded and pelvic floor neurophysiology was performed antenatally and postnatally. Repeat neurophysiological tests and questionnaires were completed by those relocated 7 and 15 years later. Prevalence of stress incontinence was highest during pregnancy and had increased seven years after the first postnatal period (P = 0.0129). Two-thirds of women with antenatal stress incontinence had stress incontinence 15 years later. One-third of women with stress incontinence at any time appear to undergo resolution of symptoms. Motor unit potential duration increased at seven years (P = 0.036). Vaginal squeeze pressure improved during the same period (P = 0.0007). When stress urinary incontinence arises during the first pregnancy, the risk of stress incontinence occurring 15 years later is doubled. Although pelvic floor reinnervation progressed after the postnatal period, the absence of an adequate marker for pelvic floor denervation makes it of uncertain clinical significance [164].

To identify obstetric factors associated with development of levator ani injury after vaginal birth magnetic resonance images were taken of the pelvic floor of 160 women 9 to 12 months after first term vaginal delivery. Half the women had de novo stress incontinence and half were continent controls. Abnormalities of the pubovisceral portion were identified on magnetic resonance as present or absent. Defect severity was further scored in each muscle from 0 (no defect) to 3 (complete muscle loss). A summed score for the 2 sides (0 to 6) was assigned and grouped as minor (0-3) or major (4-6). Obstetric details were collected. The following increased odds ratios for levator defect were found: forceps use 14.7 (95% confidence interval [CI] 4.9-44.3), anal sphincter rupture 8.1 (95% CI 3.3-19.5) and episiotomy 3.1 (95% CI 1.4-7.2) but not vacuum delivery 0.9 (95% CI 0.19-4.3), epidural use 0.9 (95% CI 0.4-2.0), or oxytocin use 0.8 (95% CI 0.3-1.8). Women with levator injury were 3.5 years older and had a 78-minute longer second stage of labour. Injuries to the levator ani muscles in women after their first vaginal delivery are associated with several obstetric factors indicating difficult vaginal birth and with older age. LEVEL OF EVIDENCE: II-3. [165]

Baytur investigated the respective roles of the mode of delivery and strength of pelvic floor muscles in the sexual function of women. Pelvic floor muscle strength was significantly lower in the group vaginally delivered compared with the group delivered by caesarean section and the nulliparous group (P<0.05). There was no difference between the groups regarding sexual function (P>0.05), and there was also no correlation between sexual function and pelvic muscle strength [166].

To compare pelvic floor symptoms at three years following instrumental delivery and caesarean section in the second stage of labour and to assess the impact of a subsequent delivery Bahl et al. conducted a prospective cohort study of 393 women with term, singleton, cephalic pregnancies who required instrumental vaginal delivery in theatre or caesarean section at full dilatation between. 283 women (72%) returned postal questionnaires at three years. Urinary incontinence at three years post delivery was greater in the instrumental delivery group as compared to the caesarean section group (10.5% vs 2.0%), OR 5.37 (95% CI, 1.7, 27.9). There were no significant differences in ano-rectal or sexual symptoms between the two groups. Pelvic floor symptoms were similar for women delivered by caesarean section after a failed trial of instrumental delivery compared to immediate caesarean section. A subsequent delivery did not increase the risk of pelvic floor symptoms at three years in either group. An increased risk of urinary incontinence persists up to three years following instrumental vaginal delivery compared to caesarean section in the second stage of labour. However, pelvic floor symptoms are not exacerbated by a subsequent delivery [167].

Female pelvic floor dysfunction is integral to the woman’s role in the reproductive process, largely because of the unique anatomic features that facilitate vaginal birth and also because of the trauma that can occur during that event. Interventions such as primary elective caesarean delivery have been discussed for the primary prevention of pelvic floor dysfunction; however, existing data about potentially causal factors limit our ability to evaluate such strategies critically.
The risk of pelvic floor disorders is independently associated with vaginal delivery but not with parity alone. Caesarean delivery has a protective effect, similar to nulliparity, on the development of pelvic floor disorders when compared with vaginal delivery. LEVEL OF EVIDENCE: II-2. [168, 169]

Younger white primiparous women had a better recovery at 6 months than older white women [170].

The pudendal nerve terminal motor latency (PNTML) measured 48–72 h after delivery is increased in women delivered vaginally compared to nulliparous control subjects.

Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tear and high birth weight are important factors leading to pudendal nerve damage [158].

Compared with spontaneous vaginal births, women having forceps or ventouse extraction have increased odds for perineal pain, sexual problems, and urinary incontinence [159].

Vaginal delivery, notably the first, is strongly associated with later surgery for stress incontinence, but the association is modified by maternal conditions and inter-ventions during delivery [171].

Women with three or more deliveries were more likely to have incontinence and excessive pelvic floor descent [171].

There is no evidence to suggest that at five years after delivery use of the ventouse or forceps has specific maternal benefits or side effects [172].

Meyer et al. found that, after spontaneous and instrumental deliveries, 21% and 34% of women complained of stress urinary incontinence and 5.5% and 4% reported faecal incontinence, respectively. Substantial bladder neck hypermobility was present together with diminished functional urethral length and intravaginal and intra-anal pressures. Only 22% of patients with stress urinary incontinence during pregnancy had such incontinence after delivery [173].

Women with postpartum urinary stress incontinence have significantly greater antenatal bladder neck mobility than those women who were continent post partum [174].

To investigate and compare the effects of different modes of delivery on urethral sphincter volume, bladder neck mobility, and changes to levator hiatus distensibility using ultrasound imaging, 156 women underwent antenatal ultrasound pelvic floor assessment. One hundred and ten (71%) completed the 6-month follow-up. There were no differences in the urethral sphincter volume between the different modes of delivery. Overall, the urethral sphincter was smaller after delivery compared to the third trimester.

Vaginal delivery was associated with a significantly larger levator hiatus area on valsalva antenatally and at rest, squeeze, and valsalva postnatally compared to caesarean section. Antenatal and postpartum bladder neck mobility was also significantly greater in the women who delivered vaginally. Urethral sphincter changes postpartum are independent of mode of delivery. Vaginal delivery is strongly associated with a larger, more distensible levator hiatus and a greater degree of bladder neck mobility both antenatally and postpartum [175].

Displacement and recovery of the vesical neck position during pregnancy and after childbirth and to discriminate between compliance of the vesical neck supporting structures with and without pelvic floor contraction. Compliance of the supporting structures remains relatively constant during pregnancy and returns to normal values 6 months after childbirth. Hysteresis, however, showed an increase after childbirth, persisting at least until 6 months post partum [176].

### III. EPIDURAL ANALGESIA DURING LABOUR

Regional anaesthesia for the relief of labour pain has become more popular during the past 20 years. Despite interest in its possible obstetric consequences, little attention has been paid to its potential effects on the pelvic floor and perineal injury. The available published data describe conflicting results. Some studies suggest that epidural analgesia, by enabling relaxation of the pelvic floor, leads to greater control of delivery of the fetal head and consequently fewer perineal lacerations [177] but prolongation of the second stage may also increase the incidence of pudendal nerve damage [161, 178].

Robinson et al. [179] recently examined the relationship between epidural analgesia and perineal damage, and found that the rate of significant perineal injury was higher with epidural analgesia (16.1 % compared with increased use of operative intervention). Episiotomy and instrumental delivery were responsible for this difference. Such an association may partly explain why institutions are reporting increased rates of significant perineal injury, paralleling local increases in epidural usage [171].

In a study of 82 women Meyer et al assessed the effects of epidural analgesia on pelvic floor function. Eighty-two primiparous women (group 1, consisting of 41 given an epidural, and group 2 of 41 not given an epidural) were investigated during pregnancy and at 2 and 10 months after delivery by a questionnaire, clinical examination, and assessment of bladder neck behaviour, urethral sphincter function and intravaginal/intra-anal pressures. Ten months after spontaneous
delivery, there were no significant differences in the prevalence of stress urinary incontinence and decreased sexual vaginal response, or in bladder neck behaviour, urethral sphincter function and pelvic floor muscle strength between women who had or had not had epidural analgesia [180].

Comprising 70 matched pairs of primiparous mothers Sartore et al. found no significant difference in the incidence of stress urinary incontinence, anal incontinence and vaginal prolapse in the two study groups. No significant differences were found between the study groups with regard to the digital test, vaginal manometry and urine stream interruption test. The use of epidural analgesia is not associated with symptoms related to perineal trauma and pelvic floor muscle weakness [181].

1. ROLE OF EPISIOTOMY (Figure 5)

Episiotomy is a widely performed intervention in childbirth, despite equivocal scientific evidence regarding its benefit. Practice patterns vary widely, as do professional opinions about maternal risks and benefits associated with routine use. It is one of the few surgical procedures performed without the patient’s consent and is the most commonly performed surgical procedure in the United States. There is a widespread assumption that it may do more harm than good [171, 179].

Restrictive episiotomy policies appear to have a number of benefits compared to routine episiotomy policies. Proponents of routine episiotomy claim that it avoids spontaneous uncontrolled tears and long-term relaxation of the pelvic floor, but these advantages are difficult to substantiate. There is no evidence that either first or second-degree perineal tears cause long-term consequences [143].

So any argument that episiotomy prevents such spontaneous tears is inconsequential. A growing body of evidence suggests that episiotomy offers no protection against third and fourth-degree tears, which are associated with adverse sequelae. A recent overview by Myers-Helfgott and Helfgott emphasized the absence of scientific evidence to support a role for liberal elective episiotomy in the reduction of third-degree lacerations during childbirth [144].

Indeed, several reports have implicated routine episiotomy in the genesis of major perineal and anal sphincter tears, even after controlling for confounding variables [145-147, 182].

In particular, midline episiotomy is associated with significantly higher rates of third and fourth-degree perineal tears than are mediolateral episiotomies [149-151].

Midline episiotomy is not effective in protecting the perineum and sphincters during childbirth and may impair anal continence [183].

Coats et al., in a randomized controlled trial of 407 women, found that with midline episiotomy, 11, 6% of patients experienced lacerations of the anal canal versus 2% who experienced these complications in association with mediolateral episiotomies. This association is compounded when instrumental delivery is employed, with anal sphincter injury rates of 50% reported with the use of midline episiotomy and forceps [184].

In spite of these data, midline episiotomy is still bewilderingly widespread, presumably because it is perceived to heal better and cause less postnatal discomfort.

Restrictive episiotomy policies appear to have a number of benefits compared to routine episiotomy policies. There is less posterior perineal trauma, less suturing and fewer complications, no difference for most pain measures and severe vaginal or perineal trauma, although there was an increased risk of anterior perineal trauma with restrictive episiotomy [185, 186].
Women who have episiotomies have a higher risk of faecal incontinence at three and six months postpartum compared with women with an intact perineum. Compared with women with a spontaneous laceration, episiotomy triples the risk of faecal incontinence at three months and six months postpartum, and doubles the risk of flatus incontinence post partum compared with women who have a second degree spontaneous tear. The effect of episiotomy is independent of maternal age, infant birth weight, and duration of second stage of labour, use of obstetric instrumentation during delivery, and complications of labour. Therefore, midline episiotomy is not effective in protecting the perineum and sphincters during childbirth and may impair anal continence and should be restricted to specified fetal-maternal indications [183, 187-190].

Routine midline episiotomy increases the risk of third- and fourth-degree perineal lacerations, which may lead to faecal incontinence. Routine use of mediolateral episiotomy does not prevent urinary incontinence (UI) or severe perineal tears. It is possible to reduce the rate of mediolateral episiotomy to as low as 20% in primiparas without increasing the risk of anal sphincter damage.

Control of obesity before delivery, as well as pelvic floor exercises and regular physical exercise both before and after delivery, seem to reduce the risk of postpartum UI [191, 192].

In a systematic review Hartmann et al. looked for the best evidence available about maternal outcomes of routine vs restrictive use of episiotomy. Immediate maternal outcomes of routine episiotomy, including severity of perineal laceration, pain, and analgesia use, are not better than those with restrictive use. Evidence is insufficient to provide guidance on choice of midline vs mediolateral episiotomy.

Evidence regarding long-term sequelae is fair to poor. Incontinence and pelvic floor outcomes have not been followed up into the age range in which women are most likely to have sequelae. With this caveat, relevant studies are consistent in demonstrating no benefit from episiotomy for prevention of faecal and urinary incontinence or pelvic floor relaxation. Likewise, no evidence suggests that episiotomy reduces impaired sexual function—pain with intercourse was more common among women with episiotomy. Evidence does not support maternal benefits traditionally ascribed to routine episiotomy. In fact, outcomes with episiotomy can be considered worse since some proportion of women who would have had lesser injury instead had a surgical incision.

Another systematic review using the Medline Database set was performed with the key words: episiotomy, dyspareunia, faecal incontinence, urinary incontinence, maternal morbidity, pelvic floor defects and sexual function. When performed liberally, episiotomy appears to increase the risk of post partum bleeding. More restrictive use does not appear to increase the risk of serious perineal injury.

In the event of instrumental extraction, use of episiotomy appears to be associated with more severe damage. Medial episiotomy does not appear to be associated with third or fourth degree tears. Episiotomy appears to be the cause of more perineal pain and dyspareunia during the early post partum weeks [193].

2. PERINEAL TRAUMA (Figure 6)

Awareness of perineal damage after vaginal delivery has increased in recent years, due in part to better understanding of its consequences, improved methods of accurate neurophysiological evaluation and accumulation of data on prognosis. Faecal incontinence represents a distressing social handicap, and vaginal delivery is now recognized as its principal cause [194].

Obstetricians should have an awareness of the causes, symptoms, appropriate investigation and treatment options available for this complication of childbirth. Limiting episiotomy can be strongly recommended. In the absence of strong data to the contrary, women should be encouraged to engage in perineal massage if they wish and to adopt the birth positions of their choice. Factors shown to increase perineal integrity include avoiding episiotomy, spontaneous or vacuum-assisted rather than forceps birth, and in nulliparas, perineal massage during the weeks before childbirth. Second stage position has little effect [195].

Further information on techniques to protect the perineum during spontaneous delivery is badly needed. Wherever possible, women with post partum faecal incontinence should be assessed in a specialized clinic, which has developed a close liaison with physiotherapy, dietetic and colorectal surgical advisers.

Episiotomy, forceps use, and birth weight are important predictors of third and fourth-degree tears. However, determinants of sulcus tears appear to be present before pregnancy. Third and fourth-degree tears are related to physician management. Exercise mitigates the potential for severe trauma induced by episiotomy [196].

Eason et al. have systematically reviewed techniques proposed to prevent perineal trauma during childbirth and performed a meta-analysis of the evidence gathered from randomized controlled trials regarding their efficacy. The conclusion was that avoiding episiotomy decreased perineal trauma (absolute risk difference 0.23, 95% confidence interval (CI) -0.35, 0.11). In nulliparas, perineal massage during the weeks before giving birth also protected against
perineal trauma (risk difference -0.08, CI -0.12, -0.04). Vacuum extraction (risk difference -0.06, CI -0.10, 0.02) and spontaneous birth (-0.11, 95% CI -0.18, 0.04) caused less anal sphincter trauma than forceps delivery. The mothers’ position during the second stage had little influence on perineal trauma (supported upright versus recumbent: risk difference 0.02, 95% CI -0.05, 0.09).

Factors shown to increase perineal integrity include avoiding episiotomy, spontaneous or vacuum-assisted rather than forceps birth, and in nulliparas, perineal massage during the weeks before childbirth. Second-stage position has little effect. Further information on techniques to protect the perineum during spontaneous delivery is needed [197].

Reduction in both perinatal and maternal mortality rates in recent decades has focused increasing attention on maternal morbidity and the long-term sequelae of childbirth. Antenatal education encourages expectant mothers to anticipate normal vaginal delivery, leading to an early restoration of normal pelvic function after the performance of routine pelvic floor exercises. Not least because of improved investigative techniques available during the past decade, the incidence and mechanisms of obstetric injury to the pelvic floor have come under scrutiny. A survey of female British obstetricians [137] revealed that one third indicated a personal preference for elective caesarean delivery of their own hypothetical uncomplicated singleton pregnancy; a general fear of pelvic floor trauma was cited as the most common reason for this choice.

Despite being based on incomplete prognostic data, this sentiment may be echoed increasingly among obstetric patients and may lead to an unselective, and even misguided, increase in caesarean delivery rates. Epidemiological studies have reported prevalence of stress incontinence ranging from 23 to 67 percent during pregnancy and 6 to 29 percent after childbirth, but little is known about how the condition affects women at this time. However, the prevalence of urinary incontinence may be nearly the same 8 weeks postpartum as during pregnancy. It is important that contributory obstetric factors are identified and their occurrence minimized. Vaginal birth has been recognized as being potentially traumatic to the pelvic floor. Women who have sustained significant anal sphincter injury are at greater risk of further damage of faecal incontinence with subsequent deliveries.

The factors necessary for the urethra to remain closed at rest and during increased abdominal pressure have been well characterized, but their functional inter-relationships are still not fully understood. These factors include: 1) healthy, functioning striated sphincter controlled by pudendal innervation, 2) well vascularised urethral mucosa and sub-mucosa, 3) properly aligned and functioning intrinsic urethral smooth muscle, and 4) intact vaginal wall support.

Detailed descriptions of the urogenital diaphragm have been made by Max Brodel working with Howard Kelly [198], Oelrich [199] and further expanded by DeLancey [200]. These reports have provided clear descriptions of the urethral rhabdosphincter. The proximal one-third of the urethra is surrounded by a sleeve of striated muscle continuous with a longer ascending cone which extends to the vaginal introitus. Manometric and electrophysiological recordings from this proximal one-third of the urethra have shown that it generates the highest level of resting pressure and electromyographic activity.

This portion of the urethra is an intra-pelvic structure located immediately posterior to the pubic bone. In the past, much has been made of the loss of this intra-pelvic position in stress incontinence. It had been suggested that when the urethra descended away from its intra-abdominal position, intra-abdominal forces no longer constricted it during straining. This concept has survived and been modified into the “hammock hypothesis” [201] which suggests that the posterior position of the vagina provides a backboard against which increasing intra-abdominal forces compress the urethra. Data supporting this hypothesis are drawn from urethral pressure transmission studies showing that continent patients experience an increase in intra-urethral pressures during coughing. This pressure increase is lost in stress incontinence and may be restored following successful operations designed to stabilize or elevate the sub-urethral vaginal wall [202-211].

The urethra is supported posteriorly and inferiorly by the anterior vaginal wall. The superior vaginal sulcus, most clearly found in nullipara, exists at this junction
of the lower and middle third of the vaginal wall. This point represents the two lateral insertion points of the vaginal "hammock". Portions of the pubococcygeus muscle attach to these sulci within the pelvis and can produce elevation during voluntary contraction.

Immediately anterior to the proximal urethra are found the reflections of the endopelvic fascia. The most prominent of these, the pubo-urethral ligaments, are sufficiently condensed to form distinct and recognizable ligaments on either side of the pubis. Although these structures form one continuous complex, they are distinguished by their names, as posterior and anterior pubo-urethral ligaments. The posterior pubo-urethral ligaments, which can be seen at the time of retropubic surgery, are the more familiar of these. These are strong fascial condensations which most likely maintain their characteristics throughout life. Previous investigators, however, have suggested that elongation of these structures may be responsible for the loss of urethral support seen in stress incontinence.

While the lower one-third of the vagina is oriented more vertically in the nullipara, the upper two-thirds of the vagina deviate horizontally. This orientation is due:

1) to the posterior attachments of the cervix by the cardinal and utero-sacral ligaments and 2) to the anterior position of the levator hiatus. Barium vaginograms have demonstrated this horizontal angulation of the upper two-thirds of the vagina, and show that during coughing and stressful manoeuvres, the levator hiatus is shortened in an anterior direction by the contraction of the pubococcygeus muscles.

Thus, the pelvic organs receive support from the shape and active contraction of the levator muscles. Modifications of the genital hiatus determining an increase in the genitohiatal distance can be associated with urodynamic stress incontinence. In a retrospective study of 396 women with urodynamic stress incontinence [212], pelvic floor ultrasound revealed a negative association of the genitohiatal distance to urodynamic functional urethral parameters such as the functional profile length, the maximum urethral closure pressure and a low Valsalva leak-point pressure ($r = -0.148$, $P = 0.018$ and $r = -0.227$, $P = 0.009$, $r = -0.199$, $P = 0.02$ respectively).

### II. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE

Labour and delivery alter vaginal and pelvic anatomy and innervation in several ways as has been discussed in other sections of this chapter. Each of these may contribute to the eventual development of urinary incontinence (Figure 7):

1. Direct crushing or traction on the pudendal nerve has been discussed above and has previously been suggested as a primary cause of sphincter incompetence in stress incontinence.

2. Cardinal and utero-sacral ligaments may be stretched or torn, resulting in anterior displacement of the uterus during straining or under the influence of gravity.

*Figure 7: Anatomical and functional interaction of the urethra, bladder and the anterior vaginal wall (PCM = Pubococcygeus muscle, PUL = Pubourethral ligaments)*
The vagina itself may be torn away from its intrapelvic attachments with subsequent loss of the superior vaginal sulcus. There may be direct attenuation of the vaginal wall itself, manifested by loss of vaginal rugae and a thin appearance. Cullen Richardson has suggested four distinct kinds of vaginal injuries: paravaginal, central, distal, and cervical, the first two being the most commonly seen in women with stress incontinence. These defects have been identified by sonographic examination [213].

Finally, stretching, tearing and avulsion of the levator muscles result in a longer and wider levator hiatus. Consequently, the perineum is displaced anteriorly and posteriorly under stress and temporarily fails to support the pelvic organs. These changes in the levator hiatus with or without associated relaxation of cervical support result in chronic anterior displacement of pelvic organs with a loss of both active and passive organ support during rest and especially during straining.

In the patient with stress urinary incontinence these changes typically give rise to a rotational descent of the proximal urethra away from its retropubic position. Radiographic images of stress urinary incontinence in women have noted this and generated our earliest concepts of this condition. Jeffcoate and Roberts [214], using lateral cystourethrograms, concluded:

“…the most common characteristic anatomical change, present in four out of five cases of incontinence, is loss of the posterior urethro-vesical angle so that the urethra and trigone tend to come into line."

In 2002, fifty years later, perineal sonographic studies of urethrovaginal angle differences in incontinent and normal patients have found excellent correlation identified between angle and degree of incontinence, supporting these original observations [215].

Hodgkinson, using a suspension of barium paste placed in the bladder and a small bead chain in the urethra, produced images of the urethra at rest and during maximum straining in women with stress urinary incontinence [216, 217]. He concluded:

“...it is clear that the distinguishing topographic pathological feature is depression of the urethrovaginal junction to the lowest level of the bladder during the peak of the straining effort. It is also clear that the spatial relationships of the bladder and urethra to the symphysis make no difference in either the incidence or severity of stress incontinence."

These kinds of radiographic studies, however, cannot distinguish between lateral or central defects in vaginal wall support. Therefore, while urethral movement can be identified as an important finding in stress incontinence, one cannot determine the exact location of the vaginal defect. Because the proximal urethra rotates out of the focal plane of ultrasonographic probes or MRI, coronal images of vaginal relaxation have not yet shown anatomical detail at the moment of incontinence. They cannot distinguish central from paravaginal defects. For this, an examination of the patient is required.

Although we have considerable knowledge about anatomical defects in the majority of patients with urodynamic stress incontinence (USI), less is understood about the exact effect of these defects, and indeed, vaginal position itself, on urethral closure. Early experience with operations for stress incontinence showed that not all women with stress urinary incontinence had vaginal prolapse, that correction of vaginal relaxation did not always correct stress incontinence, and that women who redeveloped stress incontinence symptoms after apparently successful surgery did not necessarily show a recurrence of their prolapse [218].

The greater involvement of the urethral mechanism in the occurrence of post-partum stress incontinence was confirmed in a case control study evaluating urethral closure pressure and bladder neck movement assessed with ultrasound [220]. Eighty primiparous women complaining of de-novo stress incontinence 9-12 months after delivery were compared with 80 primiparous continent and 80 nulliparous continent women. Lower maximal urethral closure pressure was most associated with de novo stress incontinence after first vaginal birth followed by vesical neck mobility.

III. EMERGING CONCEPTS OF URETHRAL WEAKNESS AND ISD

The idea that primary urethral weakness could cause urinary incontinence independent of vaginal weakness appeared in a proposed classification by Blaivas et al [221]. In their classification, they named this Type III incontinence to distinguish it from Types I and II, each of which showed movement, while Type III did not. This term still remains in the contemporary literature, although it has now been largely replaced by the term intrinsic sphincter deficiency (ISD), focusing attention on urethral elements which appear to be independent of vaginal position and mobility. These elements include pudendal innervation, striated sphincter mass and function, and urethral smooth muscle, mucosa and submucosal cushions.
When ISD was first introduced as a concept to explain surgical failures and the presence of stress incontinence in the absence of vaginal mobility, the diagnostic tendency was to consider the cause of stress incontinence as a dichotomy, due either to hypermobility (displacement, or prolapse of the vaginal wall) or ISD. The typical patient with ISD was described as having low urethral closure pressures, a “stovepipe” appearance on cystoscopy, and opening or funnelling of the urethra under resting or minimal increases in intra-abdominal pressures on radiographic images. The common causes were thought to be surgical injury, ischemia following previous pelvic or vaginal surgery or radiation damage.

It appears now, that these examples of ISD may have represented the most advanced or extreme forms.

IV. HYPERMOBILITY VS. ISD: FROM DICHOTOMY TO CONTINUUM

Currently, there appears to be a shift away from this simple categorization of stress incontinence as being due either to hypermobility or ISD. This has arisen in part because of the development of the concept of Valsalva Leak Point Pressure (VLPP) [222, 223] and more recent analyses of long term results of stress incontinence surgery [224].

VLPP emerged as an alternative method to study urethral closure during stress for studies of urethral bulking with collagen. Investigators recognized that improvements in continence following urethral bulking did not correlate with urethral closure pressures, but did correlate with the amount of pressure required to produce leakage in the absence of intrinsic detrusor contraction. Although VLPP still lacks specific anatomic or theoretical grounding and many uncertainties related to standardization of recording methods and associated prolapse remain, low VLPP (without specified or established values) has been widely embraced as an indicator of ISD.

Just as the concept of VLPP blurred the previous distinction between simple ISD and simple hypermobility, long term outcome studies of correction of hypermobility have suggested that there may be more urethral weakness among patients with hypermobility than had been previously considered. Long term outcome studies of stress incontinence surgery have shown that there is a much greater failure rate of many of the commonly performed stress incontinence operations than had been generally appreciated, and that slings providing direct sub-urethral support seemed to give the greatest long term protection against recurrence of incontinence [224]. Since slings had traditionally been the procedure of choice for recurrent incontinence or “Type III” (now ISD) incontinence, the possibility that ISD was more common than previously thought was more widely considered. Recently, Horbach and Ostergaard have found that age is a significant, independent predictor of ISD in the setting of urodynamic stress incontinence [225], suggesting that age-related reduction in muscle mass, slowed reflexes or repeated episodes of prolapse may all contribute to the condition.

In two interesting studies Perucchini et al [226, 227] showed that aging can cause a decrease in the number and density of urethral striated muscle fibres at the bladder neck and along the ventral wall of the urethra. (Figure 8 and 9 [226])

These two developments have led to a growing clinical impression that some degree of ISD may exist in many patients who, until recently, were thought to have only hypermobility as a cause of their incontinence. A typical expression of this approach can be found in the conclusion of Kayigil et al. [228]
following examination of 50 patients; “The high rate of intrinsic sphincter deficiency in patients with urethral hypermobility indicates that the incidence with stress incontinence may be greater than previously believed, and may influence the apparently higher failure rates after bladder neck suspension.” In contemporary clinical practice, this impression has given rise to a growing tendency to recommend suburethral sling surgery as a form of primary surgical treatment for all women with stress incontinence, whereas as formerly this approach was reserved almost exclusively for patients with recurrent stress incontinence or significant ISD [229, 230].

1. DIRECT STUDIES OF URETHRAL FUNCTION

As recognition of the importance of urethral function has increased, so too have the number of investigations of urethral position, urethral closure and transmission pressure profiles, Valsalva leak point pressure measurements and electromyographic examinations of the pudendal nerve and the striated sphincter.

a) Studies of urethral position

Stress incontinence is frequently associated with loss of urethral position. This has been the primary pathophysiological paradigm since the observations of Hodgkinson and Jeffcoate and Roberts. Similar observations are still reported today [231, 232]. Even when some displacement is seen in continent nulliparous females, continent women show a greater degree of mobility [233].

Successful suspensory operations, whether by sling or paraurethral suspension stabilize urethral position [218] and, when studied, increase pressure transmission during stress. It is not clear if the active contraction of urethral support seen in the female is restored after surgery, nor is it known if it is necessary for continence. It has been suggested that passive support alone is what restores continence after suspension.

b) Studies of urethral pressure and resistance

Stress incontinence is generally thought to be characterized by a decrease in urethral transmission profiles and resting closure pressure. The correlation between low resting pressures and low leak point pressures is still controversial. With a bladder filled up to 200ml Almeida et al [234] reported a significant correlation between MUCP and LPP. Patients with a LPP of 60 cm H2O or less also had shorter urethral functional length and lower sphincter activity. Moreover Sinha et al [235] showed that women with urodynamic stress incontinence were more likely to leak at cough leak point pressure than the Valsalva manoeuvre, with the opposite happening for women with detrusor overactivity. On the contrary Martan et al [236] could not find any significant correlation between MUCP and VLPP.

Different urodynamics parameters have also been considered to assess urethral function and to correlate with women with stress incontinence. Digesù et al [237] showed that urethral resistance pressure (URP) and pressure flow parameters were reduced in women with stress incontinence. Salvatore et al [238] found that the opening vesical pressure is significantly correlated to ISD.

Sonographic studies have recently shown a relationship between low urethral resistance and decreased urethral smooth and skeletal muscle layers [239].

Improvement in transmission pressures is associated with successful outcomes after suspensory operations for STRESS URINARY INCONTINENCE[202, 206, 209, 210, 240, 241]. The exact mechanism for this increase in transmission is not clear. Increased exposure to intra-abdominal forces has been suggested [211, 242, 243]. Compression against the pubis by the pelvic viscera has also been suggested [244]. The final position of the urethra, however, may not be the key variable [202].

c) Electrophysiological studies of urethral function

Snooks and Swash [245, 246] first brought attention to the importance of urethral denervation after childbirth and its possible contribution to urinary and faecal incontinence. Stress incontinence is frequently associated with a decline in the electrophysiological function of the pudendal nerve [247], the striated urethral sphincter [248], and the pelvic floor muscles [249, 250]. Most recent studies continue to support the finding of prolonged pudendal nerve terminal motor latency in STRESS URINARY INCONTINENCE [251].

Electromyographic studies of normal sphincter function show that in continent women, pressures begin to rise in the urethra before rising in the bladder, suggesting an active muscular component [252]. Women with stress incontinence have an altered pattern of pelvic floor muscle response during successive coughing efforts [253] with a sharp decrease in MUCP after repeated coughs [254]. EMG studies have also shown that women with persistent stress incontinence after previous surgery have poorer urethral neuromuscular function than naïve stress incontinent women [255]. Experimental studies of urethral function and the role of Onuf’s nucleus in the sacral spinal cord have led to recent practical innovations in the development of serotonin uptake inhibitor agents in the treatment of stress incontinence [256]. Most electrophysiological studies have concentrated on motor rather than sensory innervation, however, and the role of urethral sensation in urodynamic stress incontinence is unknown.

d) Genetic factors

Recent research is now focusing on the identification
of factors related to stress incontinence which might be genetically determined. Chen et al [257] reported that genes involved in elastin metabolism were differentially expressed in vaginal tissue from women with stress incontinence, suggesting that elastin remodelling may be important in the molecular etiology of stress incontinence. Wen et al [258] recently reported a decreased expression of alpha2-M mRNA and protein and protease inhibitory activity in the vaginal wall tissues of women with stress incontinence. There is a need for a hypothesis which would integrate these various observations regarding hypermobility, ISD and pudendal nerve function, place them within the context of an abnormal pelvic floor and provide a model to guide research and studies of the natural history of the condition.

2. ROLE OF ADVANCED IMAGING IN UNDERSTANDING PATHOPHYSIOLOGY

Radiographic imaging has provided considerable insight into pathophysiology of stress incontinence, ever since the advent of bead chain cystograms and simple static and straining lateral cystograms.

Magnetic resonance imaging (MRI) and real time ultrasonography, in addition to showing the events of stress incontinence on both a global pelvic and local urethral scale, have suggested a relationship of the proximal urethra to vaginal wall movement.

a) Magnetic resonance imaging

Dynamic fastscan MRI can visualize all compartments of the female pelvis during increased intraabdominal straining [259]. MRI is comparable to standard cystography in demonstrating cystocele defects [260]. Using the pubococcygeal line as a reference marker, the normal displacement of bladder base, cervix or cervical cuff, and the rectum can be identified and compared to women with prolapse. The urethra is shown in the context of global pelvic relaxation [261]. Although most MRI studies have been descriptive rather than quantitative, they still show far more soft tissue detail than earlier radiographic studies and continue to offer promising research opportunities. Recent studies have utilized an endovaginal coil to obtain higher resolution images of the urethra [262].

Dynamic MRI with cine-loop reconstruction produces vivid, intuitively appealing images which can show movement of all compartments of the relaxed pelvis during straining [261]. Static MRI shows details of urethral and peri-urethral anatomy and the striated sphincter can be clearly seen [263]. Pending further improvements in resolution, MRI remains a most promising tool for studying details of urethral movement [264].

Ultrasonography, however, is simpler and less expensive, and, for now, provides better visualization of moving structures.

Functional MRI has recently been evaluated to assess the efficacy of pelvic floor muscle training with EMG-biofeedback in women with stress incontinence. After a 12-week training period a more focused activation in the primary motor and somatosensory cortical representation sites of the lower urogenital tract was found [265]. (Figure 10)

b) Real time ultrasonography

Several sonographic approaches have been used for the study of stress incontinence: suprapubic, translabial and transperineal. As resolution of sonographic probes has improved, the detail previously best seen with the transrectal approach may now be seen by a transperineal approach (Figure 11).

Earlier studies with a transrectal approach have shown that funnelling of the proximal urethra was the sonographic sign most-frequently associated with loss of urine [266]. In about half the patients with stress incontinence in this study, funnelling was seen
only with straining. In the other half, some degree of funnelling was already present at rest, increasing with straining and present with actual leakage. Enhanced views of the urethra are possible with sonographic contrast material [267]. Most recently, 3-D reconstruction from translabial views of the urethra has been used to compare findings in normal volunteers and those with ISD [268].

The most recent sonographic study of women with stress urinary incontinence found funnelling at rest in 109 of 330 patients, and found that the degree of vaginal relaxation as well as the parameters of intrinsic urethral function, including VLPP and urethral closure pressures, were worse in patients with funnelling than without. The authors of this study concluded that: “In primary genuine stress incontinence, bladder neck funnelling on ultrasound cystourethrography implies the potential coexistence of poor anatomic support and an intrinsic sphincter defect. [269].” Ghoniem et al [270] also found that urethral funnelling was more likely to be associated with low closure pressures, low VLPPs, and a higher incidence of ISD in patients with stress urinary incontinence. However, recently, Tunn et al [271] could not find an association between the ultrasound findings of urethral funnelling with stress incontinence using an introital approach, demonstrating it only in 59% of the patients with stress urinary incontinence.

Ultrasound has been used to identify paravaginal defects prior to Burch colposuspension to guide surgical modification, and then repeated after surgery to show correction of the defects [272].

Urethral movement and funnelling seen by ultrasound resemble the rotational descent previously described by Nichols and Randall [273]. It is also consistent with the previously cited descriptions of Jeffcoate and Roberts, and that of Hodgkinson. Improved soft tissue detail seen with ultrasound has permitted an extension of these original observations. The anterior and posterior walls of the proximal urethra appear to move differently during increases in intra-abdominal pressure. At first, they appear to move together: the urethra begins its descent as a single unit. At some point, however, the anterior urethra becomes arrested in its rotational movement and appears to move more slowly. The posterior portion of the urethra continues to descend along with the vaginal wall [266, 274]. This difference in movement suggests a shearing apart of the two walls, leading to the appearance of funnelling, which can be seen as urine leaks out of the urethra.

Anatomic correlation suggests that the pubourethral ligaments may restrict the movement of the anterior urethral wall, facilitating downward traction by the prolapsing vagina during stress, contributing to the shear. At the level of the pubis, the posterior portion of the pubourethral ligament travels beneath the pubis to form an anterior portion, which supports the clitoris in women, and the corpora cavernosa in men. Both Nichols and Milley [275] and Zacharin [276-278] have previously suggested that the posterior pubourethral ligaments might support the urethra, and their laxity might contribute to the descent of the urethra in stress incontinence. These studies, however, suggest a different interpretation. Longitudinal and cross-sectional views of the proximal urethra show that the ligaments travel along only the anterior portion of the urethra as they pass beneath the pubis to emerge as the anterior pubourethral ligaments. The vagina and its bilateral attachments forming the lateral sulcus support the posterior part of the urethra. It is more likely that the vaginal wall and its attachments become weaker than the strong condensations of endopelvic fascia forming these ligaments. Therefore, the pubourethral complex, even if attenuated, probably remains stronger than the underlying vaginal wall. Sonographic examination of the prolapsing urethra thus suggests arrest of anterior urethral wall movement by the pubourethral complex, while the vaginal wall continues to rotate, pulling the posterior wall of the urethra along with it.

These anatomical considerations, combined with current knowledge about pudendal nerve activity in normal, prolapse or stress incontinence, suggest an inter-relationship regarding urethral closure and vaginal movement. As intra-abdominal pressure increases, the proximal urethra experiences two kinds of forces, which may lead to opening. The first of these is a shearing force produced by the unequal separation of the anterior and posterior urethral walls from the pubis during straining. This is the effect of vaginal mobility on urethral closure. The second is an expulsive force, produced by the transmission of intra-abdominal forces to the bladder, which must be resisted by the urethra if opening is to be prevented. The urethra
resists this primarily by intrinsic closure of the pudendally innervated striated sphincter, aided by vaginal support.

3D ultrasound has been recently introduced new insights in the image of urethral sphincters. Athanasiou et al [279], using a transvaginal approach, reported a close correlation between the urethral sphincter volume and the degree of incontinence assessed on videocystourethrography (r = -.65; P < .001).

Urethral vasculature has also been postulated to play a role in the continence mechanism and different Doppler parameters have been studied to evaluate correlation with STRESS URINARY INCONTINENCE. However, also for this aspect, results are controversial since some authors [280] reported less periurethral vessels and flow in women suffering from stress urinary incontinence whereas others [281] could not find any difference in the appearance of the urethral vasculature in subjects with or without stress urinary incontinence.

It is likely that these shearing and expulsive forces are generated simultaneously as intra-abdominal pressure rises. One can easily imagine that the urethra can be brought to a continence threshold beyond which urethral closure cannot be maintained.

One can further imagine that repeated episodes of prolapse may eventually stretch, tear or attenuate sphincter mass and contribute to a chronically weakened urethra manifested by low VLPP or low urethral closure pressures, characteristic of ISD.

After severe or prolonged untreated prolapse and stress incontinence, vaginal support alone may not be sufficient to correct the deficiencies of an exhausted sphincter. Although theoretical rather than evidence-based, such considerations may direct future research efforts towards a more integrated hypothesis regarding stress incontinence in women.

The relative contributions of abnormal vaginal mobility and intrinsic urethral function should be considered as part of a continuum rather than a dichotomy. Current research and interest has concentrated mostly on ISD as the primary cause of stress urinary incontinence in women, but the relationship of the many factors affecting urethral support and function should remain a perspective in interpreting emerging findings.

V. CONCLUSIONS

We are approaching a new classification of stress incontinence which will integrate hypermobility and urethral dysfunction as inter-related elements on a spectrum of change. Certain concepts have stood the test of time, and they are included below, along with conclusions:

1. Many patients with urodynamic stress incontinence show urethral mobility (Level 2), though it is not yet known what it is about that mobility which permits urethral opening during stress.

2. Some patients who present with minimal mobility or who have recurred after successful surgery have primary or residual sphincter insufficiency.

3. Sphincter insufficiency is related to a decline in striated sphincter muscle mass and function as measured by electrophysiological studies of pudendal nerve and sphincter function, and MRI and sonographic estimates of muscle mass (Level 1). If repeated episodes of vaginal traction can be shown to enhance sphincter damage, then the effect of early treatment of stress incontinence and prolapse on future development of ISD should be investigated, since advanced ISD remains difficult to treat.

4. Successful operations can restore urethral position but probably do not restore urethral function. A good surgical outcome probably requires a certain reserve of urethral function. It is in the area of functional understanding of urethral anatomy that the greatest progress is likely to be made.

D. PELVIC ORGAN PROLAPSE

I. PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

Normal pelvic organ support depends on the integrity of the endopelvic fascia, i.e. connective tissue, the pelvic floor muscles and adequate nerve supply. Theoretically, if one of these factors fails, the others might be able to compensate to a certain degree. Our knowledge as to which structure fails and why remains limited. Table 1 lists structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. In Table 2 anatomical and functional determinants of normal pelvic organ support are listed. The possible nature of failure and its potential causes, established and theoretical risk factors are also summarised.

For many years vaginal delivery has been considered the most important causal factor in the development of pelvic organ prolapse [282-287]. However, some large community-based epidemiological studies have described pelvic floor symptoms in women who gave birth by caesarean section only [283, 288]. It seems that pregnancy itself plays an important role in the development of pelvic floor dysfunction. Still not sufficiently investigated, the hormonal and enzymatic preparation of the connective tissue to soften and

278
Table 1. Structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. The levels of support and anatomical defects are derived from the anatomical studies of DeLancey. [357-359]

<table>
<thead>
<tr>
<th>Structure</th>
<th>Failure / Defects</th>
<th>Anatomical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterosacral ligaments (Level 1 support)</td>
<td>?Disruption, ?overdistension and elongation</td>
<td>Uterine prolapse</td>
</tr>
<tr>
<td>• Anterior endopelvic fascia</td>
<td>• Attenuation of fascia Disruption from attachment</td>
<td>Midline cystocele</td>
</tr>
<tr>
<td>• Lateral attachment at arcus tendineus fascia pelvis with proximal attachment at ischial spine (Level 2 support)</td>
<td>• Disruption of bulbocavernosus muscles</td>
<td>Paravaginal defect-cystocele</td>
</tr>
<tr>
<td>Perineum (Level 3 support)</td>
<td>Disruption from endopelvic fascia</td>
<td>Excessive perineal descent</td>
</tr>
<tr>
<td>Levator ani muscle</td>
<td>• Disruption/avulsion from pubic ramus</td>
<td>Rectocele</td>
</tr>
<tr>
<td>• Reduced tone/attenuation</td>
<td>• Paravaginal defect-cystocele</td>
<td></td>
</tr>
<tr>
<td>• Perineal descent</td>
<td>• Vertical course of vagina</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Determinants of normal pelvic organ support. Possible sites of failure and possible causes, established and theoretical risk factors.

<table>
<thead>
<tr>
<th>Normal support</th>
<th>Failure</th>
<th>Possible cause / risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal connective tissue including normal tone (smooth muscle cells)</td>
<td>• Reduced tone</td>
<td>Genetic LEVEL OF EVIDENCE 2</td>
</tr>
<tr>
<td></td>
<td>• Pathological type and cross linking LEVEL OF EVIDENCE 2</td>
<td>Pregnancy (connective tissue remodelling) LEVEL OF EVIDENCE 3</td>
</tr>
<tr>
<td></td>
<td>• Disruption LEVEL OF EVIDENCE 2</td>
<td>Chronic pelvic floor stress (straining, constipation, asthma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td>Normal attachment of connective tissue and pelvic floor musculature</td>
<td>• Disruption, detachment LEVEL OF EVIDENCE 2</td>
<td>Vaginal birth LEVEL OF EVIDENCE 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hysterectomy, pelvic operations LEVEL OF EVIDENCE 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic pelvic floor stress LEVEL OF EVIDENCE 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelvic trauma (accidents, falls) LEVEL OF EVIDENCE 3</td>
</tr>
<tr>
<td>Normal tone of the pelvic floor muscle</td>
<td>• Hypotonic pelvic floor muscle LEVEL OF EVIDENCE 4</td>
<td>Pregnancy, childbirth (ischemic, mechanical, hormonal) LEVEL OF EVIDENCE 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced connective tissue tone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic pelvic floor stress</td>
</tr>
<tr>
<td>Normal, nearly horizontal, axis of the vagina</td>
<td>• Vertical course of the vagina LEVEL OF EVIDENCE 3</td>
<td>Hysterectomy, pelvic operations including Burch-colposuspension LEVEL OF EVIDENCE 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic pelvic floor stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal birth LEVEL OF EVIDENCE 2</td>
</tr>
<tr>
<td>Normal innervation and pre-programming of abdominal capsule and pelvic floor muscle</td>
<td>• Denervation/re-innervation LEVEL OF EVIDENCE 1</td>
<td>Vaginal birth LEVEL OF EVIDENCE 1</td>
</tr>
<tr>
<td></td>
<td>• Loss of pre-programming LEVEL OF EVIDENCE 4</td>
<td>Pelvic trauma/pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed or lack of pelvic floor contraction during increased abdominal pressure LEVEL OF EVIDENCE 3</td>
</tr>
</tbody>
</table>
stretch adequately during vaginal birth might be an imperative factor. Although muscular, neural and connective tissue damage has been demonstrated in women after vaginal deliveries, these changes do not automatically result in pelvic floor dysfunction. Epidemiological studies have also emphasised the contributing effects of ageing, genetic predisposition, obesity, constipation and hormone therapy.

1. GENETIC AND ETHNIC PREDISPOSITION

Comparative studies have drawn attention to the higher incidence of pelvic floor dysfunction amongst relatives, most notably amongst identical twins [289-292]. Familial incidence of POP was reported as high as 30% [292].

Genetic variants have been documented that run in families with an increased incidence of pelvic organ prolapse [293]. One study examined gene expression of structural proteins that are related to actin and myosin in five women with and five women without pelvic organ prolapse in the pubococcygeal muscle. There were several genetic differences between subjects and controls with under and overexpression of genes [294]. Altered gene expression of elastin has also been described in women with pelvic organ prolapse [295]. In mice, HOXA11 has been identified as the gene that is responsible for the development of the uterosacral ligaments [296]. In HOXA11-null mice the uterosacral ligaments were absent. HOXA11 and collagen expression were significantly decreased in the uterosacral ligaments of women with pelvic organ prolapse [296].

Also, it has long been suspected and recently been studied that connective tissue diseases like Ehlers-Danlos and Marfan’s syndrome predispose to pelvic organ prolapse [297]. Young women with pelvic organ prolapse are more likely to have neurological or connective tissue diseases and congenital abnormalities [298]. Intrinsic joint hypermobility is another well recognised connective tissue disease that is associated with pelvic organ prolapse [299-302].

Differences between ethnic groups have been described in some studies with regard to pelvic floor function. White women seem to have a higher risk of pelvic organ prolapse compared with Afro-American women [303]. However, prolapse is highly prevalent in rural Gambia, West Africa e.g. with 14% of 1067 having moderate to severe prolapse [287]. In one study Hispanic women had an increased risk for prolapse compared to white women [304]. The thickness of the puborectalis muscle measured on perineal ultrasound varies between Caucasian and Chinese women [305].

Signs of a rectocele on ultrasound examination were found in 12% of young nulliparous women in a small observational study raising the question of a congenital fascial defect [306]. Pelvic organ prolapse in young women has also been linked with abdominal hernias [292]. As a deep pouch of Douglas is frequently present in young nulliparous women, without pelvic organ prolapse this implies a congenital variation and may be predisposition [307].

2. ALTERATIONS OF COLLAGEN, ELASTIN AND SMOOTH MUSCLE OF THE VAGINAL AND SUPPORTIVE TISSUES

Many studies have found alterations in supportive tissues in women with pelvic organ prolapse [308]. One study revealed that the general amount of collagen in the parametria is reduced in pre and postmenopausal women with pelvic organ prolapse compared with women without prolapse. In biopsies from the vaginal apex there were no differences [309].

Type III collagen is the primary collagen subtype in the vagina and its supportive structures. The ratio of collagen I to III is an indicator of tensile strength. The higher the amount of collagen type III the lower the mechanical strength. A lower collagen I/III ratio due to increased type III collagen has been demonstrated in women with pelvic organ prolapse in the vaginal subepithelium and uterosacral and cardinal ligaments, independent of age and parity [310-312]. Menopause seems to decrease the collagen I/III ratio [311, 313]. Type I collagen content was similar in women with and without uterine prolapse, but the quality of the fibres was different. In this study, hormonal status did not affect collagen content [314]. Unfortunately there are only cross-sectional studies and the direction of the association between pelvic organ prolapse and increased collagen III is not clear. Is the decreased collagen I/III ratio a response to the prolapse or does it cause it? However, due to the reduced tensile strength of the connective tissue progression of pelvic organ prolapse is likely.

Other studies have focussed on examining active components and factors suggestive of connective tissue remodelling. Active remodelling of vaginal connective tissue in women with prolapse has been suggested as a result of “biomechanical stress” [310]. A higher expression of tenascin -a glycoprotein that is involved in tissue repair – was found in cardinal and uterosacral ligaments of prolapsed uteri [311, 315]. This implies traumatic factors caused by the prolapse. The activity of matrix metalloproteinases (MMP) has been examined in women with and without pelvic organ prolapse with different results emphasising the heterogeneity of pelvic floor dysfunction as well as difficulties with standardisation of specimens, sites and tests [316-318]. Results do however show an active remodelling of the connective tissue in women with prolapse.

Elastin also plays an important role in connective tissue and pelvic floor integrity. As it is thought to be
very stable with little turnover during a woman's lifetime apart from childbirth, demonstrated elastin differences between women with and without pelvic organ prolapse are suggestive of a structural defect rather than a secondary result of prolapse [319].

In mice it has been shown that impaired homeostasis of elastin after parturition due to insufficient LOXL1 expression (lysyl oxidase) leads to prolapse [320]. LOXL1-deficient mice seem to develop prolapse due to a global defect in connective tissues that correlates with inferior biomechanical properties with a decrease of ultimate load at failure [321]. Altered elastin metabolism and elastin gene expression were found in women with pelvic organ prolapse [295, 315, 322] (Figure 12).

The significance of highly prevalent smooth muscle in pelvic floor supportive tissues is not clearly understood. In women with normal pelvic organ support smooth muscles fibres in the anterior vaginal wall are organised in "tightly-packed" bundles orientated in circular and longitudinal directions [323]. In comparison, in women with pelvic organ prolapse the bundles were smaller, fewer and disorganised [323]. These features were also demonstrated in biopsies from the upper posterior vaginal wall after hysterectomy in women with prolapse [324]. Loss of smooth muscle content was related to the degree of prolapse [324]. Smooth muscle content was also reduced in the round ligament of women with prolapse [325]. Caldesmon, a protein in smooth muscle that inhibits actin-activated myosin adenosine triphosphatase, plays a role in regulating smooth muscle contractility. As it has been found to be increased in vaginal tissues in women with prolapse, it may have led to impaired smooth muscle contractility and force maintenance [326].

Biomechanical factors have been assessed with different techniques. The tensile strength of the connective tissue is significantly reduced in women with pelvic organ prolapse [327] whereas extensibility was shown to be greater. Interestingly these differences of extensibility were not demonstrated in the skin of the forearms implying that prolapse in these women was related to local rather than systemic connective tissue alterations [328]. Elongation of vaginal apical tissues of women during pelvic reconstructive surgery seems very variable between 15 to 42 mm [329]. The authors concluded that this might be a reason for otherwise unexplained failure of prolapse surgery [329].

3. NEUROLOGICAL FACTORS

Intact innervation of the levator ani muscle, anal, and urethral sphincters is critical to normal pelvic function. It has been suggested that neurological damage induced by transvaginal reconstructive surgery results in suboptimal outcome [330]. Perineal terminal motor latency served as a surrogate parameter. However, the authors have reported rather low success rates after bilateral sacrospinous ligament fixation which emphasises the importance of surgical technique [331].

Vaginal birth is an established factor for nerve damage. Prospective EMG studies performed before and after childbirth substantiated the evidence of childbirth induced pelvic floor denervation detecting increased fibre density after vaginal delivery. Ageing leads to further deterioration of pelvic floor denervation [164, 332].

Histologically, there were smaller and fewer nerve bundles in women with posterior vaginal wall prolapse compared with women without prolapse [324]. The density of peptide-containing nerves in the periurethral tissue and in the levator ani muscle in women with prolapse was reduced [333, 334] (Figure 12: Tissue sample of a 54 old woman with POP. Black areas show fragmented elastic connective tissue fibres as a sign of pelvic floor tissue defect. [291])
4. PREGNANCY- EPIDEMIOLOGY AND CONNECTIVE TISSUE AND PELVIC FLOOR MUSCLE REMODELLING

Recently some studies have drawn attention to the occurrence of clinically significant pelvic organ prolapse during pregnancy in nulliparous women [335-338]. These studies employed the validated quantitation of pelvic organ prolapse of the International Continence Society. Pelvic organ prolapse stage 2 was found in 26-48% whereas none of the 21 age and race matched non-pregnant controls demonstrated stage 2 prolapse [336, 337]. Prolapse stage increased during pregnancy and persisted postpartum in women who were delivered vaginally [335-338]. The most frequent site of prolapse was the anterior vaginal wall in all of these studies.

The causes of the development of pelvic organ prolapse during pregnancy might be multifactorial but certainly hormones and enzymes are involved. Progesterone is known to reduce the tone in ureters, bladder and urethra because of its smooth muscle relaxing and estrogen antagonising effects [339]. Relaxin, a peptide hormone similar to insulin, increases markedly during pregnancy. It modifies the connective tissue and has a collagenolytic effect to allow for appropriate stretching during vaginal birth in guinea pigs [340]. As a likely result of connective tissue remodelling in preparation for birth, Landon and colleagues [341] found that the connective tissue of the rectus sheath fascia and the obturator fascia could be stretched to greater length during pregnancy, but it is also much weaker. In some women these changes may be irreversible or further stretching beyond physiological limits may result in permanent dysfunction.

5. CHILDBIRTH

Vaginal birth has long been considered the most important risk factor for pelvic organ prolapse. Most epidemiological studies demonstrate an association with parity in general [283, 286, 287, 342-344] and specifically with vaginal birth [168, 283, 303, 345]. Mechanical damage to the pelvic floor musculature, connective tissue and nerve supply occurs particularly during the second stage of labour when the fetal head distends and stretches the pelvic floor. Apart from direct muscle rupture and muscle and connective tissue stretching there might also be biochemical damage to the soft tissue, especially during long second stages. The recent development of three and four dimensional ultrasound has enabled us to directly study pubovisceral muscle detachment after vaginal delivery. Dietz et al., in a small study, revealed levator avulsion in 36% of 39 women after vaginal birth. This injury was associated with stress incontinence [155].

Employing the ICS pelvic organ prolapse standardisation, Sze et al. [337] prospectively studied nulliparous women and found that postpartum, 52% had stage 2 prolapse, 37% of women developed a new prolapse and 15% revealed a more severe prolapse compared to antenatal examinations.

Childbirth in mice has been investigated in an intriguing study analysing the elastin and LOXL1 expression [346]. There is degradation before and a high turnover of elastic fibres after childbirth that allows the tissues to recover. During parturition monocytes are present in the vagina which may induce elastolysis by chemotaxis. Mice injected with elastases into the posterior vaginal wall post partum demonstrated protrusion 2-4 hours later. Fibulin, an elastin-binding protein that is crucial for elastogenesis and effective cross linking is thought to be important for regeneration and to counteract elastin degradation. In 33 of 36 mice with null mutations in fibulin-5 pelvic organ prolapse was found to progress with age. Drewes et al. concluded that there might be different factors initiating prolapse like ageing, smoking and childbirth but the final pathway seems to be a reduction in number of functional elastic fibres [346].

6. CAESAREAN SECTION- ONLY PARTIALLY PROTECTIVE

In most post partum as well as long-term studies caesarean section might reduce but not totally prevent urinary and anal incontinence. Pelvic organ prolapse however seemed considerably lower after caesarean section [283, 343] but was still described in a rare prospective study before and 6 weeks after childbirth in 35% of 26 women after caesarean section during active labour compared to 32% of 41 women who had spontaneous vaginal deliveries [337]. The influence of labour versus no-labour pure caesarean delivery on pelvic organ prolapse has been negated in one epidemiological study using validated questionnaires [168].

7. OBSTETRICAL AND MATERNAL FACTORS

Age at first delivery may theoretically have an impact on the development of pelvic organ prolapse. However, studies are controversial considering younger age (25 versus 28 years of age) [347] as well as older age (more than 30 years) [348] at first delivery a risk factor. Another large study did not reveal an association at all [303].

A higher birth weight especially more than 4000g has been shown to increase the risk for pelvic organ prolapse in univariate and multivariate analyses [303, 304, 343, 349]. An extensive vaginal rupture has also been associated with prolapse [349]. Instrumental delivery is an established risk factor for anal incontinence but has only been shown in one study to be associated with prolapse [347] A mediolateral episiotomy did not prevent or result in a higher incidence of pelvic organ prolapse three months post partum [303, 350].
8. HORMONES

Hormone therapy has been shown to increase urogenital symptoms in some studies [351-353]. Whereas the negative effect of systemic hormone therapy on incontinence status seems established this has not been clearly demonstrated for pelvic organ prolapse. Most epidemiological studies did not reveal a significant association [286, 304, 343]. In a univariate analysis of self-reported prolapse symptoms in a population-based study, current estrogen use increased the risk. However, multivariable regression did not confirm this [303].

In prolapse patients, the cardinal ligaments and levator ani fascia express more estrogen receptors than in women without prolapse [354, 355]. Long term estrogen treatment however led to a decline in estrogen receptor expression [282, 284, 287, 344]. Menopause seems to decrease the collagen I/III ratio [313].

9. AGE

Most epidemiological studies have determined age as a main risk factor for pelvic organ prolapse [286, 342, 343, 356]. However, the interaction of age, menopause and hormonal status seems inseparable.

10. OBESITY: BODY MASS INDEX AND WAIST CIRCUMFERENCE

Many studies have examined the influence of obesity on pelvic organ prolapse prevalence, some studies also of progression and regression. Body mass index and waist circumference are the most commonly measured variables. An increased BMI increases the risk for prolapse [285, 304, 306, 347, 357] and specifically for progressive rectoceles [342]. Increased waist circumference was associated with more pelvic organ prolapse in some studies [342, 343]. Handa et al. demonstrated this for cystoceles [342]. Whereas some studies do and some do not reveal obesity as a risk factor, no study found overweight protective.

11. CONSTIPATION

Similar to obesity, constipation has frequently been described to increase the risk for pelvic organ prolapse [303, 306, 357, 358] and has never been found to be protective.

12. CHRONIC PELVIC FLOOR STRESS

Occupational heavy lifting has long been associated with pelvic organ prolapse [359]. Prolapse was more prevalent in labourers or factory workers compared with housewives or service workers [360, 361] Chronic lung disease seems likely to increase prolapse but has rarely been shown to be an independent risk factor [284].

13. PREVIOUS OPERATIONS

Whether previous hysterectomy increases the risk for subsequent pelvic organ prolapse is not clear. In some epidemiological studies previous hysterectomy seems to predispose to prolapse and further reconstructive surgery [285, 362] One case-control study (114/6214 women who had undergone hysterectomy, 236/6100 controls randomly selected) looked at the risk factors for reconstructive pelvic surgery. The incidence was 4.3 per 1000 women years if pelvic organ prolapse was grade 2 before the initial hysterectomy but only 0.6 if it was grade 0 or 1. Vaginal hysterectomy itself did not increase the risk [356]. The empirical fact that younger women and women operated on for severe prolapse are more likely to have recurrent prolapse has been confirmed in one follow up study of 389 women [363]. Previous surgery for pelvic organ prolapse appears to be a consistent risk factor.[364, 365]

Isolated enteroceles may occur after pelvic surgery. The classical example is the development of enteroceles after Burch colposuspension in up to 32% [366-369] Symptoms suggestive of a rectocele like digitation to defecate were more frequently observed after hysterectomy [370]. The anterior compartment is the main site of recurrence after sacrospinous fixation. In two comprehensive reviews the apical success rates after a follow up of 12 or more months were 79 – 97% (mean 92%) but the failure rate for cystoceles was 10-30% (mean 21%) [371].

14. THE BONY PELVIS

There is evidence from several case control studies that variations in axial and pelvic skeletal structure can be associated with increased risks of POP. These include increasing degrees of thoracic kyphosis, a decrease in lumbar lordosis and in vertical orientation of the pelvic inlet, and an increase in the transverse diameter of the pelvic inlet [372-374]. In a case control study Handa [375] compared 59 women with pelvic floor disorders with controls using standardized pelvimetry techniques during MRI.

After controlling for age, race and parity, using a multiple logistic regression analysis, pelvic floor disorders were significantly associated with a wider transverse inlet (odds ratio 3.4) and a shorter obstetrical conjugate (odds ratio 0.23). The association between early age, advanced stage POP and the severe disruption of pubic bone and pelvic muscle structure in women with bladder extrophy is well recognized [376].
15. CONCLUSION AND RECOMMENDATIONS

There are genetic alterations that predispose to pelvic organ prolapse (LEVEL OF EVIDENCE 2). Differences in collagen type and ratios as well as smooth muscle organisation and neurogenic structures between women with and without prolapse are well-known but the cause and effect remain unclear (LEVEL OF EVIDENCE 2). Altered metabolism and gene expression of elastin is thought to be the cause of pelvic organ prolapse (LEVEL OF EVIDENCE 2) whereas active remodelling of the connective tissue (increase in tenascin e.g.) is likely to be a result of biomechanical stress due to the prolapse (LEVEL OF EVIDENCE 2).

POP increases with age (LEVEL OF EVIDENCE 2). Modifiable risk factors for POP are obesity (increased BMI and waist circumference), occupational heavy lifting and constipation (LEVEL OF EVIDENCE 3). Previous pelvic floor surgery increases the risk of prolapse (LEVEL OF EVIDENCE 2).

Pregnancy itself can lead to prolapse (LEVEL OF EVIDENCE 2). Vaginal delivery increases the risk for prolapse further (LEVEL OF EVIDENCE 1) but caesarean section is only partially protective (LEVEL OF EVIDENCE 2). Obstetrical aspects that are associated with loss of pelvic organ support are birth weight of more than 4000g and instrumental delivery (LEVEL OF EVIDENCE 3). The effect of maternal age at delivery remains unclear. There is no association between episiotomy and POP.

Further research should focus on modifiable risk factors and their impact on the development and prevention of pelvic organ prolapse and its recurrence. The course of pregnancy with hormonal changes cannot be altered and caesarean section is not a universal alternative to vaginal delivery. Although we should aim to make vaginal birth safer for mother and child, the mainstay of prevention of prolapse are modifiable risk factors.

II. ASSOCIATED PELVIC FLOOR CONDITIONS

Pelvic organ prolapse (POP) has a strong inter-relationship with the urinary tract and urinary incontinence commonly co-exists with POP. Thus, it is important for incontinence specialists to have a well-grounded understanding of POP in order to provide optimal patient care for the many women worldwide whose quality of life is impacted by pelvic floor disorders.

1. BLADDER FUNCTION

In a large community-based questionnaire survey, 44% (104/239) of women who had prolapse symptoms (239/3799) also complained of stress urinary incontinence and 37% of overactive bladder [377]. Animal experiments performed by Barrington in the first half of the twentieth century have suggested a mechanism by which urethral relaxation may evoke reflex detrusor contraction: when urine enters a relaxed proximal urethra, the desire to void may be evoked, an extension of his experimental observations in anesthetized rabbits, that water running through the urethra, or mechanical distension of the urethra produced a bladder contraction [378-380]. This mechanism might explain the high co-occurrence-rate of POP and bladder symptoms.

Schick et al [381] looked at 255 women with urodynamic stress incontinence and found a statistically significant correlation between urethral hypermobility and the degree of urethral incompetence assessed with the abdominal leak point pressure. However, with greater degrees of anterior vaginal wall prolapse (Stage III and IV) fewer women have symptoms of stress incontinence [382]. Increased prolapse stages (especially point Ba on the POPQ) are associated with obstructive symptoms, as severe prolapse can descend and obstruct the urethra, making assessment and management of the continence mechanism in such patients problematic [282, 382-384] [385].

Multiple studies have described an occult stress incontinence rate after various methods of reducing the prolapse during preoperative testing of [258-261]. However, Bump et al described an only 4% de novo incontinence rate in women with Stage III or IV prolapse who had been randomized to a bladder neck plication procedure as their only prophylaxis, also concluding that preoperative barrier testing was not useful in identifying women who required a urethropexy [386]. Klutke et al determined that preoperative barrier testing was most useful in identifying those women who do not leak with reduction of the prolapse, since such patients did not undergo urethropexy and had better outcomes with regard to both USI and DO rates [387]. Because of this uncertainty, the least invasive method of bladder neck stabilization seems preferred for such patients [388].

Pelvic organ prolapse can negatively affect voiding function [385, 389], although one study noted that the majority of women with severe prolapse still void effectively [390]. Looking at 228 women with urinary tract disorders and/or prolapse, Dietz et al [391] found that enterocele had the worst effect on voiding function (P<0.001), whereas the relationship between anterior vaginal wall prolapse and voiding was complex: using ultrasound the finding of an intact retrovesical angle was related to difficulties in voiding (P<0.001);
funnelling and opening of the retrovesical angle was associated with improved voiding (P<0.001). Fitzgerald found that preoperative voiding studies with the prolapse reduced by a pessary was the best predictor of normalization of residuals post operatively [392]. The impact of pelvic organ prolapse on the upper urinary tract is not well described in the surveyed literature, consisting primarily of case reports of acute or chronic renal failure attributed to urethral obstruction by Stage IV uterine or vaginal vault prolapse. Hydroureter and hydronephrosis was demonstrated in such cases, resolving post repair [393-397].

2. BOWEL FUNCTION

Bowel symptom like incontinence of flatus and obstructed defecation are common in women with POP. In several surveys, the incidence of anal incontinence ranges from 15-50% ([398-402], [377, 398, 403-405]. Faecal incontinence was reported in 5-22% of women with prolapse [398, 404, 405] which was significantly more than bowel symptoms in a control group [404]. There were no associations found between prolapse stages and symptoms after adjusting for age and BMI [403, 405].

There are also disparities between the degree of pelvic organ prolapse, pelvic floor symptoms and defecography results [406, 407]. Two series of defecographies in consecutive patients with prolapse and/or evacuation disorders describe defecographic findings that changed the patients diagnosis (though not always the management) in 46 of 62 of cases and noted enteroceles that were not found on physical exam in approximately 50% of cases [408-410]. Sigmoidoceles are present in 4-11% of reported series, and are nearly always missed on physical examination [410, 411]. Their clinical impact and management remain however unclear. Defecography is not a routine investigation in women with POP and interpretation may be difficult in some cases since normal asymptomatic women may have focal defecographic abnormalities demonstrated [407].

The prevalence of abnormal colonic transit time is approximately 20% in patients presenting with evacuation disorders [412]. An abnormal preoperative colonic transit study is the most consistently cited risk factor for failure of rectocele repair to relieve evacuatory symptoms, regardless of the surgical technique [413-415]. Recently Goh et al [416] reviewed the management of rectocele and clearly describe the complexity of clinical conditions resulting from the possible combination of various gynaecological and colorectal symptoms with anatomical abnormalities and the different surgical approaches.

3. SEXUAL FUNCTION

Dyspareunia, coital incontinence and vaginal dryness are common complaints in women with pelvic floor disorders [417, 418]. Although sexual dysfunction appears to be more frequently observed in these women, pelvic organ prolapse did not negatively impact on sexual satisfaction when controlled for confounders like age [418-420].

E. FAECAL INCONTINENCE: GASTROENTEROLOGICAL PERSPECTIVE

Faecal incontinence is maintained by the structural and functional integrity of the anorectal unit. Consequently, disruption of the normal anatomy or physiology of the anorectal unit leads to faecal incontinence. Faecal incontinence is often due to multiple pathogenic mechanisms and rarely due to a single factor [421].

I. STRUCTURE AND FUNCTION OF THE ANORECTUM

The rectum is a hollow muscular tube, 12 cm to 15 cm long, composed of a continuous layer of longitudinal muscle that interlaces with the underlying circular muscle [422]. The anus is a muscular tube 2 cm to 4 cm long. At rest, it forms an angle with the axis of the rectum of approximately 90°; during voluntary squeeze the angle becomes more acute, approximately 70°; during defecation, the angle becomes more obtuse, about 110° to 130°.

1. THE ANAL SPHINCTER

The anal sphincter consists of two muscular components: the internal anal sphincter (IAS), a 0.3 cm to 0.5 cm thick expansion of the circular smooth muscle layer of the rectum, and the external anal sphincter (EAS), a 0.6 cm to 1.0 cm thick expansion of the striated levator ani muscles. Morphologically, both sphincters are separate and heterogenous [423]. The EAS is a predominantly slow-twitch, fatigue resistant muscle [424, 425]. The IAS generates mechanical activity, with a frequency of 15 to 35 cycles per minute, and ultra-slow waves at 1.5 to 3 cycles per minute [426, 427]. The ultra-slow waves generate pressures fluctuating between 20 mm Hg and 50 mm Hg in 10% of control subjects [428-430]. The IAS contributes approximately 70% to 85% of the resting sphincter pressure, but only 40% after sudden distension of the rectum and 65% during constant rectal distension [431]. Thus, the IAS is chiefly responsible for maintaining anal continence at rest [431].

The anus is normally closed by the tonic activity of the IAS. This barrier is reinforced during voluntary squeeze by the EAS. The anal mucosal folds, together with the expansive anal vascular cushions, provide a tight
These barriers are further augmented by the pubourethral muscle, which forms a flap-like valve that creates a forward pull and reinforces the anorectal angle [434].

2. NERVE STRUCTURE AND SENSATION

The anorectum is richly innervated by the sensory, motor, and autonomic nerves and by the enteric nervous system. The principal nerve is the pudendal nerve, which arises from the second, third, and fourth sacral nerves (S2, S3, S4) and innervates the EAS. The pudendal nerve is a mixed nerve that subserves both sensory and motor function [435]. Pudendal nerve block creates a loss of sensation in the perianal and genital skin and weakness of the anal sphincter muscle, but it does not affect rectal sensation [431]. It also abolishes the rectoanal contractile reflexes, suggesting that pudendal neuropathy may affect the rectoanal contractile reflex response. It is not completely understood how humans perceive stool contents in the anorectum. Earlier studies failed to demonstrate rectal sensory awareness [436, 437]. But more recent studies have confirmed that balloon distension is perceived in the rectum and that such perception plays a role in maintaining continence [438, 439]. Furthermore, sensory conditioning can improve both hypo-sensitivity [440, 441] and hypersensitivity [442] of the rectum. Mechanical stimulation of the rectum can produce cerebral evoked responses [443] confirming that the rectum is a sensory organ. Although there are no organized nerve endings, both myelinated and unmyelinated nerve fibres are present in the rectal mucosa, and the myenteric plexus [437, 444]. These nerves most likely mediate the distension or stretch-induced sensory responses as well as the viscerovisceral, [445] the recto-anal inhibitory, and the recto-anal contractile reflexes [444]. The sensation of rectal distension is most likely transmitted along the S2, S3, and S4 parasympathetic nerves [444]. Rectal sensation and the ability to defecate can be abolished completely by resection of the nervi erigentes [446]. If parasympathetic innervation is absent, rectal filling is only perceived as a vague sensation of discomfort. Even paraplegics or persons with sacral neuronal lesions may retain some degree of sensory function, but virtually no sensation is felt if lesions reach the higher spine [439, 447]. Thus, the sacral nerves are intimately involved with the maintenance of continence. It has been suggested that bowel contents are periodically sensed by anorectal “sampling,”[448, 449] the process by which transient relaxation of the IAS allows the stool contents from the rectum to come into contact with specialized sensory organs, such as the Krause end-bulbs, Golgi-Mazzoni bodies and genital corpuscles, and the sparse Meissner’s corpuscles and Pacinian corpuscles in the upper anal canal [436, 444, 450]. Specialized afferent nerves may exist that subserve sensations of touch, temperature, tension, and friction, but are incompletely understood [444]. Incontinent patients appear to sample rectal contents infrequently [449]. The role of anorectal temperature sensation is also subject to debate [451-453]. The likely role of anal sensation is to facilitate discrimination between flatus and faeces and the fine-tuning of the continence barrier, but its precise role needs to be characterized.

3. RECTAL DISTENSION

Rectal distension is associated with a fall in anal resting pressure known as the rectoanal inhibitory reflex. The amplitude and duration of this relaxation increases with the volume of rectal distension [454]. The arrival of flatus mimics sudden rectal distension and this is associated with a fall in anal pressure [455]. Although this process may facilitate discharge of flatus, rectal distension is also associated with an anal contractile response, a subconscious reflex effort to prevent release of rectal contents, such as flatus [456-458].

The amplitude and duration of the rectoanal contractile reflex also increases with rectal distension up to a maximum volume of 30 ml [454]. Abrupt increases in intra-abdominal pressure, such as those caused by coughing or laughing, are associated with increases in anal sphincter pressure [459]. This may be achieved through multiple mechanisms, including reflex contraction of the pubourethra [460].

4. ANAL ENDOVASCULAR CUSHIONS

The blood-filled vascular tissue of the anal mucosa also plays an important role in producing a more perfect closure of the anus. An in vitro study showed that even during maximal involuntary contraction, the internal sphincter ring was unable to close the anal orifice completely and a gap of approximately 7 mm was left open. This gap was filled by the anal cushions [461]. Anal cushions may exert pressures of up to 9 mmHg and thereby may contribute 10% to 20% of resting anal pressure [462].

II. PATHOGENIC MECHANISMS AND ETIOLOGY

Faecal incontinence occurs when one or more mechanisms that maintain continence is disrupted to an extent that other mechanisms are unable to compensate. Hence, faecal incontinence is often multifactorial [421, 463]. In a prospective study, 80% of patients with faecal incontinence had more than one pathogenic abnormality [421]. Although the pathophysiological mechanisms often overlap, they may be categorized under the four subheadings shown in Table 3. For each category, the probable cause(s) and the mechanism through which it leads to faecal incontinence is also summarized in Table 3.
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CAUSE</th>
<th>MECHANISTIC EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal sphincter muscle</td>
<td>Haemorrhoidectomy, anal dilatation</td>
<td>Loss of sampling reflex due to neuropathy</td>
</tr>
<tr>
<td>Rectum</td>
<td>Inflammation, IBD/ radiation; Prolapse; aging; IBS</td>
<td>Lost accommodation and sensation; hypersensitivity</td>
</tr>
<tr>
<td>Puborectalis</td>
<td>Excessive perineal descent; aging; trauma</td>
<td>Obtuse anorectal angle sphincter weakness</td>
</tr>
<tr>
<td>Pudendal Nerve</td>
<td>Obstetrical/surgical injury excessive straining</td>
<td>Sphincter weakness sensory loss/impairment, perineal descent</td>
</tr>
<tr>
<td>CNS, Spinal cord, ANS</td>
<td>Head or spinal cord injury, Back surgery, MS, DM, stroke, avulsion</td>
<td>Lost sensation/reflexes secondary myopathy, loss of accommodation</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorectal sensation</td>
<td>Obstet, CNS, ANS injury</td>
<td>Loss of stool awareness, Rectoanalagnosia</td>
</tr>
<tr>
<td>Faecal impaction</td>
<td>Dyssynergic defecation</td>
<td>Faecal retention and overflow; Impaired sensation</td>
</tr>
<tr>
<td><strong>Stool characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume and consistency</td>
<td>Infection, IBD, IBS, drugs, metabolic abnormalities</td>
<td>Diarrhoea and urgency Rapid stool transport Impaired accommodation</td>
</tr>
<tr>
<td>Irritants</td>
<td>Bile salt malabsorption/ laxatives</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Hard stool/Retention</td>
<td>Dyssynergia/drugs</td>
<td>Faecal retention and overflow</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility/cognition</td>
<td>Aging, dementia, disability</td>
<td>Multifactorial changes</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Willful soiling</td>
<td>Multifactorial changes</td>
</tr>
<tr>
<td>Drugs</td>
<td>Anticholinergics; Laxatives; Antidepressants; Caffeine/muscle relaxants</td>
<td>Constipation; Diarrhoea; Altered sensation/constipation; Relaxed sphincter tone</td>
</tr>
<tr>
<td>Food intolerance</td>
<td>Lactose, fructose, sorbitol</td>
<td>Diarrhoea/flatus malabsorption</td>
</tr>
</tbody>
</table>
1. STRUCTURAL ABNORMALITIES

a) Anal sphincter muscles

Disruption or weakness of the EAS muscle causes urge-related or diarrhoea-associated faecal incontinence. In contrast, damage to the IAS muscle or the anal endovascular cushions may lead to a poor seal and an impaired sampling reflex. These changes may cause passive incontinence or faecal seepage, often under resting conditions. In most patients, both sphincters may be defective. The extent of muscle loss can influence the severity of incontinence.

The most common cause of anal sphincter disruption is obstetric trauma [464, 465]. However, it is unclear why most women who have sustained an obstetric injury in their 20’s or 30’s typically present with faecal incontinence in their 50’s. The injury may involve the EAS, the IAS, the pudendal nerves, or a combination of these structures. In a prospective study, 35% of primiparous (normal anti-partum) women showed evidence of anal sphincter disruption following vaginal delivery [465, 466]. Other important risk factors include forceps-assisted delivery, prolonged second stage of labour, large birth weight, and occipito posterior presentations [465, 467, 468]. Furthermore, perineal tears, even when carefully repaired, can be associated with incontinence and patients may either present several years following delivery [468]. Episiotomy is believed to be a risk factor for anal sphincter disruption. In one study, medial episiotomy was associated with a nine-fold higher risk for anal sphincter dysfunction [469]. However, in a large 30 year retrospective cohort study, the prevalence of frequent faecal incontinence was 6.9% for women whose index delivery was complicated by anal sphincter disruption, 18% for the control group, and 0% for women who had caesarean section; bothersome incontinence was experienced by 27.6%, 25.8%, and 15.2% of the respective groups. This study suggests that regardless of the type of delivery, faecal or flatus incontinence occurs in a surprisingly large number of middle-aged women. This raises the issue of whether age-related changes that affect the pelvic floor are a predisposing comorbid problem in the pathogenesis of faecal incontinence [470]. Whether anal sphincter pressures change with aging is debatable [471]. In both men and women 70 years of age there was a 30% to 40% decrease in sphincter pressures compared to patients 30 years [472]. In another study, elderly subjects were found to have lower sphincter pressures, [473] but many were taking medications that may have affected muscle function. In contrast, other studies that have examined anal pressures have reported only insignificant decreases with age [474]. However, in all age groups squeeze pressure has been shown to be significantly lower in women than in men [471, 474, 475]. Furthermore, in women, there appears to be a rapid fall in squeeze pressure after menopause [475, 476]. Recently, estrogen receptors have been identified in the human striated anal sphincter [477]. In an experimental study of adult rats, ovariectomy led to atrophy of the striated anal sphincter muscle, [477, 478] which suggests that the strength and vigour of the pelvic floor muscles is influenced by hormones. Also, in older women, pudendal nerve terminal motor latency [PNTML] is prolonged [472, 479] and there is excessive pelvic floor descent on straining [472, 473]. These mechanisms may lead to progressive damage to the striated anal sphincter muscle due to repeated stretch injury during straining [479-481]. An anal endosonography study also showed that aging was associated with an increase in the thickness and echogenicity of the internal sphincter muscle [482].

Other causes of anatomic disruption include iatrogenic factors such as anorectal surgery for haemorrhoids, fistula, or fissures. Anal dilation or lateral sphincterotomy may result in permanent incontinence due to fragmentation of the anal sphincter apparatus [483, 484]. Contrary to the belief of many surgeons, haemorrhoidectomy can cause incontinence by inadvertently damaging the IAS [485] or through the loss of endovascular cushions. Accidental perineal trauma or a pelvic fracture may also cause direct sphincter trauma leading to faecal incontinence. Interestingly, a study of homosexual men showed that although the anal resting pressure of the subjects was lower and the anal sphincters were thinner than those of controls, there was no evidence of sphincter injury from anoreceptive intercourse [486]. These results suggest that anal intercourse may not cause sphincter trauma, at least in men. Finally, in the absence of traumatic structural defects, internal sphincter dysfunction may also occur because of myopathy, [464] internal sphincter degeneration, [487] or as a complication of radiotherapy [488].

b) Puborectalis muscle

Sir Allan Parks believed that the pressure exerted by the anterior rectal wall together with the puborectalis muscle was fundamental to maintaining continence as it formed a flap valve mechanism [489]. This concept was disputed in another study that imaged the rectum radiologically while simultaneously measuring rectal and anal canal pressures, as well as anal electromyogram (EMG) activity, during defecation manoeuvres [490]. The authors concluded that continence was maintained primarily by increased activity of the EAS muscle and the puborectalis muscle and that rectal pressures were consistently lower than those generated within the anal canal [490]. Similar observations were made by another group [491].

Also, after successful sphincter repair, continence was associated with higher sphincter pressures and not with an altered ano-rectal angle [492]. These findings suggest that an obtuse ano-rectal angle may represent an epiphenomenon in patients with
incontinence. The nerve supply for the upper portion of the puborectalis muscle arises from direct branches of the anterior S3 and S4. Thus, the puborectalis muscle and the external anal sphincter have separate neurological innervation. Consequently, pudendal blockage does not abolish voluntary contraction of the pelvic floor [493] but completely abolishes EAS function.11, [431, 493] It has been suggested that continence can be preserved following division of the EAS and IAS provided the puborectalis muscle is intact [494]. Moreover, division of the puborectalis muscle posteriorly does not produce incontinence as long as anal sphincter pressures are normal [495]. Thus, although the puborectalis plays an integral role in maintaining continence, its precise role is poorly understood.

c) Neuropathy

An intact innervation of the pelvic floor is essential for maintaining continence. Sphincter degeneration secondary to pudendal neuropathy and obstetric trauma may cause faecal incontinence in women [481]. The neuropathic injury is often sustained during childbirth, probably due to stretching of the nerves during elongation of the birth canal or through direct trauma during the passage of the fetal head. The nerve damage is more likely to occur when the fetal head is large, when the second stage of labour is prolonged, and when forceps are applied, especially high forceps delivery or if there is prolonged labour [465, 468, 481, 491, 496, 497]. Damage to the innervation of the pelvic floor musculature is usually asymmetrical [498]. Subsequent vaginal deliveries may further damage the pudendal nerves [466]. In another study of women who sustained obstetric sphincter injury, the only risk factor associated with the development of faecal incontinence was prolonged PNTML [499].

III. AUTONOMIC NEUROPATHY

The role of extrinsic autonomic innervation is somewhat controversial. Animal studies have shown that the pelvic nerves convey relaxatory fibres to the rectum [500]. Consequently, these nerves may play a role in accommodating and storing faeces and gas [501]. Damage to the pelvic nerves may lead to impaired accommodation and rapid transit through the rectosigmoid region, overwhelming the continence barrier mechanisms. Sympathetic efferent activity, as studied by stimulating the pre-sacral sympathetic nerves, tends to relax the IAS, [501, 502] whereas parasympathetic stimulation may cause contraction of the anal sphincter. The upper motor neurons for voluntary sphincter muscle lie close to those innervating the lower limb muscles in the parasagittal motor cortex adjacent to the sensory representation of the genitalia and perineum in the sensory cortex [497]. Consequently, damage to the motor cortex from central nervous system (CNS) lesions may lead to loss of bowel control and to incontinence. In some patients with neurogenic incontinence there is damage to both the sensory and motor nerve fibres, resulting in sensory impairment [438, 503, 504]. This can impair conscious awareness of anal filling [505] as well as the associated reflex responses in the striated pelvic floor sphincter muscles. Approximately 10% of patients with faecal incontinence may have lesions more proximal than the intrapelvic or perianal nerves. The primary abnormality in these patients is cauda equina nerve injury [497] which may be occult and not evident through clinical evaluation. These patients have a prolongation of nerve conduction along the cauda equina nerve roots without an abnormality in PNTML muscles [497, 506, 507]. In a minority of patients, however, there is a combination of peripheral and central lesions [506]. Other disorders such as multiple sclerosis, diabetes, and demyelination injury (or toxic neuropathy from alcohol or traumatic neuropathy) may also lead to incontinence [508-514].

a) Rectal accommodation and reservoir function

The rectum is a compliant reservoir that stores stool until social conditions are conducive for its evacuation [514, 515]. If rectal wall compliance is impaired, a small volume of stool material can generate high intrarectal pressure that can overwhelm anal resistance and cause incontinence [516]. Etiologies include radiation proctitis, ulcerative colitis, [516, 517] or Crohn's disease, an infiltration of the rectum by tumour or following radical hysterectomy [518]. Likewise, rectal surgery, in particular pouch surgery, [519] and spinal cord injury, [520, 521] may also be associated with loss of rectal compliance.

IV. FUNCTIONAL MECHANISMS

1. ANORECTAL SENSATION

An intact sensation not only provides a warning of imminent defecation, but also helps to discriminate between formed stool, liquid faeces, or flatus. Elderly persons, [522] physically and mentally challenged individuals, and children with faecal incontinence [523] often show blunted rectal sensation. This impaired sensation may lead to excessive accumulation of stool, causing faecal impaction, mega-rectum (extreme dilation of the rectum), and overflow [522, 523]. Impaired rectal sensation may also occur as a result of neurological damage such as multiple sclerosis, diabetes mellitus, or spinal cord injury [511, 520]. Less well known is the fact that analgesics (particularly opiates) and antidepressants may also impair rectal sensation and produce faecal incontinence. That the rectum is important in preserving continence has been shown elegantly through surgical studies in which preservation of the distal 6 cm to 8 cm of the rectum,
along with its parasympathetic nerve supply, helped subjects avoid incontinence [450]. In contrast, both rectal sensation and the ability to defecate can be abolished completely by resection of the nervi erigentes [446]. An intact “sampling reflex” allows the individual to choose whether to discharge or retain rectal contents. Conversely, an impaired “sampling reflex” may predispose a subject to incontinence [449]. However, the role of the sampling reflex in maintaining continence remains unclear. In children who have had colonic pull through surgery, some degree of sensory discrimination is preserved [524].

Because the anal mucosal sensory zone is absent, it has been suggested that sensory receptors (possibly located in the puborectalis muscle) may play a role in facilitating sensory discrimination [524]. Also, traction of this muscle is a more potent stimulus for triggering both defecation and rectal distension [524].

I. NEUROGENIC TRAUMA

The mechanism that maintains continence is complex and affected by various factors such as mental function, lack of a compliant rectal reservoir, enhanced colonic transit and changes in stool consistency and volume. However the most important factors appear to be an anatomically intact anal sphincter complex and neurological function. In about 80% of women with presumed “idiopathic” anorectal incontinence there is histological evidence of denervation of the striated pelvic floor muscles, particularly the puborectalis and external anal sphincter (EAS) [530]. This feature has also been demonstrated electrophysiologically by means of an increased fibre density in patients with idiopathic faecal incontinence indicating re-innervation following denervation [531]. Another finding in these patients is a conduction delay in pudendal nerves as measured by pudendal nerve terminal motor latency (PNTML) [532].

Although Hertz in 1909 suggested that pelvic floor damage may result from a normal vaginal delivery, objective scientific evidence for this was only produced in 1984 [245] and a follow-up of 14 patients 5 years later [332]. These authors studied 122 women, 71 after delivery with manometry, perineometry, PNTML and EMG, and 51 before and after delivery with EMG. This study demonstrated an increase in anal sphincter striated muscle fibre density in the vaginal delivery group at 2 months post-partum indicating evidence of re-innervation following denervation. The fibre density was not altered following elective caesarean section. Thirty three percent of primiparae and 50% of multiparae had prolonged PNTML within 48 hours of delivery. However by 2 months, the PNTML had returned to normal in 60% of these women, indicating that damage to pudendal nerve conduction is reversible. Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tears and high birth weight were important factors leading to pudendal nerve damage. In the 5 year follow-up study of 14 women, only multiparae who did not have a forceps delivery were selected; the denervating process was found to be progressive in the majority of women and 5 women suffered from stress incontinence of urine, 3 of whom were also incontinent to flatus.

In another prospective neurophysiological study, Allen et al [157] reported on 96 nulliparous women with EMG, PNTML and vaginal pressure measurements during pelvic floor contraction. They found evidence of re-innervation in the pelvic floor muscles of 80% of primiparae 2 months after vaginal delivery. The only obstetric factors associated with re-innervation were a high birth weight and a longer active stage of labour. Forty five of the original 96 women were studied again 6 years later and they concluded that changes in

F. CHILDBIRTH AND FAECAL INCONTINENCE

Pregnancy and childbirth have a significant impact on the emotional and physical wellbeing of a woman. It is reported that as many as 91% of women report at least one new symptom eight weeks post-partum [525]. A fall in maternal mortality accompanied by an increase in female life expectancy (80 years in the UK) has now shifted the focus of attention towards identification of factors that may minimise morbidity. Although pre-existing bowel symptoms may be aggravated during pregnancy and childbirth, the development of symptoms de novo is a more frequent occurrence. Obstetric trauma is the most common cause of faecal incontinence.

However the onset of symptoms may occur many years after delivery with a peak incidence in the perimenopausal years. This may reflect the effect of contributory factors such as the process of aging, the effect of the menopause or progression of neuropathy. This section focuses on the association between obstetric trauma and faecal incontinence. However to avoid confusion, the term anal incontinence is used to include incontinence to flatus, liquid and solids.

Anal incontinence has been reported to occur between 5 [465, 526] to 26 [527] percent of women during the first year following vaginal delivery. In a Canadian study [528] involving 949 consecutive women who delivered vaginally, 26% reported anal incontinence while 3% reported faecal incontinence. They identified forceps delivery and third/fourth degree tears as independent risk factors. In a population based study of 8774 women in Oregon, USA, more than 25% reported faecal incontinence within 6 months of childbirth [529].
pelvic floor neurophysiology occur with time and do not appear to be related to further childbearing [533].

A third prospective study [534] measured anal pressures, anal sensation and the perineal plane in 72 antenatal women and repeated 72 hours postpartum and in 41 women 2 months postpartum. Anal sensation was unchanged. Cornes et al [535] measured anal sensation in 96 primiparous within 10 days after delivery and measurements were repeated in 74 women 6 months after delivery. They found that at 6 months anal sensation had returned to normal. Anal sensation remained unchanged after caesarean section. In women who had a torn EAS, only impairment of sensation in the upper anal canal persisted at 6 months. More than half the women who admitted to persistent anal incontinence had normal anal sensation. Chaliha et al [536] measured anal electrosensitivity before and after childbirth and found it unchanged. Anal sensation in isolation therefore probably plays a minor role in the development of obstetric related faecal incontinence.

II. MECHANICAL TRAUMA

Until the recent advent of anal ultrasound, mechanical trauma to the anal sphincters was only suspected when there was history of a difficult vaginal deliveries and particularly recognised third or fourth degree tears collectively known as obstetric anal sphincter injuries (OASIS). Consequently, when anal endosonography was performed in patients believed to be suffering from "neurogenic" faecal incontinence unsuspected internal anal sphincter (IAS) and EAS defects were identified [537]. The sonographic appearance of EAS defects has been verified histologically to represent fibrosis [538] while the appearance of IAS defects have been validated prospectively in patients undergoing lateral internal anal sphincterotomy [539]. Trauma as identified by ultrasound may be unrecognised (previously referred to as occult) or recognised OASIS.

1. UNRECOGNISED (OCCULT) ANAL SPHINCTER TRAUMA

Sultan et al [465] performed the first prospective study (before and after childbirth) to demonstrate both “occult” anal sphincter trauma (Figure 10) and pudendal nerve damage during childbirth in both primiparous and multiparous women (n=150). In 35% of primiparous and 44% of multiparous women anal sphincter defects were identified at 6 weeks postpartum by anal endosonography that were not present before vaginal delivery. Thirteen percent and 23% respectively developed defecatory symptoms (faecal urgency and/or anal incontinence) after delivery. Only 2 of the 150 women (both primiparous) had recognised tears of the anal sphincter at the time of delivery. A strong association was demonstrated between the presence of any defect and the development of symptoms. Only 4% of multiparous women sustained new sphincter damage following a subsequent delivery. The single independent factor associated with anal sphincter damage was forceps delivery. The 23 women delivered by caesarean section remained asymptomatic and none developed sphincter defects. No relationship was demonstrated between PNTML measurements and defecatory or urinary symptoms.

Donnelly et al [540] interviewed 219 nulliparae regarding bowel habit in the third trimester and performed anal vector manometry. At 6 weeks postpartum 184 women returned and the same bowel symptom questionnaire was completed and anal vector manometry plus PNTML measurements were performed. Anal endosonography was performed in 81 women with altered faecal continence or abnormal physiology. Instrumental vaginal delivery and a passive second stage of labour prolonged by epidural analgesia were significantly associated with the greatest risk of anal sphincter trauma and impaired faecal continence. As instrumental delivery is a known risk factor (8 fold increased risk of sphincter trauma), early use of oxytocin was recommended to shorten the second stage. A continuation of the same study [541] reported that PNTML was prolonged and the squeeze pressure increment was reduced in women who had a caesarean section in the late first stage (>8cm cervical dilatation) or second stage.

Chaliha et al [536] measured anal sensation and manometry in 286 nulliparous during the third trimester and repeated it in 161 women postpartum when anal endosonography was also performed. Anal endosonography revealed sphincter defects in 38% of women and this was associated with the presence of a lowering of anal squeeze and resting pressures. Threshold anal electrosensitivity remained unchanged and bore no relationship to symptoms. Postpartum sphincter defects were associated with perineal lacerations and vaginal delivery.

Abramowitz et al [542] performed a prospective study of 233 women who had anal endosonography performed before and 6 to 8 weeks after childbirth Of the 233 women (118 primiparae) 202 had a vaginal delivery. Postpartum anal incontinence in the 233 women was reported by 13% of primiparae and 8.5% of multiparae and anal sphincter defects in 21% and 12% respectively. However the prevalence of anal sphincter defects amongst those who had a vaginal delivery (n=202) was 26% and 13% respectively. Previous studies [543, 544] including others mentioned in Table 4 and 5 have shown that the first delivery is at greatest risk for anal sphincter trauma but this study is at variance as it claimed that secundiparous females have the same risk as primiparous women. However this finding remains unsubstantiated and is further disputed by a subsequent prospective study [544].
Table 4. Prospective studies before and after vaginal delivery of “occult” anal sphincter injury and anal incontinence but excluding faecal urgency.

<table>
<thead>
<tr>
<th>Study</th>
<th>Parity</th>
<th>Vaginal delivery Numbers</th>
<th>FU in weeks postpartum</th>
<th>Sphincter Defects</th>
<th>Anal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sultan et al 93 [465]</td>
<td>Primi</td>
<td>79</td>
<td>6</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>*Donnelly et al 98 [540]</td>
<td>Primi</td>
<td>168</td>
<td>6</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Rieger et al 98 [550]</td>
<td>Primi</td>
<td>37</td>
<td>6</td>
<td>41%</td>
<td>8%</td>
</tr>
<tr>
<td>Zetterstrom et al 99 [551]</td>
<td>Primi</td>
<td>38</td>
<td>9</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>*Fynes et al 99 [545]</td>
<td>Multi</td>
<td>59</td>
<td>6-12</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>Abramowitz et al 00 [542]</td>
<td>Primi</td>
<td>202</td>
<td>8</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Multi</td>
<td>including multi</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaliha et al 01 [536]</td>
<td>Primi</td>
<td>130</td>
<td>12</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Belmonte-Montes et al 01 [548]</td>
<td>Primi</td>
<td>78</td>
<td>6</td>
<td>13%</td>
<td>?</td>
</tr>
<tr>
<td>Nazir et al 02 [547]</td>
<td>Primi</td>
<td>73</td>
<td>20</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>Willis et al 02 [546]</td>
<td>Primi</td>
<td>42</td>
<td>12</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Multi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN (excluding Willis et al)</td>
<td>Primi</td>
<td></td>
<td></td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Multi</td>
<td></td>
<td></td>
<td>31%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*modified continence score questionnaire used and may include urgency

Table 5. Postnatal studies of “occult” anal sphincter injury sustained during vaginal delivery and anal incontinence excluding faecal urgency.

<table>
<thead>
<tr>
<th>Study</th>
<th>Parity</th>
<th>Vaginal delivery Numbers</th>
<th>FU in weeks postpartum</th>
<th>Sphincter Defects</th>
<th>Anal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Varma et al 99 [549]</td>
<td>78</td>
<td>Primi</td>
<td>4 weeks 4weeks</td>
<td>11.5%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>Multi</td>
<td></td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Damon 00 [552]</td>
<td>197</td>
<td>Primi</td>
<td>3 months</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>**Faltin 00 [553]</td>
<td>150</td>
<td>Primi</td>
<td>3 months</td>
<td>28%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Ultrasound performed < 1 week after delivery
** Anal ultrasound performed immediately after delivery before perineal repair
Fynes et al [545] undertook a prospective study of 59 previously nulliparous women through 2 successive pregnancies and found that 34% had anal sphincter injury after their first delivery but only 2 new injuries occurred after the second delivery confirming the findings in Sultan's study [465]. An important finding in this study was that 42% of women (5 of 12) who had occult sphincter injury during their first delivery (squeeze pressure increment < 20mmHg or anal sphincter defect > one quadrant) developed anal incontinence after the second delivery.

Willis et al [546] performed anal vector manometry, endosonography, PNTML and rectal sensitivity at the 32 weeks and 6 weeks postpartum. Using the Kelly-Holschneider score they reported anal incontinence in 5% and identified occult injuries in 19%. PNTML and rectal sensitivity was unaffected by vaginal delivery.

Nazir [547] et al performed vector manometry and endoanal ultrasound in 73 nulliparous woman at 25 weeks and 5 months postpartum (Table 4). There was no correlation between vector manometry and anal endosonography or clinical variables.

Belmonte-Montes [548] performed anal endosonography in 98 nulliparous women 6 weeks before and 6 weeks after delivery and after excluding 20 third degree tears found occult sphincter injuries in 13%. Seventy five percent of women with defects were symptomatic and there was a good correlation between defects and symptoms. However it is not clear how many with occult defects were symptomatic (Table 4).

In 3 further studies [549-551] anal ultrasound was performed only after delivery and defects were identified in 11.5 to 34% (Table 5). Varma et al [549] studied 159 postnatal women (105 primiparous and 54 secondiparous) and found occult anal sphincter defects in 11.5% of primiparous and 19% of secondiparous vaginal deliveries but 80% of forceps deliveries. None of their patients suffered faecal incontinence but only 72% of questionnaires were returned. However their cohort had a high caesarean section rate (25%) and a low forceps rate (4%).

Some 15 years after having first coined the term “occult” OASIS Sultan [465] questioned whether the 28% sonographic anal sphincter defects (Table 6) were genuine occult defects in that they were not visible following delivery. They therefore conducted a prospective study [585] in which 241 women having their first vaginal delivery had their perineum re-examined by an experienced research fellow and endoanal ultrasound was performed immediately after delivery and repeated 7 weeks postpartum. When OASIS was identified by the research fellow, the injuries were confirmed and repaired by the duty registrar or consultant. The prevalence of clinically diagnosed OASIS increased from 11% to 25% (n=59).

Every clinically diagnosed injury was identified by postpartum endoanal ultrasound. However there were 3 women with sonographic defects in whom the injury was not identified clinically. Two of these had only small IAS defects that were not considered clinically significant. The other was a combined defect of both the IAS and EAS and while this could be classified as an occult tear it is most probably an undiagnosed tear. At 7 weeks no de novo defects were identified by ultrasound. This study concluded that most sphincter defects that have previously been designated as “occult” injuries (Table 6) were in fact OASIS that could have been identified by a trained clinician [586] and that less than one percent are genuine occult OASIS (if they exist). Interestingly, 87% of midwives and 27% of junior doctors failed to recognise OASIS clinically. Although it is likely that some of these injuries would have been detected at the time of suturing the tear, it is concerning that clinical recognition of OASIS is suboptimal [586]. However this finding is not unique as Groom and Patterson [587] also found that the rate of third degree tears rose to 15% when all “2nd degree tears” were re-examined by a second experienced person.

These studies [585, 587] confirm inadequate training that was previously highlighted by Sultan et al [588] who reported that 91% of doctors who had done at least 6 months of training in obstetrics and 60% of midwives indicated inadequate training in perineal anatomy and 84% and 61% respectively reported inadequate training in identifying 3rd degree tears. Another possible reason for under-diagnosis is that tears of the anal sphincter have been wrongly classified and therefore anal sphincter tears have been under-reported. Any involvement of the anal sphincter should be classified as third degree. However 41% of doctors and 16% of midwives classified a torn anal sphincter as a 2nd degree tear [588]. Sultan and Thakar [589] reviewed every relevant text book (n=65) in the library of the Royal College of Obstetricians and Gynaecologists (RCOG) and found that there was a lack of consistency in classification and in about 40% the classification was omitted or wrong. Furthermore previous classifications were incomplete because they did not incorporate depth of EAS rupture or involvement of the IAS. This therefore has epidemiological, clinical and medicolegal implications. If a third degree tear is incorrectly classified as second degree, then inappropriate repair could result in sub-optimal outcome (see below). Sultan [590] has therefore proposed the following classification [591] that has been incorporated into the 29th RCOG green top guidelines [585] and the first edition of this book:

**First degree:** laceration of the vaginal epithelium or perineal skin only.

**Second degree:** involvement of the perineal muscles but not the anal sphincter.
Table 6. Prevalence of anal incontinence following primary repair of obstetric anal sphincter rupture (faecal incontinence ie. excluding flatus incontinence only is shown in parentheses)

<table>
<thead>
<tr>
<th>Authors (n=33)</th>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Follow-up Months</th>
<th>Anal (Faecal) incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangalli et al [554]</td>
<td>2000</td>
<td>Switzerland</td>
<td>177</td>
<td>13 years</td>
<td>15% (10%)</td>
</tr>
<tr>
<td>Wood J et al [555]</td>
<td>1998</td>
<td>Australia</td>
<td>84</td>
<td>31</td>
<td>17%* (7%)</td>
</tr>
<tr>
<td>Walsh et al [556]</td>
<td>1996</td>
<td>UK</td>
<td>81</td>
<td>3</td>
<td>20% (7%)</td>
</tr>
<tr>
<td>Sander et al [557]</td>
<td>1999</td>
<td>Denmark</td>
<td>48</td>
<td>1</td>
<td>21% (4%)</td>
</tr>
<tr>
<td>Pretlove et al [558]</td>
<td>2004</td>
<td>UK</td>
<td>41</td>
<td>?</td>
<td>22% (22%)</td>
</tr>
<tr>
<td>Crawford et al [559]</td>
<td>1993</td>
<td>USA</td>
<td>35</td>
<td>12</td>
<td>23% (6%)</td>
</tr>
<tr>
<td>Sorensen et al [560]</td>
<td>1993</td>
<td>Denmark</td>
<td>38</td>
<td>3</td>
<td>24% (?)</td>
</tr>
<tr>
<td>Mackenzie et al [561]</td>
<td>2003</td>
<td>UK</td>
<td>53</td>
<td>3</td>
<td>25% (7%)</td>
</tr>
<tr>
<td>Nichols et al [562]</td>
<td>2005</td>
<td>USA</td>
<td>56</td>
<td>3</td>
<td>25% (11%)</td>
</tr>
<tr>
<td>Nielsen et al [563]</td>
<td>1992</td>
<td>Denmark</td>
<td>24</td>
<td>12</td>
<td>29% (?)</td>
</tr>
<tr>
<td>Go &amp; Dunselman [564]</td>
<td>1988</td>
<td>Netherland</td>
<td>20</td>
<td>6</td>
<td>30% (15%)</td>
</tr>
<tr>
<td>Fenner et al [565]</td>
<td>2003</td>
<td>USA</td>
<td>165</td>
<td>6</td>
<td>30% (?)</td>
</tr>
<tr>
<td>DeLeeuw et al [566]</td>
<td>2001</td>
<td>Netherland</td>
<td>125</td>
<td>14 years</td>
<td>31% (?)</td>
</tr>
<tr>
<td>Wagenius et al [567]</td>
<td>2003</td>
<td>Sweden</td>
<td>186</td>
<td>4 years</td>
<td>33% (25%)</td>
</tr>
<tr>
<td>Uustal Fornell et al [568]</td>
<td>1996</td>
<td>Sweden</td>
<td>51</td>
<td>6</td>
<td>40% (16%)</td>
</tr>
<tr>
<td>Poen et al [569]</td>
<td>1998</td>
<td>Netherland</td>
<td>117</td>
<td>56</td>
<td>40% (?)</td>
</tr>
<tr>
<td>Sultan et al [468]</td>
<td>1994</td>
<td>UK</td>
<td>34</td>
<td>2</td>
<td>41% (9%)</td>
</tr>
<tr>
<td>Zetterstrom et al [527]</td>
<td>1999</td>
<td>Sweden</td>
<td>46</td>
<td>9</td>
<td>41% (2%)</td>
</tr>
<tr>
<td>Sorensen et al [570]</td>
<td>1988</td>
<td>Denmark</td>
<td>25</td>
<td>78</td>
<td>42% (?)</td>
</tr>
<tr>
<td>Tetzschner et al [499]</td>
<td>1996</td>
<td>Denmark</td>
<td>72</td>
<td>24-48</td>
<td>42% (17%)</td>
</tr>
<tr>
<td>Williams et al [571]</td>
<td>2003</td>
<td>UK</td>
<td>124</td>
<td>?</td>
<td>42% (?)</td>
</tr>
<tr>
<td>Norderval et al [572]</td>
<td>2004</td>
<td>Norway</td>
<td>156</td>
<td>25</td>
<td>42% (17%)</td>
</tr>
<tr>
<td>Garcia et al [573]</td>
<td>2005</td>
<td>USA</td>
<td>26</td>
<td>3</td>
<td>42% (15%)</td>
</tr>
<tr>
<td>Kammerer-Doak et al [574]</td>
<td>1999</td>
<td>USA</td>
<td>15</td>
<td>4</td>
<td>43% (13%)</td>
</tr>
<tr>
<td>Haadem et al [575]</td>
<td>1988</td>
<td>Sweden</td>
<td>62</td>
<td>3</td>
<td>44% (?)</td>
</tr>
<tr>
<td>Rieger et al [576]</td>
<td>2004</td>
<td>Australia</td>
<td>51</td>
<td>3</td>
<td>45% (25%)</td>
</tr>
<tr>
<td>Bek &amp; Laurberg [577]</td>
<td>1992</td>
<td>Denmark</td>
<td>121</td>
<td>?</td>
<td>50% (?)</td>
</tr>
<tr>
<td>Davis et al [578]</td>
<td>2003</td>
<td>UK</td>
<td>52</td>
<td>3.6</td>
<td>50% (?)</td>
</tr>
<tr>
<td>Fitzpatrick et al [579]</td>
<td>2000</td>
<td>Ireland</td>
<td>154</td>
<td>3</td>
<td>53% (6%)</td>
</tr>
<tr>
<td>Nazir et al [580]</td>
<td>2003</td>
<td>Norway</td>
<td>100</td>
<td>18</td>
<td>54% (17%)</td>
</tr>
<tr>
<td>Gjessing H et al [581]</td>
<td>1998</td>
<td>Norway</td>
<td>35</td>
<td>12-60</td>
<td>57% (23%)</td>
</tr>
<tr>
<td>Savoye-Collet et al [582]</td>
<td>2003</td>
<td>France</td>
<td>21</td>
<td>4</td>
<td>57% (29%)</td>
</tr>
<tr>
<td>Goffeng et al [583]</td>
<td>1998</td>
<td>Sweden</td>
<td>27</td>
<td>12</td>
<td>59% (11%)</td>
</tr>
<tr>
<td>Nygaard et al [470]</td>
<td>1997</td>
<td>USA</td>
<td>29</td>
<td>30 years</td>
<td>59% (28%)</td>
</tr>
<tr>
<td>Pinta et al [584]</td>
<td>2004</td>
<td>Finland</td>
<td>52</td>
<td>15</td>
<td>61% (10%)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39% (14%)</td>
</tr>
</tbody>
</table>

*Includes 2 with secondary sphincter repair
Third degree: disruption of the anal sphincter muscles (Figures 13 & 14) and this should be further subdivided into:

3a: <50% thickness of external sphincter torn.
3b: >50% thickness of external sphincter torn.
3c: internal sphincter torn also.

Fourth degree: Third degrees tear with disruption of the anal epithelium.

An isolated rectal tear without involvement of the anal sphincter is rare and should not be included in the above classification.

2. RECOGNISED OBSTETRIC ANAL SPHINCTER INJURIES

Primary repair of OASIS (third and fourth degree tears) are usually performed by obstetricians using the end-to-end repair technique [468]. However as shown in Table 6, anal incontinence occurs in 39% (range 15 to 61%) and in addition, urgency can affect a further 6 [468] to 28% [579]. Frank faecal incontinence affected 14% [468] (range 2 [527] to 29% [581]). In five studies [468, 569, 574, 579, 583] anal endosonography was performed to demonstrate persistent anal sphincter defects following repair in 40 to 91% of women. The extent of the sphincter injury may be related to outcome of repair. However in some studies (Table 6) the data was not interpretable [560], incomplete [583] or inclusive of symptoms other than anal incontinence [575]. Forceps delivery, first vaginal delivery, large baby, shoulder dystocia and a persistent occipito-posterior position have been identified as the main risk factors for the development of OASIS [468, 542, 543, 569].

The most popular method of EAS repair is the end-to-end technique but colorectal surgeons prefer the overlap technique for secondary repair because of better outcome [592]. It is now known that like other incontinence procedures, outcome can deteriorate with time and one study has reported 50% continence at 5-year follow-up [593]. However, at least one third of women in this study had more than one attempt at sphincter repair and therefore these findings cannot be extrapolated to that following primary repair of acute injury [593]. Sultan et al [592] were the first to describe the overlap technique for acute EAS rupture and in addition advocated the separate identification and repair of the IAS. Until then very little importance was given to torn IAS during primary repair. However subsequently in a study involving 500 consecutive women with OASIS it has been shown that sonographic evidence of IAS injury was predictive of faecal incontinence [594]. When a patient presents with faecal incontinence, it is almost impossible to perform a successful IAS repair highlighting the importance of identification and repair immediately after delivery [591]. Compared to matched historical controls [468] who had an end-to-end repair, Sultan et al [592] found that anal incontinence could be reduced from 41% to 8% when the overlap technique was used for EAS repair with separate repair of the torn IAS [592] and therefore they recommended a randomised trial.

The first published randomised trial by Fitzpatrick et al [579] reported no significant difference between end-to-end and overlap repair although there appeared to be trend towards more symptoms in the end-to-end group. However there were methodological differences in that the torn IAS was not identified and repaired separately and they used a constipating agent for 3 days after the repair. Unfortunately they included partial EAS tears in their randomised study. A true overlap [591, 592] is not possible if the sphincter ends are not completely divided and it would be expected that if an overlap is attempted, the residual intact sphincter muscle would have to curl up and hence there would be undue tension on the remaining torn ends of muscle that would be overlapped. This technique would therefore go against the general principles of surgery of deliberately placing tissue under avoidable tension [591].

Garcia et al [573] also performed a randomised trial of the two techniques and took great care to include only complete ruptures of the EAS (full thickness 3b,3c and 4th degree tears). There were 23 women in the end-to-end group and 18 in the overlap group. Unfortunately only 15 and 11 women respectively returned for follow-up which was only at 3 months. No significant difference was found between the groups in terms of symptoms of faecal incontinence or transperineal ultrasound findings. However the authors acknowledged that the major limitations of their study were that randomization was inaccurate and that their study was underpowered.

Recently, Williams et al [595] performed a factorial randomized controlled trial (n=112) in which women were randomized into 4 groups: overlap with polyglactin (Vicryl; Ethicon, Edinburgh, UK); end-to-end repair with Vicryl; overlap repair with polydioxanone (PDS; Ethicon, Edinburgh, UK); end-to-end repair with PDS. This trial was specifically designed to test the hypothesis regarding suture related morbidity (need for suture removal due to pain, suture migration or dyspareunia) using the two techniques. At six weeks there were no differences in suture related morbidity. The authors claim that there were no differences in outcome based on repair technique. Unfortunately the majority of patients included in this trial were partial tears of the EAS (3a tears and as mentioned above, a true overlap [591, 592] cannot be performed if the EAS is only partially torn. Furthermore their follow up rate at 12 months was only 54%. This data therefore needs to be interpreted by caution.

Fernando et al [596] performed a randomized
Figure 13: Anal ultrasound image of the mid anal canal. EAS = external anal sphincter. IAS = internal anal sphincter. The area between the arrows at 10 and 10 o’clock represents an external anal sphincter defect.

Figure 14: Schematic representation of 3rd and 4th degree tears (with permission from Springer) [620]
controlled trial of end-to-end vs overlap technique. The study had adequate power (n=64) and the primary outcome was faecal incontinence at one year. All repairs were performed by two trained operators and superficial partial tears of the EAS (3a) were excluded. At 12 months (81% follow-up rate), 24% in the end-to-end and none in the overlap group reported faecal incontinence (p=0.009). Faecal urgency at 12 months was reported by 32% in the end-to-end and 3.7% in the overlap group (p=0.02). There were no significant differences in dyspareunia and quality of life between the groups. At 12 months 20% reported perineal pain in the end-to-end and none in the overlap group (p=0.04). During twelve months 16% in end-to-end and none in the overlap group reported deterioration of defeatory symptoms (p=0.01). Further calculation revealed that four women need to be treated with the overlap technique to prevent one woman with OASIS developing faecal incontinence. On the basis of this randomized trial one can conclude that the overlap technique of external sphincter repair accompanied by separate repair of the torn internal sphincter is performed by trained clinicians it is superior to the end-to-end repair. However as the other randomized trials included 3a tears and did not evaluate operator expertise [595] it remains to be established whether the same results would be obtained when the repair is performed by trainees.

3. MANAGEMENT OF SUBSEQUENT PREGNANCY AFTER OASIS

All women who sustained a third/fourth degree tear should be assessed in hospital by a senior obstetrician 6 to 8 weeks after delivery. Some centres have established dedicated multidisciplinary perineal clinics. It is important that a careful history is taken regarding bowel, bladder and sexual function. As these symptoms are embarrassing, a structured questionnaire may be useful. A careful vaginal and rectal examination should be performed to check for complete healing, scar tenderness and sphincter tone [585, 597, 598]. Mild incontinence (faecal urgency or flatus incontinence) may be controlled with dietary advice, constipating agents (loperamide or codeine phosphate), physiotherapy or biofeedback. However women who have severe incontinence should, in addition, be offered secondary sphincter repair by a colorectal surgeon. Asymptomatic women must be advised to return if symptoms develop [591].

There are no randomised studies to determine the most appropriate mode of delivery. Women who have had a successful secondary sphincter repair for faecal incontinence should be delivered by caesarean section [599]. Some women with faecal incontinence may choose to complete their family prior to embarking on anal sphincter surgery. It remains to be established whether these women should be allowed a vaginal delivery as it could be argued that damage has already occurred and risk of further damage is minimal and possibly insignificant in terms of outcome of surgery.

Until recently [591] the management in a subsequent pregnancy after OASIS has not been discussed in any detail [589]. It has been suggested that a caesarean section should be performed even after transient anal incontinence [499] but this has been questioned [599].

In order to counsel women with previous 3rd/4th degree tears appropriately, we find it useful to have a symptom questionnaire, anal ultrasound and manometry results. If vaginal delivery is contemplated then these tests should be performed during the current pregnancy unless performed previously and found to be abnormal. In a prospective study over a 5 year period, Scheer et al [600] found that when women who had no evidence of significant anal sphincter compromise based on anal endosonography and manometry were allowed a vaginal delivery (the others offered caesarean section) there was no deterioration in symptoms, anorectal function or quality of life. Although 11% of textbooks recommend a prophylactic episiotomy [589] there is limited evidence that an elective episiotomy prevents subsequent anal sphincter disruption [566] while other studies have indicated that episiotomy may increase the prevalence of anal sphincter disruption.

III. INSTRUMENTAL VAGINAL DELIVERY

Although only 4% of women delivered by forceps sustain a 3rd/4th degree tear, up to 50% of those that do tear have an instrumental delivery [468]. Vacuum extraction is associated with fewer 3rd/4th tears than forceps and this view is supported by 2 large randomised studies [601, 602]. A UK study [601] where mediolateral episiotomy is practised reported severe vaginal lacerations in 17% of forceps compared to 11% of vacuum deliveries and a Canadian study [602] where midline episiotomy is practised reported 3 3rd/4th tears in 29% of forceps compared to 12% of vacuum deliveries. In a Cochrane review (ten trials) [603] use of the vacuum extractor instead of forceps was associated with significantly less maternal trauma (odds ratio 0.41, 95% confidence interval 0.33 to 0.50) and with less need for general and regional anaesthesia. There were more deliveries with vacuum extraction (odds ratio 1.69, 95% confidence interval 1.31 to 2.19) and fewer caesarean sections were carried out in the vacuum extractor group. However the vacuum extractor was associated with an increase in neonatal cephalhaematomas and retinal haemorrhages. Serious neonatal injury was uncommon with either instrument.

The reduction in cephalhaematomas and retinal haemorrhages seen with forceps may be a com-
IV. EPISIOTOMY

There is now considerable observational data to indicate that a reduction in episiotomy rate is not associated with an increase in OASIS [608]. The Cochrane database [185] shows that restricting the use of episiotomy is associated with less posterior trauma. Although anterior perineal trauma was increased it had no effect on the development of urinary incontinence. Henriksson et al [609, 610] performed an observational study in which they noted when midwives who previously had a high episiotomy rate reduced their rate, the prevalence of OASIS also reduced. However this beneficial effect was abolished when midwives with a low rate of episiotomy attempted to reduce it even further. Based on this evidence, it was suggested that the ideal episiotomy rate should lie between 20 to 30% and no more. Midline episiotomies are more popular in North America as it is believed that they are more comfortable and recovery is less complicated. However Coats et al [611] performed a quasi-randomised study of 407 primiparae and found 12% of midline episiotomies extended into the anal sphincter compared to 2% of mediolateral episiotomies. Although the perineum was significantly less bruised in the midline group and sexual intercourse commenced earlier, pain and wound breakdown was similar in both groups. However care needs to be taken to ensure that mediolateral episiotomies are performed correctly as Andrews et al [612] have shown that only 22% of doctors and no midwife made the incision commencing from the posterior fourchette with a 40 to 60 degree angle from the midline. Another study demonstrated for every six degrees away from the midline there was a 50% reduction in OASIS [613].

V. DELIVERY TECHNIQUES

Pirhonen et al [614] compared the frequency of anal sphincter rupture in low risk deliveries between two Scandinavian countries (26 541 vaginal deliveries) and found the risk to be 13 times higher in Sweden (Malmo) vs Finland (Turku). They speculated that the only explanation for this was a difference in manual support given to the baby's head during crowning and pushing the perineum under the chin. The following interventions with randomized controlled trials evidence regarding effectiveness demonstrated no effect on OASIS: antenatal perineal massage, pelvic floor exercises in pregnancy, water births, positions during labour and birth, epidural analgesia, early vs delayed pushing with epidural and second stage pushing advice [607].

VI. TRAINING

McLennan et al [615] who surveyed 1177 fourth year residents and found that the majority of residents had received no formal training in pelvic floor anatomy, episiotomy or perineal repair and supervision during perineal repair was limited. Stepp et al [616] found that textbooks used in American practice offered little in terms of prevention and repair of perineal trauma. There is evidence from one study [588] that perineal anatomy is poorly understood by midwives and trainee doctors, who perform the bulk of deliveries in the UK. In this study 41% of trainees and 16% of midwives incorrectly classified a partial or complete tear of the EAS as 'second degree'. Inconsistency in classification of tears would allow many injuries to pass, unre-
cognised. It has been shown that hands-on workshops on perineal repair (www.perineum.net) can change practice [617, 618] and therefore intensive and focused training in perineal anatomy and repair should therefore become an essential module in the programme for trainees.

**VII. IRRITABLE BOWEL SYNDROME (IBS)**

IBS affects 3-17% in selected populations and the cause remains unknown. Donnelly et al [619] recruited 312 primiparous women and reported that 11% of young primiparous women (n= 34 of 208) suffered from pre-existing IBS prior to their first pregnancy. Twenty four percent reported symptoms of impaired faecal continence in the puerperium but symptoms were found significantly more frequently in those with IBS compared to those with normal bowel habit (71% vs 18%). However women suffering from IBS are no more likely to incur mechanical or neurologic injury to the anal sphincter. Women with IBS delivered by caesarean section did not have altered continence postpartum. However 6 months postpartum there were no symptomatic differences between those with IBS and those without but only 90 of the 107 women who had either impaired faecal continence or abnormal anal manometry were studied. Treatment is directed towards the predominant symptom and although antispasmodics such as hyoscine, mebeverine and dicyclomine are used widely to relax intestinal smooth muscle, they should be avoided during pregnancy.

**VIII. CONCLUSIONS AND RECOMMENDATIONS**

a) Compared to forceps the vacuum extractor is associated with less perineal and anal sphincter trauma and should therefore be the instrument of choice. (*Level 1*)

b) Compared to midline episiotomy, mediolateral episiotomy is associated with a lower risk of anal sphincter rupture (12% vs 2%). (*Level 1*)

c) Liberal use of episiotomy is not beneficial (*Level 1*) and restricting the rate of episiotomy to about 30% may reduce the risk of trauma to the anal sphincter. (*Level 4*)

d) A prolonged active second stage of labour is associated with denervation of the pelvic floor and one study has suggested that this also occurs with a prolonged passive second stage of labour with epidural analgesia. In these circumstances, early use of oxytocics in the second stage of labour may be useful. (*Level 4*)

e) Selective use of caesarean section particularly in those who have evidence of compromised anal sphincter function and those who have had previous successful continence or prolapse surgery. (*Level 5*)

f) Modification in techniques of delivery of the baby may reduce anal sphincter injury and further research is needed (*Level 5*)

g) A more focused training program for doctors and midwives needs to implement. There is a poor understanding of perineal and anal sphincter anatomy and hence identification of anal sphincter trauma, incorrect classification and poor outcome of repair (*Level 5*)

h) In experienced hands the overlap technique of external anal sphincter repair is superior to the end-to-end technique and further studies await completion to establish whether these findings can be generalized (*Level 1*)

**G. PATHOPHYSIOLOGY OF INCONTINENCE IN MEN**

Urinary incontinence in men as in women may be caused by either an abnormality of the bladder, an abnormality of the bladder outlet (sphincter), or a combination of both [621-623]. Changes in bladder ultrastructure and function that can occur as a result of neurological disease or aging (that can cause detrusor overactivity or underactivity) are similar in men and women. However there are causes of bladder and sphincter dysfunction that are unique to men. Many of these center around benign and malignant diseases of the prostate and their treatment. For example, the prevalence of detrusor overactivity and impaired compliance causing incontinence is associated with obstruction (usually caused by benign prostatic obstruction) far more often in men than in women. Also sphincter incontinence does not generally occur as the result of aging or other associated normal conditions such as pregnancy and childbirth, but rather is usually attributed to surgery or radiation of the prostate (for benign or malignant conditions) or neurological injury. Extra-urethral incontinence, which is very rare in men, is caused only by urinary fistula. Because of embryological considerations, ectopic ureter in the male does not cause incontinence as its insertion into the lower urinary tract is always proximal to the distal urethral sphincter.

In this section, we will focus on the Pathophysiology of incontinence as it relates to prostatic obstruction and its treatment and the treatment of prostate cancer.
The proximal urethral sphincter (PUS) extends from the bladder neck through the prostatic urethra above the verumontanum. The distal urethral sphincter (DUS) extends from the prostatic urethra below the verumontanum through the membranous urethra. DUS includes the rhabdosphincter (intrinsic skeletal and smooth muscle) and extrinsic paraurethral skeletal muscle. (Modified from Hadley HR, Zimmern PE, Raz S: The treatment of male urinary incontinence. In Walsh PC, Gittes RF, Perlmutter AD (Eds) Campbell’s Urology, Eds 5. B.: London, WB Saunders, 1986, p 2658) (Figure 15).

For simplicity, the normal male urinary sphincter mechanism may be divided into two functionally separate units, the proximal urethral sphincter (PUS) and the distal urethral sphincter (DUS) [624]. The PUS consists of the bladder neck, prostate and prostatic urethra to the level of the verumontanum. It is innervated by autonomic parasympathetic fibres from the pelvic nerve. This portion of the continence mechanism is removed during prostatectomy, leaving only the DUS to prevent urinary leakage. The DUS extends from the verumontanum to the proximal bulb and is comprised of a number of structures that help to maintain continence. The male DUS urethral sphincter complex is composed of the prostatomembranous urethra, cylindrical rhabdosphincter (external sphincter muscle) surrounding the prostatomembranous urethra, and extrinsic paraurethral musculature and connective tissue structures of the pelvis. The rhabdosphincter is a concentric muscular structure consisting of longitudinal smooth muscle and slow-twitch (type I) skeletal muscle fibres which can maintain resting tone and preserve continence [625, 626]. The striated muscle of the rhabdosphincter is considerably thicker ventrally and thins dorsally. Skeletal muscle fibres of the rhabdosphincter have been shown to intermingle with smooth muscle fibres of the proximal urethra, suggesting a dynamic and coordinated interaction [627]. The rhabdosphincter is invested in a fascial framework, and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle [627]. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments [628]. This dorsal and ventral support probably contributes to the competence of the sphincter. The striated fibres of the extrinsic paraurethral muscle (levator ani complex), on the other hand, are of the fast-twitch (type II) variety [625]. During sudden increases in abdominal pressure, these fibres can contract rapidly and forcefully to provide continence. Continence has been showed to be maintained after inducing paralysis of the striated sphincter [629] indicating that this structure is not solely responsible for continence. Unlike in the female where urethral support can be compromised as a result of childbirth and aging, in the male compromise to the rhabdosphincter usually occurs after trauma or surgery (e.g. prostatectomy). The striated muscle fibres of the rhabdosphincter intermingle with smooth muscle fibres of the proximal urethra and in fact have been shown to be inseparable from each other in the

I. CONTINENCE MECHANISM IN THE MALE

Figure 15: Functional anatomy of the male continence mechanism.
human male fetus [630]. However the smooth muscle fibres, which are continuous with the bladder, are divided during radical prostatectomy and the muscular vesico-prostatico-urethral continuance is interrupted. Thus continence is maintained primarily by the striated muscle of the rhabdosphincter (Figure 16).

The innervation of the DUS has been extensively studied; however, the exact details remain a point of controversy amongst anatomists. It is generally agreed that the DUS is innervated by both the autonomic (via the pelvic nerve) and somatic (by the pudendal nerve) nervous systems. Nerve fibres are seen proximally in a dorsolateral position (5 to 7 o’clock), while more distally, they are located primarily laterally, and at varying distances from the urethra [627, 631]. The intrinsic smooth muscle of the proximal urethra receives parasympathetic innervation from pelvic nerve branches of the inferior hypogastric plexus [631, 632]. The rhabdosphincter may also receive somatic innervation. Hollabaugh and colleagues described the so-called “putative continence nerves” as branches of the pelvic nerve travelling under the endopelvic fascia which pick up intrapelvic branches of the pudendal nerve, given off before it enters the pudendal canal [631]. It has also been proposed that somatic innervation from the pudendal nerve after it exits the pudendal canal is primarily sensory in origin, facilitating reflex contraction of the sphincter complex to maintain continence. [633].

A recent elegant histological and immunohistochemical study with three dimensional reconstruction in the male fetus has confirmed mixed autonomic and somatic innervation [630]. Unmyelinated (autonomic) nerve fibres destined for smooth muscle fibres run alongside of the myelinated (somatic) fibres. The majority of the unmyelinated fibres approach the smooth muscle layers at 5 and 7 o’clock while the majority of myelinated fibres penetrate the striated sphincter at 3 and 9 o’clock.

Structure and innervation are important components of sphincter function. In addition, Tuygun and associates [634] have found a much higher incidence of periurethral (or peri-sphincter) fibrosis in incontinent vs. continent men after prostatectomy. Using MRI at least 6 months after prostatectomy they discovered that all 22 incontinent men had periurethral fibrosis while only 4/14 (29%) continent men did.

In summary, sphincter continence is dependent on the integrity of the PUS and/or DUS, its support structures and neural innervation. Following removal of the PUS with prostatectomy, continence is maintained by the DUS mechanism, consisting of soft tissue supportive structures, smooth muscle, and striated muscle. The smooth muscle and slow twitch skeletal muscle of the rhabdosphincter is probably most responsible for sphincter continence; however, skeletal muscle contractions of the periurethral and paraurethral muscle are likely assist. After radical prostatectomy, the integrity or continuity of the smooth muscle fibres is lost, which may have a significant effect on their contribution to continence. Damage to the innervation (parasympathetic and somatic) of the

Figure 16: The rhabdosphincter is invested in a fascial framework, and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments. This dorsal and ventral support likely contributes to the competence of the sphincter. (From Burnett AL, Mostwin JL. In situ anatomical study of the male urethral sphincter complex: relevance to continence preservation following major pelvic surgery. J Urol 1998; 160:1301-1306). [627]
smooth and skeletal muscle may indirectly contribute to post-prostatectomy incontinence. In addition compromise of the sphincter support mechanism or post operative changes such as fibrosis can compromise sphincter function.

II. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT

Benign prostatic hyperplasia (BPH) and benign prostatic obstruction (BPO) and their treatments have long been associated with incontinence in men. Detrusor overactivity (DO), impaired compliance and urge incontinence are prevalent in men with BPO. In men undergoing urodynamic testing detrusor overactivity is present in 40-80% of patients with obstruction [635-637]. In addition, impaired compliance, another potential cause of incontinence has been shown to have a high correlation with outlet obstruction in men [638]. Thus even before treatment of BPH and BPO there is a notable incidence of bladder dysfunction and incontinence.

Incontinence after the treatment of BPH may be related to persistent bladder dysfunction, new onset bladder dysfunction or sphincter dysfunction (injury). Turner-Warwick et al. [639] first directed attention to the relationship of bladder outlet obstruction, the symptoms of frequency, urgency and urge incontinence (now commonly known as LUTS: Lower Urinary Tract Symptoms) and the correlation of these symptoms with detrusor overactivity seen on cystometry. They noted that in 75% of men, symptoms were relieved by prostatectomy. Leng and McGuire [640] showed improvement in compliance after relief of obstruction in 7/9 men with severely impaired compliance (< 5 ml/cmH2O), but only one man was restored to "normal" compliance. Several contemporary explanations for the cause of persistent overactivity after obstruction endure. These include denervation supersensitivity of the bladder muscle [33, 89, 641], alterations in collagen composition of the obstructed bladder [642], emergence of altered and increased sensory reflexes mediating the micturition reflex [22, 51], and physical changes in detrusor myocytes affecting electrical transmission [39]. In addition, the bladder itself and particularly the trigone may be inadvertently resected during surgery, causing bladder dysfunction. Causes of sphincter damage after transurethral resection or open prostatectomy for BPH include direct damage to endolumenal tissue distal to the verumontanum because of surgical error or loss of landmarks, unexpected infiltration of the sphincter by carcinoma with loss of urethral compliance, and electrocautery or thermal injury to the sphincter [643].

Recently, Han et al [644] conducted a retrospective data analysis using a managed care data set (Integrated Healthcare Information Services National Benchmark Database) from 1997 through 2003. They identified a cohort of men this BPH using International Classification of Diseases, Ninth Revision (ICD-9) codes. From a total of over 12 million men, 411,658 men with BPH (3.3%) were identified. The group then determined the nature of incontinence in these men with BPH focusing on its incidence, prevalence, and management. Furthermore they stratified patients by therapeutic subgroups of watchful waiting, alpha blockers, 5-alpha reductase inhibitors and surgery. Of the total cohort, 2.7% had a diagnosis of incontinence. Most of these men (87.5%) did not have prior BPH surgery, but of those who did have surgery 12.5% were diagnosed with incontinence. The rates were almost identical whether the procedure was transurethral resection or incision, laser, transurethral needle ablation, transurethral microwave therapy or open prostatectomy. The rate of incontinence was 1.4% for both stress and mixed incontinence, 4.5% for urge incontinence and 6.5% for unspecified incontinence. Incontinence rates for men on watchful waiting, alpha-blockers, 5-alpha reductase inhibitors and combination therapy were 6.4%, 5.7%, 5.1%, and 6, 5% respectively. This study provides some interesting data but must be interpreted with caution. The diagnosis of incontinence was limited by what the patient and provider considered incontinence and was often not confirmed by objective testing. Furthermore one cannot assume cause and effect related to treatments as many of these men may have sought treatment because they were incontinent. Nevertheless, the relationship of BPH and incontinence can clearly be inferred.

Until the last decade, transurethral resection of the prostate and open prostatectomy accounted for the majority of surgical procedures to treat BPO. In 1989, the American Urological Association published two major series on TURP and its complications. The AUA cooperative study included 3,885 patients from 13 teaching centres and private practices [645], while the second consisted of a survey of all practicing urologists in the United States of whom 2,716 urologists responded [646]. Rates of post-TURP incontinence requiring a pad or collection device were 0.4% in the first and 3.3% in the second study. The AUA Cooperative study also reported mild stress incontinence in 1.2% [647]. In 1994, the Agency for Health Care Policy and Research published clinical guidelines for the diagnosis and treatment of benign prostatic hyperplasia. The guidelines panel reviewed 27 articles about transurethral prostatectomy and 30 articles reporting open prostatectomy to analyze treatment outcomes. The panel reported that the risk of total incontinence, defined as complete loss of voluntary control over micturition was of great concern to patients facing a treatment decision for BPH. In an overall ranking of 15 different outcomes, the panel’s proxy judges ranked total incontinence of urine as the fourth most important outcome influencing a
treatment decision. After TURP, 2.1% of patients experienced stress incontinence, 1.9% had urge incontinence, and 1.0% had total incontinence. The panel attempted to abstract data on urge incontinence, but found very few studies reporting this particular outcome, therefore a statistical analysis was not performed. For open prostatectomy stress incontinence occurred in 1.9%, urge incontinence in 0.5% and total incontinence in 0.5% of patients.

Most studies evaluating post TURP and open prostatectomy incontinence have found a significant incidence of sphincter and bladder dysfunction. The incidence of sphincter dysfunction ranges from 20-92% and bladder dysfunction from 56-97% [648-653]. The relatively high incidence of sphincter dysfunction may seem somewhat surprising as the incidence of DO before treatment is so high and it persists in 18-59% after surgery to relieve obstruction [636, 639]. Therefore one might expect that a large number of patients would have persistent detrusor overactivity and urge incontinence. However, in large series, sphincter dysfunction appears to be the main cause of incontinence. The high incidence of sphincter dysfunction is likely to represent a selection bias, e.g. large numbers of patients referred to tertiary centres for treatment of stress incontinence. Nitti et al [654] evaluated patients with voiding dysfunction after TURP and found that of those who had incontinence 75% had bladder dysfunction, while only 20% had sphincter dysfunction (the cause of incontinence could not be identified in 5%). Twenty-seven percent of incontinent patients with bladder dysfunction also had obstruction.

In the past decade, alternatives to TURP for the treatment of BPH have emerged. Most notably are thermal therapies and laser resection/enucleation of the prostate. Thermal therapies are considered “less invasive” and outcomes in most series are not comparable to traditional TURP with respect to efficacy. However some laser treatments provide similar efficacy in well selected patients, at least in the short term. Studies that have evaluated holmium laser enucleation (HoLEP), holmium laser resection (HoLRP) or potassium titanyl phosphate (KTP) laser vaporization of the prostate have shown a similar incidence of incontinence. Two randomized controlled trials of holmium laser versus TURP have shown rates of stress incontinence to be very similar. Westenberg, et al [655] showed the incidence of stress incontinence with or without urge incontinence to be 7% for HoLRP versus 6.7% for TURP at a minimum of 4 years follow-up. Kuntz and colleagues [656] found just 1% stress incontinence in each group at 12 months. They also showed a similar rate of resolution of preoperative urge incontinence for both groups (81% versus 85%). Two other prospective non-randomized trials of HoLEP found 0.6% -2.5% incidence of stress [657]. Two randomized controlled trials of KTP (green light) laser versus TURP reported 0% and 1% stress incontinence in each group respectively [658, 659] while a third randomized trial did not mention incontinence [660]. Retrospective studies on Green light showed a 2-3.3% incidence of stress incontinence [661, 662]. Te et al [663] reported 1 year results of green light in the first US multicenter prospective trial. At 12 months 2 of 139 men had persistent new onset urge incontinence. They reported no stress incontinence.

III. INCONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY

1. INCIDENCE

The incidence of incontinence after radical prostatectomy has been a source of controversy over the past several decades as reported rates have varied greatly depending on the definition and methodology of data collection. The incidence has probably declined over the past two decades, owing to advances in surgical technique and to earlier recognition of lower stage disease in younger patients, however the prevalence of post-prostatectomy incontinence has risen; paralleling the increase in surgical procedures performed annually [664].

In 1991, Foote et al tabulated data from series published between 1977 and 1990, and reported a range of incontinence rates from 2.5 to 87 percent after radical prostatectomy [665]. In general, older single-institution studies utilizing physician assessments to determine incontinence rates report relatively low rates (5-8%) [666-671]. A variety of definitions of incontinence were used, making comparison of data difficult. Since then, validated patient questionnaires have been developed, which help to standardize definitions of incontinence, allow easier comparison between institutions, and assess of the impact of incontinence on quality of life. This eliminates physician bias perhaps improving accuracy [672-674], although it introduces the cave at that questionnaire-based data may reflect subjective urine leakage but does not correlate with bother or actual urine, especially for mild degrees of incontinence [675, 676]. As expected these studies show the incidence of incontinence to be significantly higher, 13-65%, depending upon the definition.

In the past several years robotic radical prostatectomy has gained popularity. Similar to what is seen with open radical prostatectomy the continence rates tend to increase with longer follow-up and may continue to improve even beyond 12 months [677]. The continence rates from several large recently published series ranged from 68 to 97% at 12 months post surgery [677-681]. 20 - 27% achieving immediate continence following catheter removal [678, 680, 681]. Recently anterior vesicourethral reconstruction [682], posterior vesicourethral reconstruction [683] and total reconstruction [684] have been described to increase the continence rate and hasten time to recovery of
continence. As in earlier open prostatectomy series, robotic series tend to be single institution studies with physician reported outcomes and continence status based on no or 0-1 pads.

In 1993, The American College of Surgeons Commission on Cancer reviewed the reported results of 2,122 patients treated by radical prostatectomy performed at 484 institutions in 1990 [685]. Only 58% reported complete continence, 23% reported occasional incontinence not requiring pads, 11.2% wore 2 or fewer pads per day, 4% wore more than 2 pads per day, and 3.6% were completely incontinent. Fowler et al [686] published the results of an outcomes study on a series of Medicare patients with less encouraging results. In this series patients age >65 surveyed by mail, telephone, and personal interview, over 30 percent reported currently wearing pads or clamps to deal with wetness; over 40 percent said they dripped urine during cough or when the bladder was full; 23 percent reported daily wetting of more than a few drops. Six percent had surgery after the radical prostatectomy to treat incontinence.

There appear to be differences in physician vs. patient reported outcomes and centers of excellence versus community surgeons’ outcomes. When trying to interpret all of the data, it is clear that the varying definitions of incontinence make comparisons impossible. Even using the definition of pad free as totally continent has its limitations. Rodriguez et al [687] found that 70% of men who attained “pad-free continence” after radical prostatectomy have occasional incontinence. Conversely, Lepor et al [688] asked the single question “Do you consider yourself continent?” at 3-24 months after surgery. 97.1% of men answered yes. They found that the best correlation of objective measures with a positive were 0 or 1 pad, total control or occasional dribbling, and no or slight problem from incontinence on the UCLA/RAND questionnaire [688]. There is a dearth of good quality prospective studies evaluating incontinence after prostatectomy in an objective manner. One such study compared continence in patients undergoing open versus laparoscopic radical prostatectomy at one year, using a 24 hour pad test, symptom scores and quality of life measures [689]. Incontinence was defined as a pad weight of > 8 grams/24 hours. There were no difference in objective and subjective measures between the two groups. Urinary incontinence was present in 13% of open and 17% of laparoscopic cases. In practical terms incidence of incontinence that produces bother, no matter what its degree, is the true parameter of interest. However, because of the individual variability of bother and the way data has been collected, we must realize the limitations of the historical data in the literature. Tables 7 and 8 highlight the reported rates of post-prostatectomy incontinence.

Table 7. Incidence rates of incontinence following radical retropubic prostatectomy based on physician assessment in single institution studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>F/U (mo)</th>
<th>Mean age/ (range)</th>
<th>Subjective Leakage</th>
<th>Pad Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel, et al (2007) [678]</td>
<td>500</td>
<td>12</td>
<td>63.2</td>
<td>N/A</td>
<td>3% (not all patients had 12 month data)</td>
</tr>
<tr>
<td>Eastham, et al (1996)[667]</td>
<td>581</td>
<td>24</td>
<td>63 med</td>
<td>Stress: 5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Geary, et al (1995) [668]</td>
<td>458</td>
<td>&gt;18</td>
<td>64.1 +/- 0.3</td>
<td>N/A</td>
<td>1-2pads/day - 8.1%</td>
</tr>
<tr>
<td>Zincke, et al (1994) [671]</td>
<td>3170</td>
<td>12</td>
<td>65.3 (31-81)</td>
<td>N/A</td>
<td>3 or more pads/day:</td>
</tr>
<tr>
<td>Leandro, et al (1992) [669]</td>
<td>398</td>
<td>12</td>
<td>68 (46-84)</td>
<td>STRESS URINARY</td>
<td>5%</td>
</tr>
<tr>
<td>Steiner, et al (1991) [670]</td>
<td>593</td>
<td>12</td>
<td>? (34-76)</td>
<td>STRESS URINARY</td>
<td>&lt;1 pad/day - 2.2%</td>
</tr>
</tbody>
</table>

Total - 0

<1 pad/day - 2.2% 1 pad/day - 3.5% 2 pads/day - 1.5% >2pads/day - 0.5%
Table 8. Incidence rates of incontinence following radical retropubic prostatectomy based on data gathered from validated patient questionnaires.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>F/U (mo)</th>
<th>Age (range)</th>
<th>Subjective Leakage</th>
<th>Pad Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford, et al (2000) [690]</td>
<td>1291</td>
<td>18</td>
<td>&lt;65 - 56% &gt;65; -44%</td>
<td>Occasional - 40% &gt;Occasional - 8.4%</td>
<td>1-2 pads/day -18.3% &gt;3 pads/day - 3.3%</td>
</tr>
<tr>
<td>Kao, et al (2000) [691]</td>
<td>1069</td>
<td>N/A</td>
<td>63.6 (30 -77)</td>
<td>65.6%</td>
<td>33%</td>
</tr>
<tr>
<td>Wei, et al (2000) [672]</td>
<td>217</td>
<td>12</td>
<td>62.3 (40-80)</td>
<td>Any leakage - 47% &gt;1 episode/day - 65%</td>
<td>13% (&gt;1PPD)</td>
</tr>
<tr>
<td>Fontaine, et al (2000) [692]</td>
<td>116</td>
<td>51.6</td>
<td>65.2 (48-76)</td>
<td>14.4%</td>
<td>19.8% 1 pad/day - 74% 2 pads/day - 13% &gt;3 pads/day - 13%</td>
</tr>
<tr>
<td>McCammon, et al (1999) [673]</td>
<td>203</td>
<td>40.3 (12-144)</td>
<td>63.7 (43-73)</td>
<td>61.8%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Bates, et al (1998) [694]</td>
<td>87</td>
<td>22 (7-87)</td>
<td>65 (49-73)</td>
<td>69%</td>
<td>24% 1 pad/day - 60% 2 pads/day - 15% &gt;3 pads/day - 25%</td>
</tr>
<tr>
<td>Talcott, et al (1997) [695]</td>
<td>94</td>
<td>12</td>
<td>61.5</td>
<td>13%</td>
<td>39%</td>
</tr>
<tr>
<td>Donnellan, et al (1997) [675]</td>
<td>51</td>
<td>12</td>
<td>?</td>
<td>Mild - 14% Moderate - 4% Severe- 2%</td>
<td>Pad test Mild - 6% Moderate - 6% Severe - 4%</td>
</tr>
</tbody>
</table>
in large contemporary series using physician-gathered and self-reported data respectively. Most large series are on radical retropubic prostatectomy as opposed to radical perineal prostatectomy.

2. RECOVERY OF CONTINENCE AFTER RADICAL PROSTATECTOMY

While the majority of patients experience incontinence immediately following RRP, in most this is transient with a gradual improvement over time. Most studies report progressive return of continence up to one year after surgery and in general intervention for incontinence is usually delayed until one year after surgery unless absolutely no progressive improvement is seen. Thus, most prostatectomy series report continence rates at 1 year. Lepor and Kaci [688] showed that continence may continue to improve up to 24 months based on objective and subjective measures. They showed modest improvements in bother (UCLA RAND questionnaire) pad usage and total control rates between 12 and 24 months. Pad weights were not determined so it is possible that some “improvements” could have been related to patient tolerance and expectations over time. Smither et al [697] objectively assessed the natural history of post radical prostatectomy incontinence using a standardized 1 hour pad test. They showed a rapid improvement in urinary control during the first 18 weeks post-RRP with a flattening of the recovery curve beyond that point. Minimal incontinence defined as ≤ 1 gm on a 1 hour pad test was as demonstrated in 3, 37, 66, 85, 87 and 91% of patients at 2, 6, 18, 30, 42, and 54 weeks. They concluded that the 18 week marker appears to be the time point after which the majority of patients have achieved urinary control, although a small percentage will have continued objective improvement.

3. RISK FACTORS

An increased risk towards post-prostatectomy incontinence in older men is supported in theory by anatomical observations. With advancing age, there is evidence of atrophy of the rhabdosphincter [627] and neural degeneration [698]. Several studies have shown advancing age to be a risk factor for postoperative incontinence [666, 667, 669, 671, 690, 699]. Steiner, et al [670] found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older. Catalona et al [666] reported that “Recovery of urinary continence occurred in 92% (1,223 of 1,325 men) and was associated with younger age (p<0.0001).

Most large series have found no correlation between the stage of disease and incontinence rates [666, 667, 672, 676]. However, in certain cases, the stage of disease may affect the surgical technique (i.e. nerve sparing) and rates may be higher, but this appears to be a reflection on surgical technique and not disease stage [667]. Authors of several single-institution studies have argued that surgeon experience and surgical technique are important determinants of post-operative incontinence rates [631, 650, 667, 700, 701] and many have found that changes in their own technique have led to reduced rates of incontinence or a reduced time to continence recovery [631, 667, 684, 702-704]. This includes procedural modifications such as, nerve-sparing (probably secondary to a more careful dissection) bladder neck preservation, preservation of anterior urethral ligamentous attachments and urethrovesical junction reconstruction.

Patients who have undergone prior radiation for prostate cancer are at high risk of developing incontinence after radical prostatectomy. Rates of significant incontinence after salvage prostatectomy range from 57-64% [705, 706]. Sanderson and colleagues [707] reported that 45% of men underwent artificial urinary sphincter placement after salvage prostatectomy and another 31% without an artificial sphincter had incontinence greater than occasional dribbling. This has prompted some to recommend urinary diversion at the time of salvage radical prostatectomy [708].

4. ETIOLOGY AND PATHOPHYSIOLOGY OF POST RADICAL PROSTATECTOMY INCONTINENCE: SPHINCTER VS. BLADDER DYSFUNCTION

There is fairly extensive literature on urodynamic investigation of post prostatectomy incontinence. While it is well established that both bladder and sphincter dysfunction may be present after radical prostatectomy, most studies agree that sphincter dysfunction (stress incontinence) is the main cause. [648, 698, 709-712]. In these series the incidence of sphincter dysfunction ranges from 88–98.5%, with associated bladder dysfunction (detrusor overactivity and less commonly impaired compliance) in 26-46%. Bladder dysfunction, on the other hand, was present in 34–45% of patients but was the sole cause of incontinence in only 1.5–4%. Bladder dysfunction when present in association with sphincter dysfunction may not always be clinically significant. Ficazzola and Nitti [710] found that although 46% of patients had bladder dysfunction, incontinence on urodynamic study was demonstrated in only 27%. Even in those patients, sphincter dysfunction was the main cause of incontinence in the overwhelming majority. Groutz and colleagues [709] found a 33% incidence of bladder dysfunction, but found that it was the main cause of incontinence in only 7.25%. Two earlier series reported a higher incidence of bladder dysfunction [649, 650]. Some authors feel that in some patients with severe intrinsic sphincter deficiency bladder dysfunction may occur as a result of filling the bladder to volumes that it is not accustomed to holding [710]. Filling to capacity may produce detrusor overactivity or decreased accommodation. Thus, bladder dysfunction is in a
sense an artefact. This may explain why the outcomes for artificial urinary sphincters for the treatment of stress incontinence are not adversely affected by the presence of detrusor overactivity [713, 714]. In addition bladder dysfunction may be chronic and stem from obstructive uropathy present before prostatectomy. Table 9 summarizes the urodynamic findings in eight series. It must be emphasized that patient selection, urodynamic technique and timing of urodynamic evaluation maybe responsible for the differences seen among the different studies. It is also important to note that most of these studies are performed in men seeking treatment for there incontinence. However, it appears that sphincter dysfunction is the main cause of post-radical prostatectomy incontinence, but bladder dysfunction may be present in a significant number of men (though rarely alone) and must not be completely discounted when planning treatment.

The majority of evidence in the literature supports the conclusion that sphincter damage is the primary cause of incontinence after total prostatectomy. Direct exposure and manipulation of the sphincter during radical prostatectomy would suggest that sphincter damage is the most likely cause of incontinence. Successful treatment with the artificial urinary sphincter and male sling procedures also indirectly suggests that primary sphincter injury is the major cause of incontinence, since outcome is usually not complicated by bladder dysfunction. Bladder dysfunction after prostatectomy may have been present preoperatively, for example due to pre-existing outflow obstruction, may be caused by the operation itself, or may be due to age related changes in bladder function. Many patients who have prostate surgery have pre-existing bladder dysfunction, which may or may not be symptomatic. While it is obvious how overzealous TURP with resection into the trigone can cause detrusor overactivity; it is less apparent how radical prostatectomy affects detrusor function. Some have suggested that denervation of the urethra or the bladder may occur during radical prostatectomy. John et al [715] studied trigonal innervation by biochemical markers and found that "urinary incontinence was associated with decreased trigonal innervation, a high sensory threshold and low maximal urethral closure pressure".

**IV. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER**

Radiation therapy, whether external beam or brachytherapy, can be a cause of voiding dysfunction and incontinence. Sometimes this is a direct effect of the radiation or it can be related to the treatment of other sequelae such as urinary retention. The initial response to is primarily oedema and then gradually degeneration, fibrosis and disorganization overcomes the bladder musculature. While radiation is primarily delivered to the prostate, portions of the bladder may also be affected. Perivascular fibrosis of blood vessels may then cause vascular occlusion followed by ischemia of the bladder wall which can then progress to fibrosis within 6 to 12 months [716]. Choo et al. [717], found that urodynamic bladder capacity decreased by an average of 54 ml, 18 months after radiation therapy. Blaivas et al [718] evaluated 47 men with symptomatic LUTS after brachytherapy and found that 71% were incontinent and 85% had detrusor overactivity. Similarly, radiation can cause damage to the distal urinary sphincter which can result in incontinence. However, this usually does not manifest until the patient undergoes treatment such as transurethral resection or incision of the prostate which compromises the proximal urethral sphincter.

Urinary retention and increased obstructive LUTS are other common problems that radiation therapy and

**Table 9. Summary of several urodynamic contemporary series on post-radical prostatectomy incontinence with regard to sphincter and bladder dysfunction.**

*This study considered urodynamic diagnoses of obstruction and impaired contractility so that patients with sphincter insufficiency and impaired contractility or obstruction without bladder dysfunction are not included in this group. From Nitti [731]*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sphincter Dysfunction Total (%)</th>
<th>Sphincter Dysfunction Alone (%)</th>
<th>Bladder Dysfunction Total (%)</th>
<th>Bladder Dysfunction Alone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leach, et al [649]</td>
<td>162</td>
<td>82</td>
<td>40</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Goluboff, et al [650]</td>
<td>25</td>
<td>60</td>
<td>8</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>Chao &amp; Mayo [698]</td>
<td>74</td>
<td>96</td>
<td>57</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Gudziak, et al [712]</td>
<td>37</td>
<td>97</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>Desautel, et al [711]</td>
<td>35</td>
<td>95</td>
<td>59</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Ficazzola &amp; Nitti [710]</td>
<td>60</td>
<td>90</td>
<td>53</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Winters, et al [648]</td>
<td>92</td>
<td>98.5</td>
<td>59</td>
<td>29</td>
<td>1.5</td>
</tr>
<tr>
<td>Groutz, at al [709]</td>
<td>83</td>
<td>88</td>
<td>33*</td>
<td>34</td>
<td>4</td>
</tr>
</tbody>
</table>
particularly brachytherapy is urinary retention. The incidence of retention has been reported to range from to be 2% to 30% after brachytherapy [719-722]. Most patients with retention will have resolution of their obstruction within weeks others go on with surgical procedures. A retrospective review of over 2,100 Medicare patients who underwent brachytherapy for prostate cancer found that 8.3% required a surgical procedure to relieve bladder outlet obstruction post-brachytherapy [723]. Flam, et al [724] reported that 19 of 600 (3.1%) patients receiving brachytherapy required TURP. Kollmeier and colleagues [725] reported a similar rate of 2% in 2050 men. Most authors have found significant rates of post TURP incontinence after radiation. Incontinence following TURP after brachytherapy has been reported in 0-70% and is often severe. [724-726]. External beam radiation is also a risk factor as Green et al [727] reported a 33% incidence of incontinence following TURP in patients post-irradiation for prostate cancer. Some authors have emphasized that incontinence can be minimized by performing a limited resection [728] or by performing TURP within 2 years of brachytherapy [725]. In the latter study, two of 24 patients (8%) that underwent TURP within 2 years of treatment were incontinent and 5 of 14 patients (36%) that underwent TURP 2 years or more after brachytherapy were incontinent (p=0.04). However, others suggest that delaying TURP until 5 years after radiation can actually reduce the risk of incontinence [729, 730].

V. CONCLUSIONS

Incontinence in the male as in the female can be broadly divided into that which is caused by bladder dysfunction and that which is caused by sphincter dysfunction. The pathophysiology of incontinence as it relates specifically to the male is fairly well described; however advances in science and anatomy will undoubtedly provide a more intricate understanding in the future. For example, the causes of sphincter insufficiency are known (i.e. damage to muscle, nerve and/or supporting structures) but clinicians are not able to accurately assess the exact cause of sphincter insufficiency in any given patient. Therefore much of our understanding of post treatment incontinence “pathophysiology” is derived from reports of incontinence (incidence/prevalence) after surgery or radiation. In addition investigators have not done a good job in defining the incidence of incontinence related to interventions for prostatic disease, whether benign or malignant. Problems have been two-fold: first in defining incontinence and what is bothersome/significant and second in accurately reporting data. New technologies for the treatment of BPH have provided us with Level 1 evidence regarding the incidence of incontinence in trials comparing new technology to TURP and Level 2 evidence through meta-analysis and prospective series. Data regarding the incidence of post radical prostatectomy and post radiation incontinence has been less robust and of a lower quality – level 2-4. Even the level 2 evidence lacks a consistent definition.

VI. RECOMMENDATIONS

Level of evidence 1 regarding the incidence of post prostatectomy and post radiation incontinence is needed. It is hoped that the advent of new technologies will prompt controlled trials of different therapies for prostate cancer with incontinence as a primary endpoint. These studies must start with a standardized definition of incontinence and how it affects quality of life, thus objective and subjective measures will be necessary. Such an understanding will allow clinicians to better select, prepare and treat patients and ultimately prevent or at least limit incontinence.

H. CAUSES OF TRANSIENT INCONTINENCE IN OLDER ADULTS

Transient causes probably accounts for one-third of incontinent cases among community-dwelling older people (>65 years old), up to one-half of cases among acutely-hospitalized older people, and a significant proportion of cases among nursing home residents [732-734]. Most causes of transient incontinence in the older population lie outside the lower urinary tract but two points are worth emphasizing. First, the risk of transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, the older person also suffers from pathologic changes. Overflow incontinence is more likely to result from an anticholinergic agent in a person with a weak or obstructed bladder, just as urge incontinence is more likely to result from a loop diuretic in someone with detrusor overactivity and/or impaired mobility [735, 736].

This fact may explain why some controversy persists regarding some causes of transient incontinence. It also emphasizes that continence depends on the integrity of multiple domains-mental state, mobility, manual dexterity, medical factors, and motivation, as well as lower urinary tract function. Although in younger individuals incontinence usually results from lower urinary tract dysfunction alone, incontinence in older patients often results from deficits in multiple domains that together result in incontinence [737]. Attention to any one or more of these risk factors can restore
continence or at least improve it. Second, although termed “transient,” these causes of incontinence may persist if left untreated, and so they cannot be dismissed merely because the incontinence is of long duration.

II. QUALITY OF DATA

In older people, continence status is often not absolute, especially in those who are frail. Infrequent leakage of small amounts may appear and disappear, and reporting accuracy varies as well [738]. Furthermore, ethical constraints and methodological issues preclude robust investigations of the conditions commonly impugned as causes of transient incontinence. Thus, it is not surprising that evidence supporting the association between these conditions and transient incontinence consists predominantly of case reports and case series.

III. RESULTS OF LITERATURE REVIEW

Transient causes of incontinence in older people are shown in Table 10 and can be recalled using the mnemonic DIAPPERS [739]

Table 10. Causes of Transient Incontinence in Older People

| D | Delirium |
| I | Infection (UTI, symptomatic) |
| A | Atrophic urethritis/vaginitis |
| P | Psychological (e.g. severe depression, neurosis) |
| P | Pharmacologic |
| E | Excess urine output |
| R | Restricted mobility |
| S | Stool impaction |

1. DELIRIUM

“D” is for delirium, a confusional state characterized by fluctuating inattentiveness and disorientation. Its onset occurs over hours to days, as contrasted with dementia, which develops over years. Delirium can result from almost any medication and from virtually any acute illness, including congestive heart failure, deep vein thrombosis, or infection. Many of these conditions may present atypically in older patients, and if the patient becomes confused because of them, incontinence may be the first abnormality detected [740]. Delirium leads the list because, if unrecognized, it is associated with significant mortality. Thus, in this case, meticulous medical evaluation - not cystometry-is crucial.

2. URINARY INFECTION

Symptomatic urinary infection is another cause of incontinence, although it is an uncommon one [732]. However, asymptomatic urinary infection, is much more common in older people [741, 742].

3. ATROPHIC VAGINITIS

Atrophic vaginitis in older women is frequently associated with lower urinary tract symptoms, which occasionally include incontinence. As many as 80% of such women attending an incontinence clinic are reported to have physical evidence of atrophic vaginitis, characterized by vaginal mucosal atrophy, friability, erosions, and punctuate haemorrhages. Atrophic vaginitis has been associated with urgency and occasionally a sense of “scalding” dysuria, but both symptoms may be relatively unimpressive. More recent epidemiologic and clinical studies have called these beliefs into question since they have demonstrated an association with estrogen treatment and the onset of incontinence. Unfortunately, limitations in their design allow for the possibility of both bias and confounding factors. Further research is warranted.

4. MEDICATIONS

Pharmaceuticals are one of the most common causes of incontinence in older people, with several categories of drugs commonly implicated [743] (Tables 11 and 12). Of note, many of these agents also are used in the treatment of incontinence, underscoring the fact that most medications used by older people are “double-edged swords.” The first category of relevant drugs is the long-acting sedative/hypnotics, such as diazepam and flurazepam, which can cloud an older patient’s sensorium. “Loop” diuretics, such as furosemide or bumetanide, by inducing a brisk diuresis,

Table 11. Important anticholinergic drugs and drug side effects in the elderly

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Anticholinergic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Tricyclic Antidepressants (not SSRI’s)</td>
<td>Constipation</td>
</tr>
<tr>
<td>Anti-parkinsonian agents</td>
<td>Confusion</td>
</tr>
<tr>
<td>First generation (sedating) antihistamines</td>
<td>Drowsiness, fatigue</td>
</tr>
<tr>
<td>Anti-arrhythmics (disopyramide)</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Inhibit detrusor contractility</td>
</tr>
<tr>
<td>Opiates</td>
<td>Urinary-retention; Blurred-Vision; Increased ocular pressure</td>
</tr>
<tr>
<td>Type of Medication</td>
<td>Examples</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Sedatives/Hypnotics</td>
<td>Long-acting benzodiazepines (e.g. diazepam, flurazepam)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Dicyclomine, disopyramide, antihistamines, (sedating ones only, e.g., Benadryl®)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Thioridazine, haloperidol</td>
</tr>
<tr>
<td>Antidepressants (tricyclics)</td>
<td>Amitriptyline, desipramine; not SSRI's</td>
</tr>
<tr>
<td>Anti-Parkinsonians</td>
<td>Trihexyphenidyl, benztropine mesylate, (not L-dopa or selegiline)</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>Opiates</td>
</tr>
<tr>
<td>Adrenergic antagonist</td>
<td>Prazosin, terazosin, doxazosin</td>
</tr>
<tr>
<td>Adrenergic agonist</td>
<td>Nasal decongestants</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>All dihydropyridines*</td>
</tr>
<tr>
<td>Potent diuretics</td>
<td>Furosemide, bumetanide (not thiazides)</td>
</tr>
<tr>
<td>NSAIDs Thiazolidinediones</td>
<td>Indomethacin, COX-2 inhibitors, Rosiglitazone, pioglitazone</td>
</tr>
<tr>
<td>Angiotensinconverting enzyme (ACE) inhibitors</td>
<td>Captopril, enalapril, lisinopril</td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
</tr>
</tbody>
</table>

can also provoke leakage. Drugs with anticholinergic side effects are a particular problem and include major tranquilizers, antidepressants, antiparkinsonian agents (e.g., benztriptine mesylate or trihexyphenidyl), first generation (sedating) antihistamines, anti-arrhythmics (disopyramide), antispasmodics, and opiates. By decreasing detrusor contractility, they can cause urinary retention and overflow incontinence. They also can cause confusion. Anticholinergic agents are particularly important to ask about for two reasons. First, older patients often take more than one of them at a time. Second, they are contained in many non-prescription preparations that older people frequently take without consulting a physician.

Adrenergically-active agents have also been associated with incontinence. Many alpha-adrenergic antagonists (used mainly for treatment of hypertension) block receptors at the bladder neck and may induce stress incontinence in women (744). Older women are particularly at risk because their urethral length and closure pressure normally decline with age. Thus, prior to considering other interventions for stress incontinence in a woman taking such a drug, substitution of an alternative agent should be tried and the incontinence re-evaluated. Calcium channel blockers can cause incontinence. As smooth muscle relaxants, they can increase residual volume, especially in older adults with impaired detrusor contractility. The increased residual urine may occasionally lead to stress incontinence in women with a weak urethral sphincter, or to overflow incontinence in men with concurrent urethral obstruction. Finally, angiotensin converting enzyme inhibitors, by inducing cough (the risk of which is age-related), may precipitate stress incontinence in older women whose urethra has shortened and sphincter weakened with age.

5. DIURESIS

Excess urinary output can also cause incontinence, especially in individuals with impaired mobility, mental state, or motivation, particularly if they also have detrusor overactivity. Causes of excess output include excess intake, diuretics (including theophylline-containing fluids and alcohol), and metabolic abnormalities (e.g., hyperglycemia and hypocalcaemia). Nocturnal incontinence can be caused or exacerbated by disorders associated with excess nocturnal excretion, such as congestive heart failure, peripheral venous insufficiency, hypoalbuminemia (especially in malnourished older people), and drug induced peripheral oedema associated with NSAIDs, thiazolidinediones, and some calcium channel blockers (e.g., dihydropyridines such as nifedipine, isradipine, and nicardipine). The role of caffeine and timing of drinking fluids (e.g. in the evening or before bedtime) is still not clear, but should nonetheless be considered a possible contributing cause for nocturia and nocturnal incontinence.

6. RESTRICTED MOBILITY

Restricted mobility is an easily understood but frequently overlooked cause of incontinence. In addition to obvious causes, restricted mobility may be associated with orthostatic or postprandial hypotension, poorly-fitting shoes, poor physical state, or fear of falling, all of which are common geriatric conditions.

7. FAECAL IMPACTION

Finally, faecal impaction has been implicated as the cause of incontinence in up to 10% of older patients seen in acute hospitals or geriatric incontinence clinics. One possible mechanism involves stimulation of opioid receptors [746]. A clue to the presence of faecal impaction is the onset of both urinary and faecal incontinence, usually associated with oozing of loose stool around the impaction.

IV. SUMMARY

Apart from re-challenge data for alpha adrenergic agents (Level of Evidence = 2), the level of evidence for most of these causes is Level 3-4. Nonetheless, because they are easily addressed and contribute to morbidity beyond the lower urinary tract, they are worth identifying even if the evidence is not strong.

V. RECOMMENDATIONS

Despite the current lack of compelling data, these seven “transient” causes of urinary incontinence should be searched for in older incontinent patients before embarking on more complex assessment and management. Their prevalence is high, their treatment straightforward, and they contribute to morbidity beyond the urinary tract. Moreover, addressing them may improve the incontinence even if it does not eliminate it, and it may make the incontinence more amenable to subsequent therapy. (Grade of recommendation C)

VI. RESEARCH PRIORITIES

Further research should be performed on the mechanisms, prevalence, incidence, and remission rates of each of the known causes of transient incontinence, and possible additional causes should be identified as well. Since older people are heterogeneous, studies should be conducted among several subgroups, including independent and homebound community-dwelling older people, bedbound and mobile institutionalized older people, and acutely hospitalized older people.
REFERENCES


370. Uustal Fornell, E., G. Wingren, and P. Kjolhede, Fact ors


Committee 5

Initial Assessment of Urinary and Faecal Incontinence in Adult Male and Female Patients

Chairman
D. Taskin (USA)

Co-Chairman
C. Kelleher (U.K)

Members
K. Avery (U.K),
R. Bosch (N.L),
N. Cotterill (U.K),
K. Coyne (USA),
A. Emmanuel (U.K),
M. Yoshida (Japan)

Consultant
Z. Kopp (USA)
Committee 5 A

Initial Assessment of Urinary and Faecal Incontinence in Adult Male and Female Patients

CONTENTS

5A - A. INITIAL ASSESSMENT OF URINARY INCONTINENCE IN ADULT MALE AND FEMALE PATIENTS

I. LOWER URINARY TRACT SYMPTOMS

II. URINALYSIS IN THE EVALUATION OF THE PATIENT WITH LUTS AND UI

III. THE UTILITY OF POST-VOIDING RESIDUAL [PVR] URINE VOLUME DETERMINATION IN THE INITIAL ASSESSMENT OF INCONTINENT PATIENTS

IV. THE FEMALE PATIENT

V. THE MALE PATIENT

5A - B. INITIAL ASSESSMENT OF FAECAL INCONTINENCE

I. FAECAL INCONTINENCE ASSESSMENT

REFERENCES

Committee 5 B

Patient-Reported Outcome Assessment

CONTENTS

INTRODUCTION

5B - A. THE MEASUREMENT OF PATIENT-REPORTED OUTCOMES (PROS) OF INCONTINENCE, OTHER LOWER URINARY TRACT SYMPTOMS, AND BOWEL PROBLEMS

5B - B. RECOMMENDED PRO QUESTIONNAIRES

5B - C. INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE (ICIQ): WHAT IS THE ICIQ?

5B - D. PATIENT REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER URINARY TRACT SYMPTOMS

5B - E. RECOMMENDATIONS FOR RESEARCH

REFERENCES
Committee 5 A

Initial Assessment of Urinary and Faecal Incontinence in Adult Male and Female Patients

D. Staskin, C. Kelleher, R. Bosch, K. Coyne, N. Cotterill, A. Emmanuel, M. Yoshida, Z. Kopp

INTRODUCTION

Organization of this committee report

Urinary (UI) and faecal incontinence (FI) are a concern for individuals of all ages and both sexes. This report reviews the “initial assessment” of urinary and faecal incontinence – and in addition, reviews the available outcome measures for symptom assessment and quality of life for these disorders. Therefore, the report is divided into 2 major sections: 5A-A initial assessment of urinary incontinence (UI) in adult male and female patients, 5A-B initial assessment faecal incontinence (FI) and 5B outcome measures. The initial assessments for the conditions of incontinence in paediatric, neurogenic, and geriatric patients and for patients with pelvic pain are presented in the specific Committee reports pertaining to these sub-groups and conditions.

5A- A. INITIAL ASSESSMENT OF URINARY INCONTINENCE IN ADULT MALE AND FEMALE PATIENTS

For the purpose of this report, the ‘initial assessment’ represents the components of the history, physical examination, laboratory tests, and basic office testing to:

1. Establish a presumptive or condition specific diagnosis, and exclude underlying organ-specific related or unrelated conditions that would require intervention.
2. Assess the level of bother and desire for intervention from information obtained from the patient or caregiver.
3. Institute empiric or disease specific primary therapy based on the risk and benefit of the untreated condition, the nature of the intervention and the alternative therapies.
4. Prompt the recommendation of additional more complex testing or specialist referral.

Within the initial assessment of UI, various sub-populations / subgroups are recognized because of the differences within patient groups or the interrelationship between the conditions. The subsections in this report should be utilized in conjunction with other population or condition specific Committee Reports of the Consultation and the final recommendations of the Consultation which are presented in simplified form along with treatment algorithms in the Management Recommendations. These sub-groups include patients with lower urinary tract symptoms (LUTS) without incontinence and with pelvic pain. The requirements of specific sub-populations negate the ability to recommend a ‘universal’ initial evaluation. Pelvic organ prolapse in the female and prostatic obstruction in the male require uniquely different approaches to lower urinary tract dysfunction. Congenital and maturational issues in the paediatric subgroup and the effects of ageing on the lower urinary tract and medical co-morbidities in the geriatric group present unique challenges. Specific risks for combined storage and emptying abnormalities and upper urinary tract deterioration in the neurogenic bladder population demand a more involved initial evaluation.

This committee report is evidence based and utilizes the ICUD - EBM grades. A search of the available literature in English obtained from Medline® and Pubmed® up to June 2008 by the individual committee members utilized multiple search terms related to assessment (eg., ‘urinary incontinence’, ‘faecal incontinence’, ‘lower urinary tract symptoms’, ‘vaginal prolapse’, and terminology related to ‘outcome assessments’ and ‘quality of life measures’).
Purpose of the initial assessment

The initial assessment must consider the degree of bother, and the costs of further evaluation, balanced against the consequences of a failure to diagnose an underlying condition, the risk and benefits of conservative management or pharmacological therapy and the need for an accurate diagnosis before more complex intervention or empiric therapy. The burden of these conditions and the availability of resources to different patients, physicians, and health care systems require that primary intervention strategies be formulated, when available from evidence based findings and decisions emanating from the initial evaluation. As will be noted, especially in this committee report, the amount and sophistication of the literature that contributes to the levels of evidence that are available for determining the grades of recommendation in the area of “initial assessment” may often rely on expert opinion of the panel.

Of note, LUTS cannot be used to make a definitive diagnosis of a specific lower urinary tract condition or lower urinary tract disease (LUTD), as these symptoms may suggest and indicate pathologies such as urinary infection or more serious underlying conditions. Basic laboratory tests, such as testing for urinary or faecal infection or blood, and appropriate screening for malignancy should be considered before the decision is made to choose therapy for incontinence.

Concomitant pathology may affect urinary or faecal production as co-morbid contributory issues, by affecting fluid balance or renal function (dietary or alimentary function) and may need to be addressed. The physician should elicit neurological symptoms and signs that may indicate alterations in the control of the lower urinary tract / bowel function or the cognitive, motivational, physical, and environmental factors that determine the ability to perform toileting functions effectively.

1. STORAGE SYMPTOMS

Overactive Bladder (OAB) - Urgency with or without urge incontinence usually with frequency and nocturia in the absence of an underlying metabolic or pathological condition.

Urinary incontinence (UI) is the complaint of any involuntary leakage of urine. In each specific circumstance, urinary incontinence should be further described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measures used to contain the leakage (wearing of protection, number and type of pads and change of underwear or outer clothes) and whether or not the individual seeks or desires help because of urinary incontinence. Urinary leakage may need to be distinguished from perspiration or vaginal discharge.

Stress urinary incontinence (SUI) is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing (NIH – the patient’s or caregiver’s statement of involuntary loss of urine during physical exertion).

Urgency urinary incontinence (UUI) is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Urge incontinence can present in different symptomatic forms; for example, as frequent small losses between micturition or as a catastrophic leak with complete bladder emptying. Information should be sought on triggering events such as cold, running water and ‘latch key’ incontinence.

Mixed urinary incontinence (MUI) is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.

Continuous urinary incontinence is the complaint of continuous leakage.

Other types of urinary incontinence may be situational, for example the report of incontinence during sexual intercourse. Coital incontinence may occur during arousal, on penetration, throughout intercourse, or specifically at orgasm; although urodynamic stress incontinence is the most common urodynamic finding in each of these situations, detrusor overactivity is found more often when leakage is restricted to orgasm [3].

Urgency is the complaint of a sudden compelling desire to pass urine which is difficult to defer (NIH – the statement that the patient feels a strong need to pass urine for fear of leakage).

Increased daytime frequency is the complaint of voiding too often by day (NIH - the statement that the patient voids eight or more times in 24 hours).

Increased daytime frequency may arise in the presence of a normal bladder capacity when there is
excessive fluid intake, or when bladder capacity is restricted secondary to detrusor overactivity, impaired bladder compliance, or increased bladder sensation.

**Nocturia** is the complaint that the individual has to wake at night one or more times to void (NIH - *the statement that the patient wakes from sleep to pass urine*). The term ‘night time frequency’ differs from that for nocturias, as it includes voids that occur after the individual has gone to bed, but before he/she has gone to sleep, and voids which occur in the early morning which prevent the individual from getting back to sleep as he/she wishes. These voids before and after sleep may need to be considered in research studies. If this definition were used then an adapted definition of daytime frequency is required. Nocturia may arise for similar reasons to daytime frequency, but may also occur due to an increase in fluid output due to other physiological abnormalities resulting in ‘nocturnal polyuria’. (see Bladder diaries below).

**Nocturnal enuresis** is the complaint of loss of urine occurring during sleep. Enquiry should include previous childhood nocturnal enuresis as delayed bladder control in childhood is associated with detrusor overactivity in adulthood.

**Bladder sensation** may be categorised as:

- **Normal**: the individual is aware of bladder filling and increasing sensation towards capacity.
- **Increased**: the individual feels an early and persistent desire to void.
- **Reduced**: the individual is aware of bladder filling but does not feel a definite desire to void.
- **Absent**: the individual reports no sensation of bladder filling or desire to void.
- **Non-specific**: the individual reports no specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity. These symptoms are most frequently seen in neurological patients, particularly those with spinal cord trauma or malformation.

**2. Voiding Symptoms**

Voiding symptoms may occur in situations of overactive outlet, or under active detrusor[1]. The former may be secondary to outlet obstruction from urogenital prolapse, urethral stricture or following previous bladder neck surgery. Detrusor atonia or hypotonia is however much more common in the female, and may arise idiothetically, or secondarily to over distension after parturition or surgery, in peripheral neuropathy due to diabetes mellitus, and in other neurological conditions. Women with prolapse may require to digitate vaginally to initiate or complete voiding.

**Slow stream** is the individual’s perception of reduced urine flow, usually compared to previous performance or in comparison to others.

**Intermittent stream (intermittency)** is when the individual describes urine flow which stops and starts, on one or more occasions, during micturition.

**Hesitancy** is when an individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.

**Straining to void** describes the muscular effort used to initiate, maintain or improve the urinary stream.

**Terminal dribble** is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle.

**Post-micturition symptoms**

Post micturition symptoms are experienced immediately after micturition.

**Feeling of incomplete emptying** is a self-explanatory term for a feeling experienced by the individual after passing urine.

**Post micturition dribble** is the term used when an individual describes the involuntary loss of urine immediately after he or she has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women.

**3. Measuring the Frequency and Severity of Lower Urinary Tract Symptoms**

The frequency-volume chart or micturition diary records a patient’s voiding pattern during normal daily activities. In some women it may be therapeutic as it provides them with insight into their bladder behaviour [4]. The ICS has described three different forms of diary, namely the micturition time chart which records the timing of voids in twenty four hours; the frequency volume chart (FVC) which also includes the volumes voided , and the bladder diary which in addition includes incontinence episodes, pad usage, fluid intake, degree of urgency and degree of incontinence. However, increasing either the complexity of the diary or duration of recording is associated with poorer compliance [5]. The optimum duration of recording depends on the clinical context and the purpose of the measurement. A properly performed 1-day FVC, which includes the first morning void the following day, is a reasonable tool to gain insight into voiding habits during normal daily routine.

However, a 3-day FVC or diary is recommended for accurate assessment of lower urinary tract symptoms and for confirming a consistent clinical pattern in day-to-day practice. Although never completely diagnostic, several different diary patterns have been described which may characterise normal and abnormal states[6]. For atypical clinical scenarios, a 7-day FVC or diary should be used. Equally, a 7-day diary has been recommended for clinical research, [7] however, of note, most pharmacological studies now employ a
three day diary as a standard for improved patient compliance (see Committee Report Pharmacology for further recommendations.

The following measurements can be abstracted from frequency volume charts and bladder diaries:

**DAYTIME FREQUENCY** is the number of voids recorded during waking hours and includes the last void before sleep and the first void after waking and rising in the morning.

**NOCTURIA** is the number of voids recorded during a night’s sleep; each void is preceded and followed by sleep.

**NIGHT-TIME FREQUENCY** is the number of voids recorded from the time the individual goes to bed with the intention of going to sleep, to the time the individual wakes with the intention of rising.

**24-HOUR FREQUENCY** is the total number of daytime voids and episodes of nocturia during a specified 24 hours period.

**24-HOUR PRODUCTION** is measured by collecting all urine for 24 hours; this is usually commenced after the first void produced after rising in the morning and is completed by including the first void on rising the following morning.

**POLYURIA** is defined as the measured production of more than 2.8 litres of urine in 24 hours in adults. It may be useful to look at output over shorter time frames.

**NOCTURNAL URINE VOLUME** is defined as the total volume of urine passed between the time the individual goes to bed with the intention of sleeping and the time of waking with the intention of rising. Therefore, it excludes the last void before going to bed but includes the first void after rising in the morning.

**NOCTURNAL POLYURIA** is present when an increased proportion of the 24-hour output occurs at night (normally during the 8 hours whilst the patient is in bed). The night time urine output excludes the last void before sleep but includes the first void of the morning. The normal range of nocturnal urine production differs with age and the normal ranges remain to be defined. Therefore, nocturnal polyuria is present when greater than 20% (young adults) to 33% (over 65 years) is produced at night. Hence the precise definition is dependent on age.

**AVERAGE VOLUME VOIDED** is the mean volume of urine passed in each void. This is calculated by dividing total voided volume by number of voids.

**NORMALISED MICTURITION FREQUENCY** is a more meaningful way of expressing voided volume. This is defined as the number of micturitions required to pass 1 litre of urine, and is calculated by dividing 1000 ml by average volume voided. This is a more specific measure of bladder function than micturition frequency, since it takes into account behavioural, dietary and pharmacological factors that affect urine volume.

**MAXIMUM VOIDED VOLUME** is the largest volume of urine voided during a single micturition and is determined either from the frequency/volume chart or bladder diary.

**INCONTINENCE EPISODE FREQUENCY** is the number of episodes of accidental urine leakage that occur over a specified period (e.g. 24 hours).

**URGENCY** is the complaint of a sudden compelling desire to pass urine, which is difficult to defer, and which leads to a fear of incontinence. The impact of this symptom may be derived from a bladder diary by recording episodes of urgency, episodes of urgency leading to incontinence and severity of urgency (e.g. using a daily visual analogue scale).

**PAD USAGE** is the number of pads used over a specified period (e.g. 24 hours).

**Recommendations**

1. **Lower Urinary Tract Symptoms (LUTS) cannot be used to make a definitive diagnosis; they may also indicate pathologies other than Lower Urinary Tract Disease (LUTD).** Specific to this report, LUTS may include Overactive Bladder (OAB) a syndrome which may be associated with urgency incontinence (OAB-wet) or without incontinence (OAB-dry). Likewise, bowel symptoms should prompt consideration and as appropriate, an evaluation for other similar symptom based pathology. (Level 5 - Grade D)

2. **Urinary and faecal incontinence should be described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measures used to contain the leakage and whether or not the individual seeks or desires help.** (Level 5 - Grade D)

3. **Urinary incontinence should be categorized by symptoms into urgency incontinence, stress incontinence or mixed incontinence and conservative (non-invasive) therapies may then be started based on this classification to treat the most troublesome component, or either component of the incontinence.** (Level 5 - Grade D) More sophisticated testing (eg. urodynamic studies) is not required prior to the institution of conservative therapy (see indications for urodynamics in the Committee Report on Urodynamic Studies). (Level 3 - Grade C)
4. A bladder diary is recommended in order to document and communicate the frequency of voids and incontinence episodes experienced by the patient - as well as additional metrics. Additional information as appropriate may include volume of intake, voided volume, and/or symptoms such as urgency or discomfort. Additional metrics may be added for research purposes such as degree of urgency or time from urgency to toileting. A bladder diary is recommended for a minimum of 3 days for accuracy (Level 3 - Grade C) as the ideal duration is not clear (Level 4). The committee acknowledges the difficulty with patient compliance and acknowledges some value of shorter periods for patient compliance. (Level 5 - Grade D).

5. Referral to a specialist is recommended for hematuria (visible or microscopic), urinary tract infection (persistent or recurrent), prolapse (symptomatic or below the introitus), obstruction or retention (symptoms or findings of palpable bladder, hydronephrosis or obstructive renal insufficiency), suspected neurological disease, mass (urethral, bladder or pelvic - benign or malignant), fistula (urinary or bowel), faecal incontinence, a history of prior pelvic surgery or radiation (incontinence, oncologic) (Level 5 - Grade D).

**Future research**

1. Standardisation of the ‘definition of symptoms’ and the ‘measurements of symptom frequency, severity and bother’ are essential for patient care and research. Continued research into the appropriate scales and metrics should be accompanied by a significant attempt to establish best practice guidelines for their use and a consensus on the adoption of universal standards.

2. Recognition and resolution of the differences in common language usage and scientific utilisation of terms should continue (e.g. common use of ‘urge to void’ and the ‘desire to void’ versus the ICS terminology of “urgency”). In addition, continued research into the development of accurate measures to objectify subjective symptoms such as “urgency”. This would include resolution of the differences in the ICS and NIH definitions (in addition to other regulatory agencies) is essential for communicating data with respect to patient care, research, and treatment outcomes.

3. Further development and standardisation of symptom assessment tools (questionnaires) to improve the diagnostic accuracy of lower urinary tract symptoms. (Refer to section 2 of this committee’s report)

4. Further validation of the accuracy of specific components of the history and physical findings to establish an accurate diagnosis and initiate non-invasive conservative or pharmacological therapy. In addition, to further identify components that would indicate the need for more invasive testing, complex therapeutic interventions, and indications for referral.

**II. URINALYSIS IN THE EVALUATION OF THE PATIENT WITH LUTS AND UI**

“The urinalysis is a fundamental test that should be performed in all urological patients. Although in many instances a simple dipstick urinalysis provides the necessary information, a complete urinalysis includes both chemical and microscopic analysis” [8].

In relation to urinary incontinence, dipstick urinalysis is not a diagnostic test, but a screening test, important in order to detect haematuria, glucosuria, pyuria and bacteriuria. Haematuria can indicate important pathology such as urothelial carcinoma in situ, leading to lower urinary tract storage symptoms including incontinence [9]. Glucosuria is relevant, as a potential indicator of diabetes mellitus. This can cause symptoms via several mechanisms including polyuria secondary to osmotic diuresis, peripheral autonomic neuropathy affecting bladder innervation leading to impaired bladder emptying and chronic urinary retention and finally due to increased risk of urinary tract infection (UTI), directly related to the glucosuria and as a sequel to impaired bladder emptying.

Pyuria and bacteriuria, detected from urinary dipstick leukocyte esterase and nitrite tests respectively, are important signs of urinary tract infection. The specificity and sensitivity of these latter tests for UTI is increased when used together compared to either individual test [10,11]. Even in the absence of controlled studies, there is general expert consensus that the benefits of urinalysis clearly outweigh the costs involved, although the use of urinalysis should always be associated with prognostic significance [12]. A positive dipstick urinalysis will prompt formal urine microscopy and culture to detect UTI prior to antibiotic treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. In the evaluation of urinary incontinence and lower urinary tract symptoms, the value of urinalysis can be illustrated by the finding that 60% of women with stable bladder will develop detrusor overactivity at the time of UTI.

The importance of urinalysis in the basic assessment of patients with urinary incontinence and lower urinary tract symptoms is not dependent on gender, age or aetiology. Indeed, it has been recommended in the evaluation of geriatric patients including nursing home residents who are incontinent, [13,14] in peri- and postmenopausal women, [15] and in older women...
reporting urinary incontinence [16]. In the latter context, it has been suggested that significant urine samples can even be obtained from disposable diapers in elderly incontinent women [17].

A Norwegian survey of general practitioners’ management of female urinary incontinence suggested that urinalysis is the most frequently performed test (73%) and is far more frequent than gynaecological examination (54%) [18]. Another survey proposed that urinalysis is one of the three-part assessment of urinary incontinence together with patient history and physical examination [19].

The clinical relevance of asymptomatic bacteriuria (without pyuria) and pyuria (without bacteriuria) in the elderly is controversial, as eradication of bacteriuria appeared to have no effect on resolution of incontinence, and many suggest that it does not deserve any treatment. [20,21].

**Recommendation**

1. It is considered standard to perform a urinalysis either by using a dipstick test or examining the spun sediment. (Level 5 - Grade D)

2. If a dipstick test is used, it is recommended that a “multiproperty” strip that includes fields for haematuria, glucose, leukocyte esterase and nitrite tests be chosen. (Level 5 - Grade D)

3. Additional tests available on urine dipstick strips, such a protein, bilirubin, ketones and pH, may be helpful in the broader medical management of patients. However, they are not essential in the context of evaluation of the patient with urinary incontinence or lower urinary tract symptoms. (Level 5 - Grade D)

**Future research**

1. Determine the role of urinalysis as a screening test in various incontinent populations, specifically the elderly patient with acute or established incontinence in combination with asymptomatic bacteriuria. Specifically, to determine the relevance of asymptomatic bacteriuria without pyuria, and pyuria without bacteriuria, in elderly patients. (see Geriatric Committee Report).

2. Determine the prognostic significance of urinalysis results and the impact of therapy the outcome of treatment of urinary incontinence.

---

**III. THE UTILITY OF POST-VOIDING RESIDUAL [PVR] URINE VOLUME DETERMINATION IN THE INITIAL ASSESSMENT OF INCONSCIENT PATIENTS**

The PVR is the volume of urine remaining in the bladder following a representative void. PVR measurement can be accomplished within a few minutes of voiding either by catheterisation or by calculation of bladder volume using a portable ultrasound scanner. Several studies have compared volumes measured with portable ultrasound scanners versus catheterisation and found portable scanners to be 85-94% accurate [22,23]. A study has imaged the bladder volume after catheterisation and found that the volume of urine remaining in the bladder after catheterisation accounted for most of the difference between the two measurements [22]. Bimanual palpation cannot reliably estimate the post-void residual urine volume [24].

Since PVR may vary, one measurement of PVR may not be sufficient [25]. PVR should probably be measured several times to increase its reliability. Griffiths et al found a significant variability in PVR measurement depending on the time of the day, with the greatest volume occurring in the morning [26]. A non-representative PVR is particularly common if the patient’s bladder is not full enough to yield an urge to void.

An increased PVR alone is not necessarily problem, but if combined with high pressures it can lead to upper tract problems. If related to UTI’s, PVR may need to be treated since UTI’s may not be eradicated in the presence of an infected residual. A significant PVR also decreases the functional bladder capacity and contributes to urgency/frequency, urge incontinence and nocturia. However, a Scandinavian study in nursing home residents found that an elevated PVR was not associated with bacteruria and incontinence [27].

Review of the literature does not show an evidence-based specific maximum PVR that is considered normal, nor is there a minimal PVR that is considered abnormal. The amount of residual urine that precludes treatment by various therapies has also not been determined. The AHCPR guidelines state that, in general, a PVR less than 50 ml is considered adequate bladder emptying and over 200 ml is considered inadequate emptying (expert opinion of the panel members) [28].
“Normal values” of PVR have been determined in several groups of non-incontinent and incontinent women. Gehrich et al studied 96 women (mean age 60 ± 11 yrs) that were seen in a well-women clinic. These women had no history of incontinence, retention, symptomatic prolapse or neurologic disorders. Most (97%) had a minor (asymptomatic) degree of prolapse, 80% was post-menopausal and 30% had had a hysterectomy. The median PVR was 19 ml (range 0-145 ml; mean 24 ± 29 ml); only 5% had PVR > 100 ml. Only, age > 65 yrs was associated with higher PVR [29]. Tseng et al studied 107 women with urodynamic stress incontinence. They found a mean PVR of 62.5 ml by bladder scan and 38.5 ml by catheterization. Only 15.9% had a PVR greater than 100 ml. The PVR determined by bladder scan offered a sensitivity of 64.7% and a specificity of 94.3% in detecting PVR greater than 100 ml [30]. Haylen et al studying women with lower urinary tract dysfunction found that 81% had a PVR of less than 30 ml Postvoid residual volumes higher than this level are significantly associated with increasing age, higher grades of prolapse, and an increased prevalence of recurrent UTIs. [31]. Fitzgerald et al studied women with urgency, frequency and urge incontinence: 10% had an elevated PVR of > 100ml. In these women with OAB, the following independent risk factors of increased PVR were found: vaginal prolapse, symptoms of voiding difficulty and absence of stress-incontinence [32]. Lukacz et al found that only 11% of women with pelvic floor disorders had an elevated PVR [33]. Wu and Baguley studied 319 consecutive patients (196 women, 123 men) in a subacute general, but predominantly geriatric, rehabilitation unit. 22 had been admitted with catheter and were excluded. Of the 297 “asymptomatic” patients, 21.5% had PVR volumes of 150 mL or more. Patients with elevated PVR (> 150 ml) were significantly more likely to have a urinary tract infection at admission and have urinary incontinence on discharge [34]. Milleman et al retrospectively reviewed 201 women (mean age 55; range 20-90) who presented with complaints of urinary frequency, urgency and/or urge incontinence. 19% had an elevated PVR of more than 100 ml (mean 211 ml; range 100-997 ml). On multivariate analysis the following independent predictors of raised PVR were identified: age > 55 yrs [OR 3.71], prior incontinence surgery [OR 4.32], a history of multiple sclerosis [OR 15.32] and pelvic organ prolapse grade 2 or greater [OR 3.61] [35].

In summary, an elevated PVR > 100 ml was found in 5% of women visiting a well-women clinic, in 10-15% of women with OAB, in 11% of women with pelvic floor disorders and in 15.9% of women with urodynamic SUI.

Does a significant PVR have an impact on the outcome of treatment in patients with incontinence? Nager et al studied the predictive value of urodynamic measures on stress urinary incontinence outcomes after surgery for stress urinary incontinence. They found that urodynamic measures do not predict outcomes. However, since women with PVR > 150 ml were excluded in this study, one can only conclude that PVR volumes < 150 ml did not have an adverse impact on stress incontinence outcome [36].

**POST VOIDING RESIDUAL URINE IN THE MALE PATIENT**

PVR measurement is especially recommended in men with suggestive of bladder outlet obstruction (BOO). PVR can be measured within a few minutes of voiding by catheterization to confirm that the bladder is empty [37] or by ultrasonography [38]. The AHCPR guidelines state that, in general, a PVR less than 50ml is considered adequate bladder emptying and over 200ml is considered inadequate emptying. More recently, a dedicated ultrasound system has been developed for automatic measurement of PVR, thereby improving the accuracy over catheterization [39] which has been largely abandoned in clinical practice. International Consultation on BPH defined a range of 50 to 100 ml as the lower threshold to define abnormal PVR [40]. Both the AUA and the EAU guidelines suggest a threshold of 300 ml to identify patients at risk of unfavorable outcome following LUTS / BPO treatment [41,42].

There is no consensus about the relation between PVR and UTI in the male patient. Although the negative role of large residuals has been reported, the evidence is controversial. Large residual urine volume has been considered a bad prognostic factor for disease progression. However, in the standard patients, renal failure, acute retention and UTIs are uncommon in men with large, chronic residuals [43]. No factors are available to identify patients, with significant residual urine, who are at risk for progression [44].

Therefore, on the basis of these trials, untreated LUTS may place the male patient at risk for potential clinical deterioration. Thus, periodical measurements of PVR are recommended in such patients.

**Recommendations**

1. Female patients who present with storage specific symptoms, with normal sensation and no complaints of decreased bladder emptying, and no anatomical, neurological, organ-specific, or co-morbid risk factors for retention may be assessed for bladder emptying by history and physical examination alone, depending on the potential morbidity of the failure to diagnose and the nature of the intended therapy. (Grade B).

2. A palpable bladder on physical exam is an indication for referral to a specialist (Grade D).
3. Residual urine determination by bladder scan is preferable to catheterisation due to the increased morbidity associated with instrumentation. (Grade D).

4. Due to the increased possibility of bladder outlet obstruction due to prostatic obstruction is increased in the male patient, the threshold for investigating residual urine in the male is significantly lower (Grade D).

5. A PVR should be performed in patients where decreased bladder emptying is suspected, especially if treatments that decrease bladder contractility or increase outlet resistance are being considered. (Grade D)

Summary of recommendations

Varying degrees of decreased bladder emptying or urinary retention may be a cause of LUTS that are associated with symptoms of decreased urinary storage.

The decision to perform a PVR in disease specific sub-groups of patients (eg., male patients with bladder outlet obstruction, in neurogenic patients who demonstrate combined disorders of storage and emptying, and preoperatively in female patients being considered for incontinence surgery) should be based on an association of the condition with poor bladder emptying (Grade D), whereas in individual patients this decision may be based on symptoms or physical findings. (Grade C)

Future Research

1. Development of more specific indications for PVR testing for diagnosis and prior to instituting therapy based on history, physical examination, and disease specific findings.

2. Further development of low cost, minimally invasive, and accurate means of measurement of PVR that do not require catheterisation.

3. Continued research in subsets of patients is required to determine the need for PVR assessment and the correlation between elevated PVR and treatment outcome, generally, to determine the effect of varying levels of PVR on the outcomes of observational, conservative, pharmacological and surgical interventions, and more specifically, the female patient prior to surgeries that increase outlet resistance, the male patient with bladder outlet obstruction where medications that can potentially decrease bladder contractility are considered, and the patient with elevated residual urine where intermittent catheterization is not practical and where recurrent urinary tract infections and decreased functional bladder capacity are potential complicating factors.

IV. THE FEMALE PATIENT

1. GENERAL MEDICAL HISTORY

The general history should include questions relevant to precipitating and aggravating factors of urinary loss, time of onset and duration of symptoms, and degree of bother. Acute symptoms may be further defined by documenting patterns of fluid intake and output, acute infection, recent surgery or trauma. Chronic symptoms may be further defined by eliciting a history of congenital abnormalities, neurological disease, relevant surgery or general health. Information must be obtained on medications with known or possible effects on the lower urinary tract. The general history should also include assessment of menstrual, obstetric, sexual and bowel function. The reader is referred to the report of the Committee on Epidemiology for risk specific risk factors to be considered during the medical history and to the second section of this report for recommendations for disease specific questionnaires.

2. URINARY SYMPTOMS

Women with urinary incontinence may have had the condition for many years before presenting; they are often embarrassed in disclosing their condition and are likely to have undertaken significant adaptations to their lifestyle to ameliorate their symptoms [45]. In establishing the history the opportunity should be taken not only to describe symptoms, but also their progression, impact on lifestyle and possible risk factors. Multiple symptoms are commonly reported, [46] and during the history it is important to define the most troublesome symptoms and the patient’s expectations from treatment.

Section 2 of this Committee Report presents a complete review and evaluation of questionnaires that are applicable for clinical and research use in evaluating patient symptoms. Structured condition specific questionnaires may be used, [47]and may be either clinician or self-administered. Questionnaires may facilitate disclosure of embarrassing symptoms, ensure that symptoms are not omitted, and standardise information thereby aiding audit and research.

3. CORRELATION OF SYMPTOMS AND SIGNS WITH SOPHISTICATED TESTING

Harvey & Versi evaluated the symptom and sign of stress incontinence in predicting the presence of urodynamic stress incontinence, using the results of a MEDLINE search for ‘urinary incontinence’, ‘urodynamic’ or ‘urodynamics’ [48]. Of 42 articles evaluated, 12 yielded analysable data. The isolated symptom of stress incontinence had a positive predictive value (PPV) of 56% for the diagnosis of pure urodynamic stress incontinence (USI) and 79% for USI with other abnormalities. The PPV for stress
incontinence with other symptoms was 77% for USI with or without other abnormalities. A positive cough test had a PPV of 55% for the diagnosis of pure USI and 91% for USI with other abnormalities. They concluded that in isolation, either symptom or sign were poor predictors of USI, although in combination prediction may be more promising [48].

Horbach reviewed the literature regarding the reliability of stress symptoms in predicting USI; PPV values ranged from 64% to 90% [49]. Summitt et al reported that 53% to 71% of women with detrusor overactivity (DO) gave similar histories to those with pure USI [50]. The PPV of a history of pure urge incontinence may be as low as 37%, [51] and overactive bladder symptoms (OAB) only 54%, [52] in the diagnosis of DO. It is however of interest to note that in a secondary analysis of data from a drug study in patients with predominant stress incontinence, the main determinant of concurrent urge symptoms was not the pathophysiological condition present (i.e. the presence of concurrent detrusor overactivity) but the severity of incontinence [53].

Martin et al, have reported a systematic review of methods of assessing urinary incontinence (54). From an electronic search of MEDLINE, EMBASE and CINAHL between 1966 and 2002 they identified 6009 individual papers; only 197 were relevant, and of these 121 reached the standards required of their report. Only a limited number could be combined and synthesised, although they were able to conclude that a large proportion of women with urodynamic stress incontinence can be correctly diagnosed in primary care from clinical history alone (sensitivity 0.92; specificity 0.56). The value of validated scales and pad tests could not be determined from the available data. The urinary diary appears to be the most cost effective of tests that might be used alongside clinical history within the primary care setting (sensitivity 0.88; specificity 0.82) [54].

Holroyd-Leduc performed a systematic review concerning the most accurate way to determine the type of urinary incontinence during an office assessment was performed incorporating a review of the literature form 1966-July 2007. The authors found that “In women, simple questions modestly helped diagnose stress urinary incontinence but are more helpful in diagnosing urge urinary incontinence. They concluded that a positive bladder stress test may help diagnose stress urinary incontinence, however, a negative test is not as useful. Also, a systematic assessment combining the history, physical examination, and results of bedside tests to establish a clinical diagnosis appears to be of modest value in diagnosing stress urinary incontinence. In addition, a systematic assessment is less helpful in diagnosing urge urinary incontinence They concluded that “the most helpful component for diagnosing urge urinary incontinence is a history of urine loss associated with urgency. A bladder stress test may be helpful for diagnosing stress urinary incontinence [55].

The reader is referred to the report of the Committee on Sophisticated Testing - Urodyamics for specific indications for complex testing

4. OTHER SYMPTOMS OF PELVIC FLOOR DYSFUNCTION IN THE FEMALE PATIENT

a) Prolapse symptoms

The feeling of a lump (“something coming down”), low backache, heaviness, dragging sensation, or the need to digitally replace the prolapse in order to defaecate or micturate, are amongst the symptoms women may describe who have a prolapse. Prolapse symptoms may be associated with urinary storage or emptying symptoms. Outlet symptoms as diverse as genuine or occult stress incontinence or obstruction, and bladder overactivity or underactivity may have a common aetiology, exist as a cause or effect, or co-exist with lower urinary tract dysfunction.

b) Bowel symptoms

In addition to urinary complaints, women may have symptoms relating to bowel function, sexual function, and pelvic organ prolapse (POP). Jackson et al. evaluated 247 women with either UI or POP. Thirty one percent of women with UI and 7% with POP had concurrent anal incontinence (AI) [56]. In a report from Sweden, 62% of 21 consecutive women undergoing a Burch colposuspension for urodynamic stress urinary incontinence had concurrent faecal incontinence [57]. In a Norwegian study of women presenting with a complaint of urinary incontinence (UI), 38% of the women were found to have significant prolapse and 19% reported faecal incontinence [58]. All these aspects of the pelvic floor and pelvic floor function must be included to plan a comprehensive treatment strategy.

c) Symptoms associated with sexual dysfunction

Dyspareunia, vaginal dryness and coital incontinence are amongst the symptoms women may describe during or after intercourse. These various symptoms are reported by one third to two thirds of women with stress incontinence, and 68% report their sex life to be spoilt by their urinary symptoms [59]. Symptoms of sexual dysfunction should be described as fully as possible; it is helpful to define urine leakage as occurring during arousal, on penetration, during intercourse, or at orgasm (vide supra) [3].

5. PHYSICAL EXAMINATION

a) General examination

There are few data linking bladder, bowel, or sexual function to variations in examination findings of women seeking routine gynaecological care. Similarly data on
women with complaints of urinary incontinence do not include detailed, specific information about their pelvic examinations.

Physical examination is essential in the assessment of all women with lower urinary tract dysfunction. Height and weight should be recorded so that body mass index can be calculated (Kg/M²); this has recently been shown to be a significant risk factor for incontinence [59].

Neurological examination should be performed, with attention to the sacral neuronal pathways. Assessment of gait, abduction and dorsiflexion of the toes (S3) and sensory innervation to the labia minora (L1-L2), sole and lateral aspect of the foot (S1), posterior aspects of the thigh (S2), and perineum (S3) and cutaneous sacral reflexes (bulbo-cavernosus and anal reflexes) may be assessed. A rectal examination will provide a subjective assessment of resting and voluntary anal tone (S2-S4). For patients with possible neurogenic lower urinary tract dysfunction, a more extensive neurological examination is needed (vide infra).

The agitated patient with urgency and frequency might have a behavioural cause and those who are clinically depressed have a less successful response to surgical treatment for stress urinary incontinence. A mental state assessment will assess cognitive function, and is particularly helpful in the elderly (vide infra). Restriction in mobility may lead to functional incontinence and a lack of hand dexterity may preclude self-catheterisation and the use of prosthetic continence devices.

b) Abdominal examination

Scars from previous surgery should be noted. Increased abdominal striae may be found in association with other markers of abnormal collagen metabolism, and are more likely in patients with prolapse and stress incontinence [60].

An attempt should be made to palpate the kidneys, particularly where a voiding dysfunction or neurogenic bladder dysfunction are suspected. A distended bladder may be identified by abdominal palpation or by suprapubic percussion. In one study designed to look at the clinical utility of basic assessment in elderly women, palpable enlargement indicated a post-void residual volume of at least 300ml [61].

c) Perineal/genital inspection

Inspection of the vulva and perineum allows a description of the skin and, for example, the presence of any abnormal anatomical features, of atrophy or excoriation, and erythema due to incontinence and the wearing of pads.

The patient should be asked to cough and strain to demonstrate stress urinary incontinence and to observe urethral length, position, and mobility, and reflex contraction of the external anal sphincter. Howard and associates tested vesical neck descent during cough and Valsalva manoeuvre [62]. They found incontinent women have similar vesical neck mobility with both manoeuvres, whereas continent women have less vesical neck descent with a cough than with Valsalva.

The clinical sign of urinary incontinence is defined as urine leakage seen during examination; this may be urethral or extra-urethral.

Stress urinary incontinence is the observation of involuntary leakage from the urethra, synchronous with exertion/effort, or sneezing or coughing. If stress urinary incontinence is suspected, provocative stress testing (direct visualization) can be performed by having the individual relax and then cough vigorously while the examiner observes for urine loss from the urethra. Optimally these tests should be done when the patient's bladder is full, but they should not be performed when the patient has a precipitant urge to void. The test is usually performed initially in the lithotomy position, although if no leakage is observed, it should be repeated in the standing position, since the yield is increased when the test is repeated in the upright position. Coughing may induce a detrusor contraction, hence the sign of stress incontinence may only be a reliable indication of urodynamic stress incontinence when leakage occurs synchronously with the first cough and stops at the end of that cough. It has however been shown that following an increase in intra-abdominal pressure, and the immediate fall in urethral closure pressure, there follows a 'refractory period' of several seconds during which the urethra maintains a lower pressure than at rest [63].

The extent of pressure loss, and the time to recovery are both less in stress continent then stress incontinent women [64]. If further increases in intra-abdominal pressure occur during this time, stress leakage is more likely to be demonstrated after a series of coughs than following a single cough.

Bonney's original stress test was performed to demonstrate urinary leakage during coughing [65]. Subsequent modifications of the test require support of the urethra-vesical junction during coughing in women who leak during a stress test. These modifications are not reliable in selecting a surgical procedure or in predicting cure.

Extra-urethral incontinence is defined as the observation of urine leakage through channels other than the urethra. This may result from congenital abnormality such as ectopic ureteric opening, or from urogenital fistula.

d) Urethro-vesical junction (bladder neck) mobility

Urethro-vesical junction (bladder neck) mobility should
 postmenopausal women. 

be assessed in all women with urinary incontinence. It is generally felt that women with urodynamic incontinence fall into several categories based on assessment of urethral support and urethral function. The choice of therapy may be affected by the assessment of bladder neck mobility [66]. One method of assessing bladder neck mobility is by visual inspection. When the patient is in lithotomy position, the urethral meatus is horizontal to the floor in a woman with good bladder neck support. When she decreases intra-abdominal pressure you can observe for posterior rotation of the anterior vagina and deflection of the meatus toward the ceiling, both signs of some loss of support. You may ask her to contract the pelvic muscles to determine if urethral support improves with muscle contraction, a sign pelvic floor training may be therapeutic.

The cotton swab or Q-tip test is a simple out-patient procedure to quantify bladder neck mobility [66]. A sterile, lubricated cotton or Dacron swab (Q-tip) is inserted into the urethra until it lies just within the urethra-vesical junction. Using a goniometer, the angle circumscribed by the distal end of the swab is measured relative to the horizontal while the woman is performing a maximum Valsalva effort. Urethra-vesical junction hypermobility is defined by a maximum strain axis exceeding +30 degrees from the horizontal.

There are no published reports about the reproducibility of the cotton swab test for measuring bladder neck hypermobility, despite its widespread clinical application in the evaluation and management of women with urinary incontinence. The validity of this test for diagnosing stress urinary incontinence was not systematically evaluated until 15 years after its introduction. At that time, investigators found that a sizable minority of women with the urodynamic diagnosis of stress incontinence did not have a positive cotton swab test result [66] (considered a straining angle >30°) and that many women with a positive cotton swab test result did not have stress urinary incontinence on urodynamic testing. The test was not able to distinguish women with stress incontinence from continent control subjects [67,68], or women with stress incontinence from those with other urologic disorders [69]. The cotton swab test is now used primarily to assess results of incontinence surgery or to determine whether the degree of urethral hypermobility may influence treatment outcomes. Although the test is simple to perform, the insertion of the small cotton swab may be uncomfortable for some women. Investigators have explored other methods to assess hypermobility, including the POP-Q anatomic evaluation system and ultrasonography. In one study, the correlation coefficient between the cotton swab straining angle and point Aa (the urethro-vesical junction) on the POP-Q system was 0.47 [70]. However, the cotton swab test was positive in 95% of patients with stage II prolapse at point Aa and in 100% of patients with stages III and IV prolapse at point Aa, which suggests that the test may be unnecessary in patients with stage II or greater prolapse at point Aa.

A study evaluating the use of a urinary catheter to assess urethral hypermobility used the Q-tip test for comparison in women with urinary incontinence and pelvic organ prolapse. Results of the study showed reduced angles of excursion from resting to Valsalva manoeuvre using a catheter [71].

Ultrasoundography can be used to measure the angle between the urethra and an axis corresponding to the pubic symphysis, the urethra, the bladder base, and the position of the internal urethral meatus. Other tests to document bladder neck mobility are used, including bead-chain cystourethrography, and videocystourethrography. The report of the Committee on Imaging of the urinary tract addresses the place of these techniques.

A comparison study was conducted to assess the interobserver reliability of the Q-tip test, the Sensor-Q trade mark test and ultrasonographic measurement of urethral mobility in women. 90 women took part in the study; and underwent one method of the assessment by two different clinicians. The correlation coefficient of the Q-tip test, the Sensor-Q trade mark test and the ultrasonographic measurement was 0.83, 0.92 and 0.43, respectively. The Sensor-Q trade mark and Q-tip test showed a higher inter-observer reliability for the evaluation of urethral mobility compared to ultrason sound assessment [71,72].

The Q-tip test has been used in a number of studies evaluating changes in urethra-vesical junction hypermobility and efficacy of surgical treatment of stress incontinence including mid-urethral tapes, vaginal wall sling procedures and Burch colposuspension [73-80]. A study investigating factors associated with severity of stress incontinence in women found that reduced urethral mobility using the Q-tip test was associated with greater severity of urinary incontinence [81].

Correlation of Q-tip test and urethroscopic imaging of the f bladder neck was assessed in stress incontinent women. After the Q-tip test, patients underwent an urethroscopy; at bladder capacity the patient was asked to strain and opening or closing of the bladder neck was noted. An abnormal Q-tip test during Valsalva (> 30°) was observed in 80% of patients. The authors suggest that a Q-tip test could diagnose bladder neck opening with a sensitivity of 91% and a specificity of 35% [82]. The correlation between the straining Q-tip angle and anterior vaginal wall prolapse assessed using the POP-Q system has been investigated in a number of studies. Noblett et al assessed the correlation between urethral mobility and anterior wall prolapse, in order to determine whether the Q-tip test was necessary in patients with stage 0/1 prolapse graded using the POP-Q system.
Results of this study suggested that the POP-Q system was highly predictive of urethral hypermobility; the positive and negative predictive values were 82% and 94% respectively [83].

A retrospective analysis conducted by Larrieux et al also concluded that descent at point Aa is a strong predictor of urethropelvic junction mobility, however urethral length did not affect the correlation between Q-tip angle and point Aa [84]. Zyczynski et al investigated the correlation between POP-Q graded anterior vaginal wall prolapse and Q-tip test findings in urinary incontinent women. The study showed that on clinical examination, one third of the study participants with urethral hypermobility by Q-tip test had a well supported urethropelvic junction. The results of this study suggested that clinicians who determine urethral mobility by watching descent of the distal anterior vagina during Valsalva manoeuvre may underestimate the true incidence of urethral hypermobility [85]. Mattison et al and Rosencrantz et al conducted retrospective reviews of a clinical database in order to determine the correlation between POP-Q evaluation of anterior vaginal wall prolapse and the straining Q-tip angle [86]. Mattison et al found the correlation between Q-tip straining angle and point Aa was 0.54 (P<0.001). Rosencrantz found correlation values between 0.26 and 0.78. Both studies concluded that urethral hypermobility could not be predicted from POP-Q measurement alone [87]. The Q-tip has not been shown to be predictive of Valsalva leak point pressures in women with urethral hypermobility and stress urinary incontinence [88].

e) Vaginal examination

Presently there are few scientific data documenting the parameters of a normal pelvic examination in women of various ages and with various obstetrical histories. The components of the examination have not been universally agreed upon. It seems intuitive the examination should include an assessment of the bony architecture, pelvic floor muscle tone and muscle mass, connective tissue support, the epithelial lining of the vagina, the size, location, and mobility of the uterus, the adnexal structures, and innervation of the pelvic floor structures.

It is important to establish the oestrogen status as oestrogen receptors are present within the lower urinary tract [89], and are shown to influence cell proliferation [90]. Women with oestrogen deficiency may complain of urgency and frequency and recurrent urinary tract infections may develop because of loss of urethral mucosal coaptation. In women of reproductive age symptoms may vary with the menstrual cycle [91].

The well oestrogenised vagina has a thickened epithelium, with transverse rugae in its lower two-thirds. The poorly-oestrogenised vagina has a thinned epithelium with loss of transverse rugae [92]. A number of authors have shown that vaginal pH levels are generally 5 or less in women with no infection and other definitive signs of good oestrogen effect. The use of a pH indicator paper may help you evaluate the oestrogen status in women with no vaginal infection [93]. The appearance of vaginal secretions may suggest a vaginal infection; urine within the vagina suggests genitourinary fistula, hypospadias or ectopic ureter.

Bimanual examination is performed to determine the size of the uterus and of the ovaries. Some women have co-existent pelvic disease which may require attention in addition to the urinary incontinence. When hysterectomy or oophorectomy is indicated, there is no adverse effect on surgical success with a colposuspension procedure. Pelvic masses are rarely the cause of urinary incontinence, and rarely does hysterectomy by itself relieve incontinence.

Urethral diverticula are occasionally congenital but most are acquired. They may have either a simple or complex sacculation. Many patients with urethral diverticula are asymptomatic and need no treatment. Symptomatic patients report recurrent cystitis, frequency, dysuria, dyspareunia, urinary incontinence and voiding difficulties. On clinical examination a sub-urethral mass may be palpable; the urethra is usually tender; and, if the sacculation communicates with the urethra, it may be possible to express a purulent exudate from the urethra. Occasionally, a stone may develop within the diverticulum [94].

6. PELVIC ORGAN PROLAPSE

The anterior, superior, and posterior segments of the vagina should be examined for pelvic organ prolapse. The examiner may use a mirror to demonstrate the findings to the patient; she can then confirm that the examiner has identified the extent of prolapse that she experiences. If the patient indicates that she normally has a greater amount of prolapse that you presently see, provocative manoeuvres which normally are associated with her symptoms may be undertaken, and the examination repeated while the patient is standing.

Several systems for the description and classification of prolapse have been described. This may be quantified descriptively as slight, moderate, marked [95], or first, second and third degree, or objectively using the Baden and Walker halfway method [96], or the International Continence Society Pelvic Organ Prolapse Quantification (ICS POP-Q) [97], or modified POP-Q [98]. In the latter, utilizing the introitus as the threshold, six specific vaginal sites and the vaginal length are assessed using centimetres of measurement from the introitus. In addition, the lengths of the genital hiatus and perineal body are measured in centimetres. Figure 1 demonstrates the summary diagram of this quantitative system.
A simplified technique for use of the POP-Q system was evaluated for inter-examiner agreement and inter-system association with the standard POP-Q exam in 48 subjects. The four areas examined are the anterior and posterior vaginal walls, the apex/cuff, and the cervix. In a patient who is post-hysterectomy, only three measurements are taken: the anterior and posterior vaginal walls and the cuff scar/apex. Kappa statistics (0.86) revealed good agreement between examiners using the simplified POP-Q system. Inter-system agreement was evaluated using Kendall’s tau-b statistic (0.90) also indicating good agreement between the two classification systems [99].

The pelvic organ prolapse quantification index (POP-Q-I) has been proposed for use in the research setting, as it provides a continuous variable rather than categorical variables. The POP-Q was modified such that points Aa, Ab, C, Bp, and Ap are measured. Point D is used only for the identification of patients with cervical hyperplasia. Genital hiatus, perineal body, and total vaginal length are not assessed. The POP-Q-I has not undergone rigorous validation [100,101].

The original POP-Q system has been used extensively in research settings for the assessment of short-and long-term outcomes of pelvic floor surgeries [102-105] including the use of mesh [106-120], laparoscopic surgery [121-123], robotic assisted vault suspension [124], sexual dysfunction associated with pelvic organ prolapse, [125-128], and also in community-based prevalence studies and selected patient populations with pelvic organ prolapse [129-138].

The POP-Q has been used in the validation of the Brazilian version of the vaginal symptoms module of the ICIQ, [139] and for an interviewer-administered pelvic floor symptoms questionnaire [140].

A novel speculum has been designed to facilitate use of the POP-Q system. The top and bottom blades of the speculum are adjustable and are marked in centimeters from the tip to the base of the blade. [141] Figure 2.

**POP-Q definitions ICS report - simplified**

Pelvic organ prolapse is defined as the descent of one or more of anterior vaginal wall, posterior vaginal wall, and apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy.

**Anterior vaginal wall prolapse** is defined as descent of the anterior vaginal wall so that the urethra-vesical junction (a point 3cm proximal to the external urinary meatus) or any anterior point proximal to this is less than 3cm above the plane of the hymen.

The well-supported anterior vaginal wall should not cross the longitudinal axis of the vaginal canal. Hypermobility of the urethra-vesical junction is demonstrated by having the patient perform a maximum Valsalva effort. In women with hypermobility the increase in intra-abdominal pressure causes descent of the urethra-vesical junction (bladder neck). On vaginal examination there may be loss of the transverse crease between the lower and middle thirds of the anterior vaginal wall and descent of the anterior vaginal wall. Anterolateral protrusion into the vaginal canal may represent unilateral or bilateral detachment of the pubocervical fascia along the anterolateral vagina sulcus from its attachment to the arcus tendineus fascia pelvis (white line). Central protrusions of the anterior vaginal wall may represent defects in the pubocervical fascia below the trigone and base of the bladder. Advanced prolapse of the upper anterior vaginal wall may obstruct a well-supported bladder neck.

**Prolapse of the apical segment of the vagina** is defined as any descent of the vaginal cuff scar (after hysterectomy) or cervix, below a point which is 2cm less than the total vaginal length above the plane of the hymen. Descent of the cervix or of the vaginal apex following hysterectomy, below the level of the ischial spines is evidence of a defective vaginal suspension mechanism. In some women, the intravaginal portion of the cervix may become elongated and cause the cervix to extend into the lower vaginal canal, simulating prolapse; however the fundus may have good support. In other women the uterus may prolapse fully outside the hymen as uterine procidentia. Following hysterectomy the vaginal cuff may be well supported or may prolapse fully outside the hymen along with other vaginal segments.

**Posterior vaginal wall prolapse** is defined as any descent of the posterior vaginal wall so that a midline point on the posterior vaginal wall 3cm above the level of the hymen or any posterior point proximal to this, less than 3cm above the plane of the hymen. The well-supported posterior vaginal wall should not cross the longitudinal axis of the vaginal canal. Posterior protrusions into the vaginal canal are most commonly caused by defects in the recto-vaginal fascia allowing protrusions of the small bowel (enterocoele) and/or rectum (rectocele). Normally, the anterior vaginal wall lies upon the posterior vaginal wall. Therefore, protrusions of the posterior vaginal wall can affect the function of the urethra and bladder which lie upon the anterior vaginal wall. For example, distal loss of support in the posterior segment may result in a bulge which compresses the urethra and affects voiding.

As with most new systems, clinicians and researchers have mixed opinions regarding this system. Excellent inter- and intra-observer reliability has been established, although patient position may affect reproducibility in that the degree of pelvic organ prolapse was higher when women were examined in a birthing chair at a 45° angle rather than in dorsal lithotomy. This system has been widely adopted for
Figure 1: ICS POP-Q. Six sites (points Aa, Ba, C, D, Bp, and Ap), genital hiatus (gh), perineal body (pb), and total vaginal length (tvl) used for pelvic organ support quantitation.

Figure 2: Speculum with adjustable blades and scale markings designed to allow easier assessment of pelvic organ prolapse using the POP-Q system. (Diokno AC, Borodulin G. A new vaginal speculum for pelvic organ prolapse quantification (POPQ). Int Urogynecol J Pelvic Floor Dysfunct. 2005 Sep-
pelvic organ prolapse researchers. In addition to collecting specific centimetre measures, an ordinal stage (0-IV) can be assigned.

Absence of prolapse is categorised as stage 0 support; prolapse can be staged from stage I to stage IV. The clinical utility of such a classification might be questioned, since clearly some degree of descent is the norm especially in a parous population. In a study of 477 women attending for annual gynaecological examination, Swift et al found that the average number of positive responses to a 7-question prolapse questionnaire was 0.27 in patients with stage 0 prolapse, 0.55 for stage I, 0.77 for stage II, and 2.1 for stage III. They concluded that women with prolapse with the leading edge beyond the hymenal ring had a significantly increased likelihood of having symptoms.

In a general population of Swedish women ages 20-59, the prevalence of prolapse was found to be 31%, whereas only 2% of all women had a prolapse that reached the introitus. It might seem more reasonable therefore to define prolapse not on the basis of any finding greater than stage 0, but on the basis of findings with a significant likelihood of being associated with symptoms.

Urinary incontinence and pelvic organ prolapse are separate clinical entities which often coexist. Significant protrusions of the vagina can obstruct voiding and defecation. Surgical repair of one pelvic support defect without repair of concurrent asymptomatic pelvic support defects appears to predispose to accentuation of un repaired defects and new symptoms. Women with pelvic organ prolapse may have to reduce their prolapse in order to void. Women with pelvic organ prolapse and a large PVR should be evaluated for voiding phase dysfunction (e.g., outlet obstruction, detrusor hypotonia).

Although anatomy can be measured and assessed accurately, reproducibly and reliably, the relationship of these anatomic findings with functional abnormalities is not well understood. For example, support abnormalities in the anterior vaginal wall are common in vaginally parous women; however, stress urinary incontinence is not always associated with this anatomic alteration. Likewise, distal posterior vaginal wall support abnormalities may exist with or without defecation abnormalities. The important relationships between anatomy and function are one of the most pressing research needs in the field of physical examination for women with pelvic organ prolapse.

Other important research needs include the development of clinically relevant ordinal staging that more accurately separates meaningful prolapse from anatomic changes following vaginal delivery. Such revised staging would allow a meaningful dialog about the appropriate surgical indications for pelvic organ prolapse and development of clinically relevant anatomic outcome measures.

7. RECTAL EXAMINATION

Digital rectal examination allows the description of observed and palpable anatomical abnormalities and is the easiest method of assessing pelvic floor muscle function in children and men. In addition, rectal examination is essential in children with urinary incontinence to rule out faecal impaction. In all women a digital rectal examination is also performed to assess sphincter tone (both resting and active) and to detect faecal impaction or a rectal mass.

8. ADDITIONAL BASIC EVALUATION

a) Pad tests

The objective of pad testing is to quantify the volume of urine lost by weighing a perineal pad before and after some type of leakage provocation. This test has also been used in an attempt to distinguish continent from incontinent women. Pad tests can be divided into short-term tests, usually performed under standardized office conditions, and long-term tests, usually performed at home for 24–48 hours. Pad tests are generally performed with a full bladder or with a fixed known volume of saline instilled bladder before beginning the series of exercises. A pad weight gain >1 g is considered positive for a 1-hour test, and a pad weight gain >4 g is positive for a 24-hour test. There is wide variation in the pad weight gain in incontinent women participating in clinical trials. Although some studies have found high test-retest correlations in pad tests [142,143], other studies have reported low inter-subject and intra-subject reliability [144,148]. Traditional pad testing may be negative in women with mild leakage; an alternative “paper towel test” was shown to be a simple and reliable measure of cough-related urine loss typical of mild stress incontinence. (149) Long-term tests are more reproducible. The correlation coefficient between total leakage during two 24-hour pad tests is good, at 0.66 [150] and 0.82 [151] and increased to 0.90 in one study in which two 48-hour periods were compared. There was no correlation between the leakage volume found in the 48-hour test and a standard 1-hour test.

b) Dye testing

When it has proved impossible to confirm a patient’s complaint of urinary leakage, it may be appropriate to seek to confirm firstly that the reported discharge is in fact urinary, secondly that the leakage is extra-urethral rather than urethral, and thirdly to establish the site of leakage. Although other imaging techniques undoubtedly have a role in this regard, carefully conducted dye studies should be considered. Excessive vaginal discharge or the drainage of serum from a pelvic haematoma postoperatively may simulate a urinary fistula. If the fluid is in sufficient quantity to be collected, biochemical analysis of its urea content in comparison to that of urine and serum will confirm its origin. Phenazopyridine may be used orally (200mg
txs), or indigo carmine intravenously, to stain the urine and hence confirm the presence of a fistula. The identification of the site of a fistula is best carried out by the instillation of coloured dye (methylene blue or indigo carmine) into the bladder via catheter with the patient in the lithotomy position. The traditional ‘three swab test’ has its limitations and is not recommended; the examination is best carried out with direct inspection; multiple fistulae may be located in this way. It is important to be alert for leakage around the catheter, which may spill back into the vagina creating the impression of a fistula. It is also important to ensure that adequate distension of the bladder occurs as some fistulae do not leak at small volumes; conversely, some fistulae with an oblique track through the bladder wall may leak at small volumes, but not at capacity. If leakage of clear fluid continues after dye instillation a ureteric fistula is likely, and this is most easily confirmed by a ‘two dye test’, using Phenazopyridine to stain the renal urine, and methylene blue to stain bladder contents[152].

c) Pelvic floor muscle strength

Pelvic floor muscle function: can be qualitatively defined by the tone at rest and the strength of a voluntary or reflex contraction as strong, weak or absent or by a validated grading system (e.g. Oxford 1-5). A pelvic muscle contraction may be assessed by visual inspection, by palpation, electromyography or perineometry. Factors to be assessed include strength, duration, displacement and repeatability.

The continence mechanisms imply that integrity of the levator ani and external urethral sphincter is necessary to maintain continence [153]. It is therefore important to test the contractility of these muscles. Once the patient understands how to contract the pelvic floor muscles correctly, the evaluation is carried out during a maximum contraction [154].

**Strength** is defined as the maximum force or tension generated by a muscle or muscle group [155]. It reflects the power, endurance and functional status of the muscle.

**Weakness** is defined as failure to generate the expected force.

**Fatigue** is defined as failure to maintain the expected force with continued or repeated contraction [156].

When considering methods/devices used to measure pelvic muscle strength, cost and availability should be recognized as important factors. Four methods of assessment are considered here: observation, digital palpation, perineometry and cotton swab (Q-tip) testing.

**Observation** - This qualitative measure can detect an in-drawing of the anus, lifting of the posterior vaginal wall and narrowing of the vaginal introitus (females); an in-drawing of the anus and slight lifting of the penis (males).

**Digital palpation** - Palpation of the right and left levator ani, per vaginam. Palpation of the perineal body.

**Perineometer** - Manometric measure of change in a vaginal/anal pressure probe. Sensitivity depends on the device.

**Cotton swab (Q-tip) test** - Downward, posterior movement of stem (measured on a goniometer) is dependent on the strength of the contraction of the pubo-coccygeus muscles, and mobility of the urethra [160].

- **Advantages**: Suitable for both sexes and all age groups, where an internal evaluation may be inappropriate. Inexpensive. Able to detect reflex contraction with cough, and bulbocavernous reflex. Observe accessory muscle activity.
- **Disadvantages**: Subjective. Cannot distinguish right and left sides independently. Generally observing activity of the superficial perineal muscles, and assuming levatores are responding in a like manner. Difficult to observe when the patient is standing.

**Advanced palpatory methods**

- **Advantages**: Suitable for both sexes. Inexpensive. Able to differentiate right from left. Qualitative - using modified Oxford scale or other systems [157,158]. Able to measure strength and endurance. Can detect reflex contraction with cough and patient’s ability to hold contraction during a cough. Can be used when the patient is standing.
- **Disadvantages**: Subjective. Not sensitive.

**Invasive methods**

- **Advantages**: Suitable for both sexes. Inexpensive. Able to measure strength and endurance. Quantitative. Can be used when the patient is standing.
- **Disadvantages**: Unable to distinguish right from left. Pressure changes may be caused by increase in intra-abdominal pressure, due to co-contraction of the abdominal muscles. No ‘Gold Standard’ device; different results with different probe sizes and materials [159].

The information learned from assessment of pelvic floor muscle strength has the following practical applications:

1. The patient has good pelvic floor muscles that need skill training to help maintain continence. DeLancey and associates have described ‘knack’ teaching [161,162].
2. The patient has weak muscles that are capable of contracting but need strength and skill training.
An effective exercise program should increase resting tone (Type I fibres) as well as improve the ability of fast twitch (Type II) fibres to respond to increases in intra-abdominal pressure [163].

3. The patient has no perceptible contractions and needs further evaluation (EMG, MRI, neurophysiologic testing) or passive contraction therapy i.e., functional electro stimulation.

Recommendations

1. Although the value of individual urinary symptoms and symptom complexes in predicting the underlying abnormality of lower urinary tract function is not high, a significant proportion of women with stress incontinence can be correctly diagnosed from basic evaluation only. Grade C

2. The frequency/volume chart or urinary diary is the most effective additional test for use alongside basic evaluation in primary or secondary care. Grade C

3. In assessing patients with urinary or faecal incontinence, the clinician should consider all aspects of pelvic floor dysfunction, i.e. urinary, bowel, prolapse, and sexual function. Grade D

4. Prolapse visible at the introitus or below may be associated with symptoms (Level 3) In describing patients with pelvic organ prolapse, one of the several systems available for classification and quantification of urethral hypermobility and pelvic prolapse should be employed. The ICS recommends the POP-Q. (Grade D). In addition, an assessment of pelvic floor identification and strength should be considered. Grade D

Future research

1. Correlation of symptoms and physical findings with urodynamic and colorectal investigations, and both basic and complex evaluations with treatment outcomes.

2. The development of a clinically relevant ordinal staging that meaningfully separates significant from insignificant pelvic organ prolapse.

3. Impact of surgical interventions for incontinence on pelvic organ support, and for pelvic organ prolapse on continence mechanisms.

V. THE MALE PATIENT

1. CHARACTERISTICS OF MALE INCONTINENCE?

In the male patients, lower urinary tract dysfunction, and obstruction from benign prostatic enlargement presents a multi-factorial paradigm for symptom aetiology. Lower urinary tract symptoms (LUTS) in men have a significant effect on quality of life (QOL), as compared with the unaffected general population. [163]. Several epidemiological reports demonstrated that overactive bladder (OAB) syndrome also increase with age in men [164,165]. Older age and higher grade of obstruction has been reported in men with bladder outlet obstruction and idiopathic detrusor overactivity [166].

In the NOBLE study, a different sex-specific pattern emerged for OAB with or without urge incontinence [165]. The prevalence of OAB with urge incontinence displays a steeper age-related increase among women than among men and the gender difference is statistically significant. In women, OAB with urge incontinence increased more than nine-fold from 2.0% in those 18-24 years of age to 19.1% among those 65-74 years of age. In contrast, a substantial increase in prevalence of OAB with urge incontinence among men did not occur until 65 years of age, reaching 8.2% for ages 65-74 years and 10.2% for those 75 years and older. In men, OAB without urge incontinence increased approximately three-fold, from 8.5% below 45 years of age to 21.8% after 55 years of age, whereas OAB without urge incontinence gradually increased in women less than 44 years of age and reached a plateau in women over the age of 44 years.

‘Prevalence ratios for OAB with urge incontinence and for OAB without incontinence were significantly elevated for men who self-reported with a history of prostate problems. Thus, the evaluation of men with symptoms of OAB syndrome depends on the identification and assessment of lower urinary tract obstruction that may be a cause (in part or in entirety) of the presenting symptoms.

The aetiology of obstructive symptoms may vary, from benign prostatic hyperplasia (BPH), urethral stricture, primary bladder neck dysfunction, or abnormal voiding dynamics of detrusor. Chronic prostatic pain syndromes (e.g. non-bacterial chronic prostatitis) and other pelvic floor dysfunctions can also present with
a component of symptoms compatible with OAB. In younger men, primary bladder neck dysfunction is a common cause of LUTS, with or without pelvic pain [167]. Functional abnormalities of striated sphincter relaxation may also occur in young men [168]. The complexity of the presenting symptoms and the various differential diagnoses mandate a thorough basic assessment of the lower urinary tract in men to plan optimal therapeutic intervention.

Another important issue in male patients is incontinence after surgery or intervention for BPO and prostate cancer. A survey in England of 5276 patients who had undergone TURP found that one-third of men (n=1759 men) who were continent before surgery reported some incontinence 3 months post-TURP [169]. Recently many minimally invasive and surgical techniques in management of BPO have been reported. A systematic review of the literature showed Urinary incontinence is more often seen following TURP (1.4%). The rate of urinary incontinence after other techniques are as follows: HIFU: 0.0%, ILCP: 0.1%, TUMT: 0.1%, TUNA: 0.0%, TUVP: 0.9%, VLAP: 0.2%, HoLEP: 1.2% [170].

It has been reported that after permanent prostate brachytherapy, urinary incontinence was observed 0-19% [171]. After radical prostatectomy, Donnellan et al reported that 6 % of men were mildly incontinent, 6 % were moderately incontinent and 4 % were severely incontinent at 1 year after surgery [172]. Carson et al. reported that incontinence occurs in 0.5 to 1.0% of all patients undergoing prostatectomy for benign disease; high rates (5 to 30%) are associated with radical prostatectomy [173].

Although prostatectomy has a clinically significant beneficial effect on LUTS with significant improvements of AUA symptom index and flow rate, [174,175] urinary leakage can have a major impact on QOL. Greater degrees of urine loss are correlated with greater bother and more significant life-style changes [172]. A Medicare survey by Fowler showed that in 1072 patients, more than half of the patients with urinary leakage considered it to be a medium or large problem [176]. In spite of these findings, many investigators have been encouraged by overall patient satisfaction with surgery and patients willingness to undergo surgery again, if faced with the same situation [176].

In the immediate postoperative period, stress and urge incontinence are common. This has been attributed to varying degree of oedema and inflammation present in the healing prostatic urethra. The majority of men achieve continence without invasive intervention following total prostatectomy. Final continence status should be measured using self-administrated disease specific instruments at 24 months after operation [176]. And no factors (age, severity of LUTS, Gleason score, bilateral nerve sparing surgery and estimated blood loss) were identified that predicted early return of continence [172].

Post-prostatectomy incontinence may be caused by sphincter malfunction and/or bladder dysfunction. [177,178]. Urinary control in the adult male depends on integrity of both the internal and external sphincters. During TURP, the internal sphincter mechanism is virtually destroyed, and in some cases, the external sphincter is also damaged. Thus post-prostatectomy stress incontinence may result.

In a recent study of patients undergoing radical prostatectomy that specifically evaluated detrusor dysfunction [179] de novo detrusor underactivity and impaired or poor compliance, presumed to be a consequence of bladder denervation, occurred in a limited proportion of patients (28.6% and 18.4% respectively), and this bladder dysfunction resolved in the majority within 8 months. Detrusor underactivity and decreased bladder compliance are also pre-existing conditions in about 30% and 20% of patients.

The conditions relate to the presence of BOO, and they do not appear to be influenced by prostatectomy. Persistent detrusor overactivity after obstruction relief is probably related to concomitant sphincter deficiency and stress urinary incontinence, which increase afferent nerve activity of the proximal urethra and induce involuntary detrusor contractions [180].

Obstruction after prostatectomy, resulting from an anastomotic stricture or residual prostatic tissue (post TUR-P), may also play an important role in the development of post-prostatectomy incontinence. Obstructing stricture often causes increase in post-void residual urine, resulting in the urinary leakage and/or a weak urinary stream. It has been reported that the anastomotic stricture treatment rates after radical prostatectomy are 16% to 33% [181,182].

2. GENERAL MEDICAL HISTORY

The medical history should focus on the urinary tract, previous surgical and radiation therapy history, medical condition and symptoms that may cause to bladder dysfunction or polyuria, familial history of prostate diseases (BPH and cancer), and a review of sexual and bowel habits. Urinary incontinence is rare in men without a history of previous trauma or prostatic or pelvic surgery; therefore, neurogenic bladder dysfunction must be considered in men with no history of surgery or trauma. A critical assessment of current medications is recommended to exclude the effects of any pharmacological agents on lower urinary tract function.

In the evaluation of the patients with post-prostatectomy incontinence, an important aspect of the history should be a description of the type and severity of incontinence and precipitating events. Severity may be determined by the number of episodes per day, the
need for protection (e.g., pads, penile clamp, external catheter), and the impact of incontinence on activities of daily living. Bladder diaries and pad tests can quantify severity. The presence of other LUTS such as OAB and decreased force of urinary stream should be determined.

3. SYMPTOM ASSESSMENT

Diagnostic assessment of men with LUTS depends on an initial estimation of subjective bother and objective data on bladder emptying. Because the occurrence of LUTS does not necessarily indicate concomitant prostate enlargement and/or obstruction, specific modalities should be used to ascertain the potential for the aetiologic role of these entities. A bladder diary may be useful in almost all male patients, especially in those with OAB. Bladder diary completion by the patient provides useful evidence about the normal urinary habits of the patient, including giving some estimate of bladder capacity and diurnal and nocturnal frequency, urgency and incontinence. The data obtained from frequency-volume chart provide a strong correlation to cystometric capacities and are reasonably immune to the effect of detrusor overactivity in men with LUTS [183].

A variety of symptom scores have been described to assess male patients with LUTS. In men, the American Urological Association symptom score for BPH (AUA-7) is most commonly used in North America for assessment of subjective symptoms. However, equally reproducible data can be obtained from the International Prostate Symptom Score (IPSS), the ICSmale questionnaire (now renamed the ICIQMLUTS, long and short forms, as part of the ICIQ modular questionnaire: www iciq net).

The IPSS has been the most widely used (in many countries and languages), but neglects the symptom of urgency incontinence, a symptom that produces significant bother. The ICIQMLUTS (ICSmale-SF) is slightly longer, but takes into account the symptom of urgency incontinence, and in fact may be divided into voiding and incontinence subscores. To date, it has not been as widely used as the IPSS, but may see more widespread use as part of the ICIQ Modular Questionnaire.

Among LUTS, urgency, nocturia, and hesitancy are most bothersome, whereas weak stream, urgency, and frequency are the most prevalent in pooled populations being evaluated for BPH [184]. Post-micturition dribbling is often provoked by an obstructing disease such as BPH or urethral stricture but can also be a symptom of a urethral diverticulum. Post-void residual urine volume and careful palpation of the genitalia are recommended in these patients.

To determine the cause of post-prostatectomy incontinence, many studies have stressed the lack of reliability of symptoms and emphasised the important role of urodynamic testing [185,186]. Nevertheless, valuable information can be gained from a careful history with regard to incontinence, especially when related to sphincter dysfunction. The symptom of stress incontinence is highly predictive of the presence of sphincter dysfunction. Chao and Mayo found that 67 of 71 men with post-prostatectomy incontinence secondary to sphincteric dysfunction complained of the symptom of stress incontinence [187]. Similarly, Ficazzola and Nitti found 95% positive predictive value and a 100% negative predictive value for symptom of stress incontinence [177]. Urge incontinence as a predictor of bladder dysfunction dose not seem to be as valuable, and the presence of bladder dysfunction cannot be determined accurately without urodynamic testing [177,187].

4. PHYSICAL EXAMINATION

A general physical examination with specific attention to the presence or absence of a distended bladder, excoriation of the genitals secondary to urinary incontinence, evidence of urethral discharge and a focused neurological examination is also highly recommended.

The assessment and treatment algorithm focuses on the abdominal examination, digital rectal examination (DRE) and neurological testing of the perineum and lower extremities. In a patient suspected of neurogenic bladder, evaluation of perineal sensation and lower extremity neuromuscular function, and anal sphincter tone, which is often decreased in neurogenic patients [188] is important. A focused neurogenic examination should also assess the patient’s general mental status and ambulatory status. The examination should also include external genitalia, location of the urethral meatus, retractability of the foreskin and evidence of congenital malformation. Abdominal palpation should be performed to evaluate bladder distension, especially in elderly incontinent men, who may have overflow leakage due to obstruction. In patients suspected of urinary retention, post-void residual volume (PVR) should be measured. The patients with incontinence should be asked to cough and to perform a Valsalva manoeuvre so that the presence of stress incontinence can be ascertained.

DRE should include palpation of the prostate to assess size, symmetry and consistency of the gland and its relation to the pelvic sidewall and the rectum. The locally advanced prostatic cancer can also produce OAB-like symptoms. DRE may exclude prostatic cancer, although its specificity and sensitivity is low [189]. DRE tends to underestimate the true prostate size: if the prostate feels large by DRE, it usually also is found to be enlarged by ultrasound or other measurement technique [190, 191]. Prostate volume has been recently associated with the risk of BPH.
Epidemiological studies in community dwelling men have shown the absence of any association between BPO / BPE / BPO and chronic kidney disease [197] suggesting that screening for renal function is not justified in male patients. Recently, data from the MTOPS study showed that the risk of developing de novo renal failure in men with LUTS is low (less than 1 %) suggesting that is not necessary to monitor renal function in patients with LUTS / BPO [197].

7. MEASUREMENT OF THE SERUM PROSTATE-SPECIFIC ANTIGEN (PSA)

In most patients, a normal DRE may be sufficient to exclude locally advanced cancer as a cause of LUTS or OAB. There is no consensus as to the measurement of prostate specific antigen (PSA) in patients with LUTS. The rationale for measuring PSA is twofold: to screen for prostate cancer [198] and to measure a parameter with prognostic value for the progression of BPH and the response to treatment [192,193]. Because prostatic cancer is one of the potential causes of LUTS or OAB in men, PSA (together with DRE) is a relatively sensitive way to exclude prostatic cancer as a diagnosis [199,200]. However, it is important to understand that about 25% of men with BPH have a serum PSA greater than 4 ng/ml. Because of the overlap between serum PSA values in men with BPH and those with clinically localised prostate cancer, other parameters (PSA velocity, free/total PSA ratio, complexed PSA and PSA density) will assist diagnostic specificity [201, 202]. It has been suggested that a relationship between initial PSA level and subsequent prostate cancer detection with a stepwise increase in cancer detection rate (from <1% to 58%) in patients with <1.0 ng/ml, 1.1-2.5, 2.6-4.0, 4-1-10.0 and >10 ng/ml PSA value in over 26,000 patients enrolled in a screening programme [203]. In addition, Thompson reported data on prostate cancer prevalence from the prostate cancer prevention trial [204] confirming a stepwise increase in the risk of having a prostate cancer in patients with serum PSA from 0.5 to 4.0 ng/ml but showing the limitation of the current threshold of 4.0 ng/ml. Change of PSA threshold from 4.0 to 2.0 ng/ml has been proposed but currently no consensus exists [205]. PSA measurement is recommended in men with LUTS and a life expectancy of over 10 years in whom the diagnosis of prostate cancer would change the management of patient’s symptoms.

It has been reported that the role of IPSS score in the assessment of BOO is questionable, and that the grade of obstruction is more related to prostate volume, PVR, and Qmax [44]. It has been demonstrated that moderate-to-severe LUTS in men can result in urinary retention. The incidence of retention in men with untreated LUTS in community-based trials is 6.8 per 1000 during longitudinal follow-up of 4 years [206]. If only patients with moderate-to-severe symptoms are considered, the rate of retention increases to 25 per 1000 [207]. Moreover, in considering men with weak
urine flow, symptoms, and increased age, without urodynamic evaluation, other parameters become independently predictive of the development of acute urinary retention. In a meta-analysis of predictors of retention in pooled groups of placebo patients from clinical trials of men with LUTS undergoing active interventions (4300 patients), Roehrborn et al. found prostate-specific antigen and prostate volume to be strong independent predictors of urinary retention and the need for surgery in men with LUTS followed up longitudinally in clinical trials [191,208].

Recently, Laniado et al (2004) [209] have also tested the hypothesis that PSA level could be used to predict the presence or absence of BOO, evaluated by pressure flow studies. In patients with LUTS, those with a PSA more than 4 ng/ml are significantly more likely to have some degree of BOO. Conversely patients with PSA less than 2 ng/ml have a 33% risk of BOO.

Therefore, on the basis of these trials, untreated LUTS may place the male patient at risk for potential clinical deterioration. Thus, periodical measurements of PVR are recommended in such patients.

**Recommendations**

1. Male patients differ from female patients in the presentation of LUTS. The incidence of OAB wet is lower until the 7th decade. (Level 2)
2. Urinary stress incontinence is primarily associated with surgery of the prostate in male patients. (Level 2)
3. Disorders of bladder emptying from benign prostatic enlargement should be considered before treating male patients for OAB symptoms. (Level 2) ((Grade B).

**Future research**

1. Improve the understanding of the underlying pathophysiology and contributory clinical factors involved in the development and treatment of detrusor overactivity in the male patient, especially in differentiating the condition from female patients.
2. Development of simple, non-invasive, cost-effective methods to determine the contribution of bladder storage and bladder emptying abnormalities in male patients.

---

**5A- B. INITIAL ASSESSMENT OF FAECAL INCONTINENCE**

**I. FAECAL INCONTINENCE ASSESSMENT**

Basic assessment of faecal incontinence focuses on determining:

1. Type of incontinence
2. Functional limitations resulting from incontinence
3. Cause(s) of incontinence

**1. HISTORY**

History gathering requires particular tact in dealing with this taboo symptom, but also a willingness to ask direct questions about the complaint. In taking a history, the necessary first step is to determine the nature of the incontinence being experienced by the patient. True faecal incontinence must be differentiated from conditions that cause seepage such as external haemorrhoids, fistulas, low rectal or anal tumours, and poor perineal hygiene.

Diagnostic administration of an enema may be useful in this respect; retention of the enema suggests that the patient does not have clinically significant faecal incontinence. This serves to both clarify the patient’s history, but also begins to suggest the anatomical deficit causing the incontinence (see below). The key importance of the history and examination is to identify any conditions that are amenable to condition specific management – these are cited in logical sequence in the text below, and listed in the recommendation box.

**a) Type of incontinence**

- **Flatus incontinence** – incontinence of flatus due to inability to differentiate gas from solid or liquid
- **Passive leakage** – involuntary soiling of liquid or solid stool without patient awareness
- **Urge incontinence** – inability to defer defaecation once the urge is perceived, for long enough to find a toilet

The first two forms are primarily related to internal anal sphincter dysfunction, the latter form due to external anal sphincter dysfunction. (Grade B) [210]. Soiling after defaecation is typically related to either a defect in the internal sphincter or poor “snapping shut” of the external sphincter after voiding. (Grade C) [211]. It is also important to determine if the incontinence is for solid or only liquid stool; if for liquid stool, the possibility of a colonic cause of diarrhoea needs to be considered. (Grade B) [212].

---

353
**b) Functional status**

After confirming the nature of faecal incontinence, it is necessary to determine the impact of the condition on a patient's lifestyle and quality of life. This assessment offers the opportunity to both empathise with the patient and to understand the pertinent emotional and social factors in the manifestation of symptoms. The history should include:

- Need to wear tissues or pads in underwear – indication of severity. (Grade B) [213-215]
- Degree of soiling of tissues, pads or underwear. (Grade C) [213,215]
- Duration, frequency and timing of incontinence episodes – indication of severity. (Grade C) [213,216]

Ability to wear clothing of choice, eat food of choice, participate in work and social activity. (Grade C) [213,216]

Severity of faecal incontinence can be classified as:

- minor - if faecal seepage occurs less than once a month,
- moderate - if there is incontinence to solids more than once a month or liquids more than once a week, and
- severe - if there is loss of control of solids several times a week or liquids on a daily basis.

An alternative classification grades continence as follows:

- Grade 1: Complete
- Grade 2: Incontinence of flatus
- Grade 3: Incontinence of flatus and liquid stools
- Grade 4: Incontinence of flatus, liquid stools, and solid stools.

**c) Aetiology**

A careful, thorough history and full physical examination are essential and will identify the majority of causes of faecal incontinence. The history should include:

- Dietary history – in particular excess ingestion of sorbitol and caffeine. (Grade C) [217]
- Medical history – particularly anti-anginals, anti-hypertensives which may reduce sphincter tone, and ferrous sulphate or antacids which may provoke diarrhoea. (Grade C) [214]
- Presence of benign anal disease – haemorrhoids, fistula, anal warts. (Grade B) [218]
- History of chronic straining – suggestive of rectal mucosal prolapse, an important cause of internal anal sphincter dysfunction. (Grade B) [219]
- Obstetric history – particularly with regard to: (Grade B) [220,221]
  - number of vaginal deliveries
  - need for forceps or Ventouse
  - birth weights
  - duration of second stage(s)
  - episiotomy
- Perianal surgery history – particularly: (Grade B) [222]
- Anal fissure surgery (sphincterotomy or anal stretch)
- Fistula surgery
- Low colonic resection surgery
- History of pelvic radiation – risk of radiation proctitis (causing heightened rectal contractions) and internal anal sphincter radiation damage (Grade B) [223]
- Symptoms of other pelvic floor problems (urinary incontinence and pelvic organ prolapse), which have similar risk factors should be elicited (Grade C) [224])
- Cognitive assessment in appropriate patients (Grade C) [225]

**2. EXAMINATION**

Examination is focussed towards the detection of evidence of incontinence and identifying the cause of incontinence.

**a) Evidence of incontinence**

Physical examination should include inspection of underclothing for soiling and staining by stool, pus, or mucus.

Perianal skin should be examined for irritation and excoriation due to over-zealous hygiene. Perianal inspection should include attempts to identify the following: (Grade B) [215,226,227]

- Perianal excoriation or erythema – suggestive of chronic passive soiling
- A patulous anus or one which gapes on gentle traction of the anal verge
- A “keyhole” deformity of the anal canal – suggesting a persisting sphincter defect

**b) Cause of incontinence**

Inspection may reveal scars from previous episiotomies or obstetric tears. Abnormalities at the anal verge from previous surgery or a gaping anus suggestive of marked loss of function may be present. Perianal inspection should identify: (Grade C) [215, 226,227]
• Scars from previous surgery
• Perianal disease – prolapsing haemorrhoids, fistula, anal warts
• Absence of perineal body – suggestive of obstetric trauma; at its worst this may manifest as a cloacal deformity
• Inspection for sphincter asymmetry whilst patient contracts sphincter – suggestive of regional sphincter defect
• Function of the puborectalis muscle (palpable at the anorectal junction) is assessed by asking the patient to squeeze the sphincter at which time the puborectalis should push the examiner’s finger anteriorly.

Digital examination should identify: (Grade C) [210,226,227].
• Rectal content – if faecal impaction is present this could explain incontinence
• Resting tone – indicative of internal anal sphincter function
• Voluntary and involuntary squeeze pressure – indicative of external anal sphincter function and potential function, respectively. The latter is elicited most commonly by asking the patient to cough while assessing sphincter tone – a cough causes a near-maximal external sphincter contraction (analogous to the guarding reflex in the bladder)
• Regional sphincter defects – detected as asymmetry
• A thickened sphincter – suggestive of chronic straining and occult rectal mucosal prolapse

If suggested by earlier findings (history of straining, thickened sphincter), the patient should be asked to sit on a commode and attempt voiding – the perineum should then be inspected for evidence of a rectal mucosal or full thickness prolapse (Grade C) [219]

Proctoscopy or rectosigmoidoscopy with a rigid instrument is a bedside test of value in excluding potentially treatable causes of faecal incontinence:
• Anal tumours or polyps
• Low rectal cancers or adenoma (Grade B) [228].
• Solitary rectal ulcer syndrome – a functional disorder of evacuation, in which repeated straining at stool and rectal self-digitation results in an ulcerated area of the anterior rectal wall (Grade) [229].

Vaginal examination using a Simms speculum may show a rectocele, cystocele and/or uterine prolapse, all of which may contribute to developing faecal incontinence (Grade C) [230].

Physiological and complimentary radiological tests are used to confirm clinical suspicions and provide objective data on the function of the anorectum. Pelvic floor dysfunction is a complex problem and multiple tests may be needed based on the initial findings and complexity of the planned intervention.

KEY RECOMMENDATIONS FAECAL INCONTINENCE

• It is essential to perform a baseline assessment comprising:
  - focussed medical history
  - a general examination
  - an anorectal examination
  - a cognitive assessment (when appropriate)

• The following conditions should be specifically assessed for as they may be amenable to definitive treatment:
  - rectal prolapse or third-degree haemorrhoids
  - faecal loading
  - potentially treatable causes of diarrhoea (eg inflammatory bowel disease and irritable bowel syndrome, infection, adenomas)
  - acute anal sphincter injury including obstetric and other trauma
  - acute disc prolapse/cauda equina syndrome

Future research

• Development and validation of a digital (finger) instrument to assess anal sphincter function (analogous to the instrument in existence for urological assessment of pelvic floor musculature).
• Development of a psychometrically valid and reproducible instrument to assess quality of life in faecal incontinence.

REFERENCES

5. Gordon D, Groult A. Evaluation of female lower urinary tract


120. Gregory WT, Otto LN, Bergstrom JO, Clark AL. Surgical outcome of abdominal sacrocolpopexy with synthetic mesh versus abdominal sacrocolpopexy with cadaveric fascia lata. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Sep-Oct;16(5):369-74.


In the first three International Consultations on Incontinence reports, the impact of incontinence on quality of life (QoL) and methods of measuring these factors were described with questionnaire recommendations for use in research and clinical practice [1, 2]. This triennial update is a departure from previous reports in that the scope of this chapter encompasses not only quality of life, but all patient-reported outcomes (PRO); and will also include a review of screening tools, not just outcome measures. Additionally, this chapter will extend and update the prior literature reviews of PROs, broaden the review to include lower urinary tract (LUTS) and bowel incontinence outcomes measures, and provide recommendations for questionnaire selection for use in clinical practice and research. In addition, this summary will review the purpose and content of the ICI questionnaire (ICIQ) modules. Given the burgeoning literature in this area, a complete review of all studies with PROs will not be provided, but rather PRO highlights will be included.

The expansion in scope of this review to include all types of patient reported outcomes (PRO) is an important step in recognising the inherent conceptual differences of various PROs each with different assessment goals. A PRO is an objective assessment of the patient's subjective experience and can include aspects of the patient's health. PROs measure different aspects of disease and therapeutic impact such as: symptom frequency or symptom bother, health-related quality of life (HRQL), treatment satisfaction, or work productivity measures (Figure 1). An essential component of selecting a PRO for use is to ensure that the selected PRO is consistent with the objective of the study or clinical purpose. For example, if the goal is to assess treatment satisfaction, then a treatment satisfaction measure should be incorporated into the study design or as a clinical outcome. The matching of appropriate PRO selection with one's desired outcomes is critical to success when assessing PRO's and will be reviewed further in this chapter.

Ultimately, the last decade has been one of tremendous growth in the area of PROs with influences from scientific and regulatory communities. As such, the ICI will endeavour to continually update the recommendations it offers on the basis of emerging data and published evidence based on the sound and rigid recommendations of the previous three reviews.

A number of different electronic databases were searched, limited to adults over the age of 18 years and human studies from January 2004 to June 2008, including Pub-Med, Medline, PsychInfo, the LOCATORplus database for books, serial titles and audiovisuals, the Cochrane Library for randomised controlled trials, and the NLM Gateway database. The following keywords were used separately and/or
In combination: "urinary incontinence", "urinary symptoms", "urgency", "overactive bladder", "stress incontinence", "incontinence", "questionnaire", "epidemiology", "prostate", "prolapse", "fecal", "faecal", "bowel", "anal" and "quality of life", "sexual" and "health utilities". Questionnaires identified in previous ICI reports were also searched in PubMed and Medline.

Incontinence and other lower urinary tract symptoms (LUTS) as well as bowel problems and their impact on patients and their lives can be assessed in a number of ways. Traditionally, the clinical history has been used to gain a summary view of the symptoms experienced by patients and in some cases the impact on their lives. Increasingly however, patient-completed methods of measuring incontinence and LUTS are being used, including voiding diaries and questionnaires.

Patient self-completed questionnaires or patient reported outcomes (PROs) represent the most important clinical review of symptom impact and treatment benefit from a patient perspective. PROs provide a method for the standardised collection of data, or an objective assessment of a subjective phenomenon, from patients relating to incontinence, other LUTS, and bowel problems. Clinicians' assessments of patients' outcomes have often been shown to underestimate the degree of bother perceived by patients, and to focus on issues of lesser importance to patients [3-6].

PRO questionnaires can be used to record the presence and severity of urinary symptoms including incontinence, as well as the impact of symptoms on everyday activities and health-related quality of life (HRQL). To ensure that the results obtained with PROs are clinically useful, data must be gathered using valid and reliable instruments. Questionnaire design and development is not a simple process. Developing such instruments requires a multistep, structured process that incorporates cognitive psychology, psychometric theory, and patient and clinician input. The process begins by determining the intent and purpose of the PRO and culminates in studies that demonstrate the measure's validity, reliability, and responsiveness. The specific steps required for developing a PRO questionnaire are outlined in the following section and are shown diagrammatically in Figure 2.

The development of a PRO is a rigorous, scientific process to provide confidence that the PRO is measuring what it is intended to measure, that it does this reliably, and is appropriate for use in the patient

**Figure 2**: The development of a patient reported outcome is a multistep process. Food & Drug Administration (3). Guidance for industry - patient-reported outcome measures: Use in medical product development to support labeling claims. Silver Spring, MD: FDA; February 2006.
or population group under investigation. The final instrument must have demonstrated validity and reliability in the intended target population. PROs need to be developed with patient and clinician input and have the psychometric, or measurement, properties of the PRO evaluated to determine that it is a valid outcome measure. To be a useful measurement tool, a PRO instrument must also be easy to administer, reliable, and valid. Only PROs that have undergone this process and have published validation data are discussed in this chapter.

1. DETERMINING QUESTIONNAIRE INTENT AND PURPOSE

The first task in developing a PRO measure is to determine why the instrument is needed. Given the current number of disease-specific questionnaires available in the field of incontinence and related pelvic disorders, a new PRO measure must fill a need that has not already been met by an existing instrument. Once the need for the measure is recognised, its purpose and clinical usefulness need to be considered because the purpose dictates the validation design process. For example, a symptom- and a treatment-satisfaction measure would be developed and validated differently because the outcome is different.

The development stage would focus on the outcome of interest (eg, symptoms patients experience and the significance of each symptom, or what issues patients consider when determining how satisfied they are with treatment) with the items derived directly relating to the outcome of interest. Validation efforts would include designing a study focused on the outcome of interest with the appropriate patient inclusion/exclusion criteria to enhance generalisability while maintaining internal consistency and providing opportunities to test—at a minimum—reliability and construct validity.

2. DEVELOPING THE ITEMS

Designing a clinically useful PRO measure involves more than just developing a series of questions. In addition to clinician input and literature review, questionnaire items should be generated from patient input. This is obtained through focus groups or one-on-one interviews to provide qualitative data on issues pertinent to patients and to identify the words patients use to describe their symptoms or disease impact. Focus groups and one-to-one interviews should be carefully planned to address the goals of the questionnaire being developed. For example, if a measure is intended to assess symptom bother, interview questions should pertain to the patient’s symptom experience. Importantly, rather than using clinical terminology which patients may not comprehend, the words used during the focus groups or interviews should be common to patients. After items are generated, the newly drafted questionnaire should be reviewed by other patients and experts to ensure its readability and content validity.

An alternative approach to questionnaire development is to adapt an existing measure to meet the needs of the desired questionnaire. Although no patient input is required at the outset when adapting an existing instrument, patients need to be involved after the questionnaire is adapted to ensure that the revised measure is pertinent to the population of interest. Also, the adapted questionnaire must be validated on its own in the target population; the validity of the original questionnaire does not apply to an adapted measure.

For newly developed and adapted questionnaires, think-out-loud interviews or cognitive debriefing interviews should be used to ascertain the correctness and validity of the revised questionnaire. In a think-out-loud interview, patients are asked to review a question and describe what they are thinking as they cognitively process the question; the patients think out loud about what the question means to them. For a cognitive debriefing approach, patients review and respond to the questionnaire items, then are interviewed about what each item meant to them as they completed the questionnaire. Both approaches provide information about what patients consider when responding to each question.

3. DETERMINING THE MODE OF ADMINISTRATION OF A QUESTIONNAIRE

Once items have been generated, the mode of administration must be considered. Will the measure be completed by the patient (ie, self-administered) or administered by an interviewer (ie, interviewer-administered)? How the questionnaire will be completed needs to be determined before the validation stage because mode of administration can affect patient responses. For highly personal or intimate questions, a self-administered questionnaire is recommended to avoid response bias. Questionnaires that are self-administered are preferable to interviewer-administered questionnaires because the data collection burden is reduced and patients are more likely to provide unbiased information on self-administered questionnaires. Importantly, if a questionnaire has been validated for a particular mode of administration, this does not make the questionnaire valid for all modes of administration. Each mode of administration should be validated separately.

4. QUESTIONNAIRES’ PSYCHOMETRIC PROPERTIES

All PRO measures must demonstrate reliability, validity, and responsiveness, which are described in detail below. This can be accomplished in several ways:

1. Perform a stand-alone cross-sectional study to validate the questionnaire in the patient population for which it was designed;
2. Administer the untested questionnaire in a clinical trial and use the baseline data to perform psychometric validation (the end-of-study data can also be used to evaluate responsiveness); or

3. Perform a stand-alone longitudinal study with an intervention to determine the instrument’s psychometric performance and responsiveness in a non-clinical trial setting.

The following psychometric properties must be tested for and demonstrated in a validated questionnaire.

**Reliability** refers to the ability of a measure to produce similar results when assessments are repeated (ie, is the measure reproducible?) [4, 5]. Reliability is critical to ensure that change detected by the measure is due to the treatment or intervention and not due to measurement error [6]. One measure of reliability is the questionnaire’s internal consistency, which indicates how well individual items within the same domain (or subscale) correlate [7]. Cronbach’s alpha coefficient is used to assess internal consistency reliability, with higher alphas indicating greater correlation [6]. Typically, Cronbach’s alpha should be greater than 0.70 to indicate good internal consistency reliability [6, 7]. If the item-to-total alpha is less than 0.20, the question should be removed or rewritten [4].

**Test-retest reliability**, or reproducibility, indicates how well results can be reproduced with repeated testing. To assess test-retest reliability, the same patient completes the questionnaire more than once, at baseline and again after a period of time during which the impact of symptoms is unlikely to change (e.g., a few days or weeks) [4, 6, 7]. The Pearson correlation coefficient and intraclass correlation coefficient are used to demonstrate reproducibility. For group data, a Pearson correlation coefficient or an intraclass correlation coefficient of at least 0.70 demonstrate good test-retest reliability [6, 7].

**Interrater reliability** indicates how well scores correlate when a measure is administered by different interviewers or when multiple observers rate the same phenomenon [7]. Demonstration of interrater reliability is not necessary for self-administered questionnaires but is necessary for instruments based on observer ratings or using multiple interviewers. A correlation of 0.80 or higher between raters indicates good interrater reliability [7].

**Validity** refers to the ability of an instrument to measure what it was intended to measure [4, 6, 7]. A measure should be validated for each specific condition or outcome for which it will be used. For example a measure designed to assess stress incontinence would not be valid for OAB unless it were specifically validated in patients with OAB symptoms.

**Content validity, convergent validity, discriminant validity** and criterion validity typically are required to validate a questionnaire [7]. Content, or face, validity is a qualitative assessment of whether the questionnaire captures the range of the concept it is intended to measure [6, 7]. For example, does a measure of symptom severity capture all the symptoms that patients with a particular condition have, and if so, is the measure capturing the items in a manner meaningful to patients? To obtain content validity, patients and clinical experts review the measure and judge whether the questions are clear, unambiguous, and comprehensive [4].

**Convergent validity** is a quantitative assessment of whether the questionnaire measures the theoretical construct it was intended to measure [4, 6]. Convergent validity indicates whether a questionnaire has stronger relationships with similar concepts or variables. Stronger relationships should be seen with the most closely related constructs and weaker relationships seen with less-related constructs [6]. **Discriminant validity** indicates whether the questionnaire can differentiate between known patient groups (eg, those with mild, moderate, or severe disease) [6] - generally, measures that are highly discriminative are also highly responsive.

**Criterion validity** reflects the correlation between the new questionnaire and an accepted reference, or gold standard [6, 7]. One difficulty in establishing criterion validity is that a gold-standard measure might not be available [6, 7]. When criterion validity can be established with an existing measure, the correlation should be 0.40 to 0.70; correlations approaching 1.0 indicate that the new questionnaire may be too similar to the gold-standard measure and therefore redundant [7].

**Responsiveness** indicates whether the measure can detect change in a patient’s condition [5]. An important aspect of responsiveness is determining not only whether the measure detects change but whether the change is meaningful to the patient. This can be done by determining the **minimal important difference (MID)** of the measure. The MID is the smallest change in a PRO questionnaire score that would be considered meaningful or important to a patient [6, 8-10]. A treatment that is statistically significantly better than another may not necessarily have made a meaningful difference to the patient; the MID indicates whether the treatment made such a difference from a patient perspective [8-10].

Unfortunately, there is no scientific test for MID as it is an iterative process that involves two methodologies to determine the MID of a questionnaire: an anchor-based approach and a distribution-based approach [11, 12]. With the anchor-based approach, the MID is determined by comparing the measure to other measures (or “anchors”) that have clinical relevance [12], such as a global measure of well-being or
psychometric equivalence, should also be demonstrated after linguistic validation, demonstrating international implementation. It is also important to note that the questionnaires discussed in this chapter have multiple linguistically validated versions making them useful for use in different populations. Linguistic and cultural adaptation of a questionnaire can occur during the development phase before validation, or it can be done after the questionnaire is validated in the language in which it was initially developed, with the latter being the more common approach. Ensuring the linguistic and cultural validity of a questionnaire is especially important for measures used in multinational clinical trials [14].

The principal steps in adapting a measure for different languages and cultures are as follows:

1. Two forward translations of the original instrument into the new language;
2. Quality-control procedures that may include a backward translation (translating the instrument back into the original language) (15);
3. Adjudication of all translated versions;
4. Discussion by an expert panel to ensure clarity of the translated questionnaire; and
5. Testing the translated instrument in monolingual or bilingual patients to ensure that it measures the same concepts as the original instrument [4, 7, 14, 15].

However, if a backward translation of the measure does not produce a semantically equivalent instrument, then the instrument may need to be developed in the target language, rather than just translated [15].

After cultural and linguistic validation, PROs should also be psychometrically validated within the target language. Thus, reliability, validity, and responsiveness need to be assessed with each language translation to confirm the same measurement properties are present in the translated language(s) to ensure psychometric equivalence. If psychometric equivalence is not present (e.g., not achieving similar or better results in new language translation), the cultural and linguistic translations need to be re-evaluated and perhaps a new instrument may need to be developed.

The ICIQ questionnaires and many of the other questionnaires discussed in this chapter have multiple linguistically validated versions making them useful for international implementation. It is also important to note that the step after linguistic validation, demonstrating psychometric equivalence, should also be demonstrated to ensure that the PRO performs equivalently in different languages and cultures.

6. REGULATORY OVERSIGHT

As clinicians and scientists have begun to appreciate and accept PROs as appropriate outcome measures, regulatory authorities have issued guidance documents on current best practices in the development and implementation of PRO in clinical trial settings [3, 16]. For PROs to be acceptable outcome measures for regulatory authorities, documentation of measurement properties must be present as well as evidence of inclusion of the patient perspective and understanding of the PRO and a cohesive conceptual framework that stipulates how the PRO is related to the intervention. While PROs within this document may have a "recommended" status, they may not meet all of the required regulatory guidelines and may require additional validation work either from a qualitative or quantitative perspective. It is strongly suggested that regulatory authorities be contacted early in the process of selecting a PRO for clinical trials to ensure regulatory acceptance of the PRO.

7. QUESTIONNAIRE DEVELOPMENT - A CONCLUSION

Patient self-completed questionnaires are the most suitable method for assessing the patient's perspective of their lower urinary tract, vaginal and bowel symptoms [17]. Questionnaires may be long and detailed for use in research, but need to be short and easy to use to be relevant for clinical practice. In addition to being valid and reliable, they need to be easy to complete, and, if they are being used to measure outcome, sensitive to change. Developing a new questionnaire and testing it thoroughly takes a great deal of time and is only necessary if there is not an existing instrument available.

There are many questionnaires currently available for use and these have been reviewed and described with recommendations from the Committee for their use in the last three ICI reports.

The major purpose of the ICI has been to provide a definitive international review and consultative opinion regarding the recommended measures to assess patient reported outcomes within the area of urinary incontinence and LUTS. To this end since the First Consultation, the ICI has worked to develop a modular format for the various patient reported outcomes including health related quality of life (HRQL) allowing clinicians and researchers to select internationally recommended questionnaires for the assessment of their patients in both clinical practice and clinical trials. In this the fourth ICI review, the ICIQ modular questionnaires (supported by the International Consultation) are presented in detail and their use evaluated. Whilst some of the modular questionnaires are still currently under full evaluation their content and format are presented within this chapter.
A detailed review of recommended questionnaires was provided in the First Consultation chapter [18]. At the Second Consultation, the Committee developed standardised grades of recommendation for questionnaires which attempted to reflect the Oxford Centre for Evidence Based Medicine’s Levels of Evidence. These were applied to evaluate questionnaires concerned with urinary incontinence [19]. At the Third Consultation, these grades were revised and updated to take into account the increasing numbers of published questionnaires concerned with LUTS and incontinence, and also broadening of the field to include pelvic organ prolapse (POP) and faecal incontinence (FI) as well as LUTS and urinary incontinence (UI).

At the Second and Third Consultations, the Committee devised three grades of recommendation [19] (Table 1).

- Questionnaires were ‘highly recommended’ and given a Grade A if the Committee found “Published data indicating that the questionnaire is valid, reliable and responsive to change following standard psychometric testing. Evidence must be published on all three aspects and questionnaires must be relevant for use with persons with incontinence.”

- Questionnaires were “recommended” and given a Grade B if the Committee found “Published data indicating that the questionnaire is valid and reliable following standard psychometric testing. Evidence must be published on two of the three main aspects (usually validity and reliability).”

- Questionnaires were considered to have “potential” and given Grade C if the Committee found “Published data (including abstracts) indicating that the questionnaire is valid or reliable or responsive to change following standard psychometric testing.”

The Committee decided that evidence published in abstracts or posters could be used to indicate a developing questionnaire’s potential, but was not sufficiently peer-reviewed to provide the basis for a stronger recommendation.

This current Fourth Consultation represents a departure from the recommendation scheme of the last review. In this fourth review questionnaires will still be graded A, B, or C as outlined above. However the recommendation will be to preferably utilise questionnaires from the ICIQ modules described in detail below. Many, but not all, of these questionnaires are Grade A questionnaires by previously stipulated criteria. Within the description of the ICIQ modules below the grade assigned to each module is indicated.

Should none of the modular questionnaires be deemed appropriate for specific research or clinical purposes, ICI’s recommendation is to use a Grade A questionnaire as previously recommended and where no suitable instrument exists a Grade B or C questionnaire.

For UI and UI/LUTS, the Committee examined the quality of the psychometric evidence. Only where published data were scientifically sound was the label ‘with rigour’ allowed. Where the Committee had concerns about the quality of evidence, this is noted in the descriptions of the questionnaires below. The Committee considered that the number of high quality questionnaires means that there are now sufficient questionnaires for most purposes and it is not necessary to encourage the development of new questionnaires, except for particular patient groups (see below). As for the last Consultation, it is expected that by the next Consultation, Grade A new questionnaires will either be promoted to Grade A because of further high quality publications or relegated to Grade B if further development does not occur.

The Committee felt that the development of questionnaires in the areas of pelvic organ prolapse (POP) and faecal incontinence (FI) was at a much earlier level. This necessitated a slightly different set of grades of recommendation so that researchers are

---

**Table 1. Criteria for recommendation of questionnaires for UI and UI/LUTS at the Fourth Consultation 2008**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Evidence required (published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended (Grade A)</td>
<td>Validity, reliability and responsiveness established with rigour in several data sets</td>
</tr>
<tr>
<td>Recommended (Grade A&lt;sup&gt;new&lt;/sup&gt;)</td>
<td>Validity, reliability and responsiveness indicated with rigour in one data set</td>
</tr>
<tr>
<td>(Grade B)</td>
<td>Validity, reliability and responsiveness indicated but not with rigour. Validity and reliability established with rigour in several data sets. To be used if suitable questionnaires not available in ICIQ modular format or Grade A or Grade A new</td>
</tr>
</tbody>
</table>
encouraged to continue to work to produce questionnaires with the highest levels of evidence (see Table 2).

### Table 2. Criteria for recommendation of questionnaires for POP and FI at the Fourth Consultation 2008

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Evidence required (published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended (Grade A)</td>
<td>Validity, reliability and responsiveness established with rigour.</td>
</tr>
<tr>
<td>(Grade B)</td>
<td>Validity and reliability established with rigour, or validity, reliability and responsiveness indicated.</td>
</tr>
<tr>
<td>With potential (Grade C)</td>
<td>Early development – further work required and encouraged</td>
</tr>
</tbody>
</table>

The ICIQ modular questionnaire was developed to meet the need for a universally applicable standard guide for the selection of questionnaires for use in clinical practice and clinical research [18, 19]. The decision to develop standard questionnaire modules was taken by the Committee after the first ICI meeting in 1998, and resulted in the development of the ICIQ core questionnaire discussed in this section. It was recognised at that time that there were many good validated questionnaires each developed for a specific purpose and each subtly different. Although developers of the questionnaires were familiar with their content and use, the increasing number of questionnaires made appropriate selection difficult and limited the ability to compare similar clinical and research data due to different data collection methods.

An international advisory board was established to continue the development of the modular ICI questionnaire outside the limits imposed by triennial convening of the ICI Committee. Early discussions with the advisory board resulted in the decision to expand the concept to include wider urinary symptoms, bowel symptoms and vaginal symptoms. The advisory board consisted of clinicians and researchers with experience in the design and use of questionnaires representing the major societies involved in the assessment and research of lower genital tract, lower urinary tract and bowel function. The members of the advisory board of the ICI can be seen on the ICIQ website at www.iciq.net. The ICIQ modular questionnaire was then established.

### I. AIMS AND OBJECTIVES

The ICIQ’s objective is to provide international consensus on the use of patient completed questionnaires for the assessment of lower pelvic symptoms and their impact on patient’s lives. Three aims underpin the ICIQ in order to achieve clarity over questionnaire use:

- To recommend high quality self-completion questionnaires according to evidence of validation as stipulated by the three prior ICI Committees;
- To promote wider use of questionnaires to standardise assessment of lower urinary tract and pelvic dysfunction and its impact on patients’s lives, in order to;
- Facilitate communication in different patient settings and different patient groups both in clinical practice and wider clinical research.

The ICIQ recognised that many high quality published questionnaires already existed and, with permission from the authors, those instruments were adopted into the modular project. It was not possible to adopt all available questionnaires and where more than one option existed the most appropriate questionnaire for the purpose was included. Where high quality questionnaires were not available, the need to develop a new questionnaire/s was acknowledged. Collaborative efforts to develop new questionnaires are welcome and encouraged.

The ICIQ’s international nature requires that linguistically validated translations are available. More than 50 language versions of various modules have been validated to date, conducted according to established protocol.

Thirteen ICIQ modules/questionnaires are currently available for use, with further modules in development (discussed in detail below). Clinicians or researchers are able to select module(s) to meet the particular requirements of their study or clinical practice. In order to simplify this selection process, modules have been categorised as shown in Table 3. It must be stressed that although multiple questionnaires can and probably should be used they must be used in the format in which they were originally designed and the questionnaires cannot be merged together.

In this chapter questionnaires forming part of the ICIQ modular format are referred to as those preferred for usage. Although many of the modules are Grade A questionnaires, others are still under various phases of development and are graded appropriately.
### Table 3. The ICIQ Modular Structure

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>RECOMMENDED MODULES</th>
<th>OPTIONAL MODULES</th>
<th>RECOMMENDED ADD-ON MODULES</th>
<th>HRQL</th>
<th>Generic HRQL</th>
<th>Sexual Matters</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core Modules</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(symptom assessment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary symptoms</strong></td>
<td>Males: ICIQ-MLUTS</td>
<td>Males: ICIQ-MLUTS LF</td>
<td>ICIQ-LUTSqol</td>
<td></td>
<td>SF-12</td>
<td>SF-12</td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td>Females: ICIQ-FLUTS</td>
<td>Females: ICIQ-FLUTS LF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal symptoms and sexual matters</strong></td>
<td>ICIQ-VS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bowel symptoms and quality of life</strong></td>
<td>ICIQ-B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary Incontinence</strong></td>
<td>ICIQ-UI Short Form</td>
<td>ICIQ-UI LF*</td>
<td>ICIQ-LUTSqol</td>
<td></td>
<td>SF-12</td>
<td>SF-12</td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CONDITION</strong></td>
<td>B) Specific patient groups</td>
<td>HRQL</td>
<td>Generic HRQL</td>
<td>Sexual Matters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nocturia</strong></td>
<td>ICIQ-N</td>
<td></td>
<td></td>
<td></td>
<td>SF-12</td>
<td>SF-12</td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overactive Bladder</strong></td>
<td>ICIQ-OAB</td>
<td></td>
<td></td>
<td></td>
<td>SF-12</td>
<td>SF-12</td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurogenic</strong></td>
<td>ICIQ-Spinal Cord Disease*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term catheter users</strong></td>
<td>ICIQ-LTC*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SF-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>ICIQ-CLUTS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gray: In development; black: Grade A or A (New)
Questionnaires that are in early stages of development and have yet to reach Grade C are described as "in development". Where an ICIQ module is not available it is recommended that a Grade A or B or C questionnaire is used.

II. ICIQ SYMPTOM AND BOTHER MODULES

1. CORE MODULES

Questionnaires to assess the core symptoms of lower pelvic dysfunction:
- Lower urinary tract symptoms (male and female specific versions).
- Urinary incontinence (male and female applicable version).
- Vaginal symptoms (female version only).
- Bowel symptoms including incontinence (male and female applicable version).

Each module is intended for the comprehensive yet succinct measurement of symptoms and associated ‘bother’. The bother item attached to each symptom enables the individual to indicate areas that cause the greatest negative impact on HRQL as perceived by them. This can be a more sensitive indicator of treatment goals than frequency of symptoms alone.

2. SPECIFIC PATIENT GROUPS

Questionnaires to assess specific conditions or symptom complexes such as nocturia and overactive bladder are contained in this section. This category also includes specific patient groups, for example, children. These instruments contain only question items characteristic of the symptom complex or have been developed specifically for use in a diverse group making the items/questionnaire only utilisable in that population.
- Nocturia (male and female applicable version).
- Overactive bladder (male and female applicable version).
- Patients with spinal cord disease.
- Patients using long term catheters.

Bother sub-items are again included for all except the children’s questionnaire.

III. ICIQ HEALTH-RELATED QUALITY OF LIFE AND SEXUAL FUNCTION MODULES

1. CORE MODULES

These questionnaires incorporate modules for assessment of health-related quality of life (HRQL) and sexual matters and are recommended to be completed alongside symptom evaluations. The core symptom modules described above contain bother items indicating impact on quality of life directly related to symptoms. The HRQL questionnaires recommended here cover specific issues that are a consequence of symptoms, such as limitations on activities and impact on relationships.
- HRQL associated with lower urinary tract symptoms (male and female applicable version).
- HRQL associated with vaginal symptoms (female version only).
- HRQL associated with bowel symptoms (male and female applicable version).
- Sexual matters associated with lower urinary tract symptoms (male and female specific versions).
- Sexual matters associated with vaginal symptoms are included in the symptom questionnaire as the issues were considered too intrinsically linked to separate for evaluation.

Bother sub-items are again included to provide more detailed information about impact on quality of life than frequency of impact alone. The assessment of symptoms in combination with quality of life enables a more thorough and detailed evaluation of the patient's experience [20,21]. Given the nature of lower pelvic dysfunction, sexual matters can also be affected and questionnaires are available to evaluate this where appropriate.

2. SPECIFIC PATIENT GROUPS

In the same manner as the symptom modules, HRQL modules are available for specific symptom complexes:
- HRQL associated with nocturia (male and female applicable version).
- HRQL associated with overactive bladder (male and female applicable version).

IV. OPTIONAL MODULES

This category includes lengthier questionnaires for more exploratory evaluation of the core symptoms of lower pelvic dysfunction. Whilst these questionnaires are suitable for use in clinical practice, they have not been shortened for clinical efficiency and are therefore more widely used in research studies where exploration of broader associated symptoms may be desired.
- Lower urinary tract symptoms (male and female specific versions).
- Urinary incontinence (male and female applicable version).
V. POST-TREATMENT MODULE

The ICIQ module for post-treatment satisfaction is in the early stages of development. Assessment of a patient’s satisfaction with treatment (behavioural, surgical or medication) provides information on treatment impact on their condition and life and includes their perception of effectiveness, tolerability and convenience. It is not yet clear if satisfaction following treatment can be characterised by a set of common question items that are applicable to all disorders of the lower urinary tract and pelvic floor. As with HRQL, there are generic and disease specific questionnaires that assess satisfaction. Ongoing studies will provide further evidence on which to make suggestions regarding post treatment evaluation but it is likely that this will encompass both generic and condition specific measures. Ultimately, the development of post treatment modules will also rely on advice from regulatory authorities (eg FDA) to ensure that measures capture a recognised multidimensionality of satisfaction.

VI. GUIDANCE FOR USE OF THE ICIQ

The ICIQ recommends the use of a ‘core’, ‘symptom-specific’, or ‘add-on’ modules that match the intended purpose of a study. Whilst this may necessitate the use of a module from each section, there is no requirement to do so. The characteristics of each module is summarised below, although more extensive information can be found on the project website, www.iciq.net.

VII. ICIQ MODULES

Tables 4, 5 a,b,c

VIII. ICIQ QUESTIONNAIRE IMPLEMENTATION

The ICIQ modular questionnaire has attracted considerable attention from both clinicians and researchers worldwide since its structure was finalised in 2004. More than 500 requests for use of the various modules have been documented and over 40 published studies were identified up to April 2008, with the majority originating from Europe, particularly the UK.

The most widely applied module is the ICIQ-UI Short Form, particularly to evaluate female urinary incontinence, though a handful of studies evaluating severity of incontinence in men resulting from prostatectomy for cancer or treatment for bladder outlet obstruction related to benign prostatic enlargement have been reported [31, 32]. Most studies relate to epidemiological research, including prevalence surveys of urinary incontinence or lower urinary tract symptoms [33, 34]; and outcomes research, including prospective and randomised clinical trials of treatments including surgery [35], drug therapies [36] and conservative treatments [37]. For example, a recent placebo-controlled randomised trial found that duloxetine significantly reduced ICIQ scores in women with mixed urinary incontinence[36].

Reports on further validation and translations of the ICIQ and related educational projects have also been published. A recent study conducted by Franco, Lee and Fynes [38], for example, compared various validated subjective measures of urinary incontinence severity to the one hour pad test in women and reported that only the ICIQ correlated significantly with this clinical variable, thereby recommending its use in routine clinical practice as an alternative to pad tests. Encouraging relationships between the ICIQ and other urodynamic parameters have also been reported [39].

The ICIQ has also been applied to hospital and general practice settings, and has been adopted in national guidelines for the management of urinary incontinence in primary care by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/pdf/sign79.pdf) and in a primary care resource pack by the British Society of Urogynaecology.

IX. CONCLUSION

The ICIQ modular questionnaire project (www.iciq.net) provides a series of standardised questionnaires for the patient reported assessment of lower pelvic dysfunction symptoms and their impact on patients lives. The ICIQ provides clarity over the selection of questionnaires by recommending only those with evidence of high quality and robust psychometric validation including validity, reliability and sensitivity to change. This assurance provides the user with confidence in the results obtained, which is important in clinical practice and research where treatment decisions or trial outcomes depend on this evidence. Increasing awareness of the ICIQ aims to promote increased use of standardised questionnaires, thereby facilitating communication between clinicians and researchers and enable more widespread comparisons between different treatments and patient groups worldwide.
<table>
<thead>
<tr>
<th>Name/Grade</th>
<th>Purpose</th>
<th>Availability</th>
<th>Domains</th>
<th>Items</th>
<th>Available Translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICIQ-FLUTS Long Form (BFLUTS [23]) Grade A</td>
<td>Detailed assessment of female <strong>lower urinary tract symptoms</strong> and associated bother.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [22,23].</td>
<td>Varied lower urinary tract symptoms.</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>ICIQ-FLUTSSex (BFLUTS[23]) Grade A</td>
<td>Assessment of <strong>female sexual matters associated with urinary symptoms</strong> and related bother.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [23].</td>
<td>Pain and leakage with sexual intercourse. Overall interference.</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>ICIQ-LUTSqol (King’s Health Questionnaire [24]) Grade A</td>
<td>Detailed assessment of <strong>HRQL issues associated with urinary symptoms</strong> and related bother in both men and women.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [24].</td>
<td>Life restrictions. Emotional aspects. Preventive measures.</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>ICIQ-MLUTS Long Form (ICSmale [26,27]) Grade A</td>
<td>Detailed assessment of <strong>male lower urinary tract symptoms</strong> and associated bother.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [26,27].</td>
<td>Varied lower urinary tract symptoms.</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>ICIQ-MLUTSsex (ICSmale[27]) Grade A</td>
<td>Assessment of <strong>male sexual matters associated with urinary symptoms</strong> and related bother.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [26,27].</td>
<td>Erection and ejaculation issues. Overall interference.</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>ICIQ-Nqol (N-QoL[28]) Grade A</td>
<td>Detailed assessment of <strong>HRQL issues associated with nocturia.</strong></td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [28].</td>
<td>Issues associated with sleep disturbance. Life restrictions. Preventive measures.</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Name/Grade</td>
<td>Purpose</td>
<td>Availability</td>
<td>Domains</td>
<td>Items</td>
<td>Available Translations</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>--------------</td>
<td>---------</td>
<td>-------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>ICIQ-OABqol (OAB-q [29]) Grade A</td>
<td>Detailed assessment of <strong>health-related quality of life</strong> issues associated with <strong>overactive bladder</strong>.</td>
<td>Available for use. Published evidence of validity, reliability and responsiveness [29].</td>
<td>Coping. Concern/Worry Sleep Social Interaction</td>
<td>25</td>
<td>50+</td>
</tr>
<tr>
<td>ICIQ-UI Short Form [18] (ICIQ) Grade A</td>
<td>Comprehensive assessment of male/female <strong>urinary incontinence</strong>.</td>
<td>Available for use. Published evidence of validity, reliability and sensitivity to change¹.</td>
<td>Urinary incontinence including items on frequency and amount of leakage and overall interference. A self-diagnostic item invites respondents to indicate the perceived cause of incontinence.</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Name / Grade</td>
<td>Purpose</td>
<td>Current Status</td>
<td>Development Methodology</td>
<td>Domains</td>
<td>Items</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>----------------</td>
<td>-------------------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>ICIQ-B Grade C</td>
<td>Comprehensive assessment of male/female bowel symptoms, predominantly incontinence, and associated bother.</td>
<td>Newly developed; testing completed; awaiting publication</td>
<td>Items generated by clinical experts and patients with anal incontinence [12]. Extensive content validity testing with potential respondents and clinical experts. Psychometric testing performed; awaiting publication</td>
<td>Bowel pattern. Bowel control. Quality of life.</td>
<td>21</td>
</tr>
<tr>
<td>ICIQ-CLUTS Grade C</td>
<td>Assessment of urinary symptoms in children.</td>
<td>Criterion validity testing is currently ongoing in the UK, Italy and Germany by way of comparisons with clinical flow tests to evaluate the ability of the questionnaire to reflect clinical findings.</td>
<td>The draft instrument has been prepared through qualitative interviews with children and their parents/caregivers in combination with clinical experts in the field to establish the clinical areas of importance and the pertinent issues for those with the symptoms.</td>
<td>Domains to be determined; Questions on urinary symptom, bedwetting and incontinence</td>
<td></td>
</tr>
<tr>
<td>ICIQ-LTC Grade C</td>
<td>Assessment of urinary symptoms and impact on quality of life associated with long term catheterisation and related bother.</td>
<td>Content validity testing and full psychometric validation are underway.</td>
<td>This draft questionnaire has been prepared in collaboration with clinical experts in this area and patients who manage their urinary symptoms through long term catheterisation.</td>
<td>Domains to be determined; Questions to be assessed: leakage, blockage, bladder stones, infections; coping strategies; social functioning; attitudes; and body image.</td>
<td></td>
</tr>
<tr>
<td>Name/Grade</td>
<td>Purpose</td>
<td>Current Status</td>
<td>Development Methodology</td>
<td>Domains</td>
<td>Items</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>ICIQ-Spinal cord disease</td>
<td>Assessment of urinary symptoms and impact on quality of life associated with specific management devices and related bother.</td>
<td>Content validity testing and full psychometric validation are due to commence.</td>
<td>This draft questionnaire has been prepared in collaboration with clinical experts in this area and patients who manage their urinary symptoms with varying devices. Patients with spinal cord disease of varying causes participated in qualitative interviews to explore the effects and impact on quality of life associated with the devices used to manage their bladder symptoms.</td>
<td>IQuestions regarding the following will be asked: Bladder and bowel function, issues associated with specific management devices, sexual matters, and lifestyle interference.</td>
<td></td>
</tr>
<tr>
<td>ICIQ-UI Long Form</td>
<td>Detailed assessment of perceived causes of urinary incontinence.</td>
<td>Content validity testing has been completed preparing the developmental ICIQ-UI Long Form for full psychometric validation. Interviews with potential respondents have confirmed that the questionnaire is applicable and appropriate for a detailed assessment of urinary incontinence symptoms. Validation is underway.</td>
<td>This draft questionnaire has been prepared in collaboration with clinical experts in this area and patients with symptoms of urinary incontinence. Patients with urinary incontinence participated in qualitative interviews to explore the cause of their symptoms and the issues of importance related to this.</td>
<td>For each perceived cause of incontinence, e.g. physical activity, urgency related, nocturnal leakage, the degree of bother and amount of leakage are evaluated.</td>
<td></td>
</tr>
<tr>
<td>ICIQ-VSqol (In development)</td>
<td>Detailed assessment of HRQL issues associated with vaginal symptoms and related bother.</td>
<td>Content validity testing has been completed preparing the developmental ICIQ-VSqol. Interviews with potential respondents have confirmed that the questionnaire is applicable and appropriate for assessment of the effects of vaginal symptoms, capturing all aspects of relevance. Psychometric validation is underway.</td>
<td>This draft questionnaire has been prepared in collaboration with clinical experts in this area and women with vaginal symptoms. Patients with vaginal symptoms of varying cause participated in qualitative interviews to explore the effects and impact on quality of life associated with their symptoms.</td>
<td>Domains to be determined. Questions regarding the following will be asked: life restrictions and emotional aspects.</td>
<td></td>
</tr>
</tbody>
</table>
5B - D. PATIENT REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER URINARY TRACT SYMPTOMS

There are a variety of PRO measures available for use in clinical practice and research that assess a range of concepts (e.g. HRQL, patient satisfaction, symptom bother, etc). This section and table series provides an overview and assessment of those measures. Importantly, clinical practitioners and researchers need to clearly determine their clinical and research objectives before selecting a PRO as it is these objectives and the target patient population that will help determine which validated PRO is appropriate to use. Tables 6 to 10 provide a brief overview of all current PRO measures for urinary incontinence and LUTS, their purpose, psychometric properties, translation availability, and recommended ICI grade.

Certainly an area which has rapidly grown with PRO measures is that of urinary incontinence and HRQL assessments (Table 6). The literature supporting HRQL assessments was reviewed and a Grade A to C recommendation assigned. Please note, as instrument development and validation is an ongoing process, the tables below contain publications prior to July 2008. As additional work may have been performed on an instrument, it is always prudent to conduct a further literature search and/or contact the instrument developer prior to selecting an outcome measure for your clinical practice or study.

One trend that has become more apparent since the previous Consultations is the modification of more established urinary incontinence questionnaires for use in selected patient groups (e.g., pelvic organ prolapse; males; different cultural/language groups). When using a questionnaire in a patient group other than the group in which it was initially developed, cognitive debriefings with the new patient population should be held to review the applicability of the questionnaire to the new patient group. Several of the main questionnaires to be discussed below have now had modified versions published in the literature. The Committee’s view is that although it may be appropriate to modify established questionnaires for use with some populations, it is advisable to keep such modifications to a minimum, and to use the original versions whenever possible. Any modifications of established questionnaires may result in changes (sometimes substantial) in the psychometric performance of the instrument, and thus all modified instruments should be subjected to the same psychometric testing as that employed in developing a completely new instrument. Specifically, modified instruments should report information regarding the instrument’s construct validity, reliability, and test-retest reliability, at a minimum, and sensitivity to change, in intervention studies.

For some of the more widely used instruments listed below, several modified, shortened versions have been published. Information regarding the modified versions is provided under the original source versions of the questionnaires, but the modified versions are evaluated and graded separately, based on the available information regarding their psychometric properties and performance.

I. HEALTH-RELATED QUALITY OF LIFE MEASURES

1. BFLUTS AND BFLUTS-SF

The long form of BFLUTS [23, 26] was developed for use with women, following the pattern established for the questionnaire developed for the ICS-‘BPH’ study. The questionnaire covers the occurrence and bothersomeness of symptoms relating to incontinence and other lower urinary tract symptoms [23, 26]. It has shown good levels of validity and reliability and has been increasingly used in epidemiological and outcome studies [40-45]. Validity, reliability and responsiveness have been demonstrated, and a scored short form has been produced, which is now the recommended version [22].

2. DAN-PSS

This questionnaire was designed in Denmark to measure the degree to which men are bothered by urinary symptoms [46, 47]. A composite score is achieved by the multiplication of the ‘symptom’ by the ‘bother’ score, with a total range of 0 to 108 [46, 47]. A computer version of this questionnaire has been validated and patients seemed to appreciated more this new version than the paper version [48]. It is primarily a questionnaire for the assessment of the occurrence and bothersomeness of a wide range of LUTS in men.

3. ICSMALE AND ICSMALE SF

The ICSmale questionnaire contains 22 questions on 20 urinary symptoms, and, for most questions, the degree of problem that the symptom causes [26]. It has exhibited acceptable levels of validity, reliability and sensitivity to change following a range of treatments including surgery, minimally invasive therapies and drug treatments [26, 27, 49]. This long version has been largely replaced now by a scored short-form – ICSmaleSF [25]. A modified form of ICSmale has been used to assess LUTS and incontinence in prostate cancer [50]. It also continues
<table>
<thead>
<tr>
<th>PRO Name / Grade</th>
<th>Purpose of Tool</th>
<th>Population Sample</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsive -ness (Treatment Duration)</th>
<th>Psychometric Validation in Other Languages</th>
<th>Available Languages</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFLUTS (Bristol Female Lower Urinary Tract Symptoms Questionnaire), Currently the ICIQ-FLUTS (ICIQ-Female Lower Urinary Tract Symptoms) [23]</td>
<td>To assess female LUTS, particularly urinary incontinence, measure impact on quality of life and evaluate treatment outcome</td>
<td>Women, incontinence</td>
<td>Internal Consistency</td>
<td>Test-retest</td>
<td>Content</td>
<td>Criterion</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Contilife® (Quality of Life Assessment Questionnaire Concerning Urinary Incontinence)[102]</td>
<td>To assess the impact of urinary incontinence on quality of life. Originally developed in French and designed for women with UI (urge, stress and mixed UI)</td>
<td>Women, SUI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>DAN-PSS-1 (Danish Prostatic Symptom Score)[46]</td>
<td>To evaluate males with LUTS suggestive of uncomplicated BPH</td>
<td>Men, BPH</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>EPIQ (Epidemiology of Prolapse and Incontinence Questionnaire)[103]</td>
<td>Developed and validated in English and Spanish to assess the presence or absence of AI, OAB, SUI, and pelvic organ prolapse in female population</td>
<td>Women, PFD</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>IBS (Incontinence Bothersome Scale)[104]</td>
<td>One item questionnaire to assess the quality of life in women with urinary incontinence.</td>
<td>Women, UI</td>
<td>None Found</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICIQ-UI Short Form (International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form) [ICIQ-UI Short Form][18,25]</td>
<td>To assess the symptoms and impact of urinary incontinence in clinical practice and research</td>
<td>Men and Women, Urinary Symptoms</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>RO Name / Grade</td>
<td>Purpose of Tool</td>
<td>Population Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td>Responsiveness (Treatment Duration)</td>
<td>Psychometric Validation in Other Languages</td>
<td>Available Languages</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>----------</td>
<td>------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>IIQ</strong> (Incontinence Impact Questionnaire)[64] Grade A</td>
<td>Developed to describe the severity of incontinence in a population. Used to assess the impact of urinary incontinence on HRQL. Primarily been evaluated in patients with stress incontinence.</td>
<td>Women, UI, SUI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Available in English and Turkish</td>
</tr>
<tr>
<td><strong>IIQ-7</strong> (Incontinence Impact Questionnaire - short form)[101] Grade A</td>
<td>Used to assess the impact of urinary incontinence on HRQL</td>
<td>*validation study on men after radical prostatectomy who had UI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Available in English and Turkish</td>
</tr>
<tr>
<td><strong>IOQ</strong> (Incontinence Outcome Questionnaire)[106] Grade C</td>
<td>Developed for assessing HRQL after surgery for stress urinary incontinence</td>
<td>Women SUI</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td>None Found</td>
</tr>
<tr>
<td>Tool Name / Grade</td>
<td>Purpose of Tool</td>
<td>Population Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td>Responsiveness (Treatment Duration)</td>
<td>Psychometric Validation in Other Languages</td>
<td>Available Languages</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-------------------------------------</td>
<td>-------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>LIS (Leicester Impact Scale) [96]</td>
<td>A condition specific quality of life measure for males and females with urinary storage symptoms of urgency, frequency, nocturia and incontinence. Was originally developed for women with incontinence only.</td>
<td>Men and Women, LUTS, OAB</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
</tr>
<tr>
<td>MUDI (Male Urogenital Distress Inventory) [109,110] Grade C</td>
<td>To address the dimension of physical health, focusing on bother from multiple symptoms associated with urinary incontinence in men. Created by eliminating four gender specific items from UDI and IIQ.</td>
<td>Men with LUTS following a radical prostatectomy for prostate cancer</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
</tr>
<tr>
<td>MUSIQ (Male Urinary Symptom Impact Questionnaire) [109, 110] Grade C</td>
<td>To capture mental/psychological health, social health, and global perceptions of function and well-being in men with urinary incontinence. Created by eliminating four gender specific items from UDI and IIQ.</td>
<td>Men, UI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
</tr>
<tr>
<td>N-QoL (ICIQ-Nqol (Nocturia Quality of Life Questionnaire) [28] Grade A</td>
<td>To assess the impact of nocturia on the quality of life of patients</td>
<td>Men and Women</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>N-Qol Translated in 17 Languages. <a href="http://www.prolutsh.com">www.prolutsh.com</a></td>
</tr>
<tr>
<td>OAB-q SF (OAB-q Short Form) [29] Grade A</td>
<td>A shortened version of the OAB-q to evaluate both continent and incontinent symptoms of OAB and their impact on HRQL</td>
<td>Men and Women, OAB</td>
<td>√</td>
<td>√</td>
<td>√ (12 Weeks)</td>
<td>√</td>
<td>OAB-q SF Translated in 40 Languages. <a href="http://www.prolutsh.com">www.prolutsh.com</a></td>
</tr>
<tr>
<td>PRO Name / Grade</td>
<td>Purpose of Tool</td>
<td>Popula- tion Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td>Responsive -ness (Treatment Duration)</td>
<td>Psychometric Validation in Other Languages</td>
<td>Available Languages</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>----------</td>
<td>---------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>OAB-q (ICIQ-OABqol) (Overactive Bladder Questionnaire) [29]</td>
<td>To evaluate both continent and incontinent symptoms of OAB and their impact on HRQL. Developed from focus groups of men and women, clinician opinion, and a thorough literature review</td>
<td>Continen- and incontinent OAB</td>
<td>Internal Consi- stency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>PRAFAB (Protection, Amount, Frequency, Adjustment, Body image) [111-113]</td>
<td>5 item questionnaire widely used in the Netherlands by physiotherapists and researchers used to evaluate treatment effects for UI in women</td>
<td>Women, UI</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>IHI (Urinary Incontinence Handicap Inventory) [114]</td>
<td>To identify difficulties patients may be experiencing because of their incontinence</td>
<td>Elderly women, UI due to detrusor instability</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>UISS (Urinary Incontinence Severity Score) [115]</td>
<td>Designed by the Finnish Gynecological Society’s urologic working group to assess symptom severity and impact of urinary incontinence on everyday life</td>
<td>Women, UI</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>UQ (Urgency Questionnaire) [116,117]</td>
<td>To assess the severity and impact of urinary urgency symptoms on health-related quality of life. VAS scale is used to measure the impact of urinary urgency on overall quality of life, the severity of urgency the intensity of urgency and the discomfort experienced in conjunction with urgency.</td>
<td>Women, OAB</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>Urolife (BPHQoL9) (Benign Prostatic Hypertrophy Health-Related Quality of Life Questionnaire) [118]</td>
<td>To assess the impact of BPH and its treatment on the quality of life of patients</td>
<td>Men, BPH</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
<tr>
<td>YIPS (York Incontinence perceptions scale) [58]</td>
<td>To measure the psychosocial aspects of urinary incontinence</td>
<td>Women, UI</td>
<td>Internal Consistency</td>
<td>Test- retest</td>
<td>Con- tent</td>
<td>Crite- rion</td>
<td>Con- current</td>
</tr>
</tbody>
</table>
to be used to assess LUTS in men [51] and minimally invasive therapies and drug treatments [52-55]. It is primarily a questionnaire for the assessment of the occurrence and bothersomeness of a wide range of LUTS in men.

The scored short-form – ICSmaleSF, [25] was developed from the longer ICSmale questionnaire to assess LUTS in men. The short form has two major scored sections: ICSmaleVS (voiding subscore) containing five questions (hesitancy, straining, reduced stream, intermittency, incomplete emptying), and ICSmaleS (incontinence subscore) containing six questions (urge, stress, unpredictable and nocturnal Incontinence, urgency, postmicturition dribble). The scores are obtained by simple addition. The authors indicate that questions to assess nocturia, frequency and impact on quality of life should be added to provide full data, but these questions should not be included in the score as they are separate constructs [25]. The ICSmaleSF has been used in studies focusing on prostate cancer [56, 57] and on LUTS [51] as well as minimally invasive therapies and drug treatments [52, 53].

4. INCONTINENCE IMPACT QUESTIONNAIRE (IIQ) AND IIQ-7

This questionnaire was developed to assess the psychosocial impact of urinary incontinence in women and consists of 30 items (24 on the degree to which incontinence affects activities and 6 on the feelings engendered) [58-60]. Scores are obtained overall or for four subscales determined by factor and cluster analyses: physical activity, travel, social relationships, and emotional health. The IIQ has been found to have acceptable levels of reliability and validity across a range of studies [61-67]. The IIQ has also been produced in a short form comprising 7 items, also with evidence of validity and reliability [67, 68]. Responsiveness of the IIQ has been assessed in several intervention studies [69-74].

5. I-QOL

This questionnaire was designed to be used in clinical trials to measure the impact of incontinence on men and women [75]. Psychometric information on translated versions of the I-QOL have been reported for French, Spanish, Swedish, German, Korean and Thai language versions [76-78]. Other cultural and linguistic adaptations are available but have not been validated. In all countries, the use of three subscales, and an overall summary score was confirmed to be useful.

6. KING’S HEALTH QUESTIONNAIRE (KHQ)

The King’s Health Questionnaire (KHQ) consists of three parts. The first section contains two questions measuring general health and overall health related to urinary symptoms. The second section includes 19 questions divided into seven domains of quality of life: incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, severity coping measures, general health perception, and symptom severity. The third section of the questionnaire comprises 11 questions measuring the bother or impact of urinary symptoms. The KHQ has demonstrated reliability and validity in men and women [24] in 37 languages [82-84]. Sensitivity to change has been shown successfully in clinical trials where it has been used to assess the HRQL improvement following treatment for patients with OAB, USI and mixed incontinence symptoms [79, 85-88]. A minimally important difference has been derived to establish clinically meaningful interpretations of the KHQ scores and a QALY measure has been derived from KHQ scoring [89].

7. LEICESTER IMPACT SCALE (LIS)

The LIS is a condition-specific HRQL measure for men and women assessing the symptoms of urgency, frequency, nocturia, and incontinence. It is an interviewer-administered tool so it is not a true PRO as interviewer administration can introduce potential bias into the patient responses. The LIS does have utility in the clinical and research settings [90].

8. OVERACTIVE BLADDER SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE (OAB-Q) AND OAB-Q SF

The OAB-q is a 33-item questionnaire developed to assess the Symptom Bother (8 items) and HRQL impact of OAB (25 items; 4 domains: Coping, Concern/Worry, Sleep, and Social Interaction.). It has demonstrated reliability, validity, responsiveness in multiple clinical studies of men and women. The OAB-q is a 33-item questionnaire developed to assess the HRQL improvement following treatment for patients with OAB, USI and mixed incontinence symptoms [79, 85-88]. A minimally important difference has been derived to establish clinically meaningful interpretations of the OAB-q scores and a QALY measure has been derived from OAB-q scoring [93]. The 19-item short-form (OAB-q SF) is a six-item symptom bother scale and 13-item HRQL scale that is a single score which has also demonstrated reliability, validity, and responsiveness to change [94]. This questionnaire was developed in the US with women to assess the degree to which symptoms associated with incontinence are troubling [59]. It contains 19 lower urinary tract symptoms and has been shown to have high levels of validity, reliability and responsiveness in a community-dwelling popu-
This 3-item questionnaire is designed to assess
1. BENEFIT, SATISFACTION, AND WILLINGNESS
   (BSW) QUESTIONNAIRE

This 3-item questionnaire is designed to assess
treatment benefit, patient satisfaction with treatment, and patient willingness to continue treatment. The BSW questionnaire was validated using data from three 12-week placebo-controlled trials of tolterodine in patients with OAB [121]. In this validation study, correlations were seen between patient-reported treatment satisfaction and improvements in the OAB-q, the KHQ, and micturition variables.

2. THE OVERACTIVE BLADDER TREATMENT SATISFACTION QUESTIONNAIRE (OAB-S)

The OAB-S is a 5 domain questionnaire which evaluates control expectations, impact on daily living with OAB, OAB control, fulfillment of OAB medication tolerability and satisfaction with control. Internal reliability coefficients were good (Cronbach’s alpha 0.76-0.96), and test retest reliability has been established (reliability coefficients 0.72-0.87) [122, 123]. Cultural and linguistic differences were considered early in the development process, and the OAB-S is available in over sixteen languages [124].
<table>
<thead>
<tr>
<th>PRO Name</th>
<th>Purpose of Tool</th>
<th>Population Sample</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsive-ness (Treatment Duration)</th>
<th>Psychometric Validation in Other Languages</th>
<th>Available Languages</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSW</td>
<td>To capture patients’ perceived benefit, satisfaction with treatment, and the willingness to continue treatment</td>
<td>Men and Women, OAB</td>
<td>Internal Consistency</td>
<td>Test-retest</td>
<td>Content</td>
<td>Criterion</td>
<td>Concurrent</td>
</tr>
<tr>
<td>EPI</td>
<td>One item questionnaire to gain a patient's improvement in a percent scale</td>
<td>Women, UI, SUI, MUI</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPI</td>
<td>One item questionnaire to assess patient's improvement</td>
<td>Women, UI, SUI, MUI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAB-S</td>
<td>To assess patients’ satisfaction with OAB treatment including/or not medication. The pre-medication module is designed to assess the patient’s expectations with treatment and impact of OAB on patient’s day to day life</td>
<td>Men and Women, OAB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQ</td>
<td>One item questionnaire used to measure how satisfied a subject was with a program</td>
<td>Women, UI, SUI, MUI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBS</td>
<td>A single-item scale used to assess the patient-reported benefits of treatment of OAB</td>
<td>Men and Women, OAB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Name / Grade</td>
<td>Purpose of Tool</td>
<td>Population Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td>Sensitivity/specificity</td>
<td>Validation in Other Languages</td>
<td>Available Languages</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>---------</td>
<td>------------------------</td>
<td>-------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>B-SAQQ (Bladder Self-Assessment Questionnaire) or Bladder Control Self-Assessment Questionnaire (BCSQ)</strong> [129]</td>
<td>A screening tool for the presence of bothersome LUTS in Women</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td>B-SAQQ Translated in 14 Available languages</td>
<td><a href="http://www.mapi-research.fr/i_03_list_urol.htm">http://www.mapi-research.fr/i_03_list_urol.htm</a></td>
</tr>
<tr>
<td>Grade <strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ISQ (Incontinence Screening Questionnaire)</strong> [130]</td>
<td>5 item questionnaire developed to screen for incontinence in women</td>
<td>Women, UI</td>
<td></td>
<td></td>
<td></td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td>Grade <strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LUSQ (The Leicester Urinary Symptom Questionnaire)</strong> [127]</td>
<td>A condition-specific screener of storage LUTS (urgency, frequency, nocturia and incontinence). Was originally developed for women with incontinence only.</td>
<td>Men and Women, LUTS</td>
<td></td>
<td></td>
<td></td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td>Grade <strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade <strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAB-SS (Overactive Bladder Symptom Score)</strong> [132]</td>
<td>A 7 item questionnaire validated to measure overall symptom severity due to the four index symptoms of OAB</td>
<td>Men and Women, LUTS with or without OAB</td>
<td></td>
<td></td>
<td></td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td>Grade <strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAB-V8 (OAB Awareness Tool)</strong> [95]</td>
<td>An 8-item screening tool for use in a primary care setting to identify patients who may have OAB</td>
<td>Men and Women, OAB</td>
<td></td>
<td></td>
<td></td>
<td>OAB-V8 is Translated in 32 Languages</td>
<td><a href="http://www.oabq.com/translations.html">http://www.oabq.com/translations.html</a></td>
</tr>
<tr>
<td>Grade <strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Name / Grade</td>
<td>Purpose of Tool</td>
<td>Population Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td></td>
<td>Available Languages</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QuID (Questionnaire for Urinary Incontinence Diagnosis)</strong> [128]</td>
<td>Grade A</td>
<td>6 item questionnaire used to diagnose stress and/or urge types of urinary incontinence</td>
<td>Internal Consistency</td>
<td>Test-retest</td>
<td>Available in German</td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td><strong>3IQ (Three Incontinence Questions Questionnaire)</strong> [134]</td>
<td>Grade C</td>
<td>A three item questionnaire used to classify urge and stress incontinence</td>
<td>Psychometric evaluation not reported</td>
<td>Available in German</td>
<td>None Found</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UI (Urinary Incontinence Score)</strong> [135]</td>
<td>Grade C</td>
<td>Developed in German used to assess UI</td>
<td>Available in German</td>
<td>None Found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USP (Urinary Symptom Profile)</strong> [139]</td>
<td>Grade B</td>
<td>To assess urinary symptoms in male and female with stress, urge, frequency or urinary obstructive symptoms for use in clinical practice to complement clinical measures and diagnosis</td>
<td></td>
<td></td>
<td>None Found</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I-PSS (International Prostate Symptom Score)</strong> [137]</td>
<td>Grade B</td>
<td>8-item questionnaire used to capture the severity of urinary symptoms related to benign prostatic hyperplasia. Originally developed from the American Urological Association Symptom Index.</td>
<td>Available in German</td>
<td>I-PSS translated into 40 languages</td>
<td><a href="http://proqolid.org/instruments/international_prostate_symptom_score_i_pss">http://proqolid.org/instruments/international_prostate_symptom_score_i_pss</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
from the OAB-q questionnaire; which is a 33 item questionnaire which assess symptom bother and HRQL impact of OAB [29]. The OAB-V8 is an 8-item questionnaire, which evaluates the symptoms of overactive bladder; namely urinary frequency, nocturia, urgency and urge incontinence. Responses are graded on a 6 point Likert scale. Patients with an overall score of eight or more are directed to seek medical advice. This questionnaire is validated for use by men and women [98].

3. OAB-SS

The OAB-SS is a validated A 7-item questionnaire validated to measure overall symptom severity due to the four index symptoms of OAB. It quantifies all symptoms of OAB in men and women. The OAB-SS includes a detailed evaluation of the urgency symptom. Responses are graded on a 5 point Likert scale.

4. QUESTIONNAIRE FOR URINARY INCONTINENCE DIAGNOSIS (QUID)

The QUID is a 6-item patient administered questionnaire developed to identify and differentiate stress vs urge incontinence. There are 3 items each related to stress and urge incontinence. Scoring is 0 (not at all) to 5 (all the time) for each response. The tool was developed for use with females [128].

V. ASSESSING SYMPTOM BOTHER AND OVERALL BOTHER

Measures that can be used to assess how bothered patients are by urinary symptoms are included in Table 9. The Patient Perception of Bladder Condition [138] and the Urogenital Distress Inventory are the only Grade A recommend instrument. There are several Grade B and C measures which assess bother for incontinence and LUTS.

1. PATIENT PERCEPTION OF BLADDER CONDITION (PPBC)

The PPBC is a single item questionnaire designed to rapidly assess patients’ perception of their bladder condition [138].

The questionnaire asks patients to choose one of 6 statements that best describes their present bladder condition. The scale was validated during two large 12-week clinical studies evaluating the efficacy and tolerability of Tolterodine in patients with OAB. Patients taking part in the studies completed the PPBC, OAB-q, KHQ and bladder diaries. Baseline and week 12 data was used for statistical analysis. PPBC scores were well correlated with OAB-q questionnaire scores and bladder diary variables. Correlations of the KHQ and PPBC were significant for all KHQ domains with the exception of the general health perception domain. The scale was found to be responsive to change in OAB symptoms and to have discriminant validity as reflected in the OAB-q, KHQ score and bladder diary changes. The PPBC has also shown to have good test retest reliability [117]. This scale has been widely used in studies evaluating the use of drug therapy in patients with OAB [139-141].

2. UROGENITAL DISTRESS INVENTORY (UDI-6)

The UDI-6 is a six item questionnaire which assesses the presence and bother of 6 lower urinary tract symptoms [101]. The UDI-6 assesses types of incontinence, frequency, difficulty emptying bladder and pain/discomfort in the lower abdomen/genitalia. The response options are 0-3. The instrument has demonstrated validity, reliability and responsiveness [142].

VI. ASSESSING THE IMPACT OF URGENCY

Several instruments have been developed specifically to assess urinary urgency, which is defined by the International Continence Society as “the complaint of a sudden compelling desire to pass urine which is difficult to defer” [147]. Urgency is the principle symptom of OAB [148], and, as such, assessing the effect of treatment on this symptom and its impact on HRQL is important. With any measure designed to evaluate urgency, patients must be able to distinguish between the normal desire to urinate (urge) and the difficult-to-postpone need to urinate (urgency) [149, 150]. Wording thus becomes critical in the development of urgency assessment measures. Chapple and Wein [151] make a case for describing urgency as a “compelling desire to void in which patients fear leakage of urine” as a means of distinguishing this abnormal sensation from the normal need to void. However, some patients may have a sensation of urgency without fear of leakage, further complicating attempts to define urgency. Importantly, with some of these scales, patients have the option of indicating that they experienced UUI (an event) rather than the strongest feeling of urgency (a sensation) itself. In such cases, patients who have severe urgency, but not UUI, do not have an option for endorsing the highest (worst) value, because they are not incontinent. Urgency severity scales that include a UUI response option thus may be less useful than those that do not because such scales are trying to measure 2 things at once, both urgency and UUI.

Several instruments have been developed to assess urinary urgency these are summarized in Table 10. Given no urgency measures have a Grade A rating, a brief summary of each urgency measure is presented below.

Urgency Perception Scale was designed for use in clinical trials to evaluate patient-perceived urgency
<table>
<thead>
<tr>
<th>PRO Name / Grade</th>
<th>Purpose of Tool</th>
<th>Population Sample</th>
<th>Cite</th>
<th>Internal Consistency</th>
<th>Test-retest</th>
<th>Content</th>
<th>Criterion</th>
<th>Concurrent</th>
<th>Discriminant</th>
<th>Responsive -ness (Treatment Duration)</th>
<th>Psychometric Validation in Other Languages</th>
<th>Available Languages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PGI-I and PGI-S</strong>&lt;br&gt;(Patient Global Impression of Severity and of Improvement)&lt;br&gt;[143]&lt;br&gt;Grade C</td>
<td>Two single-question global indexes to measure symptom bother related to urinary incontinence</td>
<td>Women, SUI</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>√ (12 Weeks)</td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td><strong>POSO (Primary OAB Symptom Questionnaire)</strong>&lt;br&gt;[117]&lt;br&gt;Grade C</td>
<td>To assess which symptom of OAB is the most bothersome to patients</td>
<td>Men and Women, OAB</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None Found</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PPBC (Patient Perception of Bladder Condition)</strong>[138]&lt;br&gt;Grade A</td>
<td>To assess patients' subjective impression of their current urinary problems. Developed for patients with urinary problems as a global assessment of bladder condition and is recommended as a global outcome measure for urinary incontinence by the European Medicine Evaluation Association</td>
<td>Men and Women, OAB</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td>PPBC is translated in 22 Languages <a href="http://www.prolutssh.com">www.prolutssh.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPI (Symptom Problem Index)</strong>[144]&lt;br&gt;Grade B</td>
<td>To measure how troublesome the patients find their urinary symptoms</td>
<td>Male, BPH</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td>SPI is translated in 19 languages <a href="http://propolid.org/instruments/symptom_problem_index_spi">http://propolid.org/instruments/symptom_problem_index_spi</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSI and SII (Symptom Severity Index and Symptom Impact Index for stress incontinence in women)</strong>[145]&lt;br&gt;Grade C</td>
<td>To measure stress incontinence severity and impact or bothersome of symptoms. This questionnaire was developed and administered to women undergoing stress incontinence surgery</td>
<td>Women, SUI</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>√</td>
<td>SSI and SII translated in 5 languages <a href="http://propolid.org/instruments/symptom_severity_index_and_symptom_impact_index_for_stress_incontinence_in_women_ssi_and_sii">http://propolid.org/instruments/symptom_severity_index_and_symptom_impact_index_for_stress_incontinence_in_women_ssi_and_sii</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This instrument consists of a single question asking patients to describe their typical experience when they feel the need to urinate. The 3 possible responses are “I am usually not able to hold urine,” “I am usually able to hold urine until I reach the toilet if I go immediately,” and “I am usually able to finish what I am doing before going to the toilet.” [152]. This scale was validated in a clinical trial evaluating the efficacy of tolterodine in treating OAB symptoms; [152] however, its limited responsiveness may preclude its usefulness in clinical practice [153].

**Indevus Urgency Severity Scale** asks patients to rate their level of urgency on a 4-point scale, from 0 (no urgency) to 4 (extreme urgency discomfort that abruptly stops all activity/tasks) [154]. The scale has been validated in a clinical trial of trospium in patients with OAB, [154] but Chapple et al [153] question whether this scale actually measures urgency or just the normal urge to void.

**Urinary Sensation Scale** is a 5-point scale ranging from 1 (no urgency; can continue activities until it is convenient to use the bathroom) to 5 (urge incontinence; extreme urgency discomfort, cannot hold urine and have a wetting accident before arriving at the bathroom) [155]. The content validity of this scale was established through a physician survey and patient interviews [155].

**Urgency Rating Scale**, recommended by the European Medicines Evaluation Agency, consists of a 5-point rating scale to be rated with every void, ranging from 1 (no urgency; I felt no need to empty my bladder but did so for other reasons) to 5 (urge incontinence; I leaked before arriving at the toilet) [16]. This scale was used in a tolterodine clinical trial, in which responses on this scale were used to calculate sum urgency, a measure that accounts for changes in both urgency and frequency [156].

**Table 9. Summary of Urinary Incontinence, OAB and LUTS PRO Measures – Symptom Bother (continued)**

<table>
<thead>
<tr>
<th>Name/Grade</th>
<th>Purpose of Tool</th>
<th>Population Sample</th>
<th>Internal Consistency</th>
<th>Test-retest</th>
<th>Reliability</th>
<th>Validity</th>
<th>Psychometric Validation Other Languages</th>
<th>Other Languages</th>
<th>Reliability Validity</th>
<th>Validity</th>
<th>Psychometric Validation Other Languages</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDI (Urogenital Distress Inventory) [64]</td>
<td>To assess symptom bother related to urinary incontinence. UDI is meant to complement the IIQ, was developed at the same time as the IIQ.</td>
<td>Women, UI, SUI</td>
<td>√ √ √ √ √</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Available in 3 languages (English, Italian and Arabic)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Available in 3 languages (English, Turkish and Arabic)</td>
</tr>
<tr>
<td>UDI-6 (Urogenital Distress Inventory-6) [142]</td>
<td>To assess LUTS bother, including incontinence, in women.</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDQ11 (Urinary Distress Questionnaire) [65]</td>
<td>To assess urinary incontinence bother and quality of life impacts in women with OAB.</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Many women present with vaginal symptoms and pelvic organ prolapse (POP) is frequently implicated. A traditional clinical history is usually used in an effort to assess the symptoms experienced by the patient and a thorough clinician will try to gain insight into how these symptoms are impacting on the patient’s life. A detailed description of the clinical techniques of pelvic floor assessment are described in another chapter in this book. However, symptoms do not always correlate with objective examination findings. Indeed the clinical assessment itself can be inconsistent, depending upon the position of the patient, whether they have been standing for a
<table>
<thead>
<tr>
<th>PRO Name/Grade</th>
<th>Purpose of Tool</th>
<th>Population Sample</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsive -ness (Treatment Duration)</th>
<th>Psychometric Validation in Other Languages</th>
<th>Available Languages</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUSS (Indevus Urgency Severity) [157] Grade A</td>
<td>Used to quantify the level of urgency associated with each toilet void as measured during standard voiding diaries.</td>
<td>OAB with urgency incontinence, men and women</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√ (12 Weeks)</td>
<td>None Found</td>
</tr>
<tr>
<td>SUIQ (Stress/Urge Incontinence Questionnaire) [158] Grade C</td>
<td>Two item questionnaire used to differentiate between symptoms of stress and urge urinary incontinence</td>
<td>Women, UI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
<td>None Found</td>
</tr>
<tr>
<td>UDI (Urogenital Distress Inventory) [64] Grade B</td>
<td>To assess symptom bother related to urinary incontinence. UDI is meant to complement the IIQ, was developed at the same time as the IIQ.</td>
<td>Women, UI, SUI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>UPS (Urgency Perception Score) [159] Grade C</td>
<td>Self-report 5 item OAB questionnaire used for grading the urge to void and assessing the reason why individuals usually void</td>
<td>Men and Women</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
</tr>
<tr>
<td>UPS (Urgency Perception Scale) [152] Grade B</td>
<td>To assess the severity of urgency – whether or not urgency, the sudden and compelling desire to urinate should have a severity measure is debated. The UPS was designed for use in clinical trials to evaluate patient perceived urgency</td>
<td>OAB (double-blind), men and women</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td>URIS-24 (Urgency Impact Scale) [160] Grade C</td>
<td>To assess of the impact of the most common form of UI in older persons</td>
<td>Older persons, UI</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>None Found</td>
<td></td>
</tr>
<tr>
<td>URS (Urgency Rating Scale) [161] Grade C</td>
<td>5-point scale to be used concurrently with voiding diaries to measure the level of urgency associated with each micturition. Advocated by the EMEA CPMP</td>
<td></td>
<td></td>
<td></td>
<td>Psychometric evaluation not reported</td>
<td>None Found</td>
<td></td>
</tr>
</tbody>
</table>
prolonged time or have just used a pessary or tampon. While there is a little research defining the association between specific symptoms and support defects [164-166], measuring subjective outcome after treatment is problematic. Unlike lower urinary tract dysfunction, where increasingly patient-completed methods such as diaries and questionnaires are being used to measure outcome, there are fewer such instruments available for POP. Clinician based history is inconsistent, disease impact may not be assessed, leading questions can be asked and patients may be unwilling to volunteer symptoms, particularly after surgical intervention, for fear of appearing ungrateful or a nuisance. Consequently, despite the highly prevalent nature of this condition we have little idea how intervention, which is frequently surgical, alters symptoms and HRQL. As for incontinence, questionnaires to assess symptoms and HRQL impact of pelvic organ prolapse would be highly desirable.

For POP, the Committee examined the quality of the psychometric evidence and only where published data were scientifically sound was the label ‘with rigour’ allowed. The Committee noted that this is a developing area with few questionnaires currently reaching the highest levels of evidence. Thus three grades of recommendation were established (Table 11).

### Table 11. Criteria for recommendation of questionnaires for POP at the Fourth Consultation

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Evidence required (published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended (Grade A)</td>
<td>Validity, reliability and responsiveness established with rigour.</td>
</tr>
<tr>
<td>(Grade B)</td>
<td>Validity and reliability established with rigour, or validity, reliability and responsiveness indicated.</td>
</tr>
<tr>
<td>With potential (Grade C)</td>
<td>Early development – further work required and encouraged</td>
</tr>
</tbody>
</table>

1. **GRADE A**

   a) **Pelvic Floor Distress Inventory (PFDI) and PFIQ (Pelvic Floor Impact Questionnaire)**

   This questionnaire is an adaptation of the well-established UDI with the aim of developing a comprehensive condition specific instrument to assess impact from pelvic organ prolapse and other aspects of colorectal-anal dysfunction, as well as LUTS [167].

---

391
The PFDI retains the 19 original items of the UDI, and adds 9 items related to lower urinary tract symptoms that are common in women with pelvic floor disorders. The three original subscales of the UDI are retained (i.e., obstructive, irritative/discomfort, and stress). Psychometric testing included internal reliability (PFDI Cronbach’s alpha 0.88, PFIQ 0.98), 1 week test-retest (interclass correlation coefficient PFDI 0.87, PFIQ 0.86).

Both correlated with stage of prolapse (Spearman correlation coefficient for pelvic organ prolapse distress inventory and impact questionnaire 0.32 p<0.01, 0.33 p<0.01). Responsiveness has not yet been tested.

PFIQ is an adaptation of the IIQ to assess quality of life impact in women with pelvic floor disorders. It contains items included in the original IIQ and new items related to other pelvic floor disorders. PFIQ has 3 scales including 92 items: IIQ (30 items), Colorectal-anal impact Questionnaire (CRAIQ) (31 items) and Pelvic Organ Prolapse impact Questionnaire (POPIQ) (31 items).

Each scale includes 4 domains of travel, social, emotional and physical activity. The psychometric properties of the PFIQ were evaluated in 100 female patients with pelvic floor dys-fuction [167].

The PFIQ showed good validity; each of IIQ, CRAIQ and POPIQ revealed significant correlation with incontinence episode and number of pad use per week, faecal incontinence per week and stage of prolapse, respectively. Internal consistency was excellent (Cronbach alpha 0.98) and test-retest reproducibility was high (overall ICC 0.86 ranging from 0.69 to 0.92). A French language version has been produced [168]. Responsiveness has not yet been evaluated.

Responsiveness of the PFDI and PFIQ was tested in women with pelvic organ prolapse undergoing surgical and conservative management with vaginal pessaries. Women undergoing surgical treatment for prolapse reported significantly greater improvement in all subscales of the PDFI and PFIQ than those patients treated with pessaries.

The PFDI was found to be more responsive to change than the PFIQ [169]. French and Spanish versions of both the PFIQ and PFDI have been produced [170, 171]. Long forms of the PFDI and PFIQ have also been validated for telephone administration [172].

Short forms of the PFDI and PFIQ questionnaires have been developed. Reliability, validity and resposiveness were tested in a population of patients before and 3-6 months after pelvic floor surgery. The short form of the PFIQ and PFDI correlated well with the long form versions of the questionnaires (r=0.88-0.94) [173] (Table 12).

**Table 12. Recommended questionnaires for the evaluation of symptoms and quality of life impact of pelvic organ prolapse**

<table>
<thead>
<tr>
<th>Grade A New (recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Floor Distress Inventory (PFDI) [167]</td>
</tr>
<tr>
<td>Pelvic Floor Impact Questionnaire (PFIQ) [167]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade B</th>
</tr>
</thead>
<tbody>
<tr>
<td>The electronic Personal Assessment Questionnaire – Pelvic Floor (ePAQ-PF) [174]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade C (with potential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-QOL/St. Mary’s Questionnaire [175]</td>
</tr>
<tr>
<td>Pelvic Floor Dysfunction Questionnaire [176]</td>
</tr>
<tr>
<td>Danish Prolapse Questionnaire [164]</td>
</tr>
</tbody>
</table>

2. GRADE B

- **e-PAQ Electronic Pelvic Floor Symptoms Questionnaire**

The electronic Personal Assessment Questionnaire – Pelvic Floor (ePAQ-PF) is an interactive computerised system that comprehensively measures pelvic floor symptoms and their impact on HRQL in women. It comprises a maximum of 124 items in 4 dimensions (Urinary, Bowel, Vaginal & Sexual) and includes 19 scored domains:

The original 14 domain version underwent psychometric testing in primary and secondary care, where it was found to be valid, reliable and acceptable (Radley et al 2006) [177]. Since this initial validation study, a further 5 domains have been added including: Irritable Bowel, Dyspareunia, Vaginal Capacity, Urinary Voiding and General Sex Life [178]. Each domain is scored on a scale of zero (best possible health) to 100 (worst possible health) and the symptom domains also each provide a 4-point scale. Recent tests of data quality on this version of ePAQ-PF supported the 19 domain structure of the instrument and its reliability and validity (Jones et al, 2008) [179]. The responsiveness of the instrument has also been demonstrated [177].

3. GRADE C

Several other questionnaires of Grade C level or below have been developed in the area of POP. If the validation of these instruments progress they may be useful for researchers. These include:

- P-QOL/St Mary’s Questionnaire [175] [180] -Pelvic Floor Dysfunction Questionnaire [176]
- Danish prolapse questionnaire [164]
- Pelvic symptom inventory and quality of life questionnaire [181,182]
A range of questionnaires have been developed to identify the severity of faecal incontinence (FI) and its influence on HRQL. Despite the large number, only a few are in regular use in research practice, and few services routinely use them in clinical assessment. Due to the close overlap between faecal incontinence and other pelvic floor disorders (in particular urinary incontinence), some of those questionnaires used for other pelvic disorders also include items to cover faecal incontinence. For similar reasons, items relating to faecal incontinence have often been included in questionnaires addressing general gastrointestinal and colorectal function, as well as condition specific instruments in such areas as irritable bowel syndrome and inflammatory bowel disease, conditions which are commonplace in colorectal practice as well as in other specialties dealing with pelvic floor disorders [185, 186]. It is also important to remember that the normal range of bowel function is broad, that bowel function may be highly variable within individuals without significant pathology. Consequently instruments in this field are likely to lack a degree of sensitivity or specificity for the specific bowel disorders such as IBS, IBD evacuation disorder and constipation.

Anal incontinence and bowel evacuation are intrinsically related to pelvic floor function and it may be inappropriate to consider bowel function purely in terms of continence and constipation. Evacuatory dysfunction may result from a variety of underlying pathologies including outlet obstruction, slow transit or other mechanical, physiological, metabolic, endocrine and neurogenic abnormalities [187]. Anal incontinence occurs in both sexes, but is more common in women than men [188]. Symptoms are considered crucial to diagnosis as specific symptoms are thought to reflect the underlying pathophysiology [189]. Thus, urgency (the inability to defer defecation) and urgency incontinence are thought to indicate loss of voluntary control due to impaired external anal sphincter function, whereas passive incontinence is thought to indicate impairment of the smooth muscle of the internal sphincter.

For FI, the Committee examined the quality of the psychometric evidence and noted that this is a developing area with questionnaires currently reaching the highest level of evidence. A FI outcomes measure is currently in development by the ICIQ (Table 3). A commonly used score for FI (Wexner), for example, does not appear to have published data related to its psychometric properties and thus while it is used widely cannot be recommended by the committee. The grades of recommendation are as outlined in previous sections (Tables 13,14).

### Table 13. Criteria for recommendation of questionnaires for faecal incontinence

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Evidence required (published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Grade A)</td>
<td>Validity, reliability and responsiveness established with rigour.</td>
</tr>
<tr>
<td>(Grade B)</td>
<td>Validity and reliability established with rigour, or validity, reliability and responsiveness indicated.</td>
</tr>
<tr>
<td>With potential (Grade C)</td>
<td>Early development – further work required and encouraged</td>
</tr>
</tbody>
</table>

### Table 14. Recommended questionnaires for the evaluation of symptoms and quality of life impact of faecal incontinence

<table>
<thead>
<tr>
<th>Grade A</th>
<th>None</th>
</tr>
</thead>
</table>

| Grade B | Faecal Incontinence Quality of Life Scale [190] |
|---------| Manchester Health Questionnaire [191] |
|         | Birmingham Bowel and Urinary Symptoms Questionnaire (BBUS-Q) [192, 193] |

<table>
<thead>
<tr>
<th>Grade C (with potential)</th>
<th>Wexner score [194]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>St Mark’s score [195]</td>
</tr>
<tr>
<td></td>
<td>Faecal Incontinence Survey [196]</td>
</tr>
<tr>
<td></td>
<td>Elderly Bowel Symptoms Questionnaire [197]</td>
</tr>
<tr>
<td></td>
<td>Postpartum Flatal and Faecal Incontinence Quality of Life Scale [198]</td>
</tr>
<tr>
<td></td>
<td>Bowel Disease Questionnaire [199]</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Quality of Life Index [200]</td>
</tr>
</tbody>
</table>
1. GRADE A

No questionnaires are currently available at this level.

2. GRADE B

a) Faecal Incontinence Quality of Life Scale

The 29-item Faecal Incontinence Quality of Life Scale developed and tested by Rockwood et al. measures impact of anal incontinence over four scales of HRQL: Lifestyle (10 items), Coping/behaviour (9 items), Depression/Self perception (7 items) and Embarrassment (3 items) [190]. The instrument was designed to measure the effect on quality of life for treatment for individuals with faecal incontinence. A panel of colorectal surgeons and researchers generated the items. Psychometric properties were tested in 118 patients with faecal incontinence and 72 controls.

The questionnaire showed good discriminant validity, with significant differences between patients with faecal incontinence and those with other gastrointestinal disorders. There were also significant correlations with selected subscales of the SF-36. Test-retest reliability at a mean interval of 20 days was satisfactory, with correlations for the 4 scales of 0.8 - 0.96. Internal consistency of the 4 scales was >0.7. The instrument does not measure physical symptom severity and has not been tested in asymptomatic controls, but appears to offer a valid and reliable measure of the impact of faecal incontinence on quality of life in men and women with this condition [190]. However, in order to demonstrate discriminant validity, the researchers deemed it necessary to modify the questionnaire for use in controls. Its use in an unscreened population is as yet unreported, and no responsiveness data have yet been produced.

b) Manchester Health Questionnaire

This questionnaire consists of items adapted from the King’s Health Questionnaire [191]. It uses the same basic structure and format but items have a 5-point response scale (rather than the 4-point scale in the KHQ). It includes items in the 8 domains of HRQL as well as a symptom severity scale. Face validity was assessed by interview with 15 patients with faecal incontinence. Test-retest reliability was measured (Pearson correlation > 0.8 in all 9 domains).

The questionnaire was posted to 236 women with faecal incontinence, of which 159 returned completed questionnaires. 121 performed test-retest at a mean interval of 20 days. Cronbach’s alpha was > 0.7 in all domains tested, indicated adequate internal consistency.

Convergent validity was assessed by comparison with responses in the SF-36, which showed significant correlations between domains of the 2 instruments. Data relating to women without faecal incontinence or unscreened women are not yet available. The questionnaire’s sensitivity to change is also not yet established.

c) Birmingham Bowel and Urinary Symptoms Questionnaire (BBUS-Q)

This is a 22-item questionnaire developed to evaluate symptoms of both bowel and urinary dysfunction in women which has a published scoring manual [192, 193]. Items were generated by a panel of clinicians and scientists and following review of existing instruments in the literature. The instrument was tested in the gynaecology departments of three hospitals, a urogynaecology clinic, a functional bowel clinic and a general practice. A total of 630 women completed the questionnaire; 379 women awaiting hysterectomy, 45 women following hysterectomy, 65 women referred with functional bowel and/or urinary symptoms and 141 asymptomatic controls.

The content, construct and criterion validity, internal consistency, reliability and responsiveness of the questionnaire were measured. Low levels of missing data, peer and patient reports supported face and content validity.

Factor analysis showed a clinically relevant four-factor structure: Constipation, Evacuatory function, Anal incontinence and Urinary symptoms with low content replication able to distinguish between patient groups, indicating good internal structure. Comparison with clinical, anorectal physiological, videoproctographic, transit time and urodynamic test results supported the instrument’s criterion validity. Key domain question analysis and Cronbach’s alphas showed internal consistency. Kappa values and limits of agreement demonstrated good test-retest reliability. Some responsiveness data have been produced.

The authors recommended the questionnaire for use as both a research tool and as a useful clinical measure. This questionnaire also forms a core element in an electronic pelvic floor symptoms assessment questionnaire (e-PAQ) (see above).

3. QUESTIONNAIRES WITH POTENTIAL [GRADE C]

There are several questionnaires on faecal incontinence which have not yet reached Grade C status. They may undergo further development and be of use in future research:

- Wexner score [194]
- St. Mark’s score [195]
- Faecal incontinence survey [184,185,190,196,201,202]
- Elderly Bowel Symptom Questionnaire (EBSQ) [197].
- Postpartum Flatal and Faecal Incontinence Quality of life Scale [198].
- Bowel Disease Questionnaire [199]
- Gastro-intestinal Quality of Life index (GIQLI) [200]
Sexual function may be regarded as a dimension or aspect of overall HRQL, for which a number of dimension-specific measures have been developed and validated. There is a wide choice of available instruments, the selection of which will depend on the clinical or research setting where the instrument is to be employed. Established and widely used measures that have been shown to be valid, reliable and responsive are clearly desirable, however the feasibility and appropriateness of using a particular instrument in a particular setting must also be considered. A large number of different instruments exist in this field, which aim to evaluate specific aspects of sexual function and sexual health. A number have been specifically developed or adapted to examine sexual function in patients with pelvic floor disorders such as incontinence.

Clinicians who treat sexual problems often prefer to use unstructured rather than structured interviews or questionnaires in clinical practice as an unstructured approach allows the tailoring of questions to suit the couple or the individual being assessed. Unstructured interviews enable the clinician to support patients who feel vulnerable and encourage discussion. The experienced clinician hopes to have an appreciation of the information required to make the correct diagnosis and institute appropriate treatment. In this setting, vocabulary can be modified, as can the level of assertiveness and the depth of questioning to suit the needs of the individual. This flexibility is not readily achievable with questionnaires which individuals may also find difficult to complete due their impersonal nature or because of physical or mental impairment, cultural or language differences. However, some patients find the discussion of intimate issues with clinicians very difficult and questionnaires may allow these issues to be measured in private, at ease and more effectively before subsequently exploring questionnaire responses in the clinical interview itself (Table 15).

1. RECOMMENDED QUESTIONNAIRES
   [GRADE A]

   a) Golombok-Rust Inventory of Sexual Satisfaction

   The Golombok-Rust Inventory of Sexual Satisfaction (GRISS), is a self-report inventory which has 56 items, from them 28 are for males and 28 are for females and it takes approximately 15 minutes to complete [203]. The questionnaire was developed systematically by sex therapists at the Maudsley Hospital Sexual Dysfunction Clinic. The GRISS assesses the quality

---

**Table 15. Recommended questionnaires for the evaluation of sexual function and health in patients with urinary symptoms**

<table>
<thead>
<tr>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade C (with potential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCoy Female Sexuality Questionnaire [217, 225]</td>
</tr>
<tr>
<td>BFLUTSex [23]</td>
</tr>
<tr>
<td>Female Sexual Function Index [209]</td>
</tr>
<tr>
<td>Sexual Function Questionnaire [218]</td>
</tr>
<tr>
<td>Simple Sexual Function Questionnaire [219]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAN-PSSsex [220]</td>
</tr>
<tr>
<td>Sexual life quality questionnaire [221]</td>
</tr>
</tbody>
</table>

* Grade A new
of a sexual relationship in a heterosexual couple and an individual's functioning within it. This questionnaire is designed for people who are currently in a relationship. There are 12 domain scores, 5 of which are female specific, 5 male specific and 2 non-gender specific. The 5 female specific domains are: Anorgasemia, Vaginismus, Avoidance, Nonsexuality and Dissatisfaction. The 2 non-gender specific domains are: Frequency of sexual contact and Non-communication. The questionnaire was validated on a clinical sample recruited from sexual dysfunction clinics throughout the UK, consisting of 68 men and 63 women, and a control group of 29 men and 30 women randomly selected from primary care attendees. Split half reliability was 0.94 for the female scale and 0.87 for the male overall scale. Average internal consistency of subscales was 0.74.

Both the overall female and male scores were found to discriminate well between clinical and non-clinical samples and scores on subscales successfully discriminated specific diagnostic groups. There was also a significant correlation between therapists' ratings of severity and scores on the questionnaire. Responsiveness was assessed by comparing change in the questionnaire scores with rated improvements by sex therapists. Correlations were moderate but statistically significant (0.54 for males and 0.43 for females, p<.005 and p<.01 respectively). Test-retest reliability was assessed in 41 couples receiving either marital or sex therapy. A further two subscales apply to both males and females and cover infrequency and non-communication. An additional 2 items each for males and females contribute to the overall scores but are not included in the subscales. The GRISS has been used by Hunt & Moss (1996) in a small study exploring the relationship of unwanted sexual experience to detrusor instability and sexual dysfunction [222]. High levels of sexual dysfunction were found in incontinent subjects compared to other clinical groups. The GRISS is not applicable to homosexual couples or people without a partner, but does provide an otherwise comprehensive, effective and well-used questionnaire.

b) ICIQ-MLUTSsex (ICSsex)

This forms one of the modules of the ICIQ modular questionnaire (see above) [205]. It consists of 4 items: to what extent sex life has been spoiled by urinary symptoms, ability to have erections, ability to ejaculate, and pain or discomfort on ejaculation. As with the other ICS questionnaires each item has an additional part to each item concerning the amount of bother the symptom causes i.e. how much of a problem is this for you? It has been used in both clinic and community samples to assess the relationship between urinary symptoms and sexual function, [205] and to show that urinary symptoms most frequently associated with sexual dysfunction were those related to incontinence [223]. It has also been used in a randomised trial of treatments for LUTS to investigate sexual side effects [224]. Aspects of reliability, validity and responsiveness have been tested and found to be satisfactory.

c) International Index of Erectile Function (IIEF)

The international index of erectile function (IIEF) is a 15-item self-administered questionnaire. It was designed to assess erectile function and is culturally and linguistically validated in at least 10 languages for use in multinational clinical trials. It was initially validated in 351 patients with erectile dysfunction (ED) and found to have a high degree of internal consistency (Cronbach's alpha > 0.85) and sensitivity to change with treatment. The questionnaire was culturally and linguistically validated in the following languages: Danish, Dutch, English (American, Australian and British), Finnish, French, German, Italian, Norwegian, Spanish and Swedish. The final 15-item instrument addresses five different domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The IIEF has a high degree of internal consistency. Test-retest repeatability was high for the domains of erectile function and intercourse satisfaction and moderately high for the other domains. Discriminant validity was good for most domains (except the sexual desire domain). Construct validity was good and all five domains showed a high degree of sensitivity to change. An abridged 5-item version of the questionnaire has also been developed (IIEF-5) [225]. Of the 5 items, 4 are from the erectile function domain and one addresses sexual intercourse satisfaction. The main difference between the 5- and the 15-item version is that the former asks patients to self-assess erectile function and satisfaction over the past 6 months while the latter refers to a time frame of 4 weeks. It has been used recently in a multinational survey of male ageing [220].

d) BPH QOL9

The QOL9 is a short form of the QOL20, a questionnaire previously validated in French for men with LUTS related to BPH [118]. The short form was developed using a large-scale cohort study of 7093 men with BPH who received alfuzosin for 3 months. The items were reduced by identifying questions that contributed most to establishing the global score and that reflected the structure of the questionnaire on principal components analysis. The final, 9-item questionnaire consists of 3 items concerning general well being, 3 items assessing BPH interferences with activities, and 3 items pertaining to patients' perceptions of their sexual life. The sexual function domain covered sexual desire, erectile function and satisfaction with sex life. The QOL9 was validated in two studies, a longitudinal study of alfuzosin, having a sample size of 4259, and a smaller cross-sectional study of men having symptomatic BPH (n=48), or no
symptoms of BPH (n=42), and a group of younger men (n=23). Feasibility and acceptability of the questionnaire were assessed by completion rates that exceeded 85%. Principal components analysis confirmed the three-factor structure. Discriminant validity was measured by comparing cases and non-cases. On the sexual function domain cases scored 10.5, non-cases 15.2 and young men 26.3. The most strongly discriminating question between cases and non-cases was satisfaction with sex life. There was also a good correlation between symptom severity and the total QOL9 score. Internal consistency of the overall scale was fair with Cronbachs alpha of 0.79 for patients with BPH and 0.85 for the control groups. Test-retest reliability was good for the total score but moderate for the sexual function subscale (ICC = 0.69 - 0.88) with the reliability of the erection item having an ICC of 0.53. After treatment the effect size of the change in the sexual function domain was linked to age and initial symptoms severity but had a mean of 0.02 and 0.55 for patients treated in each of the two studies.

e) ICIQ-FLUTSsex (BFLUTSsex)

This forms one of the modules of the ICIQ modular questionnaire (see above). The questionnaire contains 4 questions related to sexual function: pain or discomfort due to dry vagina, whether sex life has been spoilt by urinary symptoms, pain on sexual intercourse, and leakage on intercourse [23]. In addition to each of these items the respondent is asked how much of a problem this is for them. It has been used to assess sexual function after hormone replacement therapy [226] and pelvic floor muscle training [40]. There are 18 linguistic translations available and there is published evidence of validity, reliability and sensitivity to change..

f) Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ)

Rogers and colleagues in the United States have reported the development and validation of a measure of sexual function in women with urinary incontinence or pelvic organ prolapse [207]. The scale consists of 31 items spread across 3 domains: behavioural/emotive, physical, and partner-related. The measure has been found to have acceptable convergent and divergent validity and to be able to discriminate between women with and without urinary incontinence or pelvic organ prolapse [207, 227]. Test-retest ranged from 0.56 to 0.93, showing some variability in the moderate to high reliability ranges [228]. The internal consistency of the total measure and the behavioural/emotive, physical and partner-related domains was .85, .86, .77 and .43, respectively [228]. Sensitivity of the PISQ-31 has now been assessed in several studies.

A short form version of the questionnaire PISQ-12 has also been developed by the same team of researchers [229]. All subsets regression analyses with \( r > 0.92 \) identified 12 items, across all three domains, that were the most highly predictive of the PISQ-31 scores. Construct validity of the PISQ-12 was examined through correlations with the long form of the questionnaire PISQ-31 \((r=0.75-0.95)\), the Sexual History Form -12, and the IIQ-7. Correlations of the PISQ-12 with these latter measures were similar to those found for the PISQ-31.

The PISQ-12 scores were lower in those patients with poorer sexual functioning and more depressive symptoms. Test-retest reliability was moderate to high. Internal consistency reliability was stated as having been done, although the values were not reported in the article. Sensitivity of the PISQ-12 was not assessed.

An initial validation of a Spanish version of the PISQ-31 was reported for 34 bilingual patients of Mexican, Central or South American, Puerto Rican and Cuban origins living in the United States [230]. Good agreement between the Spanish and English versions was achieved for 30 of the 31 items. The three-factor structure of the original measure was validated in this sample of participants [227, 231-239].

2. RECOMMENDED QUESTIONNAIRES [GRADE B]

a) The Female Sexual Function Index (FSFI)

The Female Sexual Function Index (FSFI) [209] is a 19-item self-report questionnaire for measuring female sexual function and takes approximately fifteen minutes to complete. It provides five domains of sexual function, which have been confirmed using factor analysis they include: Desire, Lubrication, Orgasm, Arousal, Pain and Satisfaction. An overall total score is also provided. The FSFI was developed using a sample of 131 female controls (between the age of 21-68) and 128 females who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) criteria for Female Arousal Disorder (FSAD). The age of the participants was matched [21-69]. Norms are available for both groups (controls and FSAD) at the individual items level, the domains level, and the full-scale scores.

The FSFI discriminated reliably between women with arousal disorder (FSAD) and a control group on each of the domains of sexual function as well as on the full-scale score. FSFI data were also compared with results from the Locke-Wallace Marital Adjustment test (1959). Correlations between the two were generally modest in magnitude, with the strongest observed for the satisfaction domain of the FSFI. Internal consistency and test-retest reliability of the FSFI have been established. Test retest reliability of the scale was assessed in women with multiple
sclerosis with associated urinary and sexual symptoms [240].

Further cross validation studies were carried out to develop cut-off scores for potential classification of female sexual dysfunction [241, 242].

The FSFI was used in a study to investigate the prevalence of sexual dysfunction in women with chronic pelvic pain and with the [243] Female sexual distress score (FSDS) to investigate sexual outcomes in women with LUTS who were successfully treated with sacral neuromodulation. A 60% increase in the FSFI overall score or 50% increase in FSDS score was regarded as significant improvement [244]. The FSFI has been used in a study of pelvic floor muscle training for women with pelvic floor disorders and a study of sexual function in women with symptomatic pelvic organ prolapse who were treated with pessaries [233, 245].

The Italian version of the FSFI has been used as a screening tool for sexual dysfunction in healthy women attending annual gynaecological health checks [246]. The impact of LUTS and urinary incontinence on female sexual dysfunction was investigated over a 3 year period in women undergoing urodynamic studies using the FSFI [247]. The Malay translation has also been validated [248].

b) The Psychosocial Adjustment to Illness Scale (PAIS)

The Psychosocial Adjustment to Illness Scale (PAIS) was designed to assess the psychological and social adjustment of male and female medical patients to their illness and is in an interview or self-report format (PAIS and PAIS-SR) [206]. It contains a sexual relationships domain consisting of 6 items assessing the quality of interpersonal sexual relationships, sexual interest, frequency of sexual activity, sexual satisfaction, sexual dysfunction and interpersonal sexual conflict. Validation was carried out on groups of patients having renal dialysis, lung cancer, cardiac problems, breast cancer, and Hodgkin’s disease.

Internal consistency of the sexual relationships domain ranged from 0.8 to 0.93 in these different clinical groups. Factor analysis confirmed the subscale structure. All 6 items in the sexual relationships domain had very marked loadings on this dimension, with no appreciable loadings from other items. Convergent validity was assessed by comparing the scale to the Global Adjustment To Illness Scale (r=0.46), the SCL-90R (r=0.13), Affect Balance Scale (r=0.42), and the Patients Attitudes, Information and Expectancies Scale (r=0.40). Discriminant validity was assessed by comparing patients screened positive and negative for lung cancer. There were differences in the mean scores between the two groups which approached significance (t=1.53, p<0.10) [206].

The PAIS has been used to investigate the impact of different types of urinary incontinence on sexual function [249] in a sample of 200 patients referred for urodynamic assessment. Compared to patients with Urodynamic stress incontinence USI, patients having detrusor overactivity DO were significantly impaired on all items of the sexual relationships subscale, apart from the ‘sexual satisfaction’ item. Some aspects of validation were also carried out in a small study of 29 patients who had been treated successfully for penile cancer [250]. Internal consistency of the sexual relationships scales was good having Cronbach alpha of 0.83. Convergent and discriminant validity was shown in significant correlations with well-being scales but not with social scales. In addition, patients who had had the most radical treatments in terms of partial or total penectomy scored lower on the sexual relationships scale as did older patients (mean age 63 years) compared to younger patients (mean age 41 years), whereas having a mental disorder showed no correlation with sexual relationship scores.

c) The Brief Index of Sexual Function for Women (BISF-W)

The Brief Index of Sexual Function for Women (BISF-W) is a 22-item self-completed questionnaire that takes 15-20 minutes to complete [208]. It is designed to assess current levels of female sexual function and satisfaction. It was originally validated in a sample of 269 sexually active women age 20-73, and used a 3-factor scoring system (Interest/desire, Sexual activity, Sexual satisfaction) with acceptable test-retest reliability. A new quantitative scoring algorithm was developed to facilitate the use of the BISF-W in clinical trials, providing an overall composite score for sexual function and 7 domain scores; Thought/desire, Arousal, Frequency of sexual activity, Receptivity/initiation, Relationship satisfaction, Pleasure/orgasm, and Problems affecting sexual function. Norms for the composite score and for each of the seven dimension scores are available, derived from a sample of 225 healthy women (age 20-55) [251]. Comparing these scores with those of 104 surgically menopausal, sexually active women who reported impaired sexual function (age 20-55), the instrument showed good discriminant validity between women with and without sexual complaints in each of the 7 sexuality domains. In a placebo-controlled study, the BISF-W was sensitive to detecting differences between treatment groups in two of the 7 sexuality domains and on the overall composite BSIF-W score.

d) Brief Sexual Function Inventory

This 22-item questionnaire concerning male sexual function was designed for clinical and research purposes in urological settings [211]. Items were generated from the literature to produce a 50-item questionnaire which was then reduced down to 22 items in a series of pilot studies prior to the final validation study. The questionnaire comprises of 5
subscases: Libido, Erectile function, Ejaculation, Assessment of significance of each domain and Overall satisfaction. Validation was carried out on a sample of 74 men with sexual dysfunction and 60 general medical patients. Mean age was 55 and 45 years respectively. The study describes development of individual subscales down to a final questionnaire of 11 items based on measures of internal consistency and test-retest reliability. Internal consistency of the subscales ranged from 0.62 to 0.95 and ICC’s from 0.79 to 0.89 for test-retest reliability.

All subscales except the drive and ejaculation subscales discriminated between patients being treated for sexual dysfunction and general medical patients, but it was not expected that drive would be reduced in patients experiencing sexual dysfunction and ejaculation did not appear to be an important issue for patients.

e) Sexual quality of life-female questionnaire (SQOL-F)

This questionnaire was developed to assess the impact of sexual dysfunction on women’s quality of life. Responsiveness to change has not been established [210]. The content validity of the SQOL-F, sexual function questionnaire (SFO) and PISQ were further assessed in a postal study of women with OAB and urinary incontinence in the United States, and the SQOL-F was rated most relevant and understandable among this group of women [252].

3. QUESTIONNAIRES WITH POTENTIAL

[GRADE C]

Several questionnaires that have potential and are currently under development or in need of further development. With further validations these instrument could provide additional resources to research:

- The Derogatis Interview for Sexual Functioning (DISF) [206]
- Sexual Behaviour Inventory (SBI) [212, 223]
- The Changes in Sexual Functioning Questionnaire (CSFQ) [213]
- Index of Sexual Satisfaction (ISS) [215]
- Multidimensional Sexuality Questionnaire (MSQ) [216, 223].
- The Sexual Interaction Inventory (SII) [214]
- McCoy Female Sexuality Questionnaire (MFSQ) [217]
- Simple Sexual Function Questionnaire [219, 219, 253]
- Sexual function questionnaire [218]
- DAN-PSSsex [220]
- Sexual life quality questionnaire (SLQQ) [221]

a) Other measures of sexual function

Many of the questionnaires assessing the psychosocial impact of LUTS and/or UI contain one or two questions related to sexual function. The majority of these are discussed above, either as symptom questionnaires or general quality of life questionnaires. Questionnaires containing just one question tend to focus on a general assessment of the overall impact of urinary symptoms on sexual functioning. The Kings Health questionnaire, [24] the Incontinence Impact Questionnaire [59] and the I-QOL [75] are recommended by the Committee for use for UI/LUTS. However, when considering the sexual items it must be borne in mind that validation of the sexual items was not always carried out or made explicit. But the questions relating to sexual function in each of the questionnaires are very similar and judgements on validity can be made by comparing questions and psychometric data between questionnaires as well as considering the psychometric properties of the scales as a whole. If more in-depth information is required concerning sexual function, the questionnaires recommended for this aspect should be used (see above).

There are other general measures of sexual function, such as the Watts Sexual Function Questionnaire, [254] and Medical Outcomes Study (MOS) Sexual Functioning Scale [255]. There are also questionnaires that have been designed for sexual dysfunction specific to particular diseases, such as Radiumhemmets Scale of Sexual Function, [256] Sexual Adjustment Questionnaire (SAQ), [257] and Prostate-targeted Health Related Quality of Life [258].

A small number of questionnaires have produced initial validation but without publications during the reporting period: Effect of Urinary Incontinence on Sexuality Questionnaire (EISQ), [259] and Effects of urinary incontinence on sexual activity [260].

X. QUESTIONNAIRES FOR SPECIFIC PATIENT GROUPS

Most studies and questionnaires have been developed for use with members of the general population or urology/gynaecology patients with incontinence or POP. However, some specific patient groups may experience particular problems with incontinence (for example, children, frail elderly or those who are severely disabled), which may require independent investigation and potentially the development of more specific measures or the addition of a new subset of items on already developed instruments. The Committee advises that researchers should use existing highly recommended or recommended questionnaires if possible as this aids comparison and to reduce the increasing proliferation of questionnaires. Many of the questionnaires developed
below for particular conditions (e.g. prostate cancer) pre-dated the development of highly recommended questionnaires, and highly recommended questionnaires should be used preferentially.

a) Older people

Urinary incontinence symptoms play an influential role on the overall HRQL in older people (>65) and causes a significant decrease in HRQL, as severe as that of many chronic disease states. Since the elderly commonly have a number of associated comorbid conditions, it may be difficult to measure the impact of urinary incontinence with generic HRQL measures. The use of incontinence specific tools to measure patient-reported outcomes in the elderly, therefore, is of considerable importance.

Validated incontinence-specific PRO questionnaires, such as IIQ, I-QOL or KHQ, are used for clinical trials or research on urinary incontinence including elderly people, but their validity has not been specifically assessed in this age group. Okamura, assessed symptoms and HRQL in older people (men and women) with lower urinary tract symptoms including incontinence, using the KHQ and IPSS. They demonstrated that symptoms and HRQL in the elderly with LUTS could be assessed by IPSS and KHQ and that urinary incontinence appeared to be more associated with a decreased HRQL in elderly women [80].

On the other hand, there are a variety of factors affecting older people, including physical, social, mental, economic or environmental conditions, which are different from those of the young. In frail elderly people with dementia or physical impairment, it may be difficult to assess the impact of urinary incontinence alone. Questionnaires specifically developed for the elderly may be of great importance in this respect. However, there is little relating to the development or validation of particular questionnaires for older people with urinary incontinence. Two questionnaires dealing with older people were found and are described below. No questionnaires dealing with patient outcomes specifically for frail older incontinent people were found.

1. The Urge Impact Scale (URIS) [Grade B]

The Urge Impact Scale (URIS) was designed and tested specifically for older persons with urgency incontinence. The URIS was developed and validated by DuBeau et al. (1999) [261] and included 32 items, reduced to 24 items (URIS-24). The URIS-24 was psychometrically assessed for validity and reliability in community-dwelling older (>65y) men and women with urge incontinence. Cronbach alpha was 0.84 for the URIS-32 and 0.94 for the URIS-24. In assessment of test-retest reliability, interclass coefficient (ICC) was 0.88. The URIS-24 had modest but nearly significant correlation with the number of urgency incontinence episodes (rho=-0.39, p=0.05). Factor analysis revealed 3 component structures corresponding to physiological burden, perception of personal control and self-concept. There was no analysis for responsiveness. They showed that the URIS-24 is an internally consistent, highly reproducible tool for the assessment of the QOL impact of urgency incontinence on older persons.

2. Swedish questionnaire [Grade C]

A questionnaire survey was conducted among men and women aged over 75 years in Sweden [262]. The questionnaire was developed specifically for the study although many questions had been used in a previous epidemiological survey [263]. The questionnaire achieved an admirable 62% response rate, but no details were published describing the psychometric properties of the questionnaire or the method of its construction.

There still remains a gap in the assessment of PROs for frail older adults by other than subjective means. Many of the commonly used measures have been used for older people as part of pharmaceutical company studies but it is not known whether these are relevant to the needs of the frail elderly or that they respond in a similar fashion when used in younger populations.

b) Children

Some questionnaires have been developed specifically to address issues for children, particularly enuresis. See Chapter (Children) and section on ICIQ modular questionnaire.

c) Spinal cord injured/neurologically damaged

Individuals who have a spinal cord injury or are neurologically damaged can experience particular difficulties with incontinence and the use of various devices. It would be useful to investigate whether Grade A questionnaires, developed for people without neurological damage, can be used in this group, or whether additional modules or instruments are required. This is an area where a small number of questionnaires are being developed with the Qualiveen being a notable exception (Also see section on the ICIQ questionnaire and below).

Qualiveen: Quality of Life Related to Urinary Problems in Spinal Cord Injury [Grade A]

The Qualiveen was developed to evaluate the specific impact of urinary dysfunction on the quality of life of spinal cord injury patients in France [264]. The initial items were developed following patient interviews, and were then assessed for validity and reliability in 281 spinal cord injury patients with urinary difficulties. The Qualiveen contains 30 items and has demonstrated good reliability and validity [264]. Further validation of the Qualiveen has occurred in multiple
sclerosis patients [265] and it has been translated and validated into English [266], German [267], and Portuguese [268]. The Qualiveen has demonstrated responsiveness in multiple sclerosis patients and has a suggested MID of 0.5 [269].

d) Prostate/bladder cancer

Many PRO questionnaires are available for assessment in this area: Post-radical prostatectomy questionnaire, [270, 271] Cancer Rehabilitation Evaluation System - Short Form (CARES-SF), [272] Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q), [273] PROSQUIOL, [274] Modified Southwest Oncology Group (SWOG), [275] Functional Assessment of Cancer Therapy - (FACT-G), Bladder form (FACT-B) and Prostate form (FACT-P), [276] Functional Assessment of Cancer Therapy Vanderviet Cystectomy Index (FACT-VCI), [277] EORTC metastatic prostate cancer, [273] Changes in Urinary Function, [277] Prostate-targeted Health Related Quality of Life [258]. While it is beyond the scope of this chapter to review and recommend PROs in this area, the principles and guidelines discussed herein apply to selecting a PRO related to prostate and bladder cancer.

e) Lower urinary tract symptoms/benign prostate disease

Many questionnaires have been developed to assess LUTS and benign prostate disease, however most do not contain a full evaluation of UI. Perhaps the most widely known urology PRO is the AUA Symptom Index, [137] I-PSS (International Prostate Symptom Score) [137, 278]. The IPSS has been utilized internationally to assess symptoms of prostate disease with documented reliability, validity and responsiveness. Additional PRO measures for BPH are as follows: Patient-completed modification of the Boyarsky [279] BPH Impact Index, [144] and BPH Health-related QoL survey [280].

XI. SELECTING PRO MEASURES FOR CLINICAL TRIALS AND CLINICAL PRACTICE

The previous sections have provided an overview of PRO measures with evidence of reliability, validity, and responsiveness. But, how does a researcher choose which instruments are most appropriate for a particular research study and/or clinical assessment? The following section provides general guidelines for use in conducting PRO assessments in clinical trials or other research investigations related to urinary or faecal incontinence.

As there are many available PROs, it is of utmost importance to select the PRO measure that is relevant and applicable to one’s desired outcome. If an intervention is designed to reduce symptom bother, then a relevant PRO would be a symptom bother measure. Multiple PROs can be included in a research study, however the designation of the PRO as a primary or secondary endpoint must be . In addition, issues of staff and participant burden, time constraints, and resources should be considered in the selection of a PRO measure.

1. SELECTING PRO MEASURES FOR RESEARCH STUDIES

a) Study Design

There are several protocol concerns that must be taken into account when using PRO measures in research studies, including the length of the study, the frequency of contact with the study participants, the timing of clinical assessments, the complexity of the trial design, the number of participants enrolled, and participant and staff burden. The goal of the PRO investigation is to "fit" the PRO measures to the protocol without compromising either the study objective or design. For example, if the study design is complex with frequent participant contacts and multiple clinical measures, it may be necessary to keep the PRO measures at a minimum or to reduce the number of times the PRO is assessed (e.g. baseline and end of study rather than during all participant contacts) to minimise participant and staff burden.

At the same time, however, PROs must be viewed as an important variable in the overall trial design and cannot be devalued in the data collection process. Consequently, PRO measures cannot be altered or reduced to accommodate study design as such alterations may yield potentially less reliable measures or may seriously diminish the integrity of the overall study design and yield useless information. Having well developed research goals and questions regarding PROs will help to guide you in the selection of measures for a study. The goal is to develop a conceptually adequate, yet practical PRO battery given the study population, the specific intervention, and the study design.

The frequency with which PRO will need to be assessed in a research study will depend upon the nature of the condition or intervention being investigated and the expected effects (both positive and negative) of treatment. At a minimum, as with all measurements collected in a research study, a baseline and end of study assessment should be completed. In addition, other PRO assessments should be timed to match expected changes in functioning due to either the intervention or the condition or the disease itself. Timing follow-up assessments to coincide with typical patient follow-up visits, if appropriate, may also reduce the costs involved in follow-up PRO and symptom assessments.
Finally, it is important to have a clear understanding of the current medications the patient population is likely to be taking prior to randomisation to the study treatment, and how these medications might interact with the trial intervention, (either a pharmacological or behavioural intervention), to influence patient outcomes.

There are two types of PRO measures: generic and condition-specific. Generic measures are designed to assess outcomes in a broad range of populations (e.g., both healthy as well as ill individuals). These instruments are generally multidimensional, and assess at least the physical, social and emotional dimensions of life. An example of this type of instrument is the Medical Outcomes Study SF-36 Health Status Profile. [281]. A second type of measure is condition-specific (e.g., instruments designed to assess the impact of specific diseases, conditions, age groups, or ethnic groups). Condition-specific measures can be similar to generic instruments in that they assess multiple outcome dimensions, but condition-specific measures also include items more specific to the particular condition or population being studied. Examples of frequently used condition specific instruments include the Incontinence Impact Questionnaire, the King’s Health Questionnaire, and the OAB-q (described above).

In general, the growing trend has been to include condition-specific outcome measures in clinical trials due to their enhanced sensitivity to change and the need to minimise participant burden. Importantly, the type of instruments selected for inclusion in a research study will depend on the goals of the intervention and the specific research questions to be addressed. In practice, clinical trials that include PROs usually incorporate a combination of PRO measures most relevant to the study population and intervention, if applicable, being mindful of resource constraints and staff and participant burden.

1. QUALITY-ADJUSTED LIFE YEAR (QALY)

Increasingly HRQL outcome measures are being used in the development of quality-adjusted life year (QALY) measures. A QALY is a universal health outcome measure applicable to all individuals and all diseases, which combines gains or losses in both life quantity (mortality) and life quality (morbidity) and enables comparisons across diseases and programs. QALYs are widely used for cost-utility analysis [282]. In the past decades, economic evaluation has been increasingly important for the decision maker to decide which treatment or intervention is more cost-effective, in order to allocate limited healthcare resources soundly. Economic evaluation aims to compare interventions in terms of their costs and benefits,
including their patient outcome impact. Health benefits can be quantified as QALYs (pronounced “qualies”), which has become a standard measure and is now recommended in most of health economics guidelines as the method of choice [283]. The economic chapter contains additional information regarding QALYs, as do the following references: [284, 285].

2. SUMMARY

In summary, some general points to consider in selecting PRO measures for lower urinary tract and pelvic floor disorder studies:

- Ensure that the PRO research questions and study endpoints are clearly defined. Determine the PROs that are most crucial to assess and which are most likely to be affected by a particular condition and/or its treatment.
- Make good use of prior literature searches in identifying past research in the area(s) of interest, as well as in identifying the types of PRO measures other researchers have used in past work. This information can provide valuable information on how particular outcome measures have performed in previous populations, as well as provide additional information to assist in defining research questions/ issues regarding the PRO components of any given study.
- Consider the characteristics of the population in selecting measures. For example, are the study subjects to be children or older adults, well educated vs. those with limited education, or persons with low literacy? Ensure that the mode of data collection is appropriate for use with the study population. Furthermore, do not assume that an instrument validated for use with Caucasian, middle-class individuals in the U.S. will be appropriate for use in other countries, and/or those of a lower socioeconomic status or of different educational backgrounds. This chapter has indicated, where possible, the extent to which specific PRO measures have been validated, and used reliably with different populations.
- Use the questionnaires recommended in this chapter whenever possible. Do not “reinvent the wheel.” Developing new PROs is a time-consuming and complicated process. If a new scale needs to be developed, ensure that the guidelines proposed by the FDA and EMEA on developing PROs are followed and that the appropriate expertise in questionnaire development and psychometrics is available to your research team in order to guide the questionnaire development process.
- Know the strengths and weaknesses of different types of PRO measures. In general, generic measures are useful in providing information on multiple patient outcome dimensions that can be compared across different populations. They may lack sensitivity, however, in addressing concerns of specific patient populations (e.g., OAB, UI, faecal incontinence). Condition-specific instruments, in contrast, do address areas of function more specific to the condition, and tend to be more responsive to changes in clinic status, due to their increased specificity in addressing the conditions of their patient populations. Weaknesses of condition-specific instruments, however, are that they are often not appropriate for use with multiple populations, and cannot be used to make direct comparisons across different patient groups.
- Know how to score your selected PRO measures and how to interpret the scores. Specifically, ensure that the scoring method of a measure provides you with the information you need to answer your research question?
- Pilot testing of PRO measures with participants/patients similar to those in the target patient population who will be assessed in a research investigation is always advisable. Adjustments can then be made in the protocol, if necessary, prior to the initiation of the study.
- Finally, train and certify your staff to administer PRO measures using either patient interview and/or self-administration techniques, depending on the method to be used in the study. The administration process needs to be standardised and completely similarly across all participants.

5B - F. RECOMMENDATIONS FOR RESEARCH

The following recommendations were unanimous:
1. The selection of a PRO questionnaire must reflect study purpose and objectives
2. Grade A recommended questionnaires should be used in all clinical trials evaluating treatments
3. The inclusion of the ICIQ modules is preferred in all studies to standardise outcome assessment
4. Continued PRO development, refinement, and use should accurately and adequately report on the methods, samples, statistical analyses and psychometric properties of questionnaires in scientific journals (i.e. validity, reliability and responsiveness), so the quality of each study can be assessed Researchers are encouraged to use existing questionnaires and refine for specific populations when needed (e.g. frail elderly, children)
5. Researchers are encouraged to collaborate with the ICIQ project on the development and refinement of modules and translations.
REFERENCES


206. Derogatis LR. The psychosocial adjustment to illness scale (PAI(S)). J Psychosom Res. 1986;30(1):77-91.


256. Helgason Å. Prostate Cancer Treatment and Quality of Life - a Three Level Epidemiological Approach Stockholm: Karolinska Institute; 1997.


274. Stockler MR, Osoba D, Goodwin P, Corey P, Tannock IF. Responsiveness to change in health-related quality of life in a randomized clinical trial: a comparison of the Prostate Cancer Specific Quality of Life Instrument (PROSQOL) with analogous scales from the EORTC QLQ-C30 and a trial


Committee 6

Dynamic Testing

Chairman
G. Hosker (U.K)

Members
P. Rosier (The Netherlands),
J. Gajewski (Canada),
P. Sand (USA)

Consultants
L. Szabo (Hungary),
A. Capewell (U.K)
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. INTRODUCTION</td>
</tr>
<tr>
<td>B. URODYNAMICS</td>
</tr>
<tr>
<td>C. URODYNAMICS: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE</td>
</tr>
<tr>
<td>D. CLINICAL APPLICATIONS OF URODYNAMIC STUDIES</td>
</tr>
<tr>
<td>E. SUMMARY OF RECOMMENDATIONS FOR CLINICAL PRACTICE RELATING TO URODYNAMICS</td>
</tr>
<tr>
<td>F. ANORECTAL PHYSIOLOGY STUDIES</td>
</tr>
<tr>
<td>G. SUMMARY OF RECOMMENDATIONS FOR CLINICAL PRACTICE RELATING TO ANORECTAL PHYSIOLOGY STUDIES</td>
</tr>
<tr>
<td>H. ACKNOWLEDGEMENTS</td>
</tr>
<tr>
<td>REFERENCES</td>
</tr>
</tbody>
</table>
The following are the words and phrases that were used by the committee members in their search of the literature. PubMed was the source predominantly used by all the committee members.

**Keywords**

- rectal balloon
- rectal barostat predicts
- rectal barostat specificity
- rectal compliance
- rectal compliance predicts
- rectal compliance specificity
- rectal distension
- rectal electrosensitivity
- rectal mucosal sensory
- rectal saline retention test
- rectal sensation
- rectoanl inhibitory reflex
- rectoanl pressure gradient
- reliability and reproducibility of urodynamics
- repeatability anal squeeze
- repeatability manometry
- repeatibility anal squeeze
- repeatibility manometry
- reproducibility anal
- reproducibility manometry
- reproducibility resting
- reproducibility squeeze pressure
- resting anal pressure
- resting anal pressure discrimination
- resting anal pressure discriminator
- resting anal pressure following
- resting anal pressure predicts
- resting anal pressure sensitivity
- resting anal pressure specificity
- resting pressure sensitivity
- resting pressure specificity
- sacral agenesis
- saline continence test
- saline enema test
- saline infusion test
- saline retention test
- spinal cord injury
- spine bifida
- squeeze pressure following
- squeeze pressure predict
- stool chart
- stool consistency
- temperature anal mucosa
- thermal anal
- thermal rectal
- thermal rectal mucosa
- urethral stricture
- variability anal
- variability anal squeeze
- variability basal
- variability manometry
- variability resting
- variability sphincter
- vectography
- vectography ultrasound
- vector manometry
- vector manometry ultrasound
- vector volume
- vector volume ultrasound
- vesicouretreal reflux

(uininary AND incontinen*) AND ((urge* OR overactiv*) OR stress) AND (urethr* AND leak OR press* OR valsal*) OR urodynam*
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPP</td>
<td>abdominal leak point pressure</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>APV</td>
<td>anal pressure vectography</td>
</tr>
<tr>
<td>ARM</td>
<td>anorectal malformation</td>
</tr>
<tr>
<td>ARPS</td>
<td>anorectal physiology studies</td>
</tr>
<tr>
<td>AUS</td>
<td>artificial urinary sphincter</td>
</tr>
<tr>
<td>AVP</td>
<td>anal pressure vectography</td>
</tr>
<tr>
<td>BOO</td>
<td>bladder outlet obstruction</td>
</tr>
<tr>
<td>BOOI</td>
<td>bladder outlet obstruction index</td>
</tr>
<tr>
<td>BPE</td>
<td>benign prostatic enlargement</td>
</tr>
<tr>
<td>BPH</td>
<td>benign prostatic hyperplasia</td>
</tr>
<tr>
<td>BPO</td>
<td>benign prostatic obstruction</td>
</tr>
<tr>
<td>BPS</td>
<td>bladder painful syndrome</td>
</tr>
<tr>
<td>CLPP</td>
<td>cough leak point pressure</td>
</tr>
<tr>
<td>CMAP</td>
<td>compound muscle action potential</td>
</tr>
<tr>
<td>DHIC</td>
<td>detrusor hyperactivity with impaired contractile function</td>
</tr>
<tr>
<td>DLPP</td>
<td>detrusor leak point pressure</td>
</tr>
<tr>
<td>DO</td>
<td>detrusor overactivity</td>
</tr>
<tr>
<td>DOI</td>
<td>detrusor overactivity incontinence</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyogram/electromyography</td>
</tr>
<tr>
<td>FDV</td>
<td>first desire to void</td>
</tr>
<tr>
<td>FSF</td>
<td>first sensation of filling</td>
</tr>
<tr>
<td>FUL</td>
<td>functional urethral length</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>HPZ</td>
<td>high pressure zone</td>
</tr>
<tr>
<td>ICI</td>
<td>International Consultation on Incontinence</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IDC</td>
<td>involuntary detrusor contraction(s)</td>
</tr>
<tr>
<td>IDO</td>
<td>idiopathic detrusor overactivity</td>
</tr>
<tr>
<td>IPAA</td>
<td>ileal pouch anal anastomosis</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prostate Symptom Score</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>ISD</td>
<td>intrinsic sphincter deficiency</td>
</tr>
<tr>
<td>IWT</td>
<td>ice water test</td>
</tr>
<tr>
<td>LPP</td>
<td>leak point pressure</td>
</tr>
<tr>
<td>LUT</td>
<td>lower urinary tract</td>
</tr>
<tr>
<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MCC</td>
<td>maximum cystometric capacity</td>
</tr>
<tr>
<td>MES</td>
<td>mucosal electrosensitivity</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>MUCP</td>
<td>maximum urethral closure pressure</td>
</tr>
<tr>
<td>MUP</td>
<td>maximum urethral pressure</td>
</tr>
<tr>
<td>NDO</td>
<td>neurogenic detrusor overactivity</td>
</tr>
<tr>
<td>NDV</td>
<td>normal desire to void</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>OAB</td>
<td>overactive bladder</td>
</tr>
<tr>
<td>POP</td>
<td>pelvic organ prolapse</td>
</tr>
<tr>
<td>PNTML</td>
<td>pudendal nerve terminal motor latency</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PVP</td>
<td>photoselective laser vaporisation prostatectomy</td>
</tr>
<tr>
<td>PVR</td>
<td>post-void residual urine (volume)</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RAIR</td>
<td>recto-anal inhibitory reflex</td>
</tr>
<tr>
<td>SCI</td>
<td>spinal cord injury</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SDV</td>
<td>strong desire to void</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>SPT</td>
<td>specificity</td>
</tr>
<tr>
<td>STV</td>
<td>sensitivity</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>TURP</td>
<td>transurethral resection of the prostate</td>
</tr>
<tr>
<td>TVT</td>
<td>tension-free vaginal tape</td>
</tr>
<tr>
<td>UDS</td>
<td>urodynamic studies</td>
</tr>
<tr>
<td>UPP</td>
<td>urethral pressure profile/profilometry</td>
</tr>
<tr>
<td>UPR</td>
<td>urethral pressure reflectometry</td>
</tr>
<tr>
<td>URP</td>
<td>urethral retro-resistance pressure</td>
</tr>
<tr>
<td>USI</td>
<td>urodynamic stress urinary incontinence</td>
</tr>
<tr>
<td>UUI</td>
<td>urgency urinary incontinence</td>
</tr>
<tr>
<td>VLPP</td>
<td>Valsalva leak point pressure</td>
</tr>
<tr>
<td>VUR</td>
<td>vesico-ureteric reflux</td>
</tr>
<tr>
<td>VV</td>
<td>voided volume</td>
</tr>
</tbody>
</table>
Dynamic Testing

G. Hosker
P. Rosier, J. Gajewski, P. Sand
L. Szabo, A. Capewell

A. INTRODUCTION

The first two reports of the International Consultation on Incontinence (ICI) contained chapters on “Urodynamic Testing”[1, 2]. Urodynamics is the umbrella term used to describe measurements of the function of the lower urinary tract. These measurements can be used in the management of urinary incontinence. The third report of the ICI expanded this topic to include physiological measurements of the lower gastrointestinal tract. These measurements can be used in the management of faecal or anal incontinence. Consequently, the chapter was then renamed ‘Dynamic Testing’. [3]

This is the successor to that chapter and, in this fourth consultation, we have further updated the evidence for the technical performance, clinical utility and responsiveness to treatment of these measurements. We have used the chapter on ‘Dynamic Testing’ from the previous consultation as a template for this report; retaining some of the original text and tables where there has been no change since the previous consultation.

The primary aim of the chapter is to discuss the value of the various tests to diagnose the mechanisms of continence in general, to discuss what tests ought to be performed to elucidate these mechanisms in the individual; and to make recommendations for what tests should be performed for certain groups of patients. Thus we have tried to present an overview of the best scientific evidence with regard to the role of urodynamics and lower gastrointestinal tract testing.

On the basis of this we provide recommendations for the current state of assessment of the patient with incontinence, and recommendations for future scientific evaluation or analysis of dynamic testing. The overview of scientific evidence in paragraphs, with conclusion(s) and recommendation(s) and topics(s) for research are highlighted in the text and are therefore also suitable for ‘express reading’.

The third ICI report expressed the hope that faecal (anal) incontinence and urinary incontinence could be dealt with by an integrated approach by future consultations. However, although the two topics clearly have much in common with regard to both pathophysiological mechanisms and clinical application, this committee thought it was appropriate to continue to address the two topics separately in this report.

Therefore, following this introduction, the chapter firstly considers urodynamics before considering dynamic testing for anal incontinence. For each, the tests are described and then there is a review of data about normal values and reliability of the measured parameters. This is followed by reviews of the literature regarding clinical urodynamic evaluation of different patient groups with urinary incontinence (women, men, children, neurogenic dysfunction, and the frail elderly). This is followed by reviews from the literature regarding the clinical evaluation of patients with anal incontinence. Each section concludes with the committee’s recommendations regarding dynamic testing.

B. URODYNAMICS

I. WHAT IS URODYNAMICS?

The term ‘Urodynamic studies’ (UDS) was defined by the International Continence Society (ICS) in 1988 and involves the assessment of the function and dysfunction of the urinary tract by any appropriate method. [4] A more recent report in 2002 did not alter the definition of ‘urodynamic studies’ or ‘urodynamics’ but did include a new definition of ‘urodynamic observations’. [5]

The conventional view – implicitly adopted in the previous standardisations and consultations – is that urodynamics is a series of more or less agreed-upon clinical tests, such as flow studies, filling cystometry, pressure-flow studies and/or urethral function measurements. These can be combined with simultaneous electromyography (EMG) recording and/or
imaging by either X-rays or ultrasound. Also implicitly agreed upon is that urodynamics is the only objective way to determine why people have lower urinary tract symptoms (LUTS). The attempt to gain understanding of lower urinary tract (LUT) behaviour, on the basis of test observations, in relation to what is known about normal – or expected abnormal– physiology, is what constitutes urodynamics.

Urodynamic studies can answer questions such as: ‘What causes the increased voiding frequency in this patient?’ as well as: ‘Why does this patient have urinary incontinence?’ These questions not only can be posed for individual patients but also can form part of clinical or laboratory research.

Conventionally, UDS involves the patient being connected to equipment in the laboratory in order to measure physiological parameters, such as pressures, inside the patient. The data is analysed as the test is being carried out and adjustments can be made to correct for technical problems and artefacts as they arise. If conventional urodynamic studies fail to provide an answer to the question being posed then ambulatory urodynamics may be employed in an attempt to obtain the answer. [6] In ambulatory urodynamics, pressures and other physiological parameters from the patient are fed into a small, body-worn solid-state recorder and the patient is free to move about and carry out normal activities. The test can last for many hours and the physiological data is analysed once the test has been completed.

II. WHAT SHOULD BE THE ROLE OF URODYNAMIC STUDIES IN CLINICAL PRACTICE?

There is an agreement among experts that the immediate aim of urodynamic testing is to reproduce the symptom(s) of the patient under controlled and measurable conditions, so that the cause of the symptoms can be determined and useful, objective information can be provided to the clinician. The role of urodynamic studies in broad clinical perspective can be:

a) to identify or to rule out factors contributing to the LUT dysfunction (e.g. urinary incontinence) and assess their relative importance
b) to obtain information about other aspects of LUT dysfunction
c) to predict the consequences of LUT dysfunction for the upper urinary tract
d) to predict the outcome, including undesirable side effects, of a contemplated treatment
e) to confirm the effects of intervention or understand the mode of action of a particular type of treatment; especially a new one

f) to understand the reasons for failure of previous treatments for urinary incontinence, or for LUT dysfunction in general.

The International Continence Society has provided standards for urodynamic terminology and techniques to optimise interpretation and facilitate comparison between different studies [5]. Some of the urodynamic terminology is given in Table 1.

Table 1. Some urodynamic diagnoses and corresponding urodynamic observations

<table>
<thead>
<tr>
<th>Urodynamic diagnosis</th>
<th>Urodynamic observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urodynamic stress urinary incontinence</td>
<td>Loss of urine as result of an abdominal pressure increase without detrusor overactivity during the storage phase of urodynamic testing.</td>
</tr>
<tr>
<td>Detrusor overactivity incontinence</td>
<td>Loss of urine as a result of involuntary detrusor activity during the storage phase of urodynamic testing.</td>
</tr>
<tr>
<td>Urodynamic mixed urinary incontinence</td>
<td>Occurrence of urodynamic stress incontinence in combination with urodynamic urgency urinary incontinence or detrusor overactivity.</td>
</tr>
<tr>
<td>Urodynamic urgency</td>
<td>Detrusor overactivity during urodynamic testing with urgency sensation that the patient reports as representative for his or her symptoms.</td>
</tr>
</tbody>
</table>

III. THE TESTS OF CONVENTIONAL URODYNAMICS

1. UROFLOWMETRY

This is the non-invasive measurement of urine flow rate. The patient micturates into a flow meter in private when they have a normal desire to empty their bladder. [7] Urine flow rate is continuously measured and displayed graphically. Various parameters from the trace are automatically calculated and printed out together with the trace. The volume voided, shape of the curve and the maximum flow rate are usually the principal determinants of whether or not the patient is emptying their bladder normally. If an abnormal recording is obtained, it is usual to repeat the assessment to check that the result is reproducible.
Several factors, such as patient apprehension, can give an abnormal recording in patients who have no voiding difficulty. Repeating the assessment can eradicate the effect of such confounding factors and will confirm or refute the validity of the first assessment.

2. FILLING CYSTOMETRY

This is the measurement of the pressure inside the bladder to assess its storage capabilities. It is an invasive test which involves a pressure sensor being placed into the bladder, usually transurethrally, and another pressure sensor being placed rectally or vaginally (or sometimes through an abdominal stoma) to measure abdominal pressure. Subtracting the abdominal pressure from the pressure measured inside the bladder (intravesical pressure) gives a representation of pressure changes due to the action of the detrusor smooth muscle.

During this assessment, the bladder is usually filled with normal saline solution (or x-ray contrast solution in the case of videourodynamics) either through a separate catheter placed transurethrally or through the filling channel of a dual lumen catheter if such is used to measure intravesical pressure. Usually the filling rate is much faster than physiological bladder filling.

The intravesical, abdominal and detrusor pressure are monitored as the bladder is filled and before the patient has been given ‘permission to void’. The storage ability of the bladder is assessed in terms of the volumes required to elicit various sensations from the patient, its capacity, its compliance and its stability. The filling (storage) phase of cystometry is also the only method of demonstrating urodynamic stress incontinence (USI).

3. PRESSURE-FLOW STUDIES (VOIDING CYSTOMETRY)

This is a measurement of the mechanics of micturition. When the filling (storage) phase of cystometry is complete, the patient is given ‘permission to void’ and will empty their bladder on a flow meter whilst intravesical, abdominal and detrusor pressures are being monitored. The simultaneous measurement of flow rate and pressure enables voiding to be assessed and, when bladder emptying is poor, it can help determine whether poor flow is due to an outflow obstruction or poor detrusor contractility.

4. URETHRAL PRESSURE PROFILOMETRY

This is a test carried out in some centres and measures the urethra’s ability to act as a valve to contain urine within the bladder. A pressure sensor is placed transurethrally into the bladder and then withdrawn along the urethra (usually by a mechanical puller at a constant rate). The pressure along the length of the urethra is measured, usually relative to the pressure inside the bladder. The maximum pressure measured in the urethra gives an indication of the closure function of the urethra and may be of help in determining the management of the patient with USI.

5. ABDOMINAL LEAK POINT PRESSURE

This is a test carried out in some centres and is another measure of the urethra’s ability to act as a valve to contain urine within the bladder. Intravesical or abdominal pressure is measured whilst the patient is asked to increase their abdominal pressure by valsalva or by coughing. The abdominal pressure required to produce leakage from the bladder gives an indication of the closure function of the urethra. The greater the pressure required to produce leakage, the better the closure function of the urethra. This test may be of help in determining the management of the patient with USI.

IV. TECHNOLOGICAL INNOVATIONS IN URODYNAMICS

1. AIR-CHARGED CATHETERS FOR PRESSURE MEASUREMENT

Air-charged catheters have been used for pressure measurement in urodynamics for many years. However, until recently, they have been the sole preserve of enthusiasts who have manufactured and used them ‘in-house’.

Recently, commercial, single-use, air-charged catheters have been developed and used for intravesical, intraurethral and abdominal pressure measurement in urodynamics (T-Doc, Wenonah, NJ). Initial reports from a female cadaveric study showed that these catheters gave more reproducible measurements of maximum urethral closure pressure compared to microtip catheters, water filled catheters and fiberoptic catheters. [8] In a more recent study in 2004 on 45 women, their performance has been shown to be comparable to microtransducers in the measurement of maximum urethral closures pressure and Valsalva leak point pressure (VLPP). [9] However, the same study showed a difference in functional urethral length (FUL) which was attributed to the different diameters of the two catheters.

A criticism of this study was that the catheters were not used in a random order. Therefore in 2008, Zehnder et al carried out a randomised comparison of these catheters with microtip catheters in 64 women. The measured MUCP and FUL and found that the air-charged catheter was as least as reliable as the microtip for measuring these parameters. However, because the air-charged catheter gives a higher reading of both parameters compared to the microtip device, they concluded that they cannot be used interchangeably for clinical purposes. [10] These devices are being actively marketed for the
measurement of intravesical and intra-abdominal pressure during filling and voiding cystometry. However, there have been no published studies in the peer-reviewed literature concerning their performance in this way; there are only the studies mentioned above which predominantly relate to the measurement of urethral pressure. There is no reason to suspect that these devices are inappropriate for the measurement of such pressures and, indeed, the measurement of VLPP by Pollak et al [9] is encouraging that they can be used to measure intravesical pressure. Nevertheless, a comparison of the air-charged catheters with the traditional fluid-filled lines for intravesical and intra-abdominal pressure measurement would be useful; particularly comparing their measurements during relatively fast events such as coughing.

Air-charged catheters have several practical advantages over fluid-filled pressure lines because there is no fluid connection between the patient and the urodynamic equipment; just air. This means there is no hydrostatic pressure effect to account for so that there is no need to position anything at the level of the symphysis pubis. There is no need to flush the system through to exclude air; a process that is essential in a fluid-filled pressure-sensing environment. There are no artefactual fluctuations in pressure produced when the patients move. Essentially, these devices are ‘plug and play’ which means they are much easier to set up and use compared to the fluid-filled system. Therefore, they have the potential to overcome one of the problem areas of urodynamics; that of setting up. However, although they may make urodynamics easier to set up, the conduct and interpretation of a urodynamic study still requires an experienced, appropriately trained practitioner.

Conclusions (level 3)

• Air-charged catheters may provide an acceptable alternative to other techniques for measuring the pressure closing the female urethra.

• There have been no studies to show whether air-charged catheters provide an acceptable alternative to fluid-filled lines for measuring intravesical and intra-abdominal pressure in urodynamics.

Recommendation (grade C)

• Investigators planning to use air-charged catheters for intravesical and intra-abdominal pressure in urodynamics would be advised to check for themselves that they have an equivalent performance to their current system for measuring pressure

Topic for research

• That a study is set up to compare the performance of air-charged catheters with fluid-filled pressure lines in the measurement of intravesical and intra-abdominal pressure during filling and voiding cystometry; particularly during ‘fast’ events such as coughing.

2. OBJECTIVE ASSESSMENT OF BLADDER SENSATION

Bladder sensation during urodynamics is usually recorded by the simple expedient of asking the patient to inform the investigator when they experience different sensations. This is a somewhat subjective measurement which can be confounded by the investigators inadvertently distracting the patient whilst bladder filling is being carried out. Investigators can also bias the measurement by inadvertent prompting of the patient.

In 2005, Craggs described a patient-activated, keypad ‘urge score’ device to measure sensations during bladder filling. [11] This enables patient perceptions of bladder filling and the successive stages of increasing bladder sensation to be recorded without prompting or intervention by the investigator. The accuracy of the ‘urge keypad’ during filling cystometrography was validated in patients with urgency incontinence, and compared with data abstracted from patient voiding diaries. Craggs concluded that the device provides reliable and repeatable measures of different bladder sensations, with excellent, statistically significant consistency between bladder volumes and corresponding levels of sensation.

The development of an objective method of recording bladder sensation during filling cystometry appears to be desirable. Whether it improves the reproducibility and sensitivity of urodynamics has yet to be determined.

3. NON-INVASIVE PRESSURE-FLOW MEASUREMENTS

Over recent years, groups in Newcastle upon Tyne (UK) and Rotterdam (The Netherlands) having been developing non-invasive techniques to measure pressure-flow in males.

The UK group has developed a penile cuff device. [12] The cuff is placed around the penis and is inflated and deflated whilst the patient voids into a urine flow meter. The pressure required to interrupt the flow is assumed to be equivalent to the bladder pressure generating the flow at that time. The group has determined that cuff widths of 40 to 50 mm are optimal for ensuring good pressure transmission from the cuff to the urethra. [13]

Further development of the technique resulted in the publication of a nomogram to classify whether individuals are obstructed or not obstructed when measured by this technique. [14]
There is apparently good agreement between experienced operators regarding the measurement of the pressure at which flow is interrupted. [15] In 2008, non-invasive measurements of pressure and flow were carried out at six different sites in the UK. [16] The measurements on individuals were repeated a median of 20 days later. Only 69% of tests produced analysable data on the two occasions. Whilst the mean differences in flow rate (0.2 ml/s) and cuff interruption pressure (4 cm H₂O) were small, 33% of men changed diagnostic category with the repeat measurement (from obstructed to non-obstructed or vice versa).

There is evidence that the method is sensitive to change. In 2007, 163 men underwent non-invasive pressure flow study using the penile cuff technique before and 4 months after transurethral prostate resection. [17] There was a significant change in flow rate and cuff-interruption pressure following removal of the obstruction in addition to 80% becoming non-obstructed on the basis of their measurements.

The same group produced retrospective evidence that categorisation of bladder outlet obstruction by the penile cuff technique improves prediction of outcome from endoscopic prostatectomy. [18] In 179 men undergoing TURP following standard assessment in the institution concerned, 37% were categorised as having bladder outlet obstruction (BOO) by the penile cuff test and 87% of these had a good outcome from TURP. Whereas of the 19% the of deemed not obstructed, 56% experienced a good outcome (p<0.01). In the remaining men not categorised in these two groups, 77% had a good outcome. However, the retrospective nature of this study weakens the argument for the prognostic ability of the penile cuff test.

The penile cuff test is now commercially available as the CT3000 (Mediplus Ltd, High Wycombe, UK).

The group in Rotterdam had a similar approach to developing a non-invasive method of measuring pressure and flow in men. However, instead of using a penile cuff to interrupt flow, they used a condom catheter through which the patient voided into a urine flow meter. During flow, the stream would episodically be diverted to a pressure transducer which would record the bladder pressure at that time. [19] They were able to correctly classify most men as being obstructed or not obstructed when compared to the ICS nomogram provided that the men did not strain during voiding.

Further work on the technique in 2003 revealed that a minimum flow rate of 5.4 ml/s was necessary to produce an accurate assessment of bladder pressure during voiding using the condom catheter technique. [20]

In 2004, the technique was reported to have a reproducibility comparable to that of invasive pressure-flow studies in an interim analysis of the first 730 patients enrolled in a study of changes in urinary bladder contractility secondary to benign prostatic hyperplasia. [21] In 618 (94%) of 659 eligible participants, one condom pressure measurement was completed; two measurements were done in 555 (84%). The maximum condom pressure ranged from 28 to 228 cm H₂O (mean 101, SD 34). A difference between the two pressures of less than ±21 cm H₂O was found in 80%. The mean difference was -1 cm H₂O (SD 18), significantly different from 0.

In the same year, the repeatability of the condom catheter technique was assessed in 457 volunteers and compared to that of the invasive pressure-flow technique in 397 comparable male patients. [22] The repeatability of the non-invasive method was found to be comparable to, or slightly better than, that of pressure-flow studies.

In 2006, the bladder volume dependency of the isovolumetric intravesical pressure measurement by the condom catheter technique was investigated. [23] In the 1,020 healthy subjects studied, it was concluded that the optimum bladder volume for isovolumetric pressure measurements, was 264 ± 122 mL (mean ± SD) and that measurements should be taken at or above this optimum volume. At volumes below the optimum volume, the pressure decreases by approximately 5% for each 10% of volume decrease. At bladder volumes smaller than 247 mL, pressure readings in 50% of subjects were suboptimal.

The same group in Rotterdam has also been exploring the measurement of perineal noise during voiding as a way of non-invasively quantifying male bladder outlet obstruction but the work has not yet progressed sufficiently beyond testing on models to determine the viability of this technique in vivo. [24, 25]

Both the penile cuff and condom catheter techniques show promise as non-invasive techniques to assess outlet obstruction in men. However, they are subject to some confounding factors and appear to give inaccurate results if the patient strains during the assessment. It remains to be seen where and if these measurements have a role in the routine clinical assessment of men with symptoms of bladder outlet obstruction.

**Conclusion (level 2)**

- Non-invasive measurements of pressure and flow in men by the penile cuff or condom catheter seem to be as clinically useful as the traditional invasive measurement of pressure and flow.

**Recommendation (grade B)**

- That non-invasive measurements of pressure and flow should be considered when the patient is not required to undergo an invasive assessment of the storage function of the lower urinary tract.
4. URETHRAL RETRO-RESISTANCE PRESSURE

In 2004, Slack et al described a ‘new clinical measure of urethral function’. [26, 27] In the measurement of urethral retro-resistance pressure (URP), a small meatal plug is inserted just inside the female urethra and saline is pumped into the urethra. The pressure in the system rises until it reaches a value sufficient to overcome the resistance offered by the urethra and the fluid then retrogradely flows into the bladder. The pressure required to achieve and maintain an open sphincter is taken to be a measure of urethral closure function. Whilst the technique is new in that modern technology is used to apply the head of pressure to the urethra and the measurement of opening pressure is automatically recorded, the basic principle behind the technique has its origins in 1923 when Bonney made a simple attempt to measure the efficiency of urethral closure. [28]

In his first paper, Slack et al studied 258 stress incontinent women with the URP technique and compared their values with incontinence severity. They also compared the URP measurements with those of maximum urethral closure pressure (MUCP) and valsalva leak point pressure (VLPP). They found that URP measurements correlated well with both MUCP and VLPP. They also found that URP measurements correlated with incontinence severity whereas neither MUCP nor VLPP did so. [26]

In the second study, Slack et al showed that the URP in a group of 61 women, without symptoms of urinary incontinence and who had negative standing stress tests, was significantly greater than the group of stress incontinent women who had been tested previously. [27] This study also provided some test-retest data which showed that URP measurements were consistent in individuals.

The authors concluded from both of these pieces of work that the technique of URP shows promise as a physiological urethral pressure measurement.

In 2006, Digesu et al carried out measurements of URP on 165 women with various urodynamic diagnoses. [29] Women with urodynamic stress urinary incontinence (USI) had significantly lower URP than women with competent urethral sphincters. Women with mixed urodynamic incontinence had values of URP intermediate between women with detrusor overactivity (DO) and those with USI. In the mixed group, URP mean values were not significantly different from those with DO and competent sphincters or those with USI.

There was no significant difference between mean URP values and different urinary symptoms. The authors concluded that whilst there are significantly different URP measurements between women with DO and those with USI, the URP is not a diagnostic tool.

In 2007, Tunn et al measured URP in 48 women with clinically and urodynamically proven SUI without prolapse before and after anti-incontinence surgery (colposuspension n = 8, tension-free vaginal tape n = 6, tension-free transoburator tape n = 34). They found that preoperative URP did not correlate with SUI in all women, had no predictive value, and did not correlate with the outcome of anti-incontinence surgery. However, they did find a positive correlation between URP and body mass index. [30]

In 2008, Roderick et al reported on URP and established measures of incontinence severity in 100 women with pure USI prior to and 3 months after the insertion of a midurethral tape. [31] They found mean URP bore no relationship to the severity of urine loss assessed by 24-hour pad loss. There was no correlation between URP and other measures of incontinence severity. Pre and postoperative URP was available in 73 women. Although 84.9% were objectively cured after surgery, pre and postoperative URP was not significantly different (62.7 ± 19.4 cm H2O vs 61.2 ± 20.4 cm H2O). They concluded that urethral retro-resistance pressure is not a useful measure of urethral function.

**Conclusion (level 2/3)**

- Urethral retro-resistance pressure measurements do not give any better information about urethral closure function than the urethral pressure profile or valsalva leak point pressure.

**Recommendation (grade B/C)**

- That urethral retro-resistance pressure measurements should be discouraged because equivalent information can be obtained from urethral pressure measurements made with conventional urodynamic equipment.

5. URETHRAL PRESSURE REFLECTOMETRY

In 2005, Klarskov et al reported on an in vitro study of pressure reflectometry; a novel technique for the simultaneous measurement of cross-sectional area and pressure in a collapsible biological tube. [32] A very thin, highly flexible 6 cm long polyurethane bag with a diameter of 5 mm when expanded was introduced into eight different test model cavities of known cross-sectional areas in the range of 4-16 mm². The cross-sectional area was measured by acoustic reflectometry while pressures of 10-200 cm H2O vs 61.2 ± 20.4 cm H2O. They concluded that urethral retro-resistance pressure measurements should be discouraged because equivalent information can be obtained from urethral pressure measurements made with conventional urodynamic equipment.

422
clinical use in the range of 4-16 mm$^2$ and at pressures from 10 to 200 cm H$_2$O.

In 2007, Klarskov and Lose used the technique of urethral pressure reflectometry (UPR) to assess the female urethra. [33] Cross-sectional area of the urethra was measured during inflation and deflation of the thin bag placed in the urethra using step-wise pressure changes within the range 0 to 200 cm H$_2$O. They showed that the technique was easy to carry out and that they could obtain measurements of opening and closing pressure, opening and closing elastance and hysteresis. They postulated that these parameters had the potential to provide more physiological information about the urethra than could be obtained from conventional urodynamic studies.

In the same year, Klarskov and Lose compared UPR with urethral pressure profilometry (UPP) in 143 women (105 patients and 38 healthy volunteers). [34] UPR was measured supine both while relaxed and during ‘squeeze’, and while upright and relaxed. UPP was carried out using the perfusion technique with the patient supine and relaxed. All the women were assessed twice with both UPR and UPP at the same setting (short-term reproducibility) and 17 patients were assessed with both methods on two different days (long-term reproducibility). The authors showed that UPR measured the same pressure as UPP but the UPR was more reproducible. With the patient relaxed the opening and closing pressure, opening and closing elastance and the hysteresis can be measured while supine and upright; while squeezing, the opening pressure and elastance can be measured.

In 2008, Klarskov and Lose measured UPR parameters in healthy and stress urinary incontinent (SUI) women and compared them with urethral pressure parameters obtained by the perfusion technique. [35] The study included 30 SUI women and 30 volunteers (23 “continent” and 7 “nearly continent”). The women were examined in the supine position both while relaxed and during squeezing, and upright position and the following UPR variables were measured; opening and closing pressure, opening and closing elastance, hysteresis (absolute) and hysteresis (percent). UPP was carried out with the women supine while relaxed and during squeezing. The maximum urethral pressure (MUP) and maximum urethral closure pressure (MUCP) were obtained. They showed that all parameters except the hysteresis (percent) were significantly decreased in the SUI group compared to the volunteers. The squeeze opening pressure increased in all women compared to the resting condition, while MUP and MUCP during squeeze increased in 78% and decreased in 22%. The separation between the continent and SUI women was better using the resting and squeezing opening pressure than the corresponding UPP parameters. They concluded that UPR is a clinically reliable technique, which provides sound physiological parameters. The resting and squeezing opening pressures separate SUI from continent women better than the UPP parameters. They also postulated that UPR parameters have the potential to provide a pathophysiologic subdivision of SUI and other dysfunctions.

**Conclusion (level 3)**

- Measurement of opening pressure from urethral pressure reflectometry appears to have more power to separate women with stress urinary incontinence from those with normal urinary control when compared to continent women.

**Recommendation (grade C)**

- That further studies are undertaken to investigate the clinical usefulness of this technique.

---

**C. URODYNAMICS: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE**

### I. REPRODUCIBILITY OF FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS

#### 1. INTER-OBSERVER, TEST-RETEST AND PRACTICE VARIATION

When different investigators judge urodynamic traces together with written clinical information in women, there is agreement between them regarding the final clinical diagnosis in about 80% of cases. In other words there is, depending on the diagnosis, some disagreement in 20% of cases when urodynamics is judged in this manner. [36].

A few studies have concluded that there is good inter and (short time) intra–rater reliability. In a single centre series of 621 urodynamic pressure flow tracings of female patients, small average differences between analysis parameters were observed by various investigators, which was interpreted as good interobserver agreement. [37] Inter-observer variability has also been tested in other ways. In a study where 4 experienced practitioners, evaluated 17 pediatric urodynamic datasets, they failed to agree on aspects of detrusor function, including DO, in a quarter of the cases. [38] This result is reminiscent of a similar study of the interpretation of urodynamic recordings of male voiding function. [39]

In a survey to determine the variation in urodynamic...
practices in the United Kingdom 100 questionnaires were sent to units known to be performing urodynamic investigations. There was a significant variation in practices with only 51% of units having a protocol for what tests should be performed, under what circumstances and how. [40]

Standardisation of urodynamic variables may result in a greater consistency of diagnosis, allowing easier comparisons of treatment regimes and outcomes, and is the conclusion of studies of this kind and reviews. [41, 42].

In a review to examine the best position during cystometry to demonstrate DO and reproduce the overactive bladder (OAB) symptoms, 16 relevant studies with good consistency were analysed. All but two showed a clear effect, with a higher incidence of DO in the vertical position (sitting or standing) or onset of DO when changing to a vertical position. Performing the UDS in a supine position would have missed a large proportion of DO diagnoses ranging from 33% to 100%. The authors noticed a substantial practice variation in position during urodynamic investigation and demanded standardisation. [43]

2. SHORT-TERM (WITHIN-SESSION) REPRODUCIBILITY

A number of authors have investigated the within-session reproducibility of cystometric measurements. Because such measurements are conducted within a short period of time, the possibility that the first measurement influences the second for example through a direct effect on the mechanical properties of the bladder (hysteresis and/or viscoelasticity) has to be considered.

Brostrom et al [44] examined 30 healthy women with a mean age of 52 years, performing 2 consecutive medium fill rate (50 mL/min) cystometries in a single session. The volumes at first desire to void (FDV) and normal desire to void (NDV) increased significantly from the first to the second measurement, by 34 and 51 mL respectively. The maximum bladder capacity showed no significant change. The proportion of these healthy subjects who showed DO decreased from 4/30 (13%) in the first cystometry to 1/30 (3%) in the second but this was not statistically significant.

In a similar study [45] of short-term repeatability in 31 female patients aged 14-74 years, two consecutive cystometries were performed with body temperature liquid at a rate of 50 mL/min. On the first cystometry, FDV occurred at a median volume of 112 mL (range 26-503 mL). The cystometric capacity had a median value of 150 mL, with a range from 39-633 mL. (These values may be compared with the normal values in Table 3). The volume at FDV increased by 46 mL from the first to the second cystometrogram, while the cystometric capacity increased by 35 mL. These changes are similar to those seen in normal volunteers, but, as the authors point out, they are not clinically important because they are much smaller than the random variability within subjects, as measured by the 95% confidence limits of ±130 and ±106 mL respectively.

Chin-Peuckert et al [46] examined the variability between two consecutive cystometries in 32 male and 34 female children with a mean age of 7. Most suffered from spinal dysraphism. A smaller number showed DO on the second study than on the first (p<0.05), and similarly the volume at which DO was first observed was larger on the second study (p<0.05). Interestingly, these results are similar to those obtained in children without overt neuropathy.[47]

Hess et al [48] did not perform repeated cystometries, but first measured the bladder pressure “as is” at whatever volume was in the bladder initially, in 21 men and 1 woman with ‘neurogenic bladder’. They then drained the bladder and refilled to the same volume and again measured the pressure. The second “cystometric” pressures were higher than the initial ‘physiological’ ones by approx 6 cm H2O (p = 0.01), although there was a strong correlation between them.

In another study where fifty consecutive individuals with spinal cord injury had 2 trials (trial 1 and trial 2) of UDS done 5 minutes apart, differences in maximum cystometric capacity, opening pressure, maximum detrusor pressure, volume voided, and post void residual (PVR) volume were evaluated. The variation observed was ± 100-150 mL for the volume parameters and ±10-20 cm H2O for the mentioned pressure parameters. [49]

Sixty men with LUTS and 35 with neurogenic bladders after spinal cord injury (SCI) were assessed. Symptom scores and uroflowmetry were obtained and filling and pressure-flow cystometry were carried out three times in succession. In men with LUTS, a significant decrease in the number and pressure of involuntary detrusor contractions (IDC) in consecutive cystometries resulted in a reduction of observed DO from 72% to 63% and 48%, in the three studies. In men with SCI, cystometric variables and DO remained consistent over sequential studies. [50].

Twenty asymptomatic women with a mean age of 41.8 years (30-55) agreed to undergo a urodynamic evaluation, repeated immediately without removing the catheters (a two-fill and void study). [51] Sixteen women of this cohort returned for an identical assessment 1-5 months later. Immediate and short-term repeatability of UDS parameters was assessed. The short time variation was ± 5 ml/s for Qmax and ± 10 cm H2O for PdetQmax. Voided volume and first sensation of filling (FSF) differed ±50 mL in the test retest situation. The authors noted that the variation of parameters in these healthy women was larger than observed in other studies with patients.
3. INTERMEDIATE-TERM REPRODUCIBILITY

Homma et al [52] found that, in 30 patients with DO, repeat cystometry carried out 2-4 weeks after initial testing showed a consistent shift toward normal. Bladder volumes increased by 10-13% (p<0.01), while DO disappeared in 10% of subjects and decreased in amplitude by an average of 18% in the remaining cases. The random variability of cystometric capacity was ± 57 mL (95% CI).

4. LONG-TERM REPRODUCIBILITY

Sørensen et al [53] investigated 10 healthy females (mean age 34 years), twice at an interval of 2 years. They carried out measurements in both supine and sitting positions. FSF occurred at a mean volume of 378 mL supine and 354 mL sitting, with intra-subject variability over two years as quantified by the standard deviation (SD) of 76 and 100 mL (SD) respectively. Maximum capacity was 512 mL supine and 502 mL seated, with intra-subject SD of approximately 75 mL in both cases. Inter-subject SD's were a little larger: 76-144 mL. No significant differences in volumes or compliance over two years could be demonstrated (Table 2).

Summary

In patients and in healthy volunteers, if cystometry is repeated either during the same session or within about 4 weeks, the bladder volumes at which various sensations are felt and the bladder capacity tend to increase by 30-50 ml, while the proportion of traces showing DO tends to fall. These systematic changes are fairly small in comparison with the random within-subject variability, which has an SD of about 50-60 mL.

Conclusions (evidence level 2)

- A number of studies have reported test retest variation of ±10-15% for various parameters (volume, pressure or flow) and observations; this can be regarded as the physiological variation of urodynamic testing.
- Various studies have demonstrated clinically relevant practice variation and inter-rater/observer variation.

Recommendations (grade B)

- The committee recommends that investigators and clinicians take into account the inherent physiological variability of urodynamic testing.
- The committee recommends investigators and clinicians evaluate the ‘representativity’ of the tests (which is an evaluation based on the patient’s perception as to how well the tests have reproduced their usual lower urinary tract function) and the committee recommends that examiners strive towards maximal representativity.

Table 2. Intra-subject variability of cystometric parameters from one test to the next, within-session, intermediate-term (2-4 weeks), and long-term (2 years)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Period between tests</th>
<th>Systematic change (test 2 - test 1)</th>
<th>Within-subject random variation from test 1 to test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brostrom [44]</td>
<td>Healthy ♀♂</td>
<td>Same session</td>
<td>ΔFDV = +34</td>
<td>MCC: ±30</td>
</tr>
<tr>
<td>Mortensen [45]</td>
<td>Patients ♀♂</td>
<td>Same session</td>
<td>+46</td>
<td>NDV: ±130 (95% CI) MCC: ±106 (95% CI)</td>
</tr>
<tr>
<td>Chin-Peuckert [46]</td>
<td>Children, spinal dysraphism ♀♂</td>
<td>Same session</td>
<td>ΔVDO = + (p&lt;0.05)</td>
<td>DO = +</td>
</tr>
<tr>
<td>Hess [48]</td>
<td>Neurogenic bladder ♀♂</td>
<td>Same session</td>
<td>ΔP = + 6 cm H2O</td>
<td>MCC: ±57 ml (95% CI)</td>
</tr>
<tr>
<td>Homma [52]</td>
<td>Patients ♀♂</td>
<td>2-4 weeks</td>
<td>ΔV = +10% -13%</td>
<td>DO = -10%</td>
</tr>
<tr>
<td>Sørensen [53]</td>
<td>Healthy ♀♂</td>
<td>2 years</td>
<td>ΔFSF:ns</td>
<td>MCC: ±75 mL (SD)</td>
</tr>
</tbody>
</table>

(SD) Key to symbols: VDO = volume at which DO occurs; Δ = increase from test 1 to test 2.
• The committee recommends persistent attention to the standardisation of techniques and interpretation of results, especially to reduce inter-practice variation and inter-observer variability.

**Topics for research**

• The committee suggests further consideration of standardisation of urodynamic tests, procedures and evaluation, especially to reduce inter-practice variation.

• The committee suggests intensive dissemination of up-to-date standards and careful training of urodynamic investigators and suggests evaluation of the effect of these standards and training on health care quality.

---

### 5. REPRODUCIBILITY OF AMBULATORY URODYNAMICS

The third ICI reported that there was no published data on the reproducibility of ambulatory urodynamic studies. This continues to be the case.

---

### II. CYSTOMETRY: NORMAL VALUES

#### 1. NORMAL VALUES: FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS

Table 3 shows normal values for cystometric variables reported by a number of authors. This has been updated since the table published in the 3rd ICI. A striking observation is that there is great inter-centre variability, even for nominally similar patients. There

---

**Table 3. Normal values (mean or median) of filling cystometry variables**

<table>
<thead>
<tr>
<th>Authors</th>
<th>population</th>
<th>parameters</th>
<th>FSF</th>
<th>FDV</th>
<th>NDV</th>
<th>SDV</th>
<th>MCC</th>
<th>DO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wyndaele [54]</td>
<td>Healthy</td>
<td>Body temp 30 mL/min</td>
<td>151</td>
<td>140</td>
<td>106</td>
<td>453</td>
<td>429±153</td>
<td>453</td>
</tr>
<tr>
<td>Van Waalwijk [55]</td>
<td>Healthy</td>
<td>Seated 35 mL/min</td>
<td>104</td>
<td>57</td>
<td>66</td>
<td>263</td>
<td>96</td>
<td>3/17</td>
</tr>
<tr>
<td>Robertson [56]</td>
<td>Healthy</td>
<td>Room temp 50 mL/min</td>
<td>342</td>
<td>(269-471)</td>
<td>500</td>
<td>(345-562)</td>
<td>475</td>
<td>(400-600)</td>
</tr>
<tr>
<td>Sørensen [57, 58]</td>
<td>Healthy</td>
<td>Supine, body temp 60 mL/min</td>
<td>347</td>
<td>101</td>
<td>482</td>
<td>103</td>
<td>0/10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-meno</td>
<td>Supine, body temp 60 mL/min</td>
<td>357</td>
<td>126</td>
<td>491</td>
<td>147</td>
<td>0/12</td>
<td></td>
</tr>
<tr>
<td>Heslington [59]</td>
<td>Healthy</td>
<td>Supine 100 mL/min</td>
<td>420</td>
<td>175-810 (range)</td>
<td>4/22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walter [60]</td>
<td>Healthy</td>
<td>Supine, body temp 30 mL/min</td>
<td>225</td>
<td>(150-300)</td>
<td>425</td>
<td>(400-490)</td>
<td>0/15</td>
<td></td>
</tr>
<tr>
<td>Hosker [61]</td>
<td>Healthy</td>
<td>Supine, body temp 100 mL/min</td>
<td>304</td>
<td>116</td>
<td>543</td>
<td>94</td>
<td>0/72</td>
<td></td>
</tr>
</tbody>
</table>

Total DO 20/252 = 8% Key to symbols: ± = SD; (xxx-yyy) = interquartile range; xxx-yyy = 95% confidence interval. All volumes are in ml
is no evidence from the table that these variations are associated with differences in filling rate, infusate temperature, or patient position. It appears that the sensations themselves are ill-defined and inadequately standardised.

Wyndaele et al [54] examined 50 volunteers. The bladder was filled at 30 mL/min with body temperature saline. For males (n=18; mean age 22 ± 3 years), FSF occurred at 222 mL ± 151 mL; FDV occurred at 325 mL ± 140 mL; and strong desire to void (SDV) occurred at 453 mL ± 94 mL, and this was taken as maximum capacity. For females (n=32; mean age 21 ± 2 years) FSF occurred at 176 ± 96 mL; FDV at 272 mL ± 106 mL; and SDV at 429 mL ± 153 mL. DO was observed in 7/50 (14%) of these normal volunteers. The group also published a study with symptom free ‘middle-aged’ female volunteers. Of their volunteers a substantial number was excluded because of asymptomatic abnormalities. The remaining had an average capacity during cystometry of 586 mL (sd 193 m) with 258 mL and 1092 mL as extremes. [63].

In 17 healthy subjects, reported in another study, with a mean age of 24 years, but a wide age range, FSF occurred at a mean volume of 104 ± 57 mL; FDV occurred at 172 ± 66 mL; NDV occurred at 294 ± 96 mL; strong desire occurred at 263 ± 93 mL; and DO was observed in 3 of 17 subjects (18%) on conventional cystometry in the seated position. The filling rate was 35 ml/min. On ambulatory monitoring the proportion showing DO rose to 69% (Table 4).

Fifty-seven postmenopausal women: 30 continent and 27 with SUI underwent urodynamic investigation in another small study. The incontinent women showed lesser bladder capacity at FDV, as well as decreased urinary volume. MUCP was lower in the patients in relation to the continent women. Other differences between the normals and the incontinent women were not observed. [64].

Robertson [65] reported on 11 male and 6 female healthy asymptomatic volunteers, age range 22-72 years, examined by conventional 20ºC saline filling cystometry and by ambulatory monitoring. In females: the ‘filling volume’ (presumably equivalent to maximum cystometric capacity) was: 342 mL median (269-471 mL IQR) at 50 mL/min; and 475 mL median (400-600 mL IQR) at 100 mL/min. In males it was: 500 mL median (345-562 mL IQR) at 50 ml/min; and 500 mL median (390-790 mL IQR) at 100 mL/min. DO was observed in 2/12 volunteers (17%) during filling cystometry at 50 mL/min; there was none at a filling rate of 100 mL/min (which preceded the 50 ml/min filling). During ambulatory monitoring DO was seen in 6/16 subjects (38%). The median volume voided during ambulatory monitoring was markedly smaller than the filling volume on conventional cystometry (compare Tables 3 and 4).

Sørensen et al [58] examined 10 younger women (mean age 34 years, range 29-46 years) at 3 points of the menstrual cycle, filling the bladder with body temperature fluid at 60 ml/min. Because the variables showed little systematic variation during the cycle, average values are given here. FSF occurred at 347 mL ± 101 mL (SD) supine and 357 mL ± 126 mL seated. MCC was 482 mL ± 103 mL, supine and 491 mL ± 147 mL seated. No DO was observed. The same authors [57] investigated 12 healthy post-menopausal females, mean age 59 years, using similar parameters. The means of 2 studies showed: FSF, supine, at 396 mL ± 163 mL (SD); and sitting at 331 mL ± 168 mL. MCC, supine, at 551 mL ± 223 mL; and sitting at 489 mL ± 196 mL. They reported no DO.

In 2004, Hosker reported on the urodynamic findings of 72 healthy female volunteers (mean age 41.4 ± SD 10.1 years and mean parity 2.3 ± 1.6) who formed the control group for a study of urethral pressures in women with urodynamic stress incontinence. Cystometry was performed in the supine position with saline at body temperature filling the bladder at a rate of 100 mL/min. The mean PVR on catheterisation was 11 ± 13 mL. The mean FDV was 304 ± 116 mL and the mean MCC was 543 ± 94 mL. He reported no DO. [61]

Twenty-four women without a history of frequent urgency and without DO (mean age 50.2 years, range 22-80 years), including 7 pre- (29.2 years), 7 peri- (48.8 years), and 10 postmenopausal (66.0 years) women were studied with uroflowmetry and video urodynamics to determine normative data for LUT.

## Table 4. Normal values – ambulatory monitoring

<table>
<thead>
<tr>
<th>Authors</th>
<th>population</th>
<th>Mean/median voided volume</th>
<th>DO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Waalwijk [55]</td>
<td>Healthy and</td>
<td>200 ± 78 ml (mean ± SD)</td>
<td>11/16</td>
</tr>
<tr>
<td>Robertson [56]</td>
<td>Healthy and</td>
<td>263 ml (201-346) (interquartile range)</td>
<td>6/16</td>
</tr>
<tr>
<td>Heslington [59]</td>
<td>Healthy</td>
<td>212 ml 100-550 (range)</td>
<td>15/22</td>
</tr>
<tr>
<td>Salvatore [62]</td>
<td>Healthy</td>
<td></td>
<td>2/21</td>
</tr>
<tr>
<td><strong>Total DO</strong></td>
<td></td>
<td></td>
<td>34/75 = 45%</td>
</tr>
</tbody>
</table>

427
function in asymptomatic continent women without DO across the age span. For all subjects, median maximum single voided volume in bladder diary was 500 mL and median MCC was 580 mL. SDV was reported at 287, 366, and 425 mL for pre-, peri-, and postmenopausal groups, respectively. The maximum flow rate was 25, 32, and 23 mL/sec in uroflowmetry and 23, 24, and 18 mL/sec during the pressure-flow study, respectively. Median PVR was below 20 mL in all groups. At maximum flow rate subjects voided with detrusor pressures of 29, 26, and 24 cm H2O, respectively and maximum urethral closure pressure was 94, 74, and 42 cm H2O, respectively. [66].

Heslington and Hilton [59] examined 22 asymptomatic healthy female volunteers, performing conventional cystometry and ambulatory study in a random order. DO was observed in 18% on conventional cystometry and 68% on ambulatory monitoring.

As indicated above, most studies of ambulatory monitoring in healthy subjects have revealed high percentages with DO (typically of modest amplitude [55, 67]). However, Salvatore et al [62] by using 2 bladder catheters simultaneously and only verifying DO if it was shown by both, suggested that some of this apparent overactivity was a measurement artifact, and that 90% of a group of 26 healthy women showed no DO on ambulatory monitoring.

Thirty healthy males aged 21-32 years volunteered for an ambulatory urodynamic 24 h investigation with a suprapubic catheter to study natural fill urodynamics. Thirty healthy males aged 21-32 years volunteered for an ambulatory urodynamic 24 h investigation with a suprapubic catheter to study natural fill urodynamics during normal and increased fluid intake. The recorded micturition data were: frequency (f), voided volume (VV), voiding time, maximum flow rate (Qmax) and time to Qmax. The number of sensed and not-sensed detrusor contractions, and their duration and time in relation to voiding were also recorded. During the recording day subjects were randomised to normal (30 mL/kg body weight per day) or larger (60 mL/kg body weight per day) fluid intake. There was a larger urine production and an increased voiding frequency in the fluid-loaded group (p<0.0001). The detrusor pressure (PdetQmax) was significantly higher in the fluid-loaded group (73 cm H2O, range 57-94) than in the normal fluid intake group (60 cm H2O, range 45-86) (p=0.003).

No other urodynamic data differed significantly between the two groups. Ambulatory urodynamics in normal young men showed a large interindividual variation. Detrusor contractions during filling were frequently recorded, and premicturition contractions were consistently found. The data found in this study were similar to previous home flow recordings in the same group. [68]

In a retrospective study of 186 selected investigations the influence of autologous urine production during filling cystometry on total bladder volume was observed. Mean filled volume (external infusion plus autologous urine production) was 346 ± 152 mL, but mean real bladder capacity (voided volume + residual urine) was 391 ± 170 mL. In all patients, 14% extra urine was produced due to autologous urine production (mean rate, 6.1 mL/min). In 42% of the investigations, the real bladder capacity was more than 110% of the infused volume. In 18% of the patients, the contribution of natural bladder filling was more than 25% of the infused volume. [69]

Urodynamic tests were, in another study, conducted on 39 asymptomatic male volunteers with a mean age of 25.8 years (range 21 to 31) and mean weight of 75.5 kg. (range 63 to 95) to examine the pressure-flow relationship and obtain evidence to support the hypothesis that fluid consumption has a role in detrusor voiding function. Volunteers were divided into 2 groups according to water consumption regimen of 30 mL/kg daily (17 patients, group 1) and 60 mL/kg daily (12, group 2). Bladder pressure was monitored via a suprapubic catheter and abdominal pressure was measured via a rectal balloon using an ambulatory system with an average duration of 20.5 hours. Doubling of water consumption increased urethral opening pressure from 51.2 ± 3.2 to 61.5 ± 5.1 cm H2O (p<0.05), maximum detrusor pressure from 58.9 ± 4.5 to 70.0 ± 6.2 cm H2O (p<0.01) and contractility from 15.4 ± 1.4 to 17.7 ± 1.4 W/m². There were no significant differences due to water consumption in maximum flow rate (24.4 ± 1.4 to 25.2 ± 1.8 mL/s) or bladder capacity (286 ± 20 to 329 ± 15 mL) but a significant increase in the number of micturitions from 5.8 ± 0.5 to 9.8 ± 0.5 per day (p<0.001) proportional to water consumption. [70]

2. COMPLIANCE

Compliance is the ratio of a change in volume measured relative to the corresponding change in pressure. Usually compliance is calculated over the change in volume from an empty bladder to that at MCC.

In 17 healthy subjects, using a filling rate of 35 mL/min, [55] the range of compliance values was very wide (range = 11-150 mL/cm H2O; mean ± SD = 46 ± 40 mL/cm H2O). Such a mean value implies only a small rise in pressure on filling (a few cm H2O), consistent with a high compliance. Sørensen et al [53] reported similar mean values for compliance in a group of healthy females: 62 mL/cm H2O initially and 58 mL/cm H2O on re-examination 2 years later. Even higher values of compliance were reported by Hosker (range = 31-800 mL/cm H2O; mean ± SD = 124 ± 150 mL/cm H2O) in 72 healthy females (age 25-75 years) and these reproduced the wide range of values already published. [61]

The results were comparable in elderly, peri and post menopausal women. [66]. In another selected group of healthy, middle aged, volunteers compliance was ‘high’ on average, however with a large variation. [63]
Similarly, Robertson showed that in 17 healthy male and female volunteers, the median detrusor pressure rise on conventional filling cystometry was 5 or 6 cm H\textsubscript{2}O at filling rates of 50 and 100 ml/min respectively. [65] On ambulatory monitoring the median pressure rise was 0 cm H\textsubscript{2}O however, a significantly smaller value.

Compliance cannot only be quantified in the units of ml/cmH\textsubscript{2}O but also as a dimensionless number measured from empty to MCC. Compliance increases with age (because bladder capacity increases with age). The dimensionless value of compliance presents a value of which is independent of age. This is especially relevant in children when intra- and inter-individual test (retest) comparisons are made. [71]

Consistently, among 22 healthy female volunteers, conventional cystometry and ambulatory study performed in random order showed a significantly larger detrusor pressure rise on conventional filling as compared with ambulatory studies. [59]

Although these figures show that conventional filling cystometry provokes higher pressure increase during filling than ambulatory monitoring with natural filling of the bladder, this is not necessarily a disadvantage because it may unmask abnormal compliance.

Robertson [65] reported cystometric variables for 6 patients with “low-compliance bladders” due to neuropathy. Conventional cystometry showed pressure rises of 18 (± 7) and 46 (± 13) cm H\textsubscript{2}O during bladder filling at rates of 20 and 100 mL/min respectively, but the pressure rise during natural (ambulatory) filling was much smaller (in fact, hardly distinguishable from normal): 6 (± 4) cm H\textsubscript{2}O. The corresponding compliance values were 8 (± 2) and 6 (± 3) mL/cm H\textsubscript{2}O for conventional cystometry (abnormally low), but 114 (± 32) mL/cm H\textsubscript{2}O for natural filling (a normal value). [67]

### 3. NORMAL SENSATIONS AND BLADDER CAPACITY - SUMMARY

Table 3 shows the striking variability from centre to centre: FSV for example occurs at about 100 ml in one centre but at about 350 ml in another, a value large enough to provoke a strong desire to void in the first.

The bladder capacity is somewhat less variable from centre to centre, its mean varying from 340 to 570 mL. Apart from this inter-centre variability, the inter-subject variability of all the parameters is also substantial, with an SD of about 100 mL in order of magnitude. Some of this variation represents genuine differences between subjects, but it should be noted that the within-subject variability is also quite large, in order of magnitude 50 mL (Table 2).

As a rule of thumb in healthy adult subjects, and omitting some of the more inconsistent values, FSF occurs at about 170-200 ml, FDV or NDV (the ICS makes no distinction [4]) at 250 ml, and strong desire to void at about 400 ml; MCC is about 480 ml. It is interesting that the mean voided volume on ambulatory monitoring falls between FSV (on cystometry) and FDV/NDV.

Thus, in daily life, the bladder is usually emptied long before a strong or even a “normal” desire to void would be felt on cystometry, although much more can be held if voiding has to be postponed. Correspondingly, there is a discrepancy in bladder capacity between daily life and urodynamic study, also depending on the method of measurement (uroflowmetry, voiding diary or cystometry).[72]

### 4. DETRUSOR OVERACTIVITY IN NORMAL SUBJECTS - SUMMARY

DO is shown during conventional cystometry by up to 17% of normal subjects with a mean percentage of about 8% (Table 3). The percentage is much higher (up to 69%, see Table 4) on ambulatory studies, although one group disputes this.

DO can be observed during urodynamic testing, in healthy subjects (without the symptoms that are usually associated with OAB) which indicates that the observation of ‘detrusor overactivity’ should not always be interpreted as ‘synonymous with pathology that demands treatment’.

**Conclusions (evidence level 2)**

- Various studies have been helpful to reveal normal values and test retest variation of urodynamic parameters in healthy volunteers.
- There is some evidence that evaluation of filling sensation may be different between laboratories, (thus: ‘may be observer dependent’), making data exchange as well as generalisation and interpretation of published data difficult.

**Recommendations (grade B)**

- The committee recommends that investigators and clinicians bear in mind the results of urodynamic testing in healthy persons and to recognise ‘normal’ test-retest variation as well as the differences and/or variations between ‘usual LUT behaviour’, ambulatory monitoring and office urodynamic testing.
- The committee suggests investigators should be sufficiently aware of the normal variation, and normal values of urodynamic studies.
- The committee recommends further standardisation and a practical objective means of recognising and recording the parameters relevant to sensation during bladder filling.
5. INFLUENCE OF CATHETER ON VOIDING

A urodynamic database of 600 consecutive women referred for the evaluation of voiding symptoms was reviewed to examine the effect of a 7F transurethral catheter on flowrate. Before urodynamic, all patients voided privately using a standard toilet and free flow was recorded. Only 100 patients who voided similar volumes varying by less than 20% on the free and pressure flow studies were included. In each voided volume category and urodynamic diagnosis, pressure-flow parameters were significantly different from the equivalent free flow parameters in all but 4 cases. Specifically the maximum flow rate was significantly less and flow time was significantly longer on pressure versus free flow studies (each p <0.01). An intermittent flow pattern was more common on pressure than in free flow measurements (43% versus 9%). [73]

Women between the ages of 30 and 70 years, without LUT complaints and without a history of surgery for urinary incontinence, were recruited to prospectively examine the effect of a 6F urethral catheter on the urinary flow rate in healthy women without LUT symptoms. After a free flow rate, cystometry and pressure-flow studies were performed twice using a 6F urethral catheter. The maximum flow rates during the first and second studies were compared with one another and with the nonintubated values. In the 20 volunteers (mean age 42 years), the mean nonintubated flow rate was 23 mL/s. With a 6F urethral catheter in place, the women had a mean maximum flow rate of 16 mL/s on the first study and 15 mL/s on the second. A significant difference was demonstrated between the free and intubated maximum flow rates for both the first (p = 0.0006) and the second (p = 0.0001) study. No significant difference was detected between the two intubated maximum flow rates (p = 0.262). [74]

The impact of three different sized (4.5-, 6- and 7F) catheters on pressure-flow studies was studied in 60 women undergoing urodynamic evaluation for LUT symptoms, divided into two groups (A and B) of 30 women each. The patients underwent non-invasive free-flow uroflowmetry with determination of PVR. In group A the two consecutive pressure-flow studies were performed using a 4.5F catheter once and a 6F catheter once; in group B the two consecutive pressure-flow studies were performed using a 4.5F catheter once and a 7F catheter once. The maximum and average flow rate in all pressure-flow studies performed were significantly lower than the equivalent free-flow parameters and the flow time was significantly longer for all pressure-flow versus free-flow studies. Furthermore, there was a significantly larger PVR for pressure-flow than for free-flow measurements. There was no significant difference in maximum flow rate, average flow rate and flow time between 4.5- and 6F pressure-flow studies (A). However, there was a statistically significant difference between 4.5- and 7F pressure-flow studies (B) in those uroflowmetry parameters. Detrusor pressure at maximum flow (p_{detQmax}) and maximum detrusor pressure (p_{detmax}) in group A did not show statistically significant differences between 4.5- and 6F pressure-flow studies whereas in group B, p_{detQmax} and p_{detmax} were significantly different between 4.5- and 7F pressure-flow studies. [75].

Conclusion (evidence level 3):

- There is evidence that, in general, flow is reduced when voiding with a urodynamic catheter in the urethra and that this reduction is partially caused by the size of the catheter.

Conclusion (evidence level 4):

- It is also the opinion of the committee that single catheters 6F incorporating both a filling channel and a pressure-sensing channel should be used for intravesical pressure measurement during cystometry (i.e double lumen catheters in the case of using fluid filled pressure lines). This is because removal of a separate filling catheter just before voiding may displace the pressure sensor and that movement of catheters within the urethra are likely to interfere with the representativity of lower urinary tract function during micturition.

Recommendations (grade B)

- The committee recommends that investigators interpret pressure-flow-voiding parameters and the subsequent post void residual together with the uncatheterised (and representative) voiding parameters.

- The committee suggests the ‘standard’ use of, as thin as possible, ‘one-catheter-systems’ for filling and pressure recording during urodynamic testing.

III. REPRODUCIBILITY, RELIABILITY AND NORMAL VALUES OF URETHRAL PRESSURE MEASUREMENTS

1. NORMATIVE AND COMPARATIVE DATA FOR MAXIMUM URETHRAL CLOSURE PRESSURE

Table 5 shows values of MUCP that have been obtained by different authors in normal (or, at least, without urodynamic stress urinary incontinence) and abnormal female populations. It has several striking features. The first is the between-centre variability in
the values reported, with mean MUCP varying from 36 to 101 cm H2O in non-stress-incontinent subjects. The second is the large between-subject SD reported in most studies (from 10 to 52 cm H2O). The third is that, in spite of this variability, in every study the mean MUCP was lower in stress-incontinent patients than in non-stress-incontinent women, sometimes significantly so and sometimes not. Although, some of the variations shown in the table are the result of different patient populations, a weighted averaging of the mean values suggests that a normal MUCP is about 54 ± 25 cm H2O. In stress-incontinent women the corresponding figures are 39 ± 24 cm H2O. Clearly there is so much overlap that this test can hardly be useful for diagnosis [90] (see section D.I.2.b - severity of stress urinary incontinence).

Eighty primiparous women with self-reported new stress incontinence 9-12 months postpartum were compared with 80 primiparous continent controls and 80 nulliparous continent controls to identify impairments specific to stress incontinence. MUCP (± SD) in primiparous incontinent women (62.9 ± 25.2 cm H2O) was lower than in primiparous continent women (83.9±21.0) who were similar to nulliparous women (90.3 ± 25.0). This lower MUCP followed by ultrasound assessment of vesical neck mobility on coughing was the measure most associated with de novo stress incontinence after first vaginal birth. [91]

Studies providing normative data for men are scant, but there are some data on the UPP in normal males.[92, 93].

2. RELIABILITY OF URETHRAL PRESSURE VARIABLES

In clinical practice, use of a fluid-perfusion technique to measure resting urethral pressure profile parameters such as MUCP yields an SD that ranges from 3.3 to 8.1 cm H2O. On average the SD is approximately 5 cm H2O (95% confidence limits ± 10 cm H2O) or ± 5%. With a microtip transducer technique the SD varies between 3.3 and 16.5 cm of water, which means that the 95% confidence limits may be as large as ± 33 cm H2O. The coefficient of variation when using the microtip transducer technique has been reported to be 17% (95% confidence limits ± 34%).
In one study using fluid perfusion the coefficient of variation of MUCP varied from 3% to 11% (95% confidence limits 6% - 23%). [94]

Another, comparative study between fluid-filled and microtip pressure transducers observed that MUCP obtained from the fluid-filled catheter was significantly higher than that obtained from the microtip catheter. However, the authors also concluded that the use of the double-lumen fluid-filled catheter for the measurement of MUCP can be considered a reliable technique since its reproducibility is as good as that of the microtip catheter. [95]

A significant difference between MUCP values recorded by microtransducer versus fiberoptic catheter systems has also been observed. Significantly lower mean MUCP's were recorded by the fiberoptic system than by the microtransducer system. No significant difference was however observed between these two systems in measurement of VLPP. [96]

As mentioned earlier, the performance of air-charged catheters in measuring MUCP has been shown to be comparable to microtransducers in the measurement of maximum urethral closures pressure in a non-randomised study. [9] However, there was a difference in FUL which was attributed to the different diameters of the two catheters.

In 2008, Zehnder et al carried out a randomised comparison of these air-charged catheters with microtip catheters in 64 women and found that the air-charged catheter was as least as reliable as the microtip for measuring both MUCP and FUL. However, they found that the air-charged catheter gave a higher reading of both parameters compared to the microtip device. [10]

3. AGING

It is well established that in women the UPP changes with age. A recent study of 255 women, ages 20-77 years, without DO, overt neuropathy or pelvic or urinary incontinence surgery, confirmed that the MUCP is negatively associated with age ($r = -0.489, P < 0.0001$). [97] This study was not a randomised trial but one that used a convenience sample of patients.

4. OTHER PARAMETERS AFFECTING THE MEASUREMENT OF URETHRAL CLOSURE PRESSURE

The 2002 ICS standardisation report relating to urethral closure pressures shows that the value of MUCP is not only dependent on the type of catheter used but also its orientation within the urethra, the degree of bladder fullness and the position of the patient. [98]

Conclusions (evidence level 2)

- Various studies have shown considerable test-retest variation of all urethral pressure measurements or parameters.
- Various studies have shown that normal and pathological values of urethral pressure parameters are largely overlapping.
- Various studies have shown that urethral pressure (s) (parameters) are affected by age.
- Studies have shown that urethral pressures depend on patient position, volume of fluid in the bladder and position of the patient.
- Studies have shown that urethral pressures depend on the pressure recording catheter used and, sometimes, its orientation within the urethra.

Recommendations (grade B)

- The committee recommends that investigators and clinicians recognise the poor sensitivity and specificity of urethral pressure measurements and their ‘normal’ test retest variation.
- The committee does not recommend urethral pressure measurement as the only urodynamic test in patients with incontinence.
- The committee recommends that the clinical relevance of urethral pressure measurements, when performed, is judged in relation to other urodynamic tests (such as cystometry) and to the clinical examination.

IV. LEAK POINT PRESSURE

1. INTRODUCTION

The detrusor pressure or the intravesical pressure ($P_{det}$ or $P_{ves}$) at which involuntary expulsion of urine from the urethral meatus is observed is the leak point pressure (LPP). The rise in bladder pressure causing leakage may originate either from the detrusor (caused for example by the filling of a low-compliance bladder) or from an increase in the abdominal pressure. Thus there are two different leak point pressures – the detrusor LPP (DLPP) and the abdominal LPP. The abdominal pressure increase during the latter is produced voluntarily by coughing (CLPP) or by Valsalva (VLPP).

LPP is not consistently defined throughout the reports in literature and we have not found any standardisation (report) of the technique. Any comparison of findings between studies is hindered by this.

The elements which could be standardised include: 1) the basic definition of LPP (baseline value of pressure; route of measurement – urethral or rectal), 2) whether Valsalva or cough is used to produce leakage, 3) the technique to confirm urine loss, 4) location of catheter, and shift in location on cough or strain, 5) calibre of catheter (if transurethral) 6) type...
of pressure sensor 7) the volume in bladder, 8) the rate of prior bladder filling and 9) patient position. [90].

2. RELIABILITY OF LEAK POINT PRESSURE MEASUREMENTS

a) Diagnosis

In a study that recruited 168 patients it was seen that women who demonstrate urodynamic SUI at lower bladder volumes do not report greater bother from incontinence than women who leak at higher volumes. The authors concluded that leakage severity ‘quantified’ by this urodynamic method, is not an adequate reflection of incontinence related quality of life and or subjective incontinence severity. [99] Another study confirms these observations. [100]

A total of 200 women with SUI were clinically evaluated and underwent urodynamic study to determine the correlation between VLPP and the UPP. A progressive correlation of VLPP with MUCP was found when UPP was performed at 50 mL (r = 0.305, p < 0.0001), at 250 mL (r = 0.483, p < 0.0001) and at maximum bladder filling (r = 0.561, p < 0.0001). The authors concluded that there is a significant correlation between MUCP and VLPP. [101] Another prospective study in 109 patients assessed the relationship between CLPP and VLPP with SUI (n=61; 56%), DO (n=21; 19%) or a combination of these (n=27 25%). More women with SUI leaked during CLPP than during the VLPP; fewer women with DO leaked during CLPP and more during the VLPP. [102] LPP’s are reported to be dependent on patient position; being lower in the standing position as compared to supine position. [103] Another study with the goal of determining the effect of position on UPP seems to have been troubled by ‘poor test retest reproducibility’ in the standing position. [104]

Two studies, one with 369 patients including some without incontinence and another study with 65 female patients with incontinence stratified into groups with various LPP’s; various grades of urethral (hyper-)mobility and various grades of incontinence severity have been performed. Both studies were unable to find strong ‘urodynamic’ discriminators for the type or severity of incontinence and concluded that all values overlapped. Patients with SUI can be characterised by LPP and change in the urethral angle and or mobility, although these variables do not always define discrete classes. [105, 106]

The results of these studies basically confirm the earlier conclusion in an expert review: ‘It is not apparent that either LPP measurement or UPP can accurately predict which patients will achieve the best outcome of surgical treatment for SUI. Other parameters assessed during urodynamic evaluation might provide prognostic information regarding the risk of voiding dysfunction postoperatively and the possibility of persistent urgency-related leakage following surgery, though not directly predict cure.’ [107]

b) Treatment

Can any value of LPP (vValsalva or cough) and/or UPP help in the selection of treatment for patients with SUI? This question has been addressed by various investigators.

In a retrospective cohort analysis of 3-month outcomes in 145 subjects (TOT = 85; TVT = 60) it was observed that relative risk of postoperative urodynamic SUI 3 months after surgery in patients with a preoperative MUCP of ≤ 42 cmH2O was 5.89 (1.02 to 33.90, 95% confidence interval) when TOT was compared with TVT tape. [108]

The value of urethral hypermobility, MUCP and urethral incompetence in the diagnosis of SUI was evaluated in 369 women with clinical symptoms suggestive of SUI without symptoms of bladder overactivity. The cohort was divided into 2 groups according to continence or incontinence status. Continent and incontinent patients differed with regards to urethral incompetence and hypermobility (each p < 0.0001). Incontinent patients had a greater probability of a higher grade of each factor. MUCP was significantly lower in the incontinent group (p < 0.001). [106]

A prospective study assessed the difference in measured urethral function before and after TVT procedure. Twenty-three (65.7%) of 35 consecutive women had a preoperative diagnosis of intrinsic sphincter deficiency (ISD) as defined by MUCP < 20 cm H2O and/or VLPP < 60 cm H2O. Subjective and objective success rates were 91% and 83%, respectively. The mean change in MUCP was -1.3 cm H2O (95% CI -5.9, 3.3), whereas the pressure transmission ratio increased 15.7% (95% CI 5.0, 26.3%). The mean decrease in straining urethral angle was 16.3 degrees (95% CI -23.9 degrees, -8.7 degrees). Cured subjects, demonstrating hypermobility preoperatively, continued to do so postoperatively. The effectiveness of the TVT did not appear to depend on a clinically significant change in the straining urethral angle. [109]

A total of 221 women 29 to 80 years old (mean age 55.2) were included in a later study to evaluate the outcome of the TVT procedure for SUI with low VLPP. Mean follow-up was 10.5 months (range 6 to 52). Patients were divided into 61 with low (<60 cm H2O) and 160 with higher (>60 cm H2O) VLPP. The overall cure rate was significantly lower in patients with low vs higher VLPP (82.0% vs 93.1%, p = 0.013). In women with low VLPP, multivariate analysis indicated that urge symptoms and low MUCP were independent factors for treatment failure (OR 15.12, 95% CI 1.90 to 120.61, p = 0.010 and OR 0.92, 95% CI 0.86 to 0.99, p = 0.018, respectively). [110]

174 consecutive patients who underwent a distal polypropylene sling procedure for the treatment of SUI were prospectively evaluated and reported in a slightly earlier study. The group was divided by VLPP
into group 1: 60 patients who did not leak on urodynamics, group 2: 27 patients with VLPP > 80 cm H2O, group 3: 71 patients with VLPP 30 to 80 cm H2O and group 4: 16 patients with VLPP < 30 cm H2O. Mean follow-up was 14.7 months (range 12 to 30) and mean patient age was 62 years (range 32 to 88). The groups were well matched before surgery with respect to age, number of previous surgeries, and severity of SUI symptoms and urge incontinence. The percentage of patients who were cured or improved was similar among groups. After surgery there was no statistical difference among patient mean self-reported symptoms of or bother from SUI or urge incontinence. The distal urethral polypropylene sling provides similar symptom improvement in all patients regardless of preoperative VLPP. LPP is helpful in the diagnosis of SUI but appears to be of minimal benefit in predicting the outcome of the distal urethral polypropylene sling procedure. [111]

A later study reported that neither MUCP nor LPP were good predictors of post-operative stress incontinence but, because this was not the primary outcome measure of this study, there may not be adequate power to make this a definitive conclusion. [112]

c) Within-patient variability

McGuire and coworkers [113] found a SD of 5.4 cm H2O yielding a true 95% confidence interval of 89-111 cm H2O. In another study where the microtip transducer technique was used the true value was found to vary between 72 and 128 cm H2O in the standing position and between 61 and 139 cm H2O when semirecumbent. [103]

The committee has found no reports on inter-observer variability.

Conclusions (evidence level 2/3)

- Different definitions and techniques to determine (urine) leak point pressure exist.
- Various studies have demonstrated a weak association of abdominal leak point pressures and the patient experienced or measured severity of incontinence.
- Studies have shown that the ‘isolated’ parameters from abdominal leak point pressure measurements are not extremely helpful as predictors of success for TVT, TOT or suburethral sling treatment of patients with stress urinary incontinence.

Recommendations (grade B/C)

- The committee does not recommend leak point pressure measurement as a single urodynamic test in patients with urinary incontinence.
- The committee recommends that the result of abdominal leak point pressure measurements, when performed on patients with urinary incontinence, should be judged in relation to other urodynamic tests such as cystometry and to the clinical examination.
- The committee considers detrusor leak point pressure in patients with neurogenic lower urinary tract dysfunction a relevant parameter. This is discussed in section III (neurogenic lower urinary tract dysfunction) and in section IV (patient evaluation: children).

V. DIAGNOSTIC PERFORMANCE OF FILLING CYSTOMETRY AND AMBULATORY MONITORING

1. SENSITIVITY AND SPECIFICITY OF FILLING CYSTOMETRY IN OVERACTIVE BLADDER SYNDROME WITH OR WITHOUT URGENCY INCONTINENCE

a) Detrusor overactivity incontinence

Table 6, reproduced from the second Consultation[2] shows that some authors have found quite high positive sensitivity, specificity and predictive value of symptoms for urodynamic SUI. Specificity, sensitivity and predictive value of symptoms were less for detrusor overactivity incontinence (DOI) or ‘mixed symptoms’ of urinary incontinence.

Van Waalwijk van Doorn et al [122] made careful tests of the sensitivity and specificity of non-ambulatory urodynamic observations (a) for any urinary incontinence and (b) for urgency urinary incontinence (UUI). Among 348 women of mean age 41 years with symptomatic urinary incontinence, urodynamics demonstrated incontinence in only 164, a sensitivity of only 164/348 = 47%. For a similar group of men of mean age 44 years the corresponding figures were 31/83 = 37%. In a similar group of 102 female patients with voiding complaints but without symptoms of urinary incontinence, urodynamics revealed no incon- tinence in 96/102, a specificity of 94%. For men the corresponding figures were 71/75 = 95%.

Among 154 female patients (in the same study [122]) in whom urodynamics reproduced urinary incontinence, the observation of pure DOI had a sensitivity of 25/28 = 89% for symptomatic pure urgency incontinence; its specificity was 103/126 = 82%; and its negative predictive value was 97%. However, the positive predictive value was only 25/48 = 52%. In large part this low value was due to a group with mixed symptoms who revealed DOI on urodynamics.
Taking account of the patients with mixed symptoms does not however improve the overall agreement between symptoms and urodynamic findings, because nearly half of them proved to have isolated urodynamic stress urinary incontinence on urodynamics. Similar findings for stress urinary incontinence are discussed in section D.I.2.

Griffiths et al [123] examined 100 older men and women, median age 79.5 years, with urinary incontinence proven on 24-hour monitoring. The type of urinary incontinence was believed to be DO in the majority. During filling cystometry (room temperature fluid, filling rate 60 mL/min, supine and seated) urinary incontinence was not demonstrated in 32%; i.e. the sensitivity of conventional urodynamics for DO with incontinence was 67% in this study.

b) Detrusor overactivity alone

The sensitivity, specificity and predictive value of symptoms for DO, given in a review of papers quoted in the third ICI [124] are shown in Table 7. (Note that this sensitivity and specificity are equal to the positive and negative predictive values of DO for corresponding symptoms.)

In spite of the wide variations shown in Table 7, all authors agree that the correlation between symptoms and DO is modest; underlining the necessity of urodynamic testing to obtain an objective diagnosis.

Van Brummen et al [143] examined the sensitivity of DO, observed during conventional cystometry, for UUI. They examined 95 women, with OAB, symptomatic stress urinary incontinence, and/or prolapse. Symptoms were assessed by a bladder diary and conventional filling cystometry was performed (sitting, fill rate 60 mL/min). Urinary frequency, urgency and UUI had similar associations with the cystometric observation of DO (Table 8). Among patients with one of these symptoms, DO was not observed in 77-81%: i.e., there were large numbers of ‘false positive symptoms’.

In another study 171 women were recruited. These women were assessed with an OAB scoring system to help discriminate between USI and DO. The scoring system had a sensitivity of 79%, a specificity of 78% and a positive predictive value of 73% to identify DO. Investigators suggested that the scoring system could be applicable in primary care. [144]

In a similar study the accuracy of a urinary incontinence questionnaire in the diagnosis of various types of urinary incontinence was classified according to the results of multichannel urodynamic testing. Using a urinary incontinence questionnaire consisting of 12 urinary symptoms questions 129 women with symptoms of urinary incontinence were interviewed. Of the 12 questions, only three questions (two SUI symptoms and one OAB symptom) were significantly associated with the urodynamic diagnoses of urodynamic SUI or DO. The sensitivity and specificity of the questions was relatively low leading to the author’s conclusion that symptoms of urinary incontinence were not sufficient to predict types of urinary incontinence and the suggestion that urodynamic testing is essential in the diagnosis and management of female urinary incontinence. [145]

In a study to determine the prevalence and associations of ‘sensory urgency’ in comparison with DO 592 women, attending for an initial urogynecological / urodynamic assessment, took part. The group was separated into those having ‘sensory urgency’; relevant symptoms, without urodynamic DO

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>USI STV</th>
<th>SPT</th>
<th>PPV STV</th>
<th>DOI STV</th>
<th>SPT</th>
<th>Mixed incontinence STV</th>
<th>SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen [114]</td>
<td>1994</td>
<td>Review</td>
<td>0.91</td>
<td>0.51</td>
<td>0.75</td>
<td>0.74</td>
<td>0.55</td>
<td>0.48</td>
<td>0.66</td>
</tr>
<tr>
<td>Handa* [115]</td>
<td>1995</td>
<td>101</td>
<td>0.77</td>
<td>0.44</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handa* [115]</td>
<td>1995</td>
<td>101</td>
<td>0.82</td>
<td>0.59</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haeusler [116]</td>
<td>1995</td>
<td>1938</td>
<td>0.56</td>
<td>0.45</td>
<td>0.88</td>
<td>0.62</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cundiff [117]</td>
<td>1997</td>
<td>535</td>
<td>0.44</td>
<td>0.87</td>
<td>0.87</td>
<td>0.71</td>
<td>0.41</td>
<td>0.68</td>
<td>0.48</td>
</tr>
<tr>
<td>Videla [118]</td>
<td>1998</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Diokno* [119]</td>
<td>1999</td>
<td>76</td>
<td>0.83</td>
<td>1.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>James [120]</td>
<td>1999</td>
<td>555</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Lemack* [121]</td>
<td>2000</td>
<td>174</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
</tbody>
</table>

STV = sensitivity, SPT = specificity, PPV = positive predictive value

* = predictive values are for type II SUI (i.e. with hypermobility)
or those with DO. The only difference in the clinical profile between to groups was increased prevalence of the symptom of UUI. The authors concluded that sensory urgency and DO appear to be part of the same clinical spectrum of bladder dysfunction. [146]

Looking just at the association between DO and UUI [44, 143], there was again a substantial number of ‘false positive symptoms’ – subjects with UUI but no DO. Correspondingly the specificity and negative predictive value of DO were found to be low, in these studies (15/67 = 22%; 27/79 = 34%).

To determine and compare the urodynamic characteristics in patients with OAB and patients with OAB plus SUI (OAB+SUI), 120 patients (60 each in OAB and OAB+SUI groups) underwent detailed history, physical examination, complete urodynamic investigation and 20-minute pad test. FDV, SDV, urgency, and the percentage of urodynamic SUI were larger in the OAB+SUI group and FUL, MUP and MUCP were significantly lower in the OAB-SUI group than those in the OAB group (P <0.03). [147]

c) Detrusor overactivity and overactive bladder syndrome

Digesu et al [148] reported a retrospective review of 4500 women aged 22-73 years. Neurological disorders were excluded. As shown in Table 8, this study highlights that there are not only a substantial proportion of ‘false positive symptoms’, but also a large number of ‘false negative symptoms’; patients with DO but without OAB symptoms. The sensitivity and specificity of DO for OAB (symptoms) were 457/843 (54%) and 2473/3657 (68%) respectively, while its positive and negative predictive values -with symptoms referred to as the ‘golden’ standard- were 28% and 86% respectively.

Sekido et al [149] retrospectively reviewed the urodynamic examination of 139 adult patients (12 males and 38 females) and looked into the correlation between detrusor function (FSF, MCC, compliance) and DO versus symptoms of uncomplicated OAB. 75% of male patients with OAB symptoms had DO on cystometrogram in supine position and only 36.8% female patients.

Table 7. Sensitivity, specificity and predictive value of symptoms obtained on patient history for the urodynamic observation of detrusor overactivity

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Awad [125]</td>
<td>108</td>
<td>0.96</td>
<td>0.25</td>
<td>0.82</td>
</tr>
<tr>
<td>Bent [126]</td>
<td>81</td>
<td>0.83</td>
<td>0.49</td>
<td>0.32</td>
</tr>
<tr>
<td>Cantor [127]</td>
<td>214</td>
<td>0.91</td>
<td>0.45</td>
<td>0.80</td>
</tr>
<tr>
<td>De Muylder [128]</td>
<td>408</td>
<td>0.62</td>
<td>0.47</td>
<td>0.62</td>
</tr>
<tr>
<td>Glezerman [129]</td>
<td>128</td>
<td>0.40</td>
<td>0.86</td>
<td>0.27</td>
</tr>
<tr>
<td>Hilton [130]</td>
<td>100</td>
<td>0.77</td>
<td>0.38</td>
<td>0.44</td>
</tr>
<tr>
<td>Jarvis [131]</td>
<td>100</td>
<td>0.91</td>
<td>0.45</td>
<td>0.54</td>
</tr>
<tr>
<td>Korda [132]</td>
<td>537</td>
<td>0.47</td>
<td>0.63</td>
<td>0.44</td>
</tr>
<tr>
<td>Lagro-Janssen [133]</td>
<td>103</td>
<td>0.84</td>
<td>0.77</td>
<td>0.67</td>
</tr>
<tr>
<td>Ouslander [134]</td>
<td>135</td>
<td>0.89</td>
<td>0.21</td>
<td>0.49</td>
</tr>
<tr>
<td>Phua [135]</td>
<td>84</td>
<td>0.84</td>
<td>0.31</td>
<td>0.82</td>
</tr>
<tr>
<td>Sand [136]</td>
<td>218</td>
<td>0.78</td>
<td>0.39</td>
<td>0.80</td>
</tr>
<tr>
<td>Summitt [137]</td>
<td>79</td>
<td>0.46</td>
<td>0.76</td>
<td>0.57</td>
</tr>
<tr>
<td>Thiede [138]</td>
<td>196</td>
<td>0.88</td>
<td>0.39</td>
<td>0.86</td>
</tr>
<tr>
<td>Valente [139]</td>
<td>102</td>
<td>0.74</td>
<td>0.97</td>
<td>0.88</td>
</tr>
<tr>
<td>Walters [140]</td>
<td>106</td>
<td>0.35</td>
<td>0.91</td>
<td>0.67</td>
</tr>
<tr>
<td>Sandvik [141]</td>
<td>40</td>
<td>0.56</td>
<td>0.96</td>
<td>-</td>
</tr>
<tr>
<td>Cundiff [117]</td>
<td>102</td>
<td>0.71</td>
<td>0.87</td>
<td>0.41</td>
</tr>
<tr>
<td>Haeusler [51]</td>
<td>130</td>
<td>0.62</td>
<td>0.56</td>
<td>0.64</td>
</tr>
<tr>
<td>Fantl [142]</td>
<td>17</td>
<td>-</td>
<td>0.64</td>
<td>0.57</td>
</tr>
</tbody>
</table>
In a retrospective study with 1,626 women with symptoms of mixed urinary incontinence were divided into stress predominant or urgency predominant symptoms; or equal severity of stress and urgency on the basis of the most severe symptom scored on the King’s Health Questionnaire. The frequency of different urodynamic diagnoses for the all women in each of the above groups was calculated. In this study 29% (464/1,626) had stress predominant symptoms, 15% (248/1,626) had urgency predominant symptoms and 56% (912/1,626) had equal severity of urgency and stress symptoms. On urodynamics 42% (665/1,626) had pure urodynamic stress incontinence (USI), 25% (414/1,626) had pure DO, 18% (299/1,626) had both DO and urodynamic SI and 15% (248/1,626) had normal urodynamic studies. In those with stress predominant symptoms, 82% had USI; in those with urge predominant symptoms, 64% had DO. The urodynamic diagnoses were significantly different for the different balance of symptoms (p<0.05). In women with equal severity of urgency and SUI, 46% had DO while 54% had USI. The relative severity of symptoms from a symptom questionnaire distinguishes between different urodynamic diagnoses. [151]

In a study 1457 adult males and females were retrospectively selected based on OAB syndrome symptoms to determine how well the symptoms of OAB syndrome correlated with urodynamic DO using ICS definitions. A better correlation in results between OAB symptoms and the urodynamic diagnosis of DO was observed in men than in women. Of men 69% and 44% of women with urgency (OAB dry) had DO, while 90% of men and 58% of women with urgency and UUI (or OAB wet) had DO. SUI seems to have accounted for the decreased rates in women since 87% of women with UUI also had the symptom of SUI. The ICS definition does not specify what constitutes abnormal voiding frequency. Analysis of results showed that increasing voiding frequency did not have any effect on increasing the accuracy of diagnosis of DO except in women with 10 or more daytime micturition episodes. The authors concluded that the bladder is a better and more reliable witness in men than in women. [152]

The association between urinary symptoms and the urodynamic diagnoses of DO and USI was calculated to describe the relationship between symptoms reported in a self-completed postal questionnaire and urinary disorders based on urodynamic investigation. The study population was selected from women aged 40 years or over living in the community, who responded to a postal questionnaire. Four hundred eighty-eight women completed urodynamic investigation; 29.1% (142/488) were found to have DO, 33.6% (164/488) USI, 20.7% (101/488) mixed incontinence, and 16.6% (81/488) no urodynamic abnormality. SUI and UUI were included in the risk model for USI. SUI reported monthly or more was associated with more frequent diagnosis of USI, and UUI reported weekly or more with less frequent diagnosis of USI (STV: 76.9%; SPT: 56.3%; PPV: 67.8%). Strong or overwhelming urgency, urinary incontinence monthly or more, and nocturia once a night or more were all significantly associated with an increased diagnosis of DO. Reporting of SUI monthly or more reduced the risk of DO (STV 63.1%; SPT 65.1%; PPV 63.1%). The conclusion was that a postal urinary symptoms questionnaire was able to predict urodynamic diagnoses with moderate accuracy. [153]

One hundred and fourteen women attending a tertiary urogynaecology clinic were included in a randomised crossover study to either an initial interview-assisted questionnaire in the clinic with a follow up postal questionnaire or an initial pre-outpatient questionnaire followed by an interview-assisted questionnaire at the clinic visit. Question responses were compared with urodynamic diagnoses. With an interview method, only severity of incontinence was significantly associated with DO (p = 0.012). With self-completion, severity of nocturia (p < 0.05), urgency (p = 0.003), UUI (p = 0.003), leakage without warning (p = 0.035) and incomplete voiding (p = 0.01) were significantly associated with detrusor activity. On interview the symptom of SUI (p = 0.002) and use of pads (p = 0.011) were significantly associated with a diagnosis of USI. Severity of SUI (p < 0.001), frequency of leakage (p = 0.004), use of protection (p < 0.018), nocturnal incontinence (p = 0.002) and quantity of leakage (p < 0.05) on self-completion were strongly associated with diagnosed USI. There was no

---

**Table 8. Overactive bladder symptoms and detrusor overactivity, from reference [148]**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Detrusor overactivity</th>
<th>No detrusor overactivity</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAB symptoms</td>
<td>457</td>
<td>386</td>
<td>843</td>
</tr>
<tr>
<td>No OAB symptoms</td>
<td>1184</td>
<td>2473</td>
<td>3657</td>
</tr>
<tr>
<td>Totals</td>
<td>1641</td>
<td>2859</td>
<td>4500</td>
</tr>
</tbody>
</table>

Hyman et al [150] examined 160 men, mean age 61 ± 15 years, without neuropathy but with symptoms “suggestive of DO.” They observed DO in 68%, suggesting a sensitivity of 43% for OAB symptoms. DO was seen more often with UUI than with symptoms of frequency, urgency, nocturia, suggesting a rather higher sensitivity for UUI.

The association between urinary symptoms and the urodynamic diagnoses of DO and USI was calculated to describe the relationship between symptoms reported in a self-completed postal questionnaire and urinary disorders based on urodynamic investigation. The study population was selected from women aged 40 years or over living in the community, who responded to a postal questionnaire. Four hundred eighty-eight women completed urodynamic investigation; 29.1% (142/488) were found to have DO, 33.6% (164/488) USI, 20.7% (101/488) mixed incontinence, and 16.6% (81/488) no urodynamic abnormality. SUI and UUI were included in the risk model for USI. SUI reported monthly or more was associated with more frequent diagnosis of USI, and UUI reported weekly or more with less frequent diagnosis of USI (STV: 76.9%; SPT: 56.3%; PPV: 67.8%). Strong or overwhelming urgency, urinary incontinence monthly or more, and nocturia once a night or more were all significantly associated with an increased diagnosis of DO. Reporting of SUI monthly or more reduced the risk of DO (STV 63.1%; SPT 65.1%; PPV 63.1%). The conclusion was that a postal urinary symptoms questionnaire was able to predict urodynamic diagnoses with moderate accuracy. [153]

One hundred and fourteen women attending a tertiary urogynaecology clinic were included in a randomised crossover study to either an initial interview-assisted questionnaire in the clinic with a follow up postal questionnaire or an initial pre-outpatient questionnaire followed by an interview-assisted questionnaire at the clinic visit. Question responses were compared with urodynamic diagnoses. With an interview method, only severity of incontinence was significantly associated with DO (p = 0.012). With self-completion, severity of nocturia (p < 0.05), urgency (p = 0.003), UUI (p = 0.003), leakage without warning (p = 0.035) and incomplete voiding (p = 0.01) were significantly associated with detrusor activity. On interview the symptom of SUI (p = 0.002) and use of pads (p = 0.011) were significantly associated with a diagnosis of USI. Severity of SUI (p < 0.001), frequency of leakage (p = 0.004), use of protection (p < 0.018), nocturnal incontinence (p = 0.002) and quantity of leakage (p < 0.05) on self-completion were strongly associated with diagnosed USI. There was no
association between the symptoms of urgency or UUI, and USI. No symptom had a high enough specificity and sensitivity to replace urodynamic testing however, postal questionnaire responses had a better relationship with urodynamics, for USI and for DO, than interview-assisted questionnaire responses. [154]

Conclusions (evidence level 2)

- Many studies have shown the weak correlation between symptoms and the result of urodynamic investigation, especially cystometry, in patients with incontinence.
- The correlation of the symptom ‘stress incontinence’ (expressed, or questioned) with the result of urodynamic investigation is somewhat better than the correlation of urgency or urgency incontinence (expressed, or questioned) with urodynamic investigation.
- The committee concludes that especially when frequent voiding, urgency and/or urgency incontinence is part of the symptom complex of patients with incontinence, urodynamic investigation is of value to obtain an objective diagnosis.
- Taking into account the variation between various institutes and the test-retest variation, the committee considers it relevant that investigators and clinicians judge the individual representativity of the results of the performed tests by comparison with the patients’ symptoms.

Recommendations (grade B)

- The committee recommends urodynamic testing in patients with incontinence when an objective diagnosis is warranted. This is commonly the case when symptoms do not exclusively direct to stress incontinence, or when (for all types of incontinence) conservative measures have not been successful, or when relevant comorbidity exists or relevant previous surgery is performed.
- The committee recommends interpretation of the results of the complete urodynamic testing in relation with the symptoms, the clinical (or other) examinations and with the voiding diary in all patients.

**d) Distinguishing or defining characteristics of detrusor overactivity**

Several groups have attempted to find characteristics of DO that may distinguish incontinence with different aetiologies, or incontinence of different severity.

One group [155, 156] examined 132 patients with OAB symptoms (with and without neurological disease) by videourodynamic. Based on the characteristics of their involuntary contractions, patients were divided into 4 categories: type 1 - no evidence of involuntary detrusor contractions on videourodynamic; type 2 - involuntary detrusor contractions present, and patient aware and able to abort them; type 3 - contractions present, patient aware and able to contract the sphincter (judged from the videourodynamic) but not to abort contractions; and type 4 - contractions present and patient unaware but unable to contract the sphincter or abort contractions. There was no significant relationship between category and severity of symptoms as judged by voiding frequency, functional bladder capacity, or pad test. The authors concluded that the characteristics of the involuntary contractions were not distinct enough to aid in differential diagnosis, but that the ability to abort DO and stop incontinent flow might have prognostic implications, especially for the response to behaviour modification, biofeedback training, and pelvic floor exercises.

Cucchi et al [157] looked into detrusor contraction strength, detrusor contraction velocity and contraction sustainability. In this retrospective review the authors separated male patient into three groups; Group 1 had no neurogenic DO, with urgency and UUI. Group 2 was similar to group 1 but did not have urgency before involuntary contractions and Group 3 consists of “normal” men. They found that detrusor contraction velocity was different in the group with urgency versus no urgency or normal, implying that this may be an underlying mechanism for urgency.

Defreitas and coworkers [158] examined three groups of patients: group 1, men with LUTS and no known neurological condition with DO (n = 22); group 2, men with Parkinson’s disease and LUTS (n = 39); and group 3, women with Parkinson’s disease and LUTS (n = 18). Patients with Parkinson’s disease had a significantly lower median volume at first detrusor contraction than those with non-neurogenic DO. The percentage of group-1 patients with UUI was significantly lower than that found in the other two groups (9% versus 54% and 56%, p <0.001 and 0.002, respectively). No statistically significant correlation between the duration or severity of Parkinson’s disease and urodynamic parameters was found. The distinction between Parkinson’s disease proper and multiple system atrophy, which appears to be important with regard to bladder dysfunction,[159] was not made in this study.

In the study cited above, [150] 160 older men without neuropathy but with symptoms “suggestive of DO” were examined. DO was seen more often with UUI than with symptoms of frequency, urgency and nocturia. The bladder volume at which DO was observed tended to be lower in those with UUI and frequency and/or urgency than in the rest (p = 0.07). The prevalence of DO was similar in men with and without bladder outlet obstruction (BOO).
Ockrim et al [50] compared the variability of DO in men with LUTS to that in men with SCI by sequentially repeating urodynamic studies three times. They observed a significant decrease in the number and amplitude of involuntary detrusor contractions in the 60 patients with non-neurogenic LUTS whilst in the 35 SCI patients, the urodynamic variables remained the same over the subsequent studies.

The urodynamic characteristics of DO in women with multiple sclerosis (MS) (n = 54) were compared with the involuntary contractions found in women with LUTS and DO (n = 42) in a retrospective study. Among other parameters, the amplitude of the first involuntary contraction, maximum detrusor contraction, and threshold volume for the first involuntary contraction were evaluated. The amplitude of the first involuntary contraction was statistically greater in the patients with MS and DO compared with patients with DO (28.3 versus 20.5 cm H2O, p = 0.003), as was the maximum detrusor contraction (46.4 versus 30.8 cm H2O, p = 0.002). The threshold volume for DO was greater among patients with neurogenic DO (186.8 versus 150.5 mL, p = 0.037), which was likely to be secondary to the elevated PVR volume noted among patients with MS (p = 0.049).

The authors concluded that additional investigation is required to determine whether these differences are due to neurogenic influences directly on the detrusor muscle through aberrant innervation or by other mechanisms. [160]

Miller et al [161] suggested that functional bladder capacity was smaller in those with more severe incontinence as judged from the voiding diary in a study to evaluate quantification of DO.

**Conclusions (evidence level 2)**

- Studies have not been able to show relevant differences in patterns or characteristics of detrusor overactivity when the cause of overactivity is neurogenic or idiopathic.
- Various studies have not been able to reliably quantify the severity of detrusor overactivity, in a clinically or scientifically applicable way.

**Recommendation (grade C)**

- The committee recommends that neither the cause (neurogenic or idiopathic) nor the severity of detrusor overactivity is diagnosed on the basis of parameters from urodynamic investigation (cystometry).

**Topics for research**

- The committee recommends further evaluation and development of objective parameters for assessing the treatment outcome of detrusor overactivity.

- The committee recommends the development of an objective and cystometry-based detrusor overactivity severity scale.

**e) Provocative manoeuvres**

Some studies have shown that 50% of DO occurs during supine cystometry without provocation and that the remaining 50% is revealed by posture change, standing cystometry, on provocation by cough, or on catheter removal. [162-164].

Awad and McGinis [125] observed DO in 30% of female patients in the supine position versus 61% in the standing position. A systematic review of the literature by Al-Hayek et al [43] concluded that supine cystometry failed to detect a significant percentage of patients with DO.

Webster et al [165] found that in 52% of women with DO, provocation by fast filling in the standing position, and with exercises such as coughing, was required to reveal it. Investigative technique, in particular the inflation of a balloon in the proximal urethra [166] or the instructions given to the patient, [167] affects the frequency of the observation of DO.

Choe et al [168] systematically examined which manoeuvres were most provocative of DO. In 134 women with symptomatic UUI they performed gas (CO2) cystometry. Six provocative manoeuvres were performed consecutively to evoke DO, including lying supine, rising to a seated position, walking toward the bathroom, handwashing, coughing and sitting on the toilet with instructions not to void. By filling to maximum capacity and performing these manoeuvres in 2 different orders, they were able to demonstrate DO in 76/134 subjects (67%). Sitting on a toilet with a full bladder and with the instruction not to void was the most provocative manoeuvre, responsible for revealing DO in 52 of the 76 (68%). Handwashing was a distant second, revealing overactivity in 15 of the 76 (20%). Other manoeuvres revealed very little DO.

An extreme provocative manoeuvre is the bladder cooling (ice water) test advocated by Geirsson et al.[169]. The empty bladder is filled with water at a temperature of less than 10 oC. This stimulates C-fibers that normally carry afferents from receptors sensitive to temperature and pain. In infants, stimulation of these receptors can initiate a detrusor contraction, but this response is normally lost at ages over 5 years. The bladder cooling test stimulated detrusor contraction (neurogenic DO) in 91-97% of patients with traumatic upper motor neuron lesion, but in only 47% of those with presumed idiopathic DO. Detrusor contraction was not observed in any patient with a lower motor neuron lesion or pure (urodynamic) SUI. Thus the bladder cooling test is highly sensitive for neurogenic DO, and highly specific for DO in general.
The bladder cooling reflex, elicited by the ice water test (IWT) was performed in patients with painful bladder syndrome (PBS, n = 17), idiopathic DO (IDO, n = 22), neurogenic DO (NDO, n = 4) and SUI (as controls, n = 21). The IWT was performed by intravesical instillation of cold saline (0 - 4 degrees C). A positive IWT was observed in IDO (27.3%) and NDO (100%) patients, but was negative in all PBS and all control patients. Thirteen (76.5%) PBS patients reported pain during the IWT, with significantly higher pain scores during ice water instillation compared to the baseline (p = 0.0002), or equivalent amount of bladder filling (100 mL) with saline at room temperature (p = 0.015). [170]

A total of 114 patients >50 years, with an International Prostate Symptom Score (IPSS) >8 and Quality of Life (QoL) >2, were evaluated by complete urodynamic workup and IWT to investigate whether DO and/or the response to the IWT were related to nighttime urinary frequency. The DO-positive IWT responders had a significantly higher bladder outlet obstruction index (BOOI) than did the DO-positive IWT nonresponders and the DO-negative IWT nonresponders. The DO-positive IWT responders had significantly more frequent nocturia and smaller nighttime maximal and minimal voided volumes than did the DO-negative IWT nonresponders without any difference in the nocturnal voided volume. The patients with nocturia two or more times had a significantly larger nocturnal voided volume and smaller nighttime minimal voided volume than the patients with nocturia less than two times. The incidence of DO-positive IWT responders had significantly greater among the patients with nocturia three or more times than that among those with nocturia less than three times. The authors concluded that high grade BOO leads to development of C-fibre reflex activity. [171]

**Conclusions (evidence level 2)**

- A systematic review concludes that more detrusor overactivity is seen when the patient is in the sitting position during cystometry, when compared to the supine position.

- There is some evidence that moving to a toilet, and also handwashing, is a strong provocative of detrusor overactivity.

- Evidence suggests that ice water cystometry can be applied to elicit detrusor overactivity in patients with neurogenic lower urinary tract dysfunction and that a detrusor contraction during filling with ice water can be interpreted as a sign of pathologic (existing only in patients with relevant neurology) C-fibre reflex activity. It has however also been shown in this regard that false-negative tests do occur.

**Recommendations (grade B)**

- The committee recommends that the results of provocative cystometry are interpreted in view of patients' symptoms and to bear in mind the representativity of the results obtained.

- The committee recommends that the position of the patient during filling cystometry is taken into account because it can influence the demonstration of detrusor overactivity. Repeating the cystometry in a different position can be helpful when it is deemed clinically necessary.

**2. AMBULATORY URODYNAMICS: SENSITIVITY AND SPECIFICITY**

Ambulatory urodynamics is performed in an effort to capture more realistic or more physiological observations, especially of incontinence episodes. Thus, similar to provocative manoeuvres, it is an attempt to increase sensitivity by providing a longer time for overactivity to manifest itself. The authors of a review article [172] concluded that ambulatory monitoring detects more actual incontinence than conventional cystometry.

Radley et al. [173] found that ambulatory monitoring revealed DO in 70/106 women with symptoms suggestive of DO (twice as many as conventional cystometry with provocation by handwashing), and that it detected DOI in 40 of the 70. The observation of DOI was correlated with symptom severity, but it was not clear how many women complaining of UI showed DOI. Therefore the sensitivity is unknown.

**3. THE ADJUNCT USE OF IMAGING AND EMG**

Videourodynamics is an investigation where cystometry is carried out simultaneously with imaging (usually x-rays) of the lower urinary tract. This can be useful in the management of some patients; particularly children and neurogenic patients and is briefly discussed in the relevant sections. There is a fuller discussion of videourodynamics in the chapter on Imaging, Neuropohysiologie and other tests.

Another adjunct to cystometry is the simultaneous measurement of muscle activity using EMG. Most frequently this is used in the investigation of neurogenic patients and often surface electrodes are placed on the perineum to detect general striated muscle activity. Amongst other uses, failure of the urethra/pelvic floor to relax and detrusor sphincter dyssynergia can be theoretically detected during voiding using this technique. Unfortunately, it is technically difficult to ensure a good quality EMG signal from the appropriate muscle during this procedure and there have been no publications in at least the last 20 years investigating the benefits of combining EMG with cystometry.
1. PREDICTION OF TREATMENT RESPONSE

a) Filling cystometry

The authors of a review of papers from 1980-2000 [124] (see Table 9), concluded that "it is not possible to correlate the results of urodynamic tests with the effects of non-invasive therapy."

Consistent with the table, Malone-Lee et al [177] reported on 356 female patients with OAB symptoms. On urodynamics, 266 showed DO. There was no significant difference (between those with and without DO) in treatment outcome after 6-8 weeks of oxybutynin and bladder retraining.

On the other hand, previous reviews have concluded that women with incontinence and DO respond less well to surgery for SUI than those without DO. [2] Friis et al [178] conducted a blinded prospective study to evaluate the usefulness of urodynamic examination compared to clinical diagnosis. The study showed that when urodynamic examination was added to the preoperative planning of treatment for female urinary incontinence a more beneficial cure rate was found if the patient was treated in accordance with the urodynamic findings. However, the patient material is small and the power of the study is weak.

A retrospective study has shown that a careful minimal evaluation may be adequate to identify ISD, predict postoperative voiding difficulties and maximise surgical outcomes. [179]. A Cochrane review concluded that current evidence is insufficient to demonstrate a clear improvement in clinical outcomes as a result of performing urodynamic studies. [180].

In men, fewer studies have been done. Golomb et al [181] examined whether preoperative urodynamic examination allows us to predict the risk of incontinence after radical prostatectomy. A small group of 20 patients underwent radical retropubic prostatectomy for prostate cancer. Urodynamics showed DO in 12/20 pre-operatively. 5 of these 12 suffered from UII post-operatively. The positive predictive value of preoperative DO for post-operative incontinence was thus only 42%.

In a literature overview of the diagnostic and therapeutic value of urodynamic investigations in patients undergoing prolapse surgery, the reviewers found a large heterogeneity of results. ‘Occult’ SUI showed large variation between studies and de novo DO after TVT as adjunct to prolapse surgery was observed in inconsistent and unpredictable percentages. It was impossible to estimate the predictive value of urodynamic testing on the basis of this review and prospective studies were demanded. [182] A later clinical study confirmed this view. [183]

A study presented a decision-analytic model that evaluated the cost-effectiveness of basic office evaluation before surgery in women with prolapse and SUI symptoms and contrasted it with that of urodynamic testing. Costs were obtained from the Federal Register; effectiveness of treatment for urinary incontinence was based on the published literature. The strategies of basic office evaluation and urodynamic testing had the same cure rate of urinary incontinence (96%) after initial and secondary treatment. Under baseline assumptions incremental cost-effectiveness (cost for single extra cure of urinary incontinence) of urodynamic testing was $328,601.

According to sensitivity analyses, basic office evaluation was more cost-effective than urodynamic testing when the prevalence of pure DO was <8% or when the cost of urodynamic testing was >$103. The analysis concluded that urodynamic testing before surgery in women with prolapse and SUI symptoms is not cost-effective relative to basic office evaluation. [184]

Table 9. Response to medical treatment for urinary incontinence in subjects with negative or positive results of urodynamic tests, from reference [124]

<table>
<thead>
<tr>
<th>First author</th>
<th># patients</th>
<th>Treatment</th>
<th>Urodynamics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagg [174]</td>
<td>290</td>
<td>Oxybutynin and retraining</td>
<td>Cystometry</td>
<td>No relationship between urodynamic variables and response to treatment</td>
</tr>
<tr>
<td>Hashimoto [175]</td>
<td>77</td>
<td>Oxybutynin 6 mg/day for 4 weeks</td>
<td>Cystometry</td>
<td>No difference in effect of oxybutynin in motor and sensory urge</td>
</tr>
<tr>
<td>Holte Dahl [176]</td>
<td>87</td>
<td>Estriol and pelvic floor exercise and bladder training + electrical pressure profile if requested</td>
<td>Cystometry + urethral pressure profile</td>
<td>Outcome similar in subjects with/without urodynamically confirmed diagnosis</td>
</tr>
</tbody>
</table>
b) Ambulatory monitoring

Brown and Hilton [185] used conventional and ambulatory urodynamic monitoring to study the incidence of DO before and after colposuspension. They showed that preoperative ambulatory monitoring was unable significantly to predict which patients would suffer from urgency postoperatively, or even which women would demonstrate DO post-surgery. Another paper addressed specifically the effect on clinical management of doing ambulatory urodynamics.[186] In this retrospective chart review of 71 women there were technical difficulties in 30/71 ambulatory studies although only 2 were not interpretable. 32/71 women showed DO and were nearly all treated with medication. Among the remainder without DO fewer received medication. However, fewer than half of those who received medication improved. The authors concluded that ambulatory urodynamics was not very helpful in deciding on management.

Conclusions (evidence level 2/3)

- Various studies have shown that the result of urodynamic investigation does not perfectly predict the outcome of relevant treatment in all patients; neither in patients with urodynamic detrusor overactivity nor in patients with urodynamic stress incontinence and also not in patients with a ‘double’ urodynamic diagnosis.
- A retrospective study with subsequent health economic modelling has shown that in patients with ‘pure symptoms of stress incontinence’ urodynamic testing might not be cost effective.

Recommendations (grade B/C)

- The committee recommends that the result of urodynamic investigation is applied to ‘optimise’ treatment strategy without attributing perfect specificity to the result of treatment, in an individual patient.
- The committee recommends that the cost effectiveness of urodynamic testing is taken into account when discussing the necessity of urodynamic investigation.

Topics for research

- The committee suggests that large multicentre (‘national’) prospective studies might be of help to better understand the cost-effectiveness of high quality urodynamic testing in health care quality for patients with incontinence.
incontinence and urgency urinary incontinence remains to be established, as does the significance of the corresponding urodynamic observations such as USI, DOI and DO. However it should be noted that besides their diagnostic potential, urodynamic investigations can contribute qualitative and quantitative information about the underlying or coexisting pathophysiology.

In the following paragraphs the committee discusses clinical application of urodynamic tests in patients with signs or symptoms of incontinence. Firstly women with stress incontinence, followed by women with overactive bladder symptoms with incontinence.

2. STRESS URINARY INCONTINENCE

a) Pathophysiology of stress urinary incontinence

There is a clear need to better understand the pathophysiology of stress urinary incontinence. Neither the clinical nor the pathophysiological value of classification into types 0-III,[189] or of distinguishing between hypermobility and ISD, has ever been documented in prospective studies. Clinically, ISD has been defined as "... sphincter weakness..." because "...the urethral sphincter is unable to coapt and generate enough resistance to retain urine...".[190] However, this clinical term has never been conceptualised into sound urodynamic parameters. Conventional static urethral parameters such as MUP or MUCP, or cough profile parameters such as pressure transmission ratio and LPP have been shown to be of limited value to characterise the extent and the type of urethral dysfunction.[90, 191] Thus conventional urethral pressure profile parameters do not consistently provide reliable pathophysiological information. One study suggests that urethral elastance may be a more useful variable to characterise intrinsic sphincter deficiency.[192]

b) Severity of stress urinary incontinence

There is no consensus on how to measure the severity of SUI clinically or urodynamiically. Severity can be expressed on the basis of simple clinical measures such as questionnaires, or on a bladder diary or on pad weighing tests. A review concludes that static urethral pressure profilometry parameters such as MUCP or cough profile parameters such as pressure transmission ratio cannot be used to characterise the severity of incontinence.[90]. One review suggested that abdominal LPP measurement might be a useful tool to quantify urethral dysfunction associated with SUI.[191]

However, other studies have found no correlation between leak point pressures and the severity of urinary incontinence as measured by bladder diaries and quality of life instruments. [100, 193-195] Leak point pressures are also limited as a diagnostic tool by the lack of standardisation of the technique. [196]

A total of 221 women, 29 to 80 years old (mean age 55.2), were included in a prospective TVT treatment study, performed mostly using local anesthesia with a mean follow-up of 10.5 months. Patients were divided into 61 with low (less than 60 cm H2O) and 160 with higher (60 cm H2O or greater) VLPP. Cure of incontinence was defined as an absent subjective complaint of leakage and absent objective leakage on stress testing. The overall cure rate was significantly lower in patients with low vs higher VLPP (82.0% vs 93.1%, p = 0.013) and, in women with low VLPP, multivariate analysis indicated that urgency symptoms and low MUCP were independent factors for treatment failure (OR 15.12, 95% CI 1.90 to 120.61, p = 0.010 and OR 0.92, 95% CI 0.86 to 0.99, p = 0.018, respectively). This led to the conclusion that women with urgency symptoms and low MUCP should be considered to be at high risk for failure after the TVT procedure. [110]

The role of preoperative VLPP in predicting the outcome of the distal polypropylene sling procedure for the treatment of SUI was prospectively evaluated in 174 consecutive patients, divided by VLPP into group 1 (60 patients who did not leak on urodynamics), group 2 (27 patients with VLPP >80 cm H2O), group 3 (71 patients with VLPP 30 to 80 cm H2O) and group 4 (16 patients with VLPP <30 cm H2O). Mean follow up was 14.7 months and mean patient age was 62 years. The distal urethral polypropylene sling provides similar symptom improvement in all patients regardless of preoperative VLPP. VLPP is helpful in the diagnosis of SUI but appears to be of minimal benefit in predicting the outcome of the distal urethral polypropylene sling procedure. [111]

In a review of recent reports and controversies concerning the use of LPP testing and urethral pressure profilometry prior to surgical treatment for SUI, it was concluded that there remains no clear consensus as to whether this testing enhances surgical outcome of SUI treatments by improving case selection or altering the surgical approach based on study findings. The reviewer found little evidence to suggest that patients with more severe forms of USI on urodynamic testing fare more poorly after the most commonly offered surgical treatment than those with less severe forms. However urodynamic testing may aid in identifying the group of women who appear to be at higher risk of voiding dysfunction following incontinence surgery. [107]

A total of 200 prospectively selected women with stress urinary incontinence (SUI) were clinically evaluated and underwent urodynamic study to determine the correlation, as well as the influence of bladder volume, between VLPP and UPP in urody-namically selected patients with USI. A progressive correlation of VLPP with MUCP was found when UPP was performed at 50 mL (r = 0.305, p <0.0001), at 250 mL (r = 0.483, p <0.0001) and at maximum bladder filling (r = 0.561,
A total of 655 women with stress predominant symptoms underwent a standardised assessment before sling or Burch procedure. Weak to moderate correlations were observed between Medical, Epidemiological and Social Aspects of Aging Questionnaire, incontinence episode frequency, pad weight, Incontinence Impact Questionnaire and Urogenital Distress Inventory. On the other hand, VLPP correlated poorly with all variables measured. The sensitivity and specificity of the supine empty bladder stress test to predict intrinsic sphincter dysfunction were 49% and 60%, respectively. Urinary incontinence severity measures correlated moderately with each other at best. VLPP did not correlate with measures of severity and quality of life. The supine empty bladder stress test did not demonstrate a clinically significant association with other severity measures. [100]

From a total of 168 women, the 31% that demonstrated SUI at lower bladder volumes (100 ml) did not report greater bother from incontinence than the 35% women who leak at higher volumes (>400 ml). The Urogenital Distress Inventory, Incontinence Impact Questionnaire, and also the MUCP and VLPP were similar in the groups. Among the 116 patients who had a sling procedure, USI persistence did not differ according to the volume at which USI occurred (p=0.72). The authors concluded that ‘bladder volume when leaking’ during a urodynamic study is not an adequate reflection of incontinence related quality of life. [99]

Most retrospective studies show higher failure rates after surgery in women with low MUCP (often defined as MUCP ≤ 20 cm H2O at MCC [90]). Other urethral closure pressure cut-points have been suggested as predictive of failure with transobturator versus retropubic midurethral slings in recent retrospective trials, but no prospective, randomised studies have been done to validate these observations.[108, 197] However, other investigators have shown that a low MUCP is not an efficient predictor of surgical failure.[187] In a recent prospective, randomised trial of women undergoing either Burch retropubic urethropexy or bladder neck slings, LPPs were not found to be predictive of surgical outcome for SUI. [198] Nevertheless, there are data to suggest that LPP may be a sensitive indicator of changes in incontinence status, reflecting treatment effect.[191]

The value of urethral hypermobility, MUCP and urethral incompetence was analysed in a study with 369 women with symptoms suggestive of SUI without symptoms of DO. Continent and incontinent patients differed with regards to urethral incompetence and hypermobility (each p <0.0001).

Incontinent patients had a greater probability of a higher grade of each factor. Even after adjusting for the older age of incontinent patients by ANCOVA, MUCP was significantly lower in the incontinent group (p <0.001). The best univariate optimised cutoff point for discriminating continence from incontinence was obtained with urethral incompetence greater than grade I. [106]

To compare the success rates of Burch colposuspension in relation to a VLPP cutoff level of 60 cm H2O and to examine other predictive factors for ISD, such as MUCP and FUL, in an attempt to define the urodynamic contraindications to Burch colposuspension 79 patients eligible for continuous postoperative follow-up were enrolled in a prospective study. The mean age was 58 ± 10 years, mean parity was 3.71 ± 4.

The success rates in 2 groups, VLPP ≥ 60 cm H2O (n=55) and < 60 cm H2O (n=24) were 94.55% and 91.67%, respectively, demonstrating no statistical significance (p > 0.05). On post-hoc analysis a VLPP level <60 cm H2O was not found to represent an absolute contraindication to Burch colposuspension, provided that other parameters, such as MUCP and FUL, are within acceptable ranges. [199]

Conclusions (evidence level 2/3)

• Various studies have shown conflicting results regarding the association of incontinence severity and urethral function tests (leak point pressures and urethral closure pressures)

• It is the opinion of the committee that contemporary urethral function tests are only modestly suited to judge the severity of incontinence or to further 'subcategorise' patients with stress (predominant) incontinence.
**Recommendations (grade B/C)**

- The committee recommends that urethral function measurements of leak point pressures and urethral closure pressures are not used as a single factor to grade the severity of incontinence.
- The committee recommends caution with the prediction of the outcome of any surgical treatment on the basis of contemporary urethral function tests.

**Topics for research**

- The committee suggests further studies with the aim to better understand urethral closure function and dysfunction, in relation to treatment for stress incontinence or stress predominant symptoms.

**c) Aspects of urodynamic studies relevant to therapy for stress urinary incontinence**

In a systematic meta analysis (only) 129 (out of 6009) studies were relevant for inclusion using the Quality Assessment of Diagnostic Studies (QUADAS) tool to identify and synthesize studies of diagnostic processes of urinary incontinence and to construct an economic model to examine the cost-effectiveness of simple, commonly used primary care tests. A clinical history for diagnosing USI in women was found to have a sensitivity of 0.92 and specificity of 0.56 and for DO a sensitivity of 0.61 and specificity of 0.87. For validated scales, question 3 of the Urogenital Distress Inventory was found to have a sensitivity of 0.88 and specificity of 0.60. Seven studies compared a pad test with multichannel urodynamics; however, four different pad tests were studied and therefore it was difficult to draw any conclusions about diagnostic accuracy. Of the four studies comparing urinary diary with multichannel urodynamics, only one presented data in a format that allowed sensitivity and specificity to be calculated. Their reported values of 0.88 and 0.83 suggest that a urinary diary may be effective in the diagnosis of DO in women.

Examination of the incremental cost-effectiveness of three primary care tests used in addition to history found that the diary had the lowest (best) cost-effectiveness ratio of between £35 and £77 per extra unit of effectiveness (or case diagnosed). Imaging by ultrasound to determine leakage was found to be effective in the diagnosis of USI in women, with a sensitivity of 0.94 and specificity of 0.83. The report found that a large proportion of women with USI can be correctly diagnosed in primary care from clinical history alone. On the basis of diagnosis, the diary appears to be the most cost-effective of the three primary care tests (diary, pad test and validated scales) used in addition to clinical history. The authors thought that ultrasound imaging may offer a valuable alternative to urodynamic investigation and that the clinical stress test is effective in the diagnosis of USI. However, they also conceded that if a patient is to undergo an invasive urodynamic procedure, multichannel urodynamics is likely to give the most accurate result in a secondary care setting. [200]

In 2006 in the UK, the National Institute of Health and Clinical Excellence (NICE) issued guidelines that urodynamics was recommended before surgery for urinary incontinence only if there is a clinical suspicion of DO or, if there has been previous surgery for stress incontinence or anterior compartment prolapse or, if there are symptoms suggestive of voiding dysfunction. [201] In other words, urodynamics is not routinely recommended for women before surgery for a ‘clearly defined clinical diagnosis of stress urinary incontinence’. This was a recommendation founded on expert opinion collated by a modified Delphi process. However, a study in 2008 by Agur et al casts some doubt on the wisdom of this recommendation. [202] In their tertiary centre, patients are referred with lower urinary tract symptoms. Information is collected and entered into a computer database at the time of history taking and before conducting urodynamic tests. The database was used retrospectively to identify women aged 18-80 years who had multichannel cystometry for urinary incontinence over a 17-year period (1 January 1990 to 31 December 2006). To apply the NICE criterion of a ‘clearly defined clinical diagnosis of pure SUI’, strict selection criteria were used to identify patients with pure SUI. The reliability of the patients’ history in predicting ‘pure’ USI in patients with ‘pure’ SUI was investigated. They found that only 324/6276 (5.2%) women had pure SUI; moreover, a quarter of those with pure SUI symptoms ultimately had urodynamic diagnoses other than USI, that could affect the outcome of continence surgery. They concluded that only a small group of women fulfil the NICE criteria of pure SUI and it seems inevitable that even with these strict criteria, a woman can go forward to a surgical procedure with potentially important urodynamic findings unaddressed.

**Conclusion (evidence level 1)**

- It is concluded in a model study, based on a selected retrospective cohort, that urodynamic testing is not cost effective in the primary health care setting for women with predominant stress incontinence symptoms. It is also shown that in the referred population, urodynamic investigation is the most accurate way to obtain an objective diagnosis in patients with predominant stress urinary incontinence symptoms.

**Conclusion (evidence level 3)**

- Symptoms of pure stress urinary incontinence do not always exclude other abnormalities of lower urinary tract function.
**Recommendation (grade A)**

- The committee recommends that the cost effectiveness of urodynamic testing is kept in mind when discussing 'cost and gain' of the various methods of diagnosis for urinary incontinence, in relation to the method of treatment.

**Recommendation (grade B)**

- The committee recommends urodynamic studies are carried out in all women prior to surgical intervention for stress urinary incontinence.

**Topic for research**

- The committee suggests that a well-designed, multicentre study should address the question as to whether women with symptoms of pure stress urinary incontinence are more at risk of failure from surgical treatment of their incontinence without pre-operative urodynamics or have more adverse events following surgery without pre-operative urodynamics than women who have pre-operative urodynamic studies.

**d) Prediction of failure of surgery**

Most retrospective studies show higher failure rates after surgery in women with low maximum urethral closure pressure (often defined as MUCP ≤ 20 cm H2O at maximum cystometric capacity). [90] Other urethral closure pressure cut-points have been suggested as predictive of failure with transobturator versus retropubic midurethral slings or pubovaginal slings in recent retrospective trials, but no prospective, randomised studies have been done to validate these observations. [108, 197, 203] When used together, Kilcarsian and colleagues found low urethral closure pressure and low leak point pressures to be predictive of failure after in situ vaginal wall slings in 58 women. The success rate was 65% in women with VLPP < 50 cm H2O and MUCP < 30 cm H2O but it was 91% in those with VLPP > 50 cm H2O and MUCP > 30 cm H2O (p< 0.05). [204] Clemons and LaSala showed that combining low urethral closure pressure and the absence of urethral hypermobility was predictive of surgical failure after a tension-free vaginal tape procedure. They found that an MUCP ≤ 15 cm H2O resulted in only a 60% cure rate after TVT with an odds ratio of 6.3 for failure (p= 0.03). The absence of urethral hypermobility, defined as a straining angle of ≤ 35°, was associated with a cure rate of 50% with an odds ratio of 7.7 (p= 0.02). When the 2 factors were combined the cure rate was only 17% (p< 0.001). [205]

However, other investigators have shown that a low MUCP is not an efficient predictor of surgical failure. [187, 206] In a recent prospective, randomised trial of women undergoing either Burch retropubic urethropexy or bladder neck slings, leak point pressures were not found to be predictive of surgical outcome for stress urinary incontinence. [198]

Leak point pressures have not been found to be predictive of surgical outcomes following bone-anchored suburethral slings, transobturator and retropubic midurethral slings. [111, 193, 207-209]

Urethral retro-resistance pressure has also been studied as a potential predictor of surgical success. However, Tunn et al failed to show any predictive value of this measurement for surgical success with colposuspension, retropubic midurethral slings and transobturator midurethral slings. [30]

Ward and colleagues carefully examined the impact of urodynamic testing on decision-making and treatment recommendations in incontinent women. They found that the probability that urodynamics would alter recommendations for medical treatments was 27% and 46% for surgical treatment. Clinicians believe that there is value to adding multichannel urodynamics studies to history, physical examination, bladder diary, assessment of urethral hypermobility, cough stress test and post-void residual urine measurement. [210]

**Conclusion (evidence level 2)**

- Leak point pressures do not appear to correlate with success rates of colposuspensions, transobturator and retropubic midurethral, bone-anchored suburethral slings

**Conclusion (evidence level 3)**

- There is some evidence that low urethral closure pressures are associated with poorer success rates of retropubic and transobturator midurethral, vaginal wall and transvaginal bone-anchored slings.

**Recommendation (grade B/C)**

- The committee recommends that measurements of urethral function (leak point pressures and urethral closure pressures) are not used to reliably predict the likelihood of success after surgical treatment for stress incontinence. However, the values of urethral closure pressure may provide some guidance in this respect.

**e) Voiding difficulties after surgery**

Surgery for SUI may lead to voiding difficulties. [211] At this time risk factors (including urodynamic risk factors) for delayed resumption of voiding are not well defined. The type of surgery clearly plays a role: retropubic midurethral slings have been found to be less obstructive than Burch colposuspensions [212]
and transobturator midurethral slings appear to be less obstructive than the retropubic midurethral slings [213]. One major problem is that at the moment there is no clear urodynamic definition of obstruction or detrusor underactivity in women. It has been reported that low maximum flow rates (< 20 mL/s) [214] or “inadequate contraction strength” defined as pdet <15 cm H2O during voiding (but note that this low pdet frequently signifies a low urethral resistance, and not necessarily a weak detrusor contraction), or significant use of the Valsalva manoeuvre when voiding, are associated with postoperative voiding difficulties.[215-217] Wheeler et al found that maximum flow rates were the best predictor of passing an initial voiding trial after retropubic and transobturator midurethral slings in multivariate analysis of 89 women (p=0.0002). [218] Similar findings were noted by Gravina and colleagues. [219] The possibility exists that, in women who do not use their detrusor during voiding, detrusor contractility may be assessed preoperatively by mechanically interrupting the flow (“Stop test”). [220, 221]

Shukla and colleagues found no urodynamic factors that were predictive of postoperative voiding difficulty following tension-free vaginal tape procedures despite a trend toward long term voiding difficulties in those with lower average flow rates in a multivariate regression analysis of 411 patients (p= 0.12). [222]

Dawson et al showed a significant relationship between the centile score for average flow rates and the risk of voiding dysfunction and the need for intermittent self-catheterisation on multivariate analysis after tension-free vaginal tape procedures in 267 women (p=0.029). [223]

**Conclusion (evidence level 3)**

- Current test methods have not been able to reliably predict patients who will develop voiding difficulties after surgery for stress incontinence.
- However, average and maximum flow rates may be useful in predicting post-operative voiding dysfunction and retention following retropubic and transobturator midurethral slings.

**Recommendation (grade C)**

- The committee recommends that patients are informed that it is difficult to predict who will develop voiding difficulty following surgery for stress incontinence. However, poor pre-operative maximum and average flow rates are more likely to result in voiding problems following retropubic and transobturator midurethral slings.

**f) Postoperative urgency**

The preoperative symptoms of UUI and urgency, and the urodynamic observation of DO, have each consistently been shown to be associated with poorer surgical outcome in patients with mixed urinary incontinence. Several studies where the amplitude of DO was graded have shown that the risk of persistent urgency was more closely associated with high-pressure DO (pdet ≥ 25 cm H2O) than low-pressure DO.[224-226] Consequently cystometry may allow a more precise selection of patients who respond well to surgery despite concurrent urge symptoms. The success rate after anti-incontinence surgery in patients with low-pressure contractions seems to be similar to the success rate in those without DO, [224-227] but the success rate in women with high-pressure contraction is less than 50%.[224-227]

On the other hand preoperative urgency symptoms resolve in a substantial proportion of patients (50-65%).[228-230] One untested hypothesis is that surgical correction of the bladder outlet may prevent ingress of urine into the proximal urethra (which if it occurs, may induce DO in some patients).[231-234]

De novo UUI has been reported to occur in 10-20% of patients after surgery.[211] There is scant information on clinical or urodynamic risk factors; possibly the type of surgery plays a role. A recent retrospective trial suggested that the incidence of de novo UUI was higher in bladder neck slings than in retropubic midurethral slings which were also associated with more de novo UUI than transobturator midurethral slings [213]. It should be remembered however that de novo DO may merely represent DO that was missed preoperatively.

**Conclusions (evidence level 2)**

- Current test methods have been unable to reliably predict which patients will develop de-novo urinary urgency (OAB syndrome) after surgery for stress incontinence.
- Post hoc evidence suggests that procedures which are more ‘obstructive’ produce a higher chance of de novo urinary urgency (OAB-syndrome).

**Recommendation (grade C)**

- The committee recommends that patients with stress incontinence are informed that the chance of developing urinary urgency (OAB-syndrome) following surgery is largely unpredictable.

**Topics for research**

- The committee suggests further work to evaluate predictors of voiding difficulties or urinary urgency after contemporary (moderately invasive) treatments of stress incontinence (e.g. trans-obturator or trans-vaginal tapes).
g) The role of urodynamic studies in predicting occult stress urinary incontinence in women due to be treated for pelvic organ prolapse

Because 11 to 22% of continent women undergoing vaginal repair for a large cystocele develop SUI following surgical repair,[235, 236] it would be helpful to devise methods to evaluate patients who are at risk for this complication.[237] Women with severe pelvic organ prolapse may develop incontinence symptoms when the prolapse is reduced; this is frequently named ‘occult’ SUI. Voiding difficulty and bladder outlet obstruction may coexist with occult SUI; all may be associated with pelvic organ prolapse, and all may be altered if the prolapse is reduced during urodynamic testing.

The overall incidence of occult SUI was 25% when videourodynamic testing was performed with and without pessary support of the bladder base during stress manoeuvres.[238]

In a small group of patients with severe genitourinary prolapse, occult incontinence was found in 59%, and about 20% (4/22) were reported to demonstrate stress pressure profiles suspect for SUI after pessary placement.[239] However, it should be remembered that stress UPPs are not particularly reliable measurements. A special technique (Scopette, Birchwood Lab) for reducing prolapse during multichannel urodynamics revealed a 56% incidence of low-pressure urethra (possibly related to ISD, but see caveats regarding UPPs above) and an overall incidence of occult SUI of 83% in women with massive pelvic organ prolapse but without clinical urinary incontinence.[240]

As expected, urethral hypermobility is correlated with the degree of prolapse.[241] Surprisingly, so too is DO (revealed by prolapse reduction), although impaired detrusor contractility and ISD were not significantly associated with prolapse in this one study.

The literature thus emphasises the importance of urodynamic assessment with prolapse reduction to assess potential occult SUI and possibly DO.[184, 237, 238, 242] However, although occult SUI is revealed in a high proportion of cases with severe prolapse, there seem to be no studies assessing reproducibility, a particularly important point since the technique of reduction is variable and non-standardised.

Many different tests (e.g. pessary test, speculum test) have been used to document occult SUI. In many studies they are positive in 50–77% of patients (which, arguably might be overestimating the risk). In various papers the Pereyra and Kelly procedures have been used prophylactically but there is no documentation that they reduce the risk of postoperative incontinence.[243-245] A prospective controlled study[246] showed that the pessary test was positive only in 50% of incontinent women and was falsely positive in 72%. Another study[219] concluded that urodynamic testing before a pelvic organ prolapse operation was not cost-effective.

More recently in 2008, the CARE trial in the United States examined 322 stress-continent women with stages II-IV prolapse who underwent standardised urodynamics. Five prolapse reduction methods were tested: two at each site and both were performed in each subject. Clinicians were masked to urodynamic results. At sacrocolpopexy, participants were randomised to Burch colposuspension or no Burch colposuspension (control). Preoperatively, only 12 of 313 (3.7%) subjects demonstrated USI without prolapse reduction. More women leaked after the second method than after the first (22% vs. 16%; p = 0.012). Preoperative detection of USI with prolapse reduction at 300ml was found with a pessary in 6% (5 of 88); with manual vaginal elevation in 16% (19 of 122); with forceps in 21% (21 of 98); proctoswabs in 20% (32 of 158); and with a speculum in 30% (35 of 118). Women who demonstrated preoperative USI during prolapse reduction were more likely to report postoperative SUI, regardless of concomitant colposuspension (controls 58% vs. 36% (p = 0.04) and Burch 32% vs. 21% (p = 0.19). [247]

Conclusions (Evidence level 1)

• Various studies have shown that symptoms of stress incontinence can appear after surgery for prolapse.

• There are a variety of methods to uncover ‘occult stress urinary incontinence’ in women with vaginal prolapse. However, they all have different sensitivities and this makes comparison of results difficult. Standardisation of these tests in clinical practice may be beneficial.

• Various studies have shown that concomitant procedures to address possible stress incontinence developing after prolapse surgery (with or without simultaneous urodynamic testing) are not reliable in preventing its occurrence.

Recommendation (Grade B)

• The committee recommends that patients with vaginal prolapse are informed about the relative unpredictable chance of developing stress incontinence after surgery for that prolapse.

3. URGENCY URINARY INCONTINENCE
a) Pathophysiology and severity of urgency urinary incontinence

It remains unclear if the chronological sequence of bladder and urethral pressure changes may distinguish between ‘true’ (idiopathic?; originating in the detrusor?)
DO and ‘secondary’ DO. Secondary DO might be due to bladder outlet relaxation and ingress of urine into the proximal urethra followed by a micturition reflex. [248]

No statistically significant relationship between the various cystometric variables and reported symptom severity has been established.

b) Prediction of treatment response

Urgency and UUI or OAB syndrome are poorly associated with the urodynamic observation of DO, as discussed previously. The positive predictive value of OAB (urgency usually accompanied by frequency and nocturia with or without UUI) for urodynamically determined DO is only around 50%. [148] On the other hand DO is reported in 10-69% of asymptomatic female volunteers, depending on the definition and type of cystometry. [55, 59, 65, 162, 187, 249] This makes it impossible to use urodynamic investigation (cystometry) to predict the outcome of treatment for UUI.

Studies on voiding difficulties or de novo SUI or combined incontinence (as a consequence of increased capacity because of treatment for UUI) have not been published.

Conclusions (level 2/3)

- Various studies have concluded that the association between overactive bladder symptoms and detrusor overactivity during urodynamic investigation is weak.
- Various studies have concluded that the prediction of treatment - for overactive bladder symptoms - response on the basis of the characterisation or quantification of detrusor overactivity during urodynamic investigation is impossible.

Recommendation (Grade B/C)

- The committee recommends that investigators and clinicians discuss with patients with detrusor overactivity that neither quantity nor specific characteristics of detrusor overactivity predicts the response of any of the therapeutic approaches.

Topics for research

- The committee suggests further studies to find predictors of response on treatment for patients with overactive bladder syndrome.
- The committee suggests further studies to find urodynamic predictors of response for patients with overactive bladder without detrusor overactivity.

4. RECOMMENDATIONS FOR URODYNAMIC STUDIES IN WOMEN WITH URINARY INCONTINENCE

a) Recommendations for clinical practice:

1) The committee recommends non-invasive urodynamics (voiding and incontinence diary, PVR, and possibly uroflowmetry) for all patients with incontinence.

2) The committee finds that invasive urodynamic studies are not necessary prior to treatment in situations where the type of urinary incontinence is clear and there are no complicating factors and planned treatment is reversible. The committee provides the following examples:

- uncomplicated symptoms of SUI with normal bladder diary, normal flowmetry and without relevant PVR. (Symptomatic pure SUI with no symptoms or signs of voiding difficulties), for treatment by, for example, pelvic floor muscle training.
- uncomplicated symptoms of UUI with a bladder diary in accordance with these symptoms, with normal flowmetry and without relevant PVR. (symptomatic pure UUI with no symptoms or signs of voiding difficulties), for treatment by, for example, bladder training.

3) The committee recommends that, whenever surgical intervention is planned, whenever there is doubt about the pathophysiology, or about whether the incontinence is uncomplicated or not, then invasive urodynamics should be performed in order to provide the knowledge on which rational treatment decisions or prognosis can be based. The investigation should be tailored to the individual patient; typically this means that it will be a comprehensive examination of multiple aspects of storage and voiding function, and not just of the incontinence itself.

4) The committee suggests for research:

- to study new or existing urodynamic tests and parameters which have a sound technical and physiological basis
2) The committee recommends that no new therapy should be introduced without extensive urodynamic testing of all accessible aspects of its effect on LUT function and dysfunction.

II. PATIENT EVALUATION: MEN

1. INTRODUCTION

Although the incidence of urinary incontinence in men is generally regarded as much lower than in women, this is not necessarily true for all patient groups, especially when dealing with the elderly (see section D.V, Patient evaluation: Frail elderly). In both sexes those who lose urine, whatever the cause may be, increase in number with advancing age.[250] In this section the characteristic pathologies that lead to incontinence in men are discussed from the point of view of urodynamic testing. Although urinary incontinence related to benign prostatic obstruction (BPO), BOO or to (radical) prostatic surgery is most frequently encountered, other important pathological conditions such as nocturnal enuresis and post-micturition dribbling are also clinically relevant.[2, 251]

This section is organised according to the suspected origin or cause of incontinence or related LUTS, reflecting the very varied aetiologies responsible for the condition in men.

2. LOWER URINARY TRACT SYMPTOMS RELATED TO BLADDER DYSFUNCTION MAINLY DETRUSOR OVERACTIVITY AND BLADDER OUTLET OBSTRUCTION

LUTS are fairly common among men of 50 years and over. Incontinence is not usually prominent but, if it is present, urodynamics can be helpful to establish the underlying vesical/urethral dysfunction, in particular, DO and/or BOO. Coexistence of BOO and DO increases with age and with the degree of BOO. [252, 253]

Non-invasive investigations such as uroflowmetry and measurement of PVR are easy to perform, but even in simple situations can only give clues to the underlying pathology. Low Q_max on uroflowmetry cannot distinguish BOO from the poor detrusor contractility. [254] There is also a significant variation in Q_max in repeated tests [255]. Moreover, since elderly people often suffer from co morbidities – e.g. insidious neurogenic ailments such as Parkinson’s disease, multiple sclerosis, cerebrovascular disease or diabetes mellitus – invasive urodynamic tests are frequently necessary to finalise the diagnosis and plan any intervention, especially if surgical treatment is considered.

The role of urodynamics and DO in predicting treatment outcome still remains controversial. Aboseif et al compared 92 men with and without DO on pre-operative urodynamics before radical prostatectomy.

They found, after one year, a significantly higher incidence of incontinence (39% v/s 3%) in patients with pre-operative DO compared to those without pre-operative DO. [256]

Similarly, Seki et al in a retrospective study of 384 patients who had undergone transurethral resection of the prostate (TURP) for symptomatic benign prostatic enlargement (BPE), showed after one year from IPSS and QoL that the baseline DO negatively affected outcome. [257]

Monoski et al found in 40 men who underwent photoselective laser vaporisation prostatectomy (PVP) for ‘BPH’ and retention that the presence of DO in patients on pre-surgery urodynamics is associated with significantly more storage symptoms requiring twice as likely anticholinergics treatment than the patient without DO. No specific distinction was given to incontinence. [258]

On the other hand, Kleinhans et al concluded (44 patients) that preoperative DO did not correlate to any of the post surgical incontinence eight months after radical prostatectomy. [259]

In 1999, Golomb et al also concluded that there was no significant association between pre-operative DO and post-operative incontinence. [181]

Urodynamics may also be useful for selecting candidates for new, emerging treatments. For example, Vandoninck et al. [260] used urodynamics to evaluate patients with OAB symptoms who were to be treated with percutaneous tibial nerve stimulation. Overall, the objective and subjective success rates of stimulation were 56% and 64%.

The treatment abolished DO only in a few cases and subjects without DO at baseline were 1.7 times more likely to preferably respond to percutaneous tibial nerve stimulation than those with DO.

a) Recommendations for urodynamic investigation in those with LUTS with incontinence related to bladder dysfunction mainly detrusor overactivity and bladder outlet obstruction

Patients with symptoms suggestive of non-complicated bladder outflow obstruction (BOO) on the basis of prostate enlargement without incontinence, need prostate size assessment, urinary flow study, PVR measurements, (International Prostate) Symptom Score and 24 hour frequency-volume charts prior to intervention, but do not always need to be investigated with invasive urodynamic study. [261-263]
Men with incontinence and a suspicion of other LUT dysfunction form a much more restricted group with complicated, disparate, and uncertain diagnoses. In some the incontinence may be an initial symptom; in others it may follow treatment (see the following section on post-prostatectomy incontinence).

Recommendation (Grade C)

- Evidence that urodynamics improves outcome is limited, but nevertheless the committee recommends that all such patients should receive a complete urodynamic evaluation in order to understand the problem that is to be treated and that surgeons should plan surgical interventions only after scrutinising the lower urinary tract by urodynamics.

3. POST-PROSTATECTOMY INCONTINENCE

a) General

After prostatectomy a noticeable number of patients suffer from urinary incontinence. The reported incidence following surgery varies widely depending on patient age, bladder function, definition or degree of urinary incontinence, benign or malignant prostatic disease and the type of surgery. Approximately 10-14% of patients, 2-5 years after radical prostatectomy complain of incontinence. [264] A prospective survey study on 1201 patients and 625 partners on outcome after treatment for prostate cancer showed that urinary incontinence was at its worst by 2 months after surgery and then improved in most patients. Factors that were associated with worse incontinence were an older age, black race, and a high PSA score at diagnosis. Patients in the brachytherapy group reported significant deterioration in ‘urinary irritation’ or obstruction and incontinence as compared with baseline (p<0.001). Incontinence after brachytherapy was reported by 4 to 6% of patients at 1 to 2 years after treatment. [265]

Understanding of prostato-vesical anatomy and the pelvic floor, and meticulous surgical technique, are of prime importance in preventing these distressing symptoms. Urodynamic studies can establish the aetiology and provide a rational basis for treatment by determination of the type of LUT dysfunction(s).

Kondo et al [251] have analysed the aetiology of urinary incontinence following surgery for ‘benign prostatic hyperplasia (BPH)’ or prostatic cancer using accumulated data from 573 patients reported in 8 articles from 1978 to 1997. Urodynamic studies suggested that the most common aetiology was sphincter weakness (causing USI), present in 34% of patients, followed by sphincter weakness plus DO in 33%, and DOI alone in 26%. Other aetiologies including low compliance and urethral stricture were responsible for the remaining 7% of patients with incontinence after surgery for BPH. Thus, although sphincter weakness was present in two-thirds of patients, a blanket assumption that it is the only cause of incontinence would be wrong in two-thirds. Clearly urodynamic testing is needed for diagnosis, and perhaps to choose treatment.

b) TURP, Open Prostatectomy and Thermal Treatments

Approximately 1% of patients who have undergone TURP suffer from post-prostatectomy incontinence.[266] Is urodynamics required prior to treatment? Das et al. [263] performed holmium laser resection of the prostate in 100 men patients for management of LUTS without performing any urodynamic studies except for a urinary flow rate. Their follow-up study 2 years later revealed that persistent incontinence remained in only 1, who required pads, and that the IPSS and maximum flow rates improved from 21.6 to 6.8 points and from 7.5 to 21.6 mL/s, respectively. This report does suggest that if patients are appropriately selected, post-operative urinary control is quite satisfactory, leaving only about 1% of cases with urinary incontinence. This implies that the role of urodynamic investigation in preventing post-operative incontinence before laser resection of the prostate may be marginal.

Kuo [267] urodynamically evaluated 185 men aged from 55 to 91 with a mean of 75 years who had had variable LUTS after TURP and had been refractory to conventional treatments. He found that urinary incontinence was present in 74 patients (40%) and that BOO and DO with impaired contractility (DHIC) were the most common findings associated with post-prostatectomy incontinence, followed by DO. Since these diagnoses imply quite different treatments, urodynamic investigation has an important role.

Conclusions (evidence level 3)

- Retrospective studies have shown that urodynamic tests cannot predict stress urinary incontinence or detrusor overactivity (with or without incontinence) after surgical treatment for benign prostatic obstruction.
- Studies have shown that urodynamic tests clearly identify the aetiology of urinary tract dysfunction after surgical treatment for benign prostatic obstruction however the predictive value towards the effects of subsequent treatment is unknown.

Recommendations (Grade C)

- The committee recommends urodynamic testing when patients have signs and/or symptoms of lower urinary tract dysfunction after surgical treatment for benign prostatic obstruction; particularly if further surgical or invasive treatment is planned.
c) Radical Prostatectomy and Radiotherapy

i) Is (invasive) urodynamic investigation of incontinence after radical prostatectomy necessary?

Radical retropubic prostatectomy for prostatic cancer results in much higher incidence of post-prostatectomy incontinence than TURP. In physician-reported studies, the incidence of total incontinence is a few percent and the incidence of SUI requiring some degree of protection is about 10%. [268] In studies based on patient self-report, however, the incidence of any degree of incontinence is 66% and the incidence of pad use is 33%. [269] One of the main determinants of prevalence is the time following surgery, since continence is regained after radical prostatectomy over the first year in many patients. [270] Continence after radical prostatectomy depends on minimizing the injury to the striated urethral sphincter and the use of well-designed surgical techniques. [271]

Patients who undergo a nerve-sparing radical prostatectomy appear to have a better chance of achieving continence than those undergoing standard radical prostatectomy. [272] Recent enhancements to the nerve-sparing prostatectomy may preserve external sphincter function and shorten the time to achieve post-operative continence. [272]

Castille et al prospectively assessed 229 men who were scheduled to undergo radical retropubic prostatectomy with preoperative urodynamics in an attempt to help physiotherapists predict postoperative incontinence. [273] They observed that all men diagnosed as having DO or BOO were incontinent 6 weeks after operation but had improved 4 months later. They stressed that DO and BOO in those undergoing radical retropubic prostatectomy are significant risk factors for postoperative incontinence, although only for a short period of time. Thus the role of pre-operative urodynamics is limited.

Groutz et al [274] evaluated 83 men of mean age 68 years, who were consecutively referred for persistent urinary incontinence following radical retropubic prostatectomy. They reported that USI was the most common urodynamic finding (73 patients, 88%), followed by DO in 6, BOO in 1, impaired detrusor contractility in 1, and normal findings in 2. Of 73 men diagnosed as having USI, 27 suffered from pure urodynamic USI, and the remaining 46 had concomitant bladder disorders such as impaired detrusor contractility (22 men), BOO (14 men) or DO (10 men). The authors reported that 25 of the 83 men had what they called “low urethral compliance”. This non-standard term expressed the fact that there was a difference of more than 10 mL/s between maximum free uroflow and maximum invasive (pressure-flow) uroflow. This term is not recommended, however, as it implies a cause for these observations that may not be correct.

Huckabay et al suggested a urodynamic protocol with video-urodynamics for patients with persistent incontinence after radical prostatectomy. They evaluated 60 men and found that twenty-four (40%) men had DO with 8 (13%) also having DOI. Only one patient had impaired bladder compliance. All men had USI, but 21 (35%) men demonstrated it only after removal of the urethral catheter. For men leaking with and without the urethral catheter, the respective abdominal leak point pressure (ALPP) was significantly different, 86.3 and 67 cmH₂O, respectively (p = 0.002). The men who leaked only in the absence of the urethral catheter had significantly higher ALPP measurements, p < 0.001. After reclassification using the fluoroscopic images of the bladder outlet and free Qmax, only 13.3% patients were obstructed. [275]

McCallum et al [276] reported that 21 of 180 men who had been treated for incontinence following radical prostatectomy still remained incontinent 2 years later. Sixteen of the 21 were evaluated, and half had USI together with UUI or decreased bladder compliance. The authors emphasised that SUI was one of the predominant symptoms but that co-morbid detrusor dysfunction had to be taken into consideration, as well as ISD, in order to properly treat persistent post-prostatectomy incontinence.

There was a very interesting study reported by Noguchi et al in 2006. [277] They evaluated a standard versus modification technique of radical prostatectomy in which the anterior attachment of the puboprostatic ligament to the pubic bone is preserved, to which the newly created vesico-urethral anastomosis is suspended. Three months after surgery ALPP, functional urethral length (FUL) and maximal urethral pressure were measured. The “suspension” group had a significant better continence rate and significantly higher ALPP.

On the other hand Twiss et al. based on study 29 men with incontinence after radical prostatectomy, concluded that ALPP is a relatively poor predictor of incontinence severity and, therefore, has limited clinical value in the urodynamic evaluation of post-prostatectomy incontinence. [278]

i) Is (invasive) urodynamic investigation of incontinence after radiotherapy necessary?

There are few manuscripts reporting the effects of radiotherapy in those with prostatic cancer, and even fewer discussing the place of urodynamics. [279, 280]

Henderson et al. [281] assessed the clinical role of urodynamics in the selection of prostate cancer patients for brachytherapy with a minimum dose of 145 Gy. One hundred consecutive patients were assessed after implantation. Prior to the treatment an unselected group of 57 of the 100 patients had been evaluated urodynamically: normal detrusor function (no DO) was found in 48 and DO in 9. No patients had
permanent urinary incontinence and 2 required surgery for BOO. Acute urinary retention developed in 7 patients, clean intermittent catheterisation was utilised by 27, and 89% of patients had a deterioration in their LUTS with the worst symptoms 6 weeks after implantation. They found that those who post-operatively had acute retention or preferred to utilise clean intermittent catheterisation had either larger prostatic volumes (> 35 mL) or were urodynamically obstructed. Consequently they concluded that urodynamics might have an important role in the selection of treatment for men with early prostate cancer, in particular to improve the outcome of brachytherapy.

In another study Beekman et al found in 204 patients that high PVR (> 100 mL) is associated with slower resolution of voiding symptoms, prolonged (more than 3 days) catheter dependency, and increased postbrachytherapy surgical intervention for BOO. [282]

Also Wehle et al suggested that the combination of urinary flow rate, prostate volume, postvoid residual urinary volume, and the American Urological Association symptom score can help identify patients with underlying voiding dysfunction. Urinary flow rate was a statistically significant predictor of genitourinary tract morbidity after brachytherapy for localised prostate adenocarcinoma. [283]

Overall there is a weak evidence to support urodynamic evaluation before radiotherapy for cancer of the prostate

**iii) Artificial urinary sphincter and male sling**

Gomha and Boone [284] treated 86 patients who were incontinent following surgery with implantation of an artificial urinary sphincter (AUS) and assessed whether or not prior radiation affected surgical outcomes in those who had or had not had radiotherapy. The aetiology of the urinary incontinence in group I (without radiation) was radical prostatectomy in 55 patients, TURP in 2, orthotopic ileal reservoir in 1; in group II (with radiation) the aetiology was radiation with salvage prostatectomy in 5, adjuvant radiotherapy after radical prostatectomy in 20, and radiotherapy and TURP in 3. Urodynamic study prior to artificial sphincter implantation revealed that DO was much more prevalent in group II (radiation, 26%) than in group I (no radiation, 5%), a significant difference (p = 0.04). In spite of this, post-operative urgency with or without urgency incontinence was found in similar proportions of the 2 groups (47% of group I and 43% of group II), and similar proportions were 0 to 1 pad a day to protect against their incontinence (60% and 64% respectively). Thus pre-operative urodynamics did not predict outcome.

Similarly, Thiel and co workers concluded that patients with incontinence post RP and DO, low compliance, decreased MCC and FSF have the same outcome after AUS implantation. [285] This was a retrospective review of 86 patients. Obviously, there could have been a selection bias in the study and the more severe cases could have been excluded from surgery.

However Ullrich & Comiter evaluated urodynamically 22 patients at a mean of 25 months after a male sling procedure and found that patients with postoperative retrograde leak point pressure < 50 cm H2O and DO are associated with increased pad use and bother. [286]

**d) Recommendations for urodynamics in those having post-prostatectomy incontinence**

Sphincter weakness, BOO, DO and mixed incontinence are significant aetiological factors contributing to post-prostatectomy incontinence.[251, 267, 276] These parameters can be only identified by urodynamics, which is considered by most.[284, 287, 288] but not all, [289] to be one of the main tools for investigating this type of incontinence. In brachytherapy for prostate cancer, urodynamics may have some value for predicting which men might develop acute urinary retention or might require intermittent catheterisation after treatment.[281]

**Conclusions (evidence level 3)**

- Retrospective studies have shown that urodynamic tests cannot predict lower urinary tract dysfunction after surgical treatment for prostatic carcinoma.
- There is weak evidence to support urodynamic evaluation before radiotherapy for cancer of the prostate
- Studies have shown that urodynamic tests clearly identify the aetiology of urinary tract dysfunction after surgical or radiotherapeutic treatment of prostatic carcinoma however the predictive value towards effect of subsequent treatment is unknown.

**Recommendations (grade C)**

- The committee recommends urodynamic evaluation before radiotherapy for cancer of the prostate.
- The committee recommends urodynamic testing when patients have signs and/or symptoms of lower urinary tract dysfunction after treatment of prostatic carcinoma; particularly if surgical or invasive treatment is planned.

**Topics for research**

- The committee suggests research to find predictors for lower urinary tract dysfunction after treatment for benign prostatic obstruction or for prostatic carcinoma.
- The committee suggests research to improve
4. NOCTURNAL ENURESIS AND PARKINSON'S DISEASE RELATED TO MALE INCONTINENCE

Several ailments or pathological conditions have been reported to be closely associated with male incontinence, e.g., neurological diseases, prior radiotherapy, neurogenic DO, diminished bladder compliance, nocturnal enuresis, post-micturition dribble and terminal dribbling. [251]

a) Nocturnal enuresis

Nocturnal enuresis in adult males is rather rare. Sakamoto and Blaivas reported important and interesting observations based on data of over 3000 patients referred for the evaluation of LUTS. [288] They found that 8 of 3277 patients (0.02%) had adult onset nocturnal enuresis without daytime enuresis. All these patients were male, with a mean age of 63 years (48 to 80 years) and all suffered from BOO with mean maximum urinary flow rate 8.5 mL/s, mean IPSS 12.6, and mean PVR urine 350 ml (50 to 489 ml). The authors identified hydronephrosis in 5 of the 8 patients, a bladder diverticulum in 3/8, VUR in 4/8 and low bladder compliance in 4/8. Five of the 8 underwent TURP resulting in improved symptoms. Thus BOO is one of the distinct pathologies that can provoke nocturnal enuresis with variable LUTS, but it is not the only pathological factor. For example, Hunsballe [290] found more delta activity in electroencephalography among adult primary enuretics compared to normal controls. Therefore, invasive urodynamics may be justified in such patients, because it is the only way of reliably identifying BOO.

Another factor contributing to nocturnal enuresis is the presence of a neobladder. Nocturnal enuresis plagues nearly 28% of such patients. Indeed, 25 of 30 patients (83%) who underwent the Stanford pouch ileal neobladder had nocturnal enuresis 1 year later. [291] Patients older than 65 years are at greater risk because of the physiological increase in LUTD nocturnal diuresis associated with aging. An orthotopic neobladder produces variable LUTD including both failure to empty the bladder and failure to store urine. The urodynamic behavior depends on the type, length, and configuration of the bowel segment used. [292] There may be overdistension, elevated PVR, lack of sensation, reduced MUCP, or more frequent and higher-pressure DO. [293] The intestinal overactivity in a neobladder resembles bowel peristalsis. [294]

e-l-Bahnasawy et al studied urodynamically 50 enuretic men at least 1 year after a radical cystoprostatectomy and ileal neobladder and compared them to 17 men with only occasional enuresis and 50 men without enuresis after similar surgery. Both enuretic groups had significantly higher residual urine volumes, pressure at mid-capacity and at maximum enterocystometric capacity, amplitude of involuntary contractions, and lower compliance than continent men. Men with occasional enuresis also had a significantly higher frequency and duration of involuntary contractions than continent men. Men with persistent enuresis had significantly lower average and maximum urinary flow rates than continent men, and significantly lower functional urethral length and maximum urethral pressure. [295]

Urodynamic investigation is important to establish the diagnosis and select treatment, although one group suggested that bed wetting could be simply alleviated by waking up at least twice per night to void. [291] Stroke is a common and well-known cause of enuresis and LUTD in the older population. The predominant symptoms are urinary frequency, urgency and UUI (including night-time incontinence) while DO is the most common finding on urodynamics. [296] In patients after a stroke, incontinence (or LUTD in general) is a serious threat for quality of life. [297] Because DO in patients with LUTD is so prevalent, conservative or pharmacologic treatment is often instituted without prior urodynamic investigation, even though the size and the site of the stroke do have an influence on urological findings. [298] Simple tests such as uroflowmetry and, especially, PVR urine assessment (by ultrasound) are however useful since elevated residual urine is to be expected in a significant amount of these patients and its evaluation can improve caregiving and quality of life. [299, 300] Cystometry has limited value: the prevalence of DO in older people is quite high even in the absence of stroke (perhaps 10% in women and 25 to 35% in men). Therefore the observation of DO alone is not definitive, while the observation of DOI merely confirms what one would suspect in any case.

b) Parkinson's disease

Parkinsonian diseases are known to significantly influence bladder function (see section D.V.6). LUTS may be the first sign, especially nocturia in male patients. Large capacity bladder (when discovered during urodynamic testing for LUTS) may also be a sign of Parkinsonism. [301-304]

DOI is common in patients with Parkinsonism, [158] but urodynamic findings differ in different diseases of this group. [305] In multiple system atrophy for example – as opposed to Parkinson’s disease – PVR urine volume > 100mL, detrusor-sphincter dyssynergia, or EMG evidence of internal or striated sphincter denervation are common. Such findings, especially (large) residual urine, may influence the choice of treatment. If there is residual urine, invasive pressure-flow studies may be indicated, particularly to diagnose...
or rule out BOO and or to confirm detrusor underactivity or dyssynergy.

Defreitas et al carried out a retrospective review of the urodynamic results in men with DO due to BOO (22 patients) and compared them to men (39 patients) and women (18 patients) with Parkinson’s disease. Patients with Parkinson’s disease had a significantly lower median volume at first detrusor contraction than those with non-neurogenic DO. The percentage of urgency incontinence was significantly lower in patient without Parkinson’s disease than in men and women with it (9.1% vs 53.8% and 55.6%). No statistically significant correlation between the duration or severity of Parkinson’s disease and UDS parameters was found. [158]

c) Recommendations for urodynamic investigation for men suffering from nocturnal enuresis or Parkinson’s disease

Conclusions (level of evidence 2/3)

- Nocturnal enuresis in adult males is rare but problematic, and it is associated with many possible aetiologies.
- Nocturia, nocturnal enuresis or lower urinary tract symptoms may be a first or an early sign of Parkinsonism in elderly male patients.
- Lower urinary tract dysfunction in patients with Parkinsonism can be the result of detrusor overactivity, (benign prostatic) bladder outlet obstruction, dyssynergic voiding or post void residual urine or any combination thereof.

Recommendations (grade B/C)

- The committee recommends that urodynamic evaluation should be conducted in all cases of nocturnal enuresis in adult males
- The committee recommends that urodynamic evaluation should be performed in patients with Parkinsonism. There should be flowmetry and postvoid residual assessment in all cases and invasive testing when abnormalities are observed in flowmetry and postvoid residual assessment.
- The committee suggests that investigators should be alert for large capacity bladder and/or detrusor underactivity (or large residual without significant bladder outlet obstruction) because it is a first or early sign of Parkinsonism.

5. POST-MICTURITION OR TERMINAL Dribbling

There are no recent manuscripts on post-micturition dribble or terminal dribbling involving urodynamics.

In 1996, Reynard et al determined the prevalence of the symptom of terminal dribbling from a symptom questionnaire completed by 165 men presenting with LUTS. Objective evidence of terminal dribbling during voiding was assessed from uroflow recordings and prostate volume was measured by transrectal ultrasonography. Combined pressure-flow studies were performed to determine the presence or absence of BOO. They found that there was relatively poor agreement between the symptom of terminal dribbling and objective evidence of its presence; 48% of the patients who reported terminal dribbling most or all of the time showed no objective evidence of terminal dribbling on uroflowmetry.

The symptom of terminal dribbling was not significantly related to the presence of BOO (p = 0.74). However, objective evidence of terminal dribbling on uroflow traces was significantly related to BOO (p < 0.001) and those patients with objective evidence of terminal dribbling had higher values of URA (median 39 compared with 28 cmH2O). Objective terminal dribbling had a specificity of 92% and positive predictive value of 88% for the presence of BOO.

Neither the symptom of terminal dribbling nor objective evidence of its presence were significantly related to prostatic enlargement. The authors concluded that while the symptom of terminal dribbling is probably not related to BOO or prostatic enlargement, objective evidence of terminal dribbling on flow curve recording is fairly specific for BOO and as such, its presence could potentially be of value in the assessment of men with LUTS. [306]

Recommendation (grade C)

- When a complaint of terminal dribbling is objectively identified in the urinary flow curve, urodynamic studies may be indicated to verify or rule out the presence of bladder outlet obstruction or urethral pathology.

III. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

1. INTRODUCTION

Neurogenic incontinence may express itself as UUI, ‘reflex incontinence’, ‘overflow incontinence’ or SUI. UUI and SUI have already been reviewed in this present chapter. ‘Reflex’ and ‘overflow incontinence’ are terms not currently recommended by the International Continence Society but they will be discussed below, together with other relevant topics for this group of patients which are not covered elsewhere in this chapter.
2. WHAT IS USUALLY EVALUATED?

Because not all patients with neurogenic conditions develop typical urinary symptoms or urodynamic findings, a specific understanding of the dysfunction in each individual is an absolute prerequisite for the correct choice of therapy.[307-309] The aim is to describe the (dys)function of the bladder, the urethra and the pelvic floor, their coordination during filling and voiding, and their influence on other pathological conditions (e.g. autonomic dysreflexia) or organ systems (e.g. renal function). Except in a few diseases where empirical, conservative therapy can safely be instituted, or where LUT dysfunction is predictable (e.g. post-stroke), urodynamic investigation is required to provide the understanding of the situation on which rational treatment must be based. Even when empirical therapy is instituted without urodynamics, the progress of the patient must be carefully reviewed to determine whether urodynamics is needed after all.

Because many patients with neurological conditions show anatomical abnormalities that involve the LUT, or detrusor-sphincter dyssynergia (lack of coordination) that can be demonstrated easily by imaging, comprehensive videourodynamics is the test of choice.[307-311]

3. SPECIAL TESTS

The ice water (bladder cooling) test is sometimes used in an attempt to identify neurogenic DO (see section C.V.1.e: provocative manoeuvres).

The carbachol test is intended to reveal supersensitivity to muscarinic agents following neurological decentralization, typically in bladders in which a voiding reflex cannot be demonstrated.[312] A subcutaneous injection of a muscarinic agonist (0.25 mg carbachol or bethanechol) is given and the detrusor pressure is monitored for 30 min or until it rises to over 20 cm H2O. The test is considered positive if the detrusor pressure increases above 20 cm H2O.[313] Results published more than 20 years ago report detrusor decentralisation in a variable proportion of patients with a positive carbachol test (from as few as 50% up to as many as 98%).[312, 314, 315] Thus in some hands (though not in all) it does not have a very good diagnostic performance and as a result it has fallen out of favour. An attempt to use it to help predict the results of sacral neuromodulation proved unsuccessful.[316]

4. NEUROGENIC DETRUSOR OVERACTIVITY

INCONTINENCE (‘REFLEX INCONTINENCE’)

DO of neurogenic origin is frequently observation in association with neurological disease, and often leads to actual leakage, i.e. incontinence. Observed on urodynamics, this type of incontinence should be termed neurogenic DOI. The corresponding symptom is variable: if the DO is accompanied by sensation (desire to void) it might be termed UUI; frequently however any sensation is absent and so the term urgency incontinence is misleading. For this reason the term ‘reflex incontinence’ was introduced,[4] implying automatic filling and emptying of the bladder without sensation or control. This term is no longer recommended.[5]

5. DETRUSOR-SPHINCTER DYSSYNERGIA

Neurogenic DO is often accompanied by detrusor-sphincter dyssynergia: a neurogenically determined failure of coordination of detrusor and urethra. The failure of the urethral sphincter to relax, when the detrusor contracts, causes a functional urethral obstruction which may not only hinder bladder emptying, but may also permit the development of high detrusor pressures. If high pressures are present for prolonged periods in daily life, renal function may be endangered (see the following subsection on “overflow incontinence”).

6. ‘OVERFLOW INCONTINENCE’

‘Overflow incontinence’ is another term that is no longer recommended.[4] It means continual leakage from a constantly overdistended bladder.[4] The presenting symptom is usually characterised by continual small amounts of incontinence, exacerbated by increased abdominal pressure, together with an inability to empty the bladder by voiding.

On urodynamics the usual corresponding observation is a bladder with low compliance and little or no detrusor activity; as the bladder is filled the detrusor pressure rises because of the poor compliance, until it reaches a value sufficient to open the urethral sphincter. Dribbling leakage then ensues. Clinically, the most important variable is believed to be the detrusor pressure at which leakage occurs, the detrusor leak point pressure (DLPP). If this pressure is elevated, and if similar pressures are attained during continual leakage in daily life, then renal function is endangered because the constantly high detrusor pressure hinders outflow from the ureters. Conventionally, DLPPs of 40 cm H2O or more are believed to be unacceptable. There is evidence (mostly from pediatric studies) that upper urinary-tract deterioration is more probable when DLPP is elevated. [317-319] However, the evidence for a cut-off at 40 cm H2O seems less clear.

7. REPRODUCIBILITY AND RELIABILITY OF TESTS

Since many patients with neurogenic dysfunction of the LUT have severe subpontine neuropathy, the influence of the emotional (limbic) nervous system on lower-tract function is reduced or eliminated; thus, urodynamic observations may be less variable and more reliable than those made in individuals with an intact nervous system. Nevertheless, the test
conditions (e.g. the rate of filling the bladder) do influence the results, and should be chosen carefully.[2]

8. DOES URODYNAMIC TESTING IMPROVE CLINICAL OUTCOME?

The aims of therapy for neurogenic lower urinary tract dysfunction are to achieve the most nearly physiological filling and voiding conditions [307-309] as well as a management situation acceptable to the patient in daily life. Long periods of elevated detrusor pressure during bladder filling or (abnormally prolonged) voiding put the upper urinary tract at risk [317-319] (Level of evidence 3). The primary aim of therapy in patients with such problems is conversion to a low pressure bladder during filling,[307, 309] even if this leads to incomplete emptying. Adequate therapy depends on whether the detrusor is overactive or has reduced compliance, and only urodynamics can answer those questions unequivocally. Timely and adequate diagnosis is of paramount importance for the patient's quality of life.[308, 309, 320, 321] Urodynamic investigation is essential for checking the efficacy of treatment and in following up any sequelae of the disease and its management. Kabay et al [322] used urodynamics to evaluate acute Posterior Tibial Nerve Stimulation in patients with MS. Stimulation improved volume at the first involuntary detrusor contraction and MCC. It remains however unclear if this translates to clinical improvement.

Conclusions (evidence level 3)

- Urodynamic testing improves clinical outcome in patients with continually elevated detrusor pressures.
- In many other types of neurogenic dysfunction rational treatment is impossible without the knowledge that invasive urodynamic testing provides.

Recommendations (grade B/C)

- The committee recommends that patients with suspected neurogenic dysfunction of the LUT should receive comprehensive urodynamic evaluation, including videourodynamic if possible, to establish the state and function of the lower tract.
- The committee recommends that anorectal function should be evaluated in addition to urinary function (see section F on Anorectal physiology studies).
- The committee recommends that urodynamic testing in this group of patients should be done in specialised centres by trained and certified personnel.

Recommendations for research:

1. Comprehensive urodynamic testing should form an essential part of the evaluation of new therapies such as botulinum toxin injection or intravesical instillation of capsaicin analogs.
2. New types of urodynamic study need to be developed to delineate more precisely the types of neurogenic dysfunction that arise from supraspinal abnormalities of the lower urinary-tract control system, which up to the present have been neglected.

IV. PATIENT EVALUATION: CHILDREN

1. INTRODUCTION

The indications for urodynamic evaluation in children in this section have been set out on neurological, anatomical and functional lines, with the types of studies to be performed being based on the underlying pathological conditions rather than on the presenting symptoms. The findings, efficacy and reliability of urodynamic studies for each of these conditions will be discussed.

Many of the conditions for which urodynamics is employed in children involve anatomical and neurological abnormalities, in which LUT dysfunction is variable, complicated, and unpredictable. Urodynamic testing is used to establish as clearly as possible the baseline situation, so that changes as a result of treatment and/or growth can be assessed, and some guidance is obtained in the choice of treatment (although the result of urodynamic testing may not necessarily be the deciding factor). Here, therefore, perhaps more clearly than in any other patient group, the aim of urodynamic studies is surely to provide objective knowledge about LUT function and dysfunction as well as to provide understanding to the care-giver and to the patient (and her or his parents).

Of course, it is still important that the tests used should be relevant, reliable and reproducible in the patient population considered, and the evidence for this will be discussed in the following paragraphs.

2. NEUROGENIC BLADDER DYSFUNCTION

a) Myelodysplasia

For the last 20 years initial urodynamic studies very early in the neonatal period have been recommended for children with myelodysplasia, the basis being that they help identify children at risk for subsequent urinary tract deterioration or a changing neurological picture.[323]. DO on cystometry, detrusor underactivity during voiding, detrusor-sphincter dyssynergia (usually established on the basis of surface EMG), DLPP, and
PVR are the key elements of a detailed urodynamic study that need to be considered.[324, 325]

In an exhaustive review of the efficacy and reliability of urodynamic studies in newborns with myelo-dysplasia [326], of 24 studies analysed, 13 focused on EMG activity of the striated urethral sphincter or pelvic floor, 7 on bladder compliance and 2 on cystometric technique. Twenty-one studies were at level of evidence 4, 2 were at level 3 and 1 was at level 1. Nine of the 24 studies were performed at international sites and the remainder within the United States. The urodynamic patterns of normal detrusor function (66%), acontractile detrusor (33%), DO (57%), and detrusor compliance, as well as detrusor-sphincter synergy (21%), dyssynergia (37%) and sphincter denervation (60%) were similar, with little variability across comparable studies.

van Meel et al have shown that repeating the Ice Water Test (IWT) will increase its positivity. Combining the IWT and electrical perception threshold (EPT) will reinforce the results of both tests and can indicate more clearly the possibility of an unsuspected neurological cause of the dysfunction in children with idiopathic DO. The IWT was positive in 46% patients with relevant neurological abnormalities if used once, this percentage became 86% when the IWT was repeated. In patients without neurological abnormalities, one IWT was positive in only 7% and when repeated, the positive test rate increased to 24%. The EPTs were not significantly different between the neurologic and nonneurologic patients with a positive IWT, except after the third instillation. In those with negative IWTs, the EPTs were significantly different between the neurologic and nonneurologic patients, independent of the number of IWTs done. [327]

Bladder capacity was studied in a group of 506 myelodysplastic children [328] and found to conform to the formula: capacity in mL = 24.5 x (age in years) + 62. This formula for the increase in bladder size with age is 20% less steep than published age-related bladder capacities in neurologically normal children [329, 330] (e.g. 30 x age + 30). However, those children who did not have DO had a bladder capacity similar to normals. Because neurological impairment affects detrusor compliance, cystometric filling rates also influence measured capacity and compliance as noted in 3 studies that addressed this issue.[328, 331, 332]. The lower the filling rate the greater the compliance and the larger the capacity.

Bladder augmentation alone without simultaneous antireflux repair is usually sufficient for the resolution of pre-existing vesico-ureteral reflux (VUR) in children with neurogenic dysfunction. A retrospective study by Juhasz et al in 2008 suggested that the various GI segments used for augmentation have no effect on the urodynamic results and the resolution of VUR. [333]

On the basis of a retrospective review of single centre data, that also included results from other centres and multicentre studies, intravesical electrotherapy was considered effective in improving bladder capacity without deterioration of compliance and without 'new onset' DO. Of the 372 patients 77% had a 20% or greater increase in bladder capacity after treatment. In this subset of patients, bladder storage pressure at capacity was below the 'critical level' of 40 cm H2O in 75%. Of the 17% of patients who had no change in bladder capacity 81% had normal bladder storage pressures after treatment. Bladder sensation developed and was sustained in 62% of patients. [334].

Rendeli et al retrospectively assessed the usefulness of urodynamic testing to determine the optimal timing of neurosurgery and to evaluate the evolution of bladder function in children with lipomeningocele. All patients underwent urodynamic testing preoperatively and during extended followup (mean 6.5 years, range 3 to 12). Bladder capacity and mean DLPP improved in all groups but particularly in children who had had neurosurgical treatment within the first year of life. At the end of the study mean bladder capacity was 420 cc in patients operated before the age of 12 months, 300 cc in those operated between 2 to 36 months old and 260 cc in those who were older than 36 months at the time of surgery (p <0.01). Mean DLPP was 37, 54 and 55 cm H2O in these groups respectively (p <0.01). At the latest followup, 65% of patients in the youngest group had improved urodynamic parameters compared to 33% of those 12 to 36 months old and 28% of those older than 36 months. Urodynamic evaluation and the presence of neurological impairment were considered to have had crucial roles in determining the optimal timing of surgery in patients with lipomeningocele, and in diagnosing the onset of tethered cord. [335]

Six studies evaluated the relationship between level of the neurological lesion (on clinical examination) and LUT function but none could predict a specific urodynamic pattern based on the level of the lesion. Sacral level lesions can be associated with an upper motor neuron urinary tract ‘urodynamic pattern’ just as readily as the expected lower motor neuron findings.[336] Similar findings have been noted for children with thoracic or high lumbar level lesions where the incidence of sacral reflex sparing is 54%. [337]

Approximately 90% of children born with spina bifida will have a normal upper urinary tract at birth. Over time many children who have not received proactive urological care develop upper and/or LUT deterioration. The deterioration is an acquired phenomenon secondary to the development or progression of various LUT hostility factors such as neurogenic DO, poor bladder compliance, detrusor-sphincter dyssynergia and/or high LPP from denervation fibrosis.
[323-325, 338] Despite the fact that only one study was at level 1, all urodynamic studies corroborated their reliability by reporting that the prediction of upper urinary tract deterioration on the basis of urodynamic testing is possible with 90% accuracy.

In 2006, Wang et al calculated a urodynamic risk score including a DLPP of >40 cmH2O, a bladder compliance of <9 mL/cmH2O and evidence of-acontractile detrusor. They postulated that the selective use of urodynamic variables might be valuable for predicting the risk of upper urinary tract dilatation in children with neurogenic bladder-sphincter dysfunction. They found that decreased bladder compliance, increased DLPP and acontractile detrusor are the main urodynamic risk factors, and they reciprocally increase the occurrence and grades of upper urinary tract dilatation. The grades of renal dilatation are compatible with increases in relative unsafe cystometric capacity and the calculated urodynamic risk score [338] Severe bladder trabeculation in incontinent children with neurogenic LUT dysfunction is reported to be associated with bladder outlet obstruction. [339]

Not all authors consider that prophylactic (high pressure prevention) treatment is beneficial, but all recommend periodic cystometry when new onset hydronephrosis, VUR or urinary incontinence develops, the latter in children on a continence program already (i.e. clean intermittent catheterisation and/or drug therapy).[340, 341] When new onset urinary incontinence not related to urinary infection nor easily treated by increasing current treatment regimens occurs, one study has shown that repetition of cystometry, urethral pressure profilometry, and EMG measurements, is helpful in management [342].

When incontinence develops in spite of strict adherence to bladder and bowel continence programs, or when changes occur in leg function or sensation, or when the child experiences back pain or increasing scoliosis, a change in neurological impairment might be expected. If striated urethral sphincter EMG is assessed periodically during the first 3 to 6 years of life and then periodically throughout puberty, changes in pelvic floor or urethral sphincter innervation can indicate changes in neurological and LUT function. Bearing this in mind, 4 studies, noted that a considerable number of myelodysplastic children (40% to 61%) regardless of their neurological level have progressive neurological deficits as they grow up and reach puberty.[336, 343-345] Two of these studies noted changes particularly early in infancy, while a third study noted changes throughout childhood. Thus, most clinicians agree that myelodysplasia is a dynamic disease process which changes as the child grows and that warrants constant vigilance of both the neurological picture and lower urinary tract function. Although its efficacy has not been proven, it is recommended that a cystometrogram/EMG be repeated 3 months following any neurosurgical intervention to correct a tethered cord, or spinal surgery to repair increasing scoliosis, for this provides a new baseline for comparison should further spinal cord tethering take place after corrective surgery.

In 2006, Schulte-Baukloh et al evaluated prospectively the efficacy and tolerability of propiverine for treating neurogenic DO in children. Twenty children with neurogenic DO due to an upper motor neurone lesion were enrolled (17 had myelomeningocele). In the urodynamic examination, the mean (SEM) volume at first detrusor activity increased from 103.8 (21.3) to 174.5 (33.7) mL (p<0.005) after 3-6 months of propiverine treatment, maximum detrusor pressure decreased from 52.5 (7.9) to 40.1 (6.2) cmH2O (p<0.05), maximum cystometric bladder capacity increased from 166 (28.8) to 231.9 (34.8) mL (p<0.005), and bladder compliance improved from 11.2 (2.8) to 30.6 (9.7) mL/cmH2O p<0.01. The incontinence score (scale 0-3) improved from 2.4 (0.2) to 1.6 (0.3) (p<0.05). [346]

Several studies that evaluated the urodynamic result of bladder augmentation have been published. Significant increase in bladder capacity and compliance were achieved and maintained in the long term. Median preoperative compliance was 1.6 mL/cm H2O and an increase of 762.5% was observed during followup. [347]

Renal transplantation in patients with myelodysplasia is a challenging issue. LUT dysfunction carries increased risks for the grafted kidney. Careful diagnosis and surveillance of LUT function by urodynamic evaluation is essential to optimise these outcomes. Recent publications suggested that renal transplantation is a safe and effective treatment modality in patient with myelodysplasia. Videourodynamic tests were performed on all patients preoperatively as well as postoperatively. Augmentation cystoplasty was required in a proportion of children to achieve a low-pressure reservoir with adequate capacity. [348-350]

\textbf{b) Occult spinal dysraphism}

Several series characterising the preoperative urodynamic evaluation of children with occult spinal dysraphisms have documented abnormalities in striated urethral sphincter function (denervation and/or detrusor-sphincter dysynergia) in 20 - 35% of babies under 2 years of age with normal neurological examinations; thus emphasising the need for urodynamic testing in these children.[351-356]. Six reports in older children revealed a greater correlation (70 – 90%) between an abnormal neurological examination and the likelihood of finding an abnormality on urodynamics. [351, 355-359] A few studies demonstrated that between 10% and 20% of patients experience a loss in function immediately postoperatively (most of whom had abnormal LUT
function preoperatively), and a variable number, usually inversely related to age, have improved sacral cord function on postoperative assessment 3 or more months after surgery.[351, 353, 357-359] Two studies, both retrospective, revealed an efficacious response in EMG activity, with stabilisation or improvement in up to 60%, on postoperative urodynamic assessment when the dysraphic state was corrected before 2 years of age.[351, 357] When children were first operated on after 2 years of age, 2 urodynamic reports documented an additional 25 to 35% with progressive changes in urethral sphincter function with axial growth, very few of whom had a detectable change on physical examination.[352, 357]

In a small prospective study in 2008, it was observed that children with open spina bifida, as compared to closed dysraphism, tended to have more bladder dysfunction as exemplified on clinical history and urodynamic assessment. Before neurosurgical closure of the defect, history indicated that the bladder was involved in 14 of the 25 children. Six of the 10 cases with an open spina bifida showed clinical involvement of the bladder as compared to 8 of 15 with a closed pattern. Urodynamic studies showed evidence of bladder dysfunction in 19 children. Of 10 with a meningocele, there were abnormal urodynamics in 9 as compared to 10 of 15 with closed dysraphism. Follow up urodynamic studies showed improvement in 9 of 20 children 3 of 7 with a meningocele and 6 of 13 with closed dysraphism. The authors concluded that a preoperative urodynamic study helps to identify severity of bladder dysfunction in clinically overt cases and also identifies subtle bladder dysfunction in clinically silent cases. Evaluation after operation tends to show better outcome in children with closed dysraphism. The study also identifies deterioration in some patients with seeming clinical improvement. [356]

In 2007, Abrahamson et al studied the urodynamic findings in a consecutively treated population of children with myelomeningocele after untethering of the spinal cord. Severe bladder dysfunction was defined as detrusor pressure at MCC > 40 cm H2O and/or amplitude of DO in the range 20 - 40 cm H2O, moderate dysfunction as detrusor pressure at MCC in the range 20 - 40 cm H2O and/or amplitude of DO in the range 20 - 60 cm H2O, and mild dysfunction as detrusor pressure at MCC < 20 cm H2O. After untethering, 35% of the patients experienced improved bladder function and 5% deteriorated. All of the patients who deteriorated before untethering improved afterward, and 90% of those who were stable preoperatively continued to be stable postoperatively. Therefore, regular evaluation of bladder function in children with myelomeningocele should be performed. [360]

**Conclusions (evidence level 2/3)**

- Retrospective and prospective studies have shown that the urodynamic diagnosis of DO and/or reduced detrusor compliance in patients with myelodysplasia or (occult) spinal dysraphism is not predictable on the basis of clinical signs or symptoms.
- Many retrospective and prospective studies have shown that urodynamic testing in patients (children) with meningomyelocele or (occult) spinal dysraphism reveals clinical relevant results with regard to detrusor storage function.
- On the basis of expert opinion, videourodynamic testing is preferable above urodynamic testing without video, however the exact advantage (eg in repeated investigation) is not substantiated.
- Various studies have shown that LUT function in children with myelodysplasia or (occult) spinal dysraphism may change over time (and physical growth).
- No studies have been published that are a help to determine the optimum of timing and frequency of urodynamic follow-up.

**Recommendations (grade B/C)**

- Comprehensive urodynamic testing is advised in all patients with myelodysplasia or (occult) spinal dysraphism.

**Recommendations (grade C)**

- Videourodynamic testing should be considered in children with myelodysplasia or (occult) spinal dysraphism.
- Timing and technique of urodynamic testing in patients with myelodysplasia or (occult) spinal dysraphism should be selected on an individual basis.
- To help identify children at risk for subsequent urinary tract deterioration or a changing neurological picture initial urodynamic studies very early in the neonatal period are recommended for children with myelodysplasia or (occult) spinal dysraphism.
- The committee recommends that anorectal function or dysfunction is simultaneously evaluated with urinary tract function in children with myelodysplasia or (occult) spinal dysraphism (see section F on faecal incontinence).

**c) Sacral agenesis**

Sacro agenesis, absence of the lowermost vertebral bony segments, is a lesion that can be missed in infancy because of its subtle clinical manifestations,
with generally no loss of lower extremity motor and sensory function, and the non-progressive nature of its pathophysiology.[361, 362] Urinary and/or faecal incontinence usually manifest themselves at an older age when the child fails to toilet train on time. A careful physical examination noting flattened buttocks and a short gluteal crease is pathognomonic for the diagnosis. In 8 reports that provided enough data, urodynamic studies had been 90% accurate in delineating the neurological deficit, which cannot be predicted by the level of absent vertebrae,[354, 363-369] and in managing the incontinence and/or upper urinary tract abnormalities (i.e., hydronephrosis, VUR). These studies reveal that between 30 and 40% of these patients have an upper motor neuron type lesion with DO and an intact but dyssynergic sphincter, while 25 to 50% have signs of a lower motor neuron deficit with acontractile detrusor and denervation in the sphincter, and 15 to 20% have normal LUT function.[361, 363, 364] Tethered cord occurs in children without sacral anomalies as well as in those with low anorectal malformation. Mosiello et al [370] recommend evaluation of all patients using MRI. When MRI shows sacral or spinal cord anomalies, UDS should be performed. They recommend a noninvasive evaluation for all other children and urodynamics when neurogenic dysfunction is suspected. It is presumed that the neurological deficit associated with this entity is fixed because no study showed any progression of the neurological disorder with increasing age.

Various studies have shown that a proportion of children with sacral agenesis have dysfunction of the LUT and that the proportion of patients is the highest in the patients with concomitant relevant neurological abnormalities.

**Conclusion (evidence level 3)**

- Case series have shown that evaluation of lower urinary tract function in children with (partial) sacral agenesis reveals a substantial incidence of dysfunction.
- There is a small, however unknown, proportion of children with lower urinary tract symptoms where (otherwise subclinical) sacral abnormalities were ultimately discovered to be the cause of the problems.

**Recommendation (grade C)**

- Clinicians should consider urodynamic testing in children with sacral agenesis when clinical signs of LUT dysfunction or relevant neurological abnormalities exist.
- Clinicians must be aware that in children with lower urinary tract dysfunction, otherwise clinically silent sacral abnormalities might also exist.

**d) Spinal cord injury**

The rarity and variability of spinal cord injuries in children makes it difficult to propose any one treatment program unless the specific type of LUT function is known. [49, 371-373]. Even if the individual regains the ability to void spontaneously and empty his/her bladder, it is imperative to know the detrusor filling and emptying pressures. Even if the child is continent on clean intermittent catheterisation, it is important to measure detrusor compliance in order to determine the potential risk for hydronephrosis and VUR. [374] A poorly compliant bladder with or without elevated voiding pressures from detrusor-sphincter dyssynergia often leads to the development of hydronephrosis and VUR; when combined with urinary tract infection progressive renal failure is often the result. [375] Four studies extol the need for urodynamic studies once spinal shock from the initial injury wears off, to determine the presence of low filling and voiding pressures and the ability for complete emptying, for the reasons cited above. [376-379] All studies are retrospective and use historical controls for comparison.

A thoracic or cervical level injury may produce an upper motor neuron deficit leading to DO, poor compliance, high voiding pressures and incomplete emptying over time, secondary to detrusor-sphincter dyssynergia. [380-382] In the presence of elevated filling and voiding pressures, there is a 30% incidence of upper urinary tract deterioration. [318] Balanced voiding with pressures below 40 cm H2O in the absence of detrusor-sphincter dyssynergia ensures a stable upper urinary tract. [378]

Generao retrospectively studied 42 children with spinal cord injury. Patients were divided into 3 groups based on level of injury-cervical (10), thoracic (26) and lumbar (6). In the cervical group, safe bladder capacity was less than the expected capacity in 80% of patients but all patients undergoing multiple urodynamics had increasing capacity with time. In the thoracic group, 58% of patients had a safe bladder capacity less than expected and 76% of those undergoing multiple urodynamics had increasing capacity. In the lumbar group 50% of patients had a safe bladder capacity less than expected and 67% of those undergoing multiple urodynamics had increasing capacity. [373]

A cauda equina injury often leads to a lower motor neuron deficit of the striated sphincter that may not require any treatment whatsoever because the bladder empties readily at low pressure, but it probably necessitates medical and/or surgical therapy to achieve continence. Urodynamic studies are considered invaluable in describing LUT function and in efficaciously managing any dysfunction to maintain a healthy upper urinary tract and long-term survival with minimal morbidity. [375, 379, 383]
Urodynamic studies should be undertaken no earlier than 6 weeks after injury, to allow for the manifestation of the extent of the neurologic injury. [377]

Periodic reassessment of the bladder and sphincter function is appropriate up to 2 years after injury, due to the potential for change during that time

**Conclusion (evidence level 2/3)**

- Retrospective studies have shown that urodynamic testing of all children with spinal cord injury is relevant.
- Retrospective studies have shown that urodynamic testing of children with spinal cord injury results in diagnoses and treatment similar to adults with spinal cord injury.

**Recommendations (grade C)**

- The committee recommends that urodynamic testing in children with spinal cord injury is planned on an individual basis, but no earlier than 6 weeks after injury.

3. IMPERFORATE ANUS

Imperforate anus is classified as high, intermediate or low depending on whether or not the rectum ends above, at or below the levator ani muscle. In the past, imperforate anus repair for high lesions frequently resulted in urinary incontinence due to a pudendal nerve injury that often occurs from a perineal approach to bringing the rectum down to the anal verge.[392] With the advent of the posterior sagittal anoplasty this complication has been eliminated as a cause for subsequent urinary incontinence, although bladder neck incompetence may be a consequence of extensive mobilisation of the sigmoid colon which helps transfer the rectum to its final location. However, recent reports of spinal MRIs reveal a 35% incidence of distal spinal cord abnormalities in children with an imperforate anus.[393-395]

Wetting after definitive repair may be the result of stress incontinence through ineffective emptying ('overflow incontinence') and bladder underactivity or acontractility rather than sphincter injury. In 2005, Shimada et al reported on the reconstruction of cloacal anomaly in a consecutive series of 11 girls. The main clinical characteristic of bladder dysfunction was a failure to empty. [396] They could not define the exact aetiology, but iatrogenic injury from extensive dissection can lead to the higher risks of peripheral nerve damage.

In 2004, Warne et al prospectively studied the effect of surgical reconstruction by posterior sagittal approach and total urogenital mobilisation in either causing or worsening bladder dysfunction in new patients with cloacal anomalies. A comparable group of patients...
with anorectal malformation (ARM) were studied as comparative controls to assess the effect of posterior sagittal approach without urogenital surgery. Natural filling urodynamics via suprapubic catheter were performed in all infants at 0.2 to 9 months (mean 3) before surgical reconstruction. This assessment was repeated 6 to 24 months (mean 14.8) after surgery. A total of 10 patients with cloacal anomalies (5 with short [less than 3 cm] and 5 with long common channel [greater than 3 cm]) and 20 patients with anorectal malformation (ARM) were consecutively studied. At presentation bladder dysfunction was present in 9 of 10 patients with cloacal anomalies and in 12 of 20 patients with ARM. After surgery there was significant deterioration in bladder function in half of the cloacal group (5 of 10 patients, p = 0.04) and in 1 of 20 patients with ARM (p = 0.7). Of the 5 patients with cloacal anomalies who had deterioration of bladder function a urodynamic pattern of DO changed to detrusor underactivity in 4, all of whom had a long common channel at presentation. The authors concluded that patients with cloacal malformation have a high incidence of innate bladder dysfunction. However, surgical reconstruction by total urogenital mobilisation can cause further deterioration of bladder function, particularly in the group with a long common channel and urodynamic assessment is necessary to detect bladder dysfunction in these patients. [397]

The VATER or VACTERL association is a group of diverse abnormalities that include Vertebral bony, Anal atresia, Cardiac, Tracheo-Esophageal fistula, Renal and Limb anomalies. [321] Imperforate anus may occur as an isolated lesion or in conjunction with this association. Spinal cord pathology occurs in 38% of cases producing a picture of upper and/or lower motor neuron deficits to the LUT. [368, 394, 398-400] By combining the incidences in 3 studies it was found that the presence of an abnormal sacrum increases the likelihood of neurogenic LUT dysfunction to as high as 76% (38 of 50 children).[368, 398, 399] When the rectum ends above the levator ani muscle there is a much greater chance of neurogenic bladder dysfunction than when it ends below the pelvic floor [370, 398] and the older the child is at the time of urodynamic assessment the more likely he/she is to have abnormal LUT function. [400, 401]

In 2006, a prospective study was carried out on children with ARM prior to and following definitive procedure, using urodynamic evaluation. Among these 19 children 13 underwent re-evaluation after definitive surgery for ARM. Of the 19 children, 14 (73.7%) were cases of high ARM and 5 (26.3%) were cases of low ARM. Baseline evaluation done in 19 children revealed seven urodynamic patterns: Normal capacity, compliant without DO (21.1%) or with DO (5.3%); Normal capacity, poorly compliant without DO (5.3%) or with DO (10.5%); small capacity, compliant with DO (5.3%) or poorly compliant with DO (26.3%) and large capacity, compliant with DO (26.3%). Thirteen patients were evaluated post operatively also and in only 23% (3 of 13) was no change in urodynamic pattern observed. In the remaining 76.9% (10 of 13) some changes in urodynamic pattern were observed. The deleterious changes observed were appearance of DO in 30.8% (4 of 13), decrease in the bladder capacity in 23% (3 of 13) and decrease in bladder compliance in 15.4% (2 of 13). Only 9 of the 19 patients had normal urodynamics pre-operatively and post-operatively, and 3 more patients worsened. [402]

Mosięjewski et al recommends evaluation of all patients with ARM using MRI. When MRI shows sacral or spinal cord anomalies, urodynamics should be performed. They recommend a noninvasive evaluation for all other children and urodynamics when neurogenic dysfunction is suspected. [370]

The reliability and reproducibility of these findings among the various studies analysed confers an important role on videourodynamic studies as an integral part of the evaluation and management of these children: it has diagnostic accuracy; it provides a reason to explore any intraspinal abnormality to improve the child’s chances of achieving urinary and faecal continence; and it is useful as a basis for future comparison if incontinence should subsequently become a problem in children not undergoing early spinal cord exploration.

Conclusions (evidence level 3)

- Various studies have shown that a proportion of children with imperforate anus have primary or secondary dysfunction of the LUT, lower urinary tract innervation abnormalities or pelvic floor dysfunction.

Recommendation (grade C)

- Clinicians should consider urodynamic testing in children with imperforate anus when clinical signs of LUT dysfunction or relevant neurological abnormalities exist, before and or after reconstructive surgery.

4. ANATOMIC ABNORMALITIES

The use of urodynamics for evaluating anatomic lesions that affect the lower and, consequently, the upper urinary tract in children is still somewhat controversial. Essentially, the evidence consists of uncontrolled case series and expert opinions. Although many clinicians now feel its usefulness is beyond question.

a) Posterior urethral valves

Nowhere is the above controversy more obvious than in boys with posterior urethral valves. [403-405] Prior to the ready availability of urodynamics, persistent
upper urinary tract dilation was managed with bladder neck resection and/or striated urethral sphincter resection. By demonstrating the presence of detrusor underactivity or DO, urodynamic studies have helped explain the radiological findings of hydronephrosis that many of the children exhibited over time despite adequate valve ablation. These studies changed the focus from increased bladder outlet resistance to altered bladder function as the aetiology.

There are only two urodynamic reports prior to valve ablation. In one, DO was seen in 60%, poor compliance in 10% and normal function in 30%. In the other, all 46 patients had ‘bladder hypercontractility’ and comparable high maximum voiding detrusor pressures. At the end of followup (mean 4.5 years) in this second study, no patient in group 1 (22 patients who underwent simultaneous valve ablation and bladder neck incision at the 6 o’clock position) had ‘bladder hypercontractility’ or DO, and the mean maximum voiding detrusor pressure was 53 ± 15 cm H2O. In comparison, 9 patients in group 2 (24 patients who underwent simple valve ablation) had ‘bladder hypercontractility’, 6 had DO and the mean maximum voiding detrusor pressure was 87 ± 45 cm H2O (p < 0.01).

In a series of urodynamic studies after valve ablation, the type of bladder function found correlates with the time elapsed from surgery; DO is the predominant pattern initially but improvement is noted in both DO and compliance over time. In 2005, a series of 30 patients showed DO with single or multiple involuntary detrusor contractions in 60%, and small capacity, reduced bladder compliance in 40%.

Myogenic failure in conjunction with increasing capacity and poor emptying are primarily a later phenomenon, most likely secondary to increased urine production and decreased frequency of voiding with advancing age. Despite early valve ablation, a large proportion of boys treated for PUV have gradual detrusor decompensation and/or secondary bladder neck obstruction leading to obstructive voiding and ultimately detrusor underactivity or acontractility. VUR was, in a small and selected series, most commonly noted in boys with DO whereas hydronephrosis is most frequently seen with a poorly compliant bladder. The persistence of upper urinary tract changes is related to the bladder’s unresponsiveness to medical therapy for the DO and/or underactivity. Several studies have shown the predictability of the development of renal failure based on specific detrusor patterns seen on urodynamic evaluation; persistent poor compliance, high detrusor pressures and failure to adequately contract during voiding with increased PVR are the most likely causes of this progressive deterioration.

b) Bladder extrophy

Once the extrophied bladder is closed it may be difficult to determine how best to manage persistent incontinence, upper urinary tract dilation or VUR, whether to further improve bladder outlet continence function or whether to perform augmentation cystoplasty for a small capacity, poorly compliant bladder. In addition, as more children undergo complete primary repair of the extrophic bladder in the neonatal period the most concrete assessment of bladder function is via urodynamics. Only a few studies characterise the change in function following bladder neck reconstruction in patients with persistent incontinence; 20% show DO preoperatively versus 37% postoperatively, and compliance worsens in up to 50% after surgery. No studies are extant that have correlated incontinence with bladder capacity, compliance, DO and/or LPP.

c) Ectopic ureterocele

Urodynamic studies in babies with an ectopic ureterocele have shown that LUT function may be altered in as many as half the affected patients; 2 reports revealed that between 55 and 70% had a larger than normal capacity bladder for age with high compliance, and poor bladder emptying due to detrusor underactivity. In another multicentre analysis of 616 children with a variety of ureterocele types, investigators found only a 6% incidence of bladder dysfunction (all in children with an ectopic ureterocele) consisting of primarily DO; less than 1% had poor bladder emptying whereas the remainder had normal bladder storage function and complete emptying. In a recent study in 2007, voiding dysfunction was suspected in 23% of patients. Urinary incontinence and/or infection following surgical incision or excision of a ureterocele is likely to be secondary to the obstructive effects of the ureterocele directly on the bladder outlet and not to any surgical complication. Patients undergoing bilateral ectopic ureterocele repair are at increased risk for postoperative voiding dysfunction. Whether this risk is present preoperatively or is a result of trigonal surgery is unclear.

d) Vesicoureteral reflux

Recent evidence has confirmed that VUR may be a secondary phenomenon resulting from DO and not a primary anatomic abnormality at the ureterovesical junction in a significant proportion of children. There is growing evidence that DO may lead to VUR in a marginally competent ureterovesical junction mechanism.

This DO may be a natural phenomenon in the infant bladder, especially males (due to the presence of high voiding pressures and/or a learned dysfunction in older children who try to withhold voiding throughout the day). Several investigators have
shown that DO tends to resolve with increasing age. [434, 438, 441]

The bladder pressure at the onset of VUR, as determined by nuclear cystometrography, is a significant independent predictor of VUR resolution in children. The pressure at the onset of VUR was also highly predictive of spontaneous resolution (p = 0.0005). VUR occurring at greater pressures was more likely to resolve spontaneously, independent of the VUR grade or bladder volume at the onset of VUR. [442] VUR occurring at greater than 75% of predicted bladder capacity had a significantly higher resolution rate (p = 0.0005). In addition to grade, bladder volume relative to predicted bladder capacity at the onset of VUR appears to provide additional prognostic information regarding the likelihood of spontaneous resolution of primary VUR. [443]

Despite this finding, there is ample evidence in 4 studies to show that treating the DO and/or voiding dysfunction with anticholinergic agents leads to a faster rate of resolution of VUR (63 - 92% within 1 year) [444-446] than it might when the child is treated with antibiotics alone to prevent recurrent infection (25 - 54%). [447]

In this setting, history-taking about voiding habits [448] and urodynamics with cystometry and uroflowmetry to confirm the abnormal bladder and possibly sphincter function, become paramount to just treating the child with antibiotics and getting yearly voiding or nuclear cystograms. Urodynamic studies have confirmed the presence of DO and/or high voiding pressures in at least half the babies studied with high grades of VUR, whereas only 38% had totally normal function [436, 440, 449-452] Upper urinary tract damage is more likely to occur in children with abnormal bladder function as reported in 4 retrospective reviews.[441, 445, 451, 453].

In 2006, videourodynamic studies were performed in 40 patients. Dysfunctional voiding was present in 76% of the children with DO, in 73% of the children with VUR, in 63% of the children with urinary incontinence, in 77% of the children with episodic urinary tract infection, and in all of the children with diurnal enuresis. Compared to children without dysfunctional voiding, the voiding pressure was significantly higher in children with dysfunctional voiding (with VUR, 61 ± 30 vs. 25 ± 16 cm H₂O, p = 0.004; without VUR, 53 ± 24 vs. 25 ± 16 cm H₂O, p = 0.010). [454] In the 5 patients who had post-treatment urodynamic studies, biofeedback pelvic floor muscle training and treatment with an antimuscarinic agent effectively decreased detrusor pressure, increased bladder capacity and maximum flow rate, and reduced the grade of VUR.

Many clinicians treating patients with VUR advocate urodynamics to assess the LUT in children with high grade VUR, especially those who have incontinence, renal damage, or who are about to undergo surgery for VUR.[445, 455-457]

e) Urethral stricture

Urethral stricture disease in boys is rare, usually arising from a previously unsuspected straddle injury. Uroflowmetry can accurately predict the presence of a urethral stricture in 88% of affected males.[458-461] In a prospective study the voided volumes at first sensation of bladder fullness were significantly greater in hypospadias patients with urethral stenosis. They had bladder outflow obstruction and had decreased sensation of bladder fullness. The significantly decreased quotient of Qmax at greater and at smaller voided volumes could demonstrate a mild outflow obstruction. [462]

Because recurrence of a stricture is often both frequent and insidious, periodic urinary flow rates, analysing the maximum flow rate in relation to volume voided, may alert the clinician to early signs of renarrowing but efficacy of periodic flow rates has not been corroborated. [463] Uroflowmetry should be integral in the management of urethral stricture and complete urodynamic investigation is repeatedly required. [464]

Conclusions (evidence level 3)

- Many studies (case series) have demonstrated frequent urodynamic abnormalities - predominantly DO and reduced bladder compliance or large capacity bladder with impaired filling sensation - in children with posterior urethral valves, urethral stricture, ectopic ureterocele, VUR or bladder extrophy.

Recommendation (grade C)

- Clinicians should consider complete urodynamic testing, at least once, in children with posterior urethral valves, urethral stricture, ectopic ureterocele, VUR or bladder extrophy.

- Clinicians should consider regular uroflowmetry and postvoid residual urine in the management and follow-up of children with posterior urethral valves, urethral stricture, ectopic ureterocele, VUR or bladder extrophy.

5. FUNCTIONAL DISORDERS OF THE LUT

When assessing functional disorders involving the LUT in children, one must take into account the dynamics of the maturing nervous system, learned habits of elimination for bladder and bowel function and social influences that might modulate the child’s behaviour in a negative or in a positive manner.[465, 466]

a) Diurnal incontinence

Urodynamics has a limited place in diurnal (day and
night) incontinence. This condition is not considered worrisome before age 5 or 6. When older, most children without an (until then unsuspected) anatomic or neurological lesion should be dry.[467] Urinary incontinence in children can have many causes and history and clinical investigation are very important in this regard. Urinary incontinence can also coincide with dysfunctional voiding and or bowel elimination problems. [468, 469] Treating these elimination dysfunctions with behavioural modification, biofeedback training, drug therapy or intermittent catheterisation (CIC) [470] and/or antibiotics to prevent further urinary infection is necessary before considering urodynamics. [471] Uroflowmetry with a PVR urine determination and cystometry are however indicated; especially if the incontinence persists despite medical therapy. In one study of girls with recurrent infection without VUR two distinct patterns of dysfunction emerged in 80% of those studied, either DO with a normal urinary flow pattern and complete emptying, or a normal detrusor with an intermittent flow pattern and incomplete emptying. [472]

In boys with persistent day and night-time incontinence, voiding cystourethrography is warranted to determine the presence of different forms of bladder outlet obstruction that may be contributing to or coincide with the DO.[473]

Faecal incontinence in the absence of any anatomical or neurological deficit often affects LUT function and contributes to urinary incontinence in a number of ways. Constipation and faecal impaction have been shown to cause DO and a reduced functional bladder capacity.[474] Understanding and eliminating this possible aetiology can normalise LUT function. There is no need for urodynamic testing, before starting treatment for faecal impaction, in these cases. [468]

Persistent daytime and night-time incontinence in the absence of urinary infection and a normal bladder and bowel emptying regimen warrants cystometry, pressure-flow studies and a urinary flow rate. A meta-analysis, over 20 years, of 460 children with daytime incontinence evaluated with urodynamic studies reveals DO in 57% (261 of 460), dysfunctional voiding (failure to relax the sphincter mechanism) in 22% (34 of 152) and normal findings in only 14% (64 of 460). [436, 475-479] In recent studies, dysfunctional voiding was present in 76% of 40 children with DO. [454, 480] These findings are not gender-specific but are age-dependent, with most children outgrowing the abnormal findings by puberty. [476] Presumably normal children without day or night-time wetting do not have a pronounced degree of DO or dyssynergia but the evidence for this is lacking due to the paucity of studies in normal children.

Urodynamic testing has clearly improved our understanding of the aetiology of diurnal incontinence but no study has shown that urodynamic characterisation of any abnormality has improved the efficiency of treatment for these children.

b) Enuresis (nocturnal)

Night-time wetting (enuresis) is a condition that is common in children aged 5 years but which improves with time, so that less than 15% of pubertal boys and 5% of pubertal girls continue to be affected.[465-467, 481] Multiple causes for the persistent wetting, ranging from genetic factors, to maturational delays, to sleep disturbances, to social causes, to attention deficit disorders, to bladder and urethral dysfunction, to excess fluid intake, to abnormal vasopressin secretion and/or to constipation, have been implicated. [468, 482-489] Although in various cultures there may be social and familial pressures to resolve the condition before puberty, in western societies it is generally not necessary to conduct urodynamics until adolescence, to determine why the wetting has not abated. Urodynamic testing in 615 enuretic children with and without daytime symptoms has identified DO in 61%.[370, 490-494] In a prospective study, bladder volume and wall thickness index was calculated based on ultrasound studies and classified as thick (less than 70), normal (70 to 130) or thin (more than 130). 96% of the patients with an index of less than 70 exhibited DO on cystometry. [495, 496] In another prospective study 116 children with primary enuresis were evaluated and urodynamic abnormalities were seen in 80/116 (69%) patients namely DO 50/116 (43%), small bladder capacity 20/116 (17%), large bladder capacity 4/116 (3%), decreased bladder compliance 3/116 (3%) and detrusor sphincter dyssynergia 3/116 (3%). The combination of abnormal micturition history stating daytime urinary urgency or frequency or dysfunctional voiding symptoms like squatting and/or abnormal voiding charts could predict abnormal results of urodynamics correctly with sensitivity of 81% and specificity of 86%.[497]

When the children are divided into those with day and night-time incontinence (non monosymptomatic) versus those with just nocturnal wetting (monosymptomatic), the incidence of DO decreases from 64% to 35% in the latter group.[492, 493] In another prospective study comparing enuretics to age-matched non-enuretic controls, bladder capacity at night (enuretic capacity) was significantly less in those who wet versus those who did not.[498] Although the authors did not speculate on aetiology they felt that enuretics were less able to hold their urination than non-enuretics. Management should be directed at improving the child’s ability to withhold urination. Treating the non monosymptomatic child using antimuscarinic agents can be very effective (as high as 77% cure) with low recidivism rates when based on the findings of urodynamic testing.[484, 488, 499-503]
Conclusions (evidence level 2/3)

- Various studies show that treatment for children with functional incontinence (and of the, frequently associated, bowel elimination problems) can be initiated on the basis of history, clinical exam and uroflowmetry and postvoid urine assessment.
- Various studies, reviews and guidelines agree on the relevance of urodynamic testing in children with incontinence and nocturnal enuresis resistant to initial (conservative) treatment.

Recommendations (grade B/C)

- The committee recommends uroflowmetry and postvoid residual urine assessment (until -for the individual child- representative values are obtained) as screening and evaluation in all children with incontinence and nocturnal enuresis.
- The committee recommends complete urodynamic testing in children with incontinence and nocturnal enuresis resistant to conservative treatment, if invasive treatments are contemplated.

6. TECHNICAL CONCERNS: RELIABILITY AND REPRODUCIBILITY OF TESTS

Often, differences in urodynamic parameters exist from one study to another or one year to the next. Chou et al provided reference ranges for “normal” variability in urodynamic parameters that can be considered as “no real change” from one study to the next. It was a retrospective chart review. Fifty consecutive individuals with spinal cord injury had 2 trials of urodynamic studies done 5 minutes apart. They established percentile ranges. Knowing these ranges of variability can be helpful in determining whether differences between filling trial 1 and filling trial 2 in a single study or year-to-year changes in urodynamic studies are significant or simply the normal variability of the urodynamic study. [49]

A reduced rate of filling, e.g. 10% of the expected bladder volume per minute, has been recommended in children to accurately determine detrusor compliance and functional bladder volume. [504] Some investigators advocate that infants should be assessed with much lower rates of filling or with natural filling cystometry. [505, 506] Several studies do show lower detrusor pressures under natural filling versus even slow filling rates during cystometry. [331, 332, 507] Even though the practicality of time management plays a role in a busy urodynamic laboratory, it is essential to perform urodynamic testing in a way that reveals what one considers clinically important. One study in particular [331, 332, 507] demonstrated that the intravesical pressure was lower when it was measured initially by catheterisation (before emptying the bladder) and then compared to the pressure at the same volume during the subsequent cystometrogram. Except for determining bladder volumes at specific pressures,[332] no study has shown that these differences are crucial in the management of children with LUT dysfunction. One study looked at the effect of the temperature of the instillate (25° versus 37.5° C) on measured detrusor pressures and found no significant differences in compliance. [46] van Meel et al have shown that repeating the Ice Water Test (IWT) will increase its positivity. [327]

The smallest dual-channel urethral catheter available should be used in children for the same reasons as specified for adults, although the measuring lumen must be large enough to measure pressures in a technically adequate manner. Although urethral catheters of moderate size do not always obstruct the urethra,[508, 509] or produce higher than the normal voiding pressures as measured with suprapubic tubes, it is prudent to employ the smallest calibre catheters that are practical when doing a cystometrogram that measures filling as well as voiding pressures. For very young infants it may be better to insert a suprapubic catheter placed under anaesthesia the day before the test to make the subsequent investigations more accurate [510, 511] but this has not been assessed with any precision.

Most children can undergo urodynamic studies without pre-medication; only the most agitated may require some degree of sedation. Even then, children should not be so heavily sedated that they cannot void around the catheter. However, there are no studies that show a difference in bladder filling pressure (whether related to compliance or to DO) in awake versus anaesthetised children.

In the previous consultation the recommendation was made that children should receive comprehensive urodynamic testing in a laboratory that is specialised in pediatric urodynamic testing with appropriately trained personnel.

Conclusions (evidence level 3/4)

- The committee concludes (on the basis of various studies to determine normal and test retest values for urodynamic testing in children) that within the limits also provided for adults, urodynamic testing in children is reliable and reproducible.
- Although it is plausible and considered useful to reduce filling speed and catheter size in relation to patient size, the exact values cannot be given and the influence of the transurethral catheter size on voiding is unknown.
Suggestions for research:

- The committee suggests that additional work is undertaken to establish normative values and reproducibility of urodynamic data, especially on voiding and voiding abnormalities, both in normal children and in well-defined groups of pediatric patients.
- The committee suggests that further integrated approaches to the diagnosis (and management) of children with anorectal (elimination) dysfunction in combination with lower urinary tract dysfunction are undertaken.

V. PATIENT EVALUATION: FRAIL ELDERLY

1. INTRODUCTION

Frail older patients are poorly represented in all studies, but especially those involving invasive interventions or medications, as they suffer from multiple impairments (eg poor mobility, cognitive impairment, renal failure) or conditions (heart failure, multiple medications) which tend to exclude them from research.

Elderly patients should not be considered differently from younger subjects simply because of their chronological age. LUT symptoms, especially storage symptoms, showed age-related alterations in the two sexes in the absence of any overt underlying disease, and bladder function in both sexes may be subject to a gender-independent aging process.[512] Urodynamic findings in the elderly tend to demonstrate DO, [513, 514] even in asymptomatic individuals. There may also be a reduction in bladder capacity, urinary flow rate and detrusor contractility.[515] Because of these changes the utility of urodynamics has to be judged against a different background in the elderly.

Older people age at different rates, with some developing a clinically recognised pattern of frailty [516, 517] characterised by impairments in a number of functions including physical activity, mobility, balance, cognition, nutrition and endurance. Such individuals tend to suffer multiple chronic medical conditions, take multiple medications, and are at risk of admission to hospital or a care home. [518, 519] They are also at greater risk of developing incontinence. As a group they are poorly represented in research studies. [519] These features need to be born in mind when considering the contributors to and investigation of incontinence. Limitations to care may also be appropriate in a frail older person who is nearing the end of their life [520] but appropriate intervention should not be denied on the basis of age. This is covered more fully in chapter on the Frail Elderly produced by committee 11.

Firstly, the invasive nature of conventional urodynamics becomes a more important factor in the old-old or frail elderly, who may be more vulnerable to any insult than younger people. For example, one study [521] showed that there was a significant association between age and the presence of asymptomatic bacteriuria before cystometry and between this bacteriuria and urgency (without DO) on cystometry. These results do not however support a policy of universal screening for bacteriuria before urodynamic investigation. Asymptomatic bacteriuria did not influence the urodynamic outcome except in patients with urgency (without DO); and the authors recommended that screening and treatment be considered individually in older women who are being investigated for storage symptoms. About 20% of this group of patients developed UTI (mostly asymptomatic) after the urodynamic investigation. The concept of ‘symptomatic’ is difficult in the frail elderly – for instance the development of delirium is a symptom of many conditions including UTI – but is not generally included in the outcome measures. This information should be included in the counselling before urodynamic investigation and should be incorporated into the patient information leaflet as part of good clinical practice. Unfortunately, there are few adequately powered studies (and none that we are aware of in this patient group) of the efficacy of antibacterial prophylaxis.

Secondly, given the multifactorial nature of incontinence in the elderly, [161] and the fact that there may be easily reversible causes or contributory factors, screening for these then conservative therapies are indicated initially.[522] Urodynamic examination is reserved for patients in whom conservative management has failed or has proved inadequate, who desire further attempts to correct or manage the incontinence, and who therefore need a detailed and objective diagnosis.

The place of urodynamics in the frail elderly with incontinence is therefore quite limited even in principle and, given that the number of studies seeking to establish its clinical utility is even smaller than in
younger adults, there is very little objective evidence for or against clinical urodynamics in this population group.

On the other hand, because of the changes in function that occur with age not only in the LUT, but in the neural system that controls it (or fails to control it), and also in other organ systems that may have an impact on urological problems, research urodynamics is essential to establish what these changes are, how they are related to other aging-associated changes, and how they may be reversed, so that there is a chance of developing new, more suitable therapies. Therefore, in academic centres at least, many geriatric patients should be examined so as to generate a steady stream of high-quality clinical urodynamic research, addressing mechanisms of disease and deterioration in all the main geriatric patient groups (including ‘normal aging’), and in the less common patient groups as well.

2. WHAT IS USUALLY EVALUATED

Among the frail elderly, incontinence is the paramount troublesome symptom in both men and women, with a steeply rising incidence after age 80.[523] The type of incontinence appears to be predominantly urge.[123, 514] SUI is relatively uncommon in men of any age (except post radical prostatectomy) and it seems to become gradually less common in women after the age of about 50, [523] for reasons that are incompletely understood.

a) Urgency incontinence

Urgency incontinence is usually the result of DO. (It is believed that occasionally it may be due to involuntary relaxation of the urethral sphincter mechanism, without a measurable detrusor contraction.[5]) Thus one possible reason to perform urodynamics might be to identify DO. The relevant test would be filling cystometry. There are reasons to question whether this is the best approach:

1. In straightforward urgency incontinence in the elderly, DO is highly probable, and it is not necessary to perform urodynamics to prove this before trying pharmacological or behavioral therapy. This is one of the reasons for the limited clinical role of urodynamics referred to above.

2. Because DO is only one contributor to urgency incontinence,[161, 524] not all individuals with DO are incontinent. In fact, DO is believed to be quite common in healthy older people who are apparently free of bladder symptoms of any kind. Thus it is important to look not just for DO, but for actual leakage caused by detrusor contraction - DOI.

3. Because only the more difficult or intractable cases are investigated with urodynamics, it is important to look for other coexisting LUT dysfunction, beyond simple DO.

4. As a group the elderly find hospital intervention more difficult to tolerate, and therefore urodynamics and even measurements of flow rates or PVRs on a single occasion are less reproducible.

Among the elderly, the most common type of DO is the ‘terminal’ pattern in which a single involuntary detrusor contraction occurs at the end of filling and leads directly to leakage (incontinence).[525][72] Quite frequently there is reduced bladder sensation also, so that the subject does not feel any sensation of bladder filling or the need to void until the contraction is about to take place.[526] and thus has very little warning of impending leakage. These characteristics are believed to have a neurological (cerebral) origin.[525, 526]

In elderly people, UUI frequently coexists with incomplete bladder emptying. Among men who have not had prostate surgery, urethral obstruction is a possible contributor to incomplete emptying. If there is no obstruction, and particularly in women in whom obstruction is rare, incomplete emptying is a sign of impaired bladder contractility.

The urodynamic abnormality underlying UUI with incomplete emptying (assuming no obstruction) has been named ‘DHIC’ (detrusor hyperactivity with impaired contractile function).[527] Its significance is that the standard pharmacological treatment of UUI – with antimuscarinics – may worsen bladder emptying and possibly cause urinary tract infection or even make the incontinence worse.

Thus the principal urodynamic tests that are done are:

1. Free uroflowmetry:
   a. may be useful as a screening test for obstruction or diminished detrusor contractility
      • A slow, prolonged or intermittent flow curve may indicate either urethral obstruction or diminished detrusor contractility; pressure-flow studies are required to distinguish between them

2. Measurement of PVR urine:
   a. to check whether anticholinergic (antimuscarinic) therapy is contraindicated because of a large residual
   b. to help identify DHIC

Observation of consistently elevated PVR thus has therapeutic consequences and so, among urodynamic investigations, measurement of PVR urine is important. Clinical experience suggests that faecal loading of the bowel is a common cause of poor bladder emptying in this group, but there are no studies to confirm this. Even if screening to rule out constipation has been carried out initially, this should be reconsidered in the presence of a large residual volume.
If a large amount of residual urine is found in the absence of faecal loading then incontinence associated with chronic overdistension or infection may be suspected, and intermittent catheterisation may be indicated. The measurement is included in the Resident Assessment Protocol (mandated for nursing homes by the US Congress) along with the stress test.[528] Even if screening to rule out constipation has been carried out initially, this should be reconsidered in the presence of a large residual volume.

If the PVR is small, significant infravesical obstruction or detrusor underactivity or acontractility is less likely, and a small dose of anticholinergic medication may be tried.

3. Filling cystometry:
   a. to demonstrate or rule out DO or – more importantly – DOI
   b. to identify the pattern of DO – terminal or phasic
   c. to identify reduced or normal bladder sensation

Cystometry is sometimes said to be an essential part of the diagnostic evaluation, both in defining underlying pathophysiology and directing treatment.[155] However, none of these aims (a.-c. above) have particular therapeutic importance except in difficult cases where initial therapy has failed and it is uncertain what the underlying problem is.

A small number of frailer older women are considered for operative intervention of SUI but as their risks are higher so should they have cystometry first, especially as pure SUI is so unusual in the frail elderly?

4. Pressure-flow studies of voiding:
   a. to identify or rule out prostatic obstruction (in men)
   b. to identify or rule out impaired contractility (reduced detrusor contraction strength)

5. Simple cystometry:

It is sometimes recommended that urodynamics in the elderly should be done by “simple cystometry” if cystometry is indicated and no equipment or referral is available.[529] The procedure needs only an open syringe attached to a single-lumen catheter, sterile water or saline and a tape measure. Fluid is infused by gravity at a pressure head of 15-20 cm H2O. Bladder capacity, sensation of filling and presence of a detrusor contraction or overactivity can be semiquantified. Pressure is measured by observing the height of the column of water. These simple measures can be carried out at the bedside and may be useful for disabled patients.[530-535] Simple cystometry, as compared with multichannel cystometry has a specificity of 75-79% and a sensitivity of 75-88% for the observation of DO.[530, 531] The accuracy can be improved by combining it with even simpler tests [531, 532] such as a stress test to exclude SUI.[536]

However the clinical significance of these findings is limited. DO is found in up to 50% of symptom-free elderly (and so it is not pathognomonic), while DOI is the most likely finding in incontinent frail elderly in any case.[123, 514, 527] Thus the test is performed only to rule out DO in a small subset of patients.

Furthermore, most of the studies recommending simple cystometry were conducted before the widespread availability of simple bedside bladder scans and before the high prevalence of detrusor hyperactivity with impaired contractility (DHIC) was recognised.[514] This dysfunction is the most common abnormality observed in the frail elderly population with incontinence.[514, 527] A total of 185 patients who had persistent LUTS after TURP were enrolled in one study, and the results revealed that a normal videourodynamic tracing was found in 9%, pure DO in 10%, low detrusor contractility in 19%, DHIC in 14%, poor relaxation of the urethral sphincter in 19%, and bladder outlet obstruction in 28%.[267] DHIC is easily misdiagnosed as a stable detrusor on simple cystometry,[536] because single-channel cystometry is less sensitive for detecting low-pressure detrusor contractions than multichannel recording. If a detrusor contraction coincides with a cough, the leakage may be regarded as the sign of a positive stress test.

By design, simple cystometry can at best recognise only DO, or DOI if actual leakage is recorded. There is no possibility of studying voiding dynamics. Furthermore, the checks on measurement quality that are part of conventional urodynamics are not available. Hence, because recognition of DO by itself has little therapeutic importance, and urodynamics in the elderly is reserved for difficult or intractable cases, it is more reasonable in such cases to conduct a full urodynamic examination of both filling and voiding phases, in which quality control can be maintained to eliminate artifacts, and the more relevant aspects of LUT behavior can be assessed, such as obstruction and reduced detrusor contractility.

b) Stress urinary incontinence

Among older men, SUI is almost entirely confined to post radical prostatectomy patients (see section D.II, Patient evaluation: Men). Among elderly women, pure SUI seems to be rare. Urodynamic testing usually follows the methods used in younger women. Frequently, it is difficult to perform an adequate examination because the patient is not able to produce a strong enough cough or Valsalva manoeuvre to cause leakage during testing, and cannot easily be examined in the upright position, which is the most likely posture to produce incontinence. On the other hand, it may be just such factors that make SUI uncommon in this population in the first place.

A weak urethral sphincter (intrinsic sphincter deficiency,
ISD) is a contributory factor to SUI. There is some evidence that a weak sphincter or inadequate sphincter control may contribute to the severity of UUI as well.\[155, 161\] Methods of assessing the sphincter include measurement of VLPP (difficult for the reasons stated above) and urethral pressure measurements. Unfortunately, urethral pressures diminish with age, whether or not there is SUI, and are not diagnostic.

3. EVIDENCE FOR REPRODUCIBILITY AND RELIABILITY OF URODYNAMIC TESTS IN THE GERIATRIC OR FRAIL ELDERLY POPULATION

There is little published evidence about reproducibility and reliability in this patient population. Two groups have recently examined specific aspects of geriatric urodynamics which have some bearing on this topic. There is a little earlier evidence on the reproducibility of some parameters.

a) Filling cystometry

One group \[537\] sought urodynamic changes associated with behavioral and drug treatment of UUI in 105 ambulatory, nondemented, community-dwelling women, of mean age 67 years (range 55-91). Although oxybutynin and behavioral treatment were both effective, and although oxybutynin increased cystometric bladder volume at strong desire to void and bladder capacity, the authors were unable to demonstrate that the improvement in incontinence was related to the urodynamic changes observed – that is, that the changes mediated the improvement. One possible explanation for this negative result is that the urodynamic parameters measured show considerable variability, as in other patient groups (see sections C.I and C.II).

b) Post-void residual urine

Residual urine is believed to depend on the presence of bladder outlet obstruction (in men) as well as on detrusor underactivity (i.e. impaired contractility).\[538\] Thus, in a man, the presence of substantial residual urine (> 100 ml) in the absence of severe bladder outlet obstruction suggests that the increased residual urine is mainly due to a reduction in detrusor contractility, with bladder outlet obstruction making only a minor contribution. There may be an age-dependent decrease in contractility in both sexes.

Residual urine varies in a given individual for no known cause: recorded values wax and wane over time \[192\]. Significant daily variations have been observed in elderly patients of both sexes, with larger residuals (up to 40% greater) being measured in the early morning. Similar changes have been described in patients with bladder outlet obstruction or detrusor underactivity \[67, 539\]. No clear predictor of deterioration of residual urine volume or of complete urinary retention has been identified. Although the presence of faecal loading may be a significant factor, there is an absence of supporting evidence from formal studies.

c) Pressure-flow studies

Another group \[221\] compared consistency, reproducibility, and responsiveness of various methods of estimating detrusor contraction strength from pressure-flow studies. They retrospectively analysed urodynamic data on 84 females 53 years old or older, with UUI, who received either a titrated dose of antimuscarinic medication or placebo in a controlled trial. Data were gathered before and at the end of treatment. Three different variations of the stop test were compared. In a stop test, flow is prevented and the isovolumetric detrusor pressure attained is taken to be a measure of detrusor contraction strength. Flow may be stopped by a voluntary contraction of the urethral sphincter midway through voiding (voluntary stop test: often impossible in stress incontinent women); by blockage of the outlet by a balloon midway through voiding (mechanical stop test); or by attempted voiding against an outlet that is already blocked by a balloon (continuous occlusion).

The voluntary stop test yielded isovolumetric detrusor pressure values inconsistent with the other 2 tests (a mean and SD of 31 ± 16 cm H2O as opposed to 47 ± 26 and 49 ± 24 cm H2O). The mechanical and continuous occlusion tests gave very similar results that were highly correlated with one another (r = 0.87). Measurements pre- and post-treatment in the 20 women who received a placebo showed that the continuous occlusion test had the highest reproducibility (r = 0.9, p <0.01), followed by the mechanical (r = 0.7, p = 0.01) and voluntary (r = 0.7, p <0.01) stop tests. Treatment with oxybutynin decreased isovolumetric detrusor pressure by up to 6 cm H2O, but the decrease was statistically significant only for the continuous occlusion test.

The authors concluded that to assess detrusor contraction strength in elderly females with UUI either a mechanical stop test or a continuous occlusion test is acceptable but the continuous occlusion test has better reliability and more sensitively detects slight drug-induced changes. Again this study is on relatively young women, this time just ‘53 years and older’, once again demonstrating the lack of data in the elderly, let alone the frail elderly!

This work demonstrates that some urodynamic measurements in a geriatric population are quite reproducible, reliable, and responsive to the effects of treatment. This means that they may be useful for research, but are not necessarily clinically relevant. For example, there is no evidence that a weak detrusor contraction strength predicts poorer response to treatment with anticholinergic medication or surgery.
4. EVIDENCE THAT PERFORMING URODYNAMIC TESTING IMPROVES CLINICAL OUTCOMES IN THE GERIATRIC POPULATION

Few relevant studies have been published in this population. One publication [540] assessed the results of tension-free vaginal tape (TVT) for the treatment of SUI in 76 consecutive women more than 70 years old (median age 76 years). 31% (24/76) of the patients had OAB symptoms and 4 (3%) had proven DO controlled by anticholinergic therapy. All patients had preoperative multichannel urodynamic evaluation. At a mean follow up of 25 months, 67% of the patients were cured. Preoperative urgency symptoms were cured in 46% of the group. Among the failures, 14 (18%) had UUI, while “de novo” urgency without incontinence was noted in 21%.

Thus, this paper provides no clear evidence that preoperative urodynamics was able to predict the outcome of a popular SUI procedure in older women. It does show that post-operative difficulties may be due to urgency and UUI, which however could not be predicted from the tests performed preoperatively.

To summarise, there is no clear evidence that urodynamic testing improves clinical outcomes in the geriatric population.

5. THE PRACTICAL INDICATIONS FOR URODYNAMIC STUDIES AND WHICH TESTS ARE NEEDED

a) Post-void residual urine

Based on the above, there is general agreement that PVR urine measurement is indicated before treatment of incontinence either with anticholinergic medication or by SUI surgery. A consistently large residual urine certainly is a reason for caution and careful monitoring of bladder emptying, and may be a relative contraindication to such treatment.

b) Uroflowmetry

Uroflowmetry is a simple and noninvasive test. A normal uroflow without much residual urine probably rules out significant urethral obstruction or impaired contractility, but this finding is unusual in the elderly. Conversely, a poor uroflow is common in the elderly irrespective of sex, and although it cannot distinguish between obstruction and poor contractility, in either case there is a relative contraindication to anticholinergic therapy. Consequently, uroflowmetry (with residual urine measurement) may be a useful screening tool prior to instituting therapy.

c) Pressure-flow studies

A frequently asked referral question, in an older man who is incontinent, has an enlarged prostate, and is cognitively impaired or has a disease such as Parkinson’s disease or multiple system atrophy, is whether the incontinence is due to prostatic obstruction or to cerebral changes. If the former condition is present, then prostate surgery might be considered. As outlined above, prostatic obstruction is not usually the “cause” of UUI, which is typically multifactorial. However, there is weak evidence to suggest that, if the obstruction is urodynamically severe, then surgery may improve the incontinence. [541] If obstruction is equivocal or absent, then there is little point in performing surgery in an attempt to eliminate it. After screening with uroflowmetry and residual urine measurement, pressure-flow studies may be indicated in older men in whom obstruction cannot be ruled out and surgery is at least contemplated. See also discussion of Parkinson’s disease below.

6. THE URODYNAMIC PARAMETERS IMPORTANT IN VARIOUS GERIATRIC CONDITIONS

Recent papers have examined the urodynamics of Parkinson’s disease and related diseases. It is important to know the characteristic urodynamic features of these diseases, because a frequently asked clinical question is whether lower urinary tract dysfunction observed in an elderly male patient is due to such a disease or to BPE/BPO. Similar questions may sometimes arise in women.

a) Parkinson’s Disease

One group [158] found that men with presumed obstruction-related lower urinary-tract symptoms were less likely to have UUI (DOI) on urodynamics than men or women with Parkinson’s disease. DO due to Parkinson’s disease occurred at smaller bladder volumes than that in obstruction-related DO, although this finding was more pronounced in women than in men. The duration and severity of Parkinson’s disease were not related to the nature or severity of urodynamic abnormalities.

Another group [305] found that the majority of patients with Parkinson’s disease (72%) or multiple system atrophy (100%) had symptoms of urinary tract dysfunction. Neurogenic DO was more common in Parkinson’s disease (81% vs 56% in multiple system atrophy). Detrusor-external sphincter dyssynergia was seen only in multiple system atrophy (in 47%). Urethral obstruction (AG number or BOOI > 40) was more common in Parkinson’s disease than in multiple system atrophy. A weak detrusor (impaired contractility) was less common in Parkinson’s disease (66% of women and 40% of men) than in multiple system atrophy (71% of women and 63% of men). PVR urine volume > 100 ml was not observed in patients with Parkinson’s disease but was present in 47% of patients with multiple system atrophy.

Thus urinary tract dysfunction was prominent in both diseases but patients with Parkinson’s disease had
less severe dysfunction: primarily DO starting at small volumes and urethral obstruction. (Unfortunately these findings may make it difficult to distinguish from dysfunction associated with BPO). However, a PVR urine volume > 100 mL detrusor-striated sphincter dyssynergia, or an open bladder neck at the start of bladder filling are suggestive of multiple system atrophy. It has to be pointed out that multi system atrophy is diagnosed using other clinical criteria, and that residuals over 100 mL in frail older people are common.

**Recommendations (grade C)**

- As urinary incontinence in frail elderly people may be the result of a number of contributory factors, many of which are reversible by simple measures, such patients should be first evaluated by a clinician skilled in the care of older people before any invasive investigations or more potentially harmful medications are given.
- Post-void residual urine measurement by a noninvasive method is recommended before institution of pharmacological or surgical treatment of incontinence. It should be repeated to monitor the effect of such treatment.
- Uroflowmetry may be used to screen for voiding abnormalities prior to such treatment.
- Filling cystometry alone has limited value in this patient population. “Simple cystometry” is not recommended unless a urethral or suprapubic catheter is already present for management but still must be interpreted with care.
- Comprehensive urodynamics including, at a minimum, filling cystometry and pressure-flow study of voiding, is recommended in difficult and intractable cases that have not responded to behavioural or pharmacological therapy, and in whom further therapy is desired; and in complicated cases or cases with complicated comorbidity, where treatment is desired but the nature and aetiology of the urinary tract problems are unclear.
- If stress urinary incontinence is suspected, extra tests of urethral function and/or pelvic floor mobility may be useful, although stress urinary incontinence is not only less common than in younger patients but may be difficult to prove or rule out in this population.
- The committee recommends that comprehensive urodynamic testing be performed in specialised centres with a special interest in incontinence, by trained and certified staff who routinely perform urodynamic testing of any patients referred with suspected lower urinary tract dysfunction.
- To maintain adequate urodynamic expertise in this difficult-to-examine patient population, and to provide a background of ‘regular’ patients against whom specific patients can be judged, it is essential that such centres examine substantial numbers of frail elderly patients.

**Topics for research**

- Study of biological mechanisms of continence and incontinence in the frail elderly, especially those related to supraspinal control or lack thereof.
- Development and testing of treatments specific to the frail elderly.
- Establishment of the reproducibility and reliability of urodynamic measurements in the frail elderly.
- Investigation of the effect of faecal loading of the bowel on detrusor contraction, overactivity and residual volumes post micturition.
- The relationship between faecal incontinence and faecal loading in the absence of impaction.
Anorectal physiology studies (ARPS) incorporate a variety of measurements in the lower gastrointestinal (GI) tract which are intended to:

1. Aid diagnosis of anal incontinence
2. Quantify the effects of therapeutic intervention for anal incontinence
3. Aid prognosis of intervention to treat anal incontinence
4. Aid identification of continent individuals who are at risk of developing anal incontinence if they undergo surgery of the anorectum.

In many ways the lower GI tract is analogous to the LUT with the rectum (a reservoir for the storage and expulsion of faeces) being the analogue of the bladder and the anal canal (which acts as a valve to contain faeces within the rectum during storage and which acts as a tube to convey faeces away from the body during defaecation) being the analogue of the urethra.

Unlike the LUT which has to retain a substance of a fairly consistent viscosity to maintain continence (urine), the lower GI tract is not as simple in that the substance it is trying to retain for continence can have a wide range of textures (from “watery” to “hard”). Therefore, sphincters which might be adequate to maintain continence in the presence of hard stool may be totally inadequate when challenged with loose stool. This may well be a significant, confounding factor in measuring lower GI tract function but this has not been investigated with any great rigor.

There are simple ways of quantifying stool consistency [542, 543] which appear to be reproducible. [544] However, more objective measures also exist. [545]

The anal sphincters act as valves to contain faeces within the rectum until defaecation is convenient.
II. BASIC ANATOMY AND
PHYSIOLOGY

1. INTERNAL ANAL SPHINCTER

The internal anal sphincter is a continuation of the smooth muscle lining of the rectum and it is under autonomic control. A study in 1979 reported a 75% contribution of the internal anal sphincter to the closure of the anal canal at rest [546] but other workers demonstrated that it is responsible for around 85% of the resting tone in the anal canal. [547, 548] However, there is some evidence that the contribution may be only between 50%-60%. [549] What is known is that the external anal sphincter does contribute to resting pressure in the anal canal [550]; probably to varying degrees in individuals.

It has long been thought that poor internal sphincter function makes an individual more likely to suffer from passive anal leakage throughout the day and night. However Deutekom et al have shown that there is also an association of passive faecal incontinence with poor external sphincter function. [551]

2. EXTERNAL ANAL SPHINCTER

The external sphincter is voluntary, striated muscle. It is this muscle that an individual activates to maintain continence when a defaecation desire is experienced but it is inappropriate to do so. Poor external sphincter function makes an individual more likely to experience urgency when a defaecation desire is experienced and often incontinence can occur on the way to the toilet.

3. PUBLORECTALIS

There have been considerations in the past that puborectalis has a role in anal control. This part of the pelvic floor slings around back of the lower GI tract and creates the anorectal angle. During times of increased abdominal pressure it has been postulated that this angle creates either [552] or both [553] a “flap” valve or “flutter” valve effect to minimise the additional pressures challenging the sphincters. However, there is scant evidence to support the existence of either of these mechanisms. Bartolo in 1986 carried out work which showed that the presence of a “flap” valve mechanism was unlikely [554] and Bannister also confirmed this finding in the following year [555]

III. ANAL INCONTINENCE AND ANORECTAL PHYSIOLOGY STUDIES

Anal incontinence can result directly from poor sphincter function, altered rectal sensation, altered rectal compliance or recto-vaginal fistulae. Problems associated with the upper GI tract, which result in intestinal hurry and diarrhoea, can also directly lead to incontinence. Indirectly, anal incontinence can result from “overflow” due to poor evacuation. Incomplete defaecation may result from an anatomical problem such as rectocele but it can be a functional problem relating to poor rectal sensation, high rectal compliance, failure of the internal sphincter to relax during defaecation or the external sphincter actively contracting rather than relaxing during defaecation.

Anorectal physiology studies involve the measurement of sphincter function, rectal compliance and sensation and will be discussed in two parts. The first tests considered are those which measure parameters of lower GI tract function that can directly cause anal incontinence; these are termed tests relating to “primary incontinence”. After that, tests which measure parameters of lower GI tract function that can indirectly cause anal incontinence will be considered; these are termed tests relating to “secondary incontinence”

IV. TESTS RELATING TO PRIMARY INCONTINENCE

1. ANAL MANOMETRY

The most common way of assessing sphincter function is by anal manometry. Pressures are measured in the anal canal at rest, during voluntary contraction of the muscles and sometimes during Valsalva or cough. A variety of devices are used to carry out manometry including air-filled [556] and water-filled balloons, water-perfused catheters, catheter-mounted pressure transducers (also known as microtips and solid state catheters). [558] In 1983, Schouten and Vroonhoven described a simple system of anorectal manometry. [559] Even a simple tube system can give measurements of pressure in the anal canal. [560]

Devices for anal manometry can be single or multi-channelled with sensors arranged radially and/or longitudinally along the length of the catheter. In many instances, the device measuring pressure in the anal canal also has a balloon at its tip which can be placed in the rectum, inflated and the effect on the anal sphincters assessed.

The performance of many of the different systems have been compared [561, 562] and different measurements can be obtained with the different devices. Size and stiffness of catheter, rate of perfusion of water-perfused systems, orientation of sensors within the anal canal can all affect the measurement of pressure. [563] Some comparison between air-charged balloons, solid state systems and water-perfused catheters have shown minimal differences in pressure measurements. [564]

A study in 1998 showed that a water-perfused catheter
and a rectosphincteric balloon gave equivalent values of pressure (in 10 patients). [565]

A ‘historical’ state-of-the-art perspective of anal manometry was carried out in 1993 by Meunier and Gallavardin. [566] They discussed the methods of recording anorectal pressures with perfused catheters, sleeve catheters, water- or air-filled balloon catheters and microtransducers. They then discussed routine anorectal manometry and the parameters resulting from this investigation. The manometric findings in constipation in adults and children, in incontinence and in the descending perineum syndrome were presented and the usefulness of anorectal manometry in surgical and various conditions was discussed.

a) Units of pressure in anal manometry

There is no universal standard for units of pressure in anal manometry. These can be cm H2O, mm Hg or kPa. Although it would be convenient to have a standard unit of measurement, conversion from one unit to another is trivial and it could be argued that a standard is not absolutely necessary. However, when authors quote values without units of measurement in even the abstract of their work [567], there is a strong argument for having a standard because without a standard, recognised unit, parameters quoted without units are meaningless.

In this chapter, pressure values will be cited in the units originally published by the authors.

b) Position for manometry

Traditionally, manometry is performed in the left lateral position. However, there are significant differences in the pressures of patients when placed in the erect position [568] and, because these measurements correlate better with symptom severity, the authors postulate that manometry may be more physiological than in any other position, particularly because most patients have their symptoms when ambulating.

Nevertheless, currently most manometry continues to be performed with the patient lying in the left-lateral position

2. RESTING PRESSURE

Pressures are recorded along the length of the anal canal with the patient at rest. As mentioned previously, the resting pressure within the anal canal arises from both internal and external anal sphincter activity; with the former thought to contribute the majority of the tone (between 50%-85% of the total). Therefore, measurement of the maximum resting pressure in the anal canal is thought to be indicative of internal sphincter function. It can be measured relative to atmospheric pressure or relative to rectal pressure (as is also encountered when measuring maximum pressure in the urethra) and, amongst others, it can be termed as ‘maximal resting pressure’, ‘basal anal pressure’, ‘maximum resting anal pressure’. The term ‘rectoanal pressure gradient’ is also used but it is most frequently used to describe the pressure difference between the rectum and anal canal on defaecatory manoeuvres.

a) Reproducibility of resting pressure

In 1989, Rogers et al studied 16 subjects (mean (s.d.) age 50.7 (12.8) years, three men) on two separate occasions by two experienced investigators in random order. No significant differences were found between the results obtained by the two investigators in the measurements of anal canal length, and canal resting pressure and squeeze pressure. [569]

In a study of 10 healthy individuals in 1998, measurement of resting pressure was shown to be reproducible on occasions four hours apart and four days apart. [570] A small study of 6 women suggested that resting pressure was not affected by the menstrual cycle. [571] Goke et al demonstrated in 12 healthy volunteers that the day to day intraindividual variability of resting pressure was 13.5 % (which was considered to be relatively low). [572]

In 1991, Ekhardt and Elmer looked at the reproducibility of sphincter pressure and length on three different days in 10 male and 10 female healthy subjects with the use of a pneumohydraulic capillary perfusion system. There was complete agreement between both observers in the analysis of anal resting pressure. The pressure profiles from different days correlated significantly (p < 0.01) with each other regardless of whether the studies were performed in the prepared or unprepared bowel. [573]

In 2004, Bharucha et al assessed the intra-individual day-to-day reproducibility of resting pressures in 19 healthy subjects and judged that they were highly reproducible on the basis of a value of r ≥0.7. [574]

In 1997, Ryhammer et al showed in 58 healthy females that the mean difference for maximum anal resting pressure was 2.2 (95% confidence interval: -3.5 - 7.8) cm H2O. They concluded that there was no systematic variation in the repeated measurements however, the nonsystematic variation was generally large. [575]

b) Normal values of resting pressure

Although there are some publications containing normal values for anal manometry, these are only specific for the type of manometer being used and how the manometric parameters were recorded. Therefore they cannot be universally applied.

Often they just include a small number of subjects (e.g. a recent determination of the normal ranges for manometry and balloon expulsion and rectal sensation determined in Thai men and women comprised 17 men and 13 women). [576] The mean resting pressure in this group of healthy Thai adults was 55.4 mm Hg
(1SD, 15.3 mm Hg). The measurements of resting pressure were similar in both men and women.

In 1987 McHugh and Diamant, using a multilumen continuously perfused catheter and a mechanized rapid pull-through technique, studied anal pressures in 143 incontinent patients and a control population of 157 healthy subjects. [577] In 10 male volunteers, pressures were determined using catheters that varied from 3 mm to 18 mm in diameter. In the control population, the resting anal pressure was significantly lower in females 40 years of age and over as compared to males. In women, parity did not correlate with resting anal pressure but aging was associated with a consistent reduction in resting anal pressure. In males, there was a similar but less impressive age-related reduction for resting anal pressure. A linear increase in resting anal pressures was recorded as catheter diameter increased from 3 to 12 mm. Normative data for the resting anal pressures are shown in Table 10.

In 1992, Cali measured resting pressures in normal volunteers; 20 males, 21 nulliparous females and 18 multiparous females. The resting pressures were similar between males and nulliparous females; the nulliparous females had higher resting pressures than the multiparous females. [578]

In 2007, Chaliha et al reported that 95% of resting pressures in 286 healthy women in the third trimester of their first pregnancy were between 29-90 mm Hg. 12 weeks after delivery 161 of these women returned for re-evaluation and 95% of these resting pressures were between 27–98 mm Hg (with similar values between those who had bowel problems and those who did not). [579]

In 1998, Wong et al produced normal values of resting pressure from 11 normal subjects. [550] In 1994 Sultan et al reported the normal values of resting pressure for 93 nulliparous women and 21 healthy men. [580]

In 1994 Benninga et al carried out some studies of resting pressure in 13 healthy children. [581]

In 1991, Felt-Bersma et al produced normal values of resting pressure for 40 men and 40 women aged 20-87 with a perfused catheter system. The mean maximum basal pressure for the men was 68 mm Hg (1SD 21 mm Hg) and for the women was 63 mm Hg (1SD 19 mm Hg). There was no significant difference between the two however, the maximum basal pressure decreased significantly with age. [582]

In 1986 Gibbons et al studied resting pressure in 14 normal males and 11 normal females using probes of between 0.4 and 3 cm in diameter. The larger the probe, the higher the pressure. [583]

Normal values of resting pressure were tabulated in a 1999 review of anorectal testing techniques. [584] These are reproduced in Table 10 along with a set of more recent data.

c) Sensitivity and specificity of resting pressure

The previous consultation noted that although resting pressure was lower in faecally incontinent patients, there was poor sensitivity to distinguish between continent and incontinent individuals [577, 591].

In 1987, McHugh and Diamant showed that although resting anal pressure was lower in 143 incontinent patients compared to a control population of 157 healthy subjects, 39% of incontinent females and

### Table 10. Normal values of maximum resting pressures in the anal canal

<table>
<thead>
<tr>
<th>Technique</th>
<th>Women</th>
<th>Age (years)</th>
<th>n</th>
<th>Men</th>
<th>Age (years)</th>
<th>n</th>
<th>Year</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Station pull-through</td>
<td>58 (±3)</td>
<td>22</td>
<td>66 (±6)</td>
<td>15</td>
<td>1979</td>
<td>[585]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 (±13)</td>
<td>18</td>
<td>63 (±12)</td>
<td>18</td>
<td>1985</td>
<td>[586]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 (±5)</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>1991</td>
<td>[587]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49 (±3)</td>
<td>12</td>
<td>49 (±3)</td>
<td>7</td>
<td>1995</td>
<td>[588]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59 (20-99) Antenatal</td>
<td>286</td>
<td></td>
<td></td>
<td>2007</td>
<td>[579]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow pull-through</td>
<td>46 (40-58)</td>
<td>35</td>
<td>60 (51-98)</td>
<td>23</td>
<td>1989</td>
<td>[589]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid pull-through</td>
<td>100 (±22)</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>1984</td>
<td>[590]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>106 (±18)</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>1984</td>
<td>[590]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>102 (±19)</td>
<td>35</td>
<td>100 (±21)</td>
<td>27</td>
<td>1987</td>
<td>[577]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76 (±24)</td>
<td>40</td>
<td>97 (±20)</td>
<td>31</td>
<td>1987</td>
<td>[577]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53 (±22)</td>
<td>17</td>
<td>72 (±23)</td>
<td>3</td>
<td>1987</td>
<td>[577]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as means in units of mm Hg with either the SEM or the range in parantheses.
44% of incontinent males fell within the 'normal' range. [577]

In 1995, Penninckx et al compared 'conventional' anal manometry in 27 control subjects (M:8, F:19; mean age: 47 yr) and in 40 incontinent patients (M:5, F:35; mean age: 49 yr). Discriminatory values of > 40 mmHg for maximum basal pressure could identify continent patients with 96%, and incontinent patients with 88% accuracy. [592]

In 1999, Osterberg et al compared maximum resting pressure in 156 patients with faecal incontinence (mean age 63 yr; 139 women, 17 men) and 25 healthy controls (mean age 54 yr; 20 women, five men) using a perfused catheter with a station pull-through technique. Although maximum resting pressure was higher in the continent group, there was not sufficient sensitivity and specificity to consider it as a diagnostic test. [593]

There has been no further evidence to dispute this although it has been suggested, in a reasonably sized study of 80 continent patients and 47 patients with idiopathic faecal incontinence that resting pressure gradient may be a more sensitive and specific discriminator than resting pressure itself. [594] However a study, 3 years earlier, in 22 individuals with normal faecal control and 36 patients with faecal incontinence suggests that resting pressure gradient is no better a discriminator than maximum resting pressure. [595]

Interestingly, Lejeune et al found that basal anal pressure had as good a sensitivity (77.2%) and specificity (82%) as cardiac criteria in assessing diabetic autonomic neuropathy [596]

**d) Resting pressure's sensitivity to change**

In 1986, Holmstrom et al showed that in 11 patients who had a Ripstein operation for procidentia, the mean maximum anal resting pressure increased from 39 to 55 mm Hg (p = 0.01). [597]

In 1991, Sainio et al studied 28 patients who underwent transabdominal repair of rectal prolapse. In the 22 patients who were incontinent prior to the procedure, they demonstrated an increase in resting anal pressure in those who achieved continence after the procedure. [598]

In 1993, Kushwaha et al showed that resting anal pressure decreased 6 months after radiotherapy of the prostate and bladder [599]

Also in 1993, Church et al showed measurable changes in resting pressure following ileal pouch-anal anastomoses in 134 patients and coloanal anastomoses in 16 patients. [600]

In 2003, Norton et al showed in a randomised study to assess the effect of biofeedback, that resting pressure improved in 171 patients with faecal incontinence; irregardless of what conservative therapy they received. These improvements were largely maintained 1 year after finishing treatment. [601]

In 2004, Torrabedella et al showed that Sildenafil reduced the resting pressure of patients with chronic anal fissure. [602]

Also in 2004, Yeoh et al showed that in 38 patients who had radiation therapy for localized carcinoma of the prostate showed progressive reductions of basal anal pressures up to 2 years following the treatment and this was associated with an increase in bowel frequency, urgency and faecal incontinence. [603]

Again in 2004, Martinez-Puente Mdel et al evaluated biofeedback for treating faecal incontinence in 53 patients. Maximum anal resting pressures significantly increased after therapy. [604]

In 2005, Ram et al found that there were changes in basal resting pressure up to a year after lateral sphincterotomy for anal fissure. 50 patients with anal fissure were included in this study and underwent sphincterotomy; 12 healthy patients served as controls. All patients were examined 1 month before surgery and 1, 3, 6, and 12 months following surgery. The control group had 3 manometric evaluations 6 months apart. They showed that the mean basal resting pressure before surgery was 138 ± 28 mm Hg. One month after surgery, the pressure dropped to 86 ±15 mm Hg (p < 0.0001) and gradually rose to a plateau at 12 months (110 ± 18 mm Hg, p < 0.0001). At 12 months, the manometric pressure was significantly lower than the baseline (p < 0.0001). However, manometric measurements in the fissure group were still significantly higher than in the control group (110 ± 18 versus 73 ± 4.8 mm Hg, p < 0.0001). All patients were free of symptoms at the 12-month follow-up. They concluded that lateral internal sphincterotomy caused a significant decline in the resting anal pressure. During the first year following surgery, the tone of the internal anal sphincter gradually increased, indicating recovery, but still remained significantly lower than before surgery. However, postoperative resting pressures were higher than those in the control group, and no patient suffered any permanent problems with incontinence, so this decrease may not be clinically significant. [605]

In 2005, Alper et al extended the above report to include resting pressures in 38 patients with third-degree or fourth-degree symptomatic haemorrhoids who underwent haemorrhoidectomy in addition to the 50 patients with anal fissure who underwent sphincterotomy, and 12 healthy patients who served as controls. Before surgery, the resting pressure in the fissure group was significantly higher than in the haemorrhoid group, which was significantly higher than in the control group (138 ± 28.4 mm Hg vs. 108.4 ± 23 mm Hg vs. 73 ± 5.9 mm Hg, p< 0.0001). Twelve
months after surgery, anal resting pressure was significantly lower than the baseline measurements in both the fissure (110 ± 18.2 vs. 138 ± 28.4, p< 0.0001) and haemorrhoid groups (103.6 ± 21.5 vs. 108 ± 23, p< 0.0001), but both remained higher than the control group (103.6 ± 21.5 mm Hg vs. 73 ± 5.9 mm Hg, p< 0.0001). [606]

In 2006, Lovegrove et al conducted a meta-analysis of stapled versus ileal pouch anal anastomosis (IPAA) following restorative proctocolectomy published between 1988 and 2003. This comprised 4183 patients (2699 hand-sewn and 1484 stapled IPAA). Anorectal physiological measurements demonstrated a significant reduction in the resting pressure in the hand-sewn IPAA group by 13.4 mm Hg, with the stapled IPAA group having improved nocturnal continence, which was reflected in a higher anal pressure. [607]

In 2007, Toyonaga et al showed that maximum resting pressure significantly decreased following fistulotomy for intersphincteric fistula-in-ano in a prospective study of 148 patients. [608]

In 2008, Brisinda et al treated 80 patients with botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Anorectal manometry at 1 month demonstrated a significant reduction in resting pressure. [609]

e) Does resting anal pressure predict outcome of intervention?

In 1993, Church et al, showed that pre-operative resting pressure was not predictive of continence following IPAA in 134 patients and coloanal anastomoses in 16. [600]

In a retrospective study in 1999, Hool et al found that preoperative resting pressure did not predict faecal continence following sphincter repair in 51 patients.

In 2000, Stadelmaier et al determined the clinical and physiologic parameters enabling the prognosis of continence after protective ileostomy closure secondary to rectal resection for rectal cancer. 65 patients who had undergone rectal resection (of whom 24 had had radiochemotherapy) were evaluated by clinical examination, anorectal manometry and orthograde contrast enema before ileostomy closure (baseline). Continence was evaluated by clinical findings 91 ± 52 weeks after stoma closure with the help of standardised questionnaires and classified according to the Wexner continence score. Correlations were found to be significant between the continence score and the level of anastomosis (r = -0.58, p < 0.001), median baseline resting pressure (r = -0.52, p < 0.001), and baseline rectal compliance (r = -0.43, p < 0.001). Additionally, radiochemotherapy impairs continence (p = 0.0001). Correlations were not significant between continence and baseline functional sphincter length, squeeze pressure, threshold for perception, urge and maximal tolerable volume, and continence for semiliquid contrast medium. Based on these findings, the continence score can be calculated before closure of a diverting ileostomy by applying multivariate analysis with the help of the following formula: Continence score = 18.23 - 0.94 x level of anastomosis - 0.18 x resting pressure + 3.72 x radiochemotherapy. [610]

In 2001, Mylonakis carried out a prospective study in 100 patients who had different types of surgery for various types of anal fistulae. The type of fistula and the preoperative anal pressures determined the operative procedure that was used. Six patients had some soiling postoperatively and 3 patients had impaired control of flatus. On the basis of this, the authors concluded that preoperative anal manometry is important in deciding the operative procedure for fistula surgery [611]

Also in 2001, Herman studied 33 patients with small, mobile rectal tumors (adenoma and carcinoma) undergoing transanal endoscopic microsurgery. They underwent anorectal motility studies (using pull-through anorectal manometry and rectal barostat) and endoanal ultrasound prior to surgery and 3 weeks and 6 months after TEM; controls were 20 healthy volunteers. The main risk factors of anorectal dysfunctions following TEM included: postoperative internal anal sphincter defects, low preoperative resting anal pressure, disturbed rectoanal coordination, extent (>50% of wall circumference) and the depth (full thickness) of tumor excision. They concluded that preoperative anorectal motility studies and anal ultrasound allow the identification of patients with the risk of postoperative anorectal dysfunctions. [612]

In 2002, Halverson et al prospectively measured perioperative resting pressures in 1439 patients undergoing ileal pouch-anal anastomosis. Postoperative functional status was assessed at various time intervals from 6 months to 8 years after the procedure. They found that perioperative resting anal sphincter pressures greater than 40 mm Hg were associated with significantly better function and quality of life after the procedure. However, a low perioperative resting pressure (< 40 mm Hg) did not preclude a successful outcome. [613]

In 2004, Pescatori found that preoperative resting pressure did not predict continence following fistulotomy in 38 males. [614]

Prather, in a review in 2004 concluded that few physiological parameters have been consistently identified as important in predicting response to either biofeedback or surgery. He states that the process of isolating these factors has been hampered by heterogeneity in the definition of fecal incontinence, lack of consensus on what constitutes a successful
outcome, lack of follow-up data, variations in the way ‘standard’ treatments are implemented, and lack of properly powered randomized controlled trials. Factors that have not been found to be important in predicting outcome following biofeedback retraining include pudendal nerve damage and pretreatment anal canal pressures. The presence of some degree of anorectal sensation is the only preoperative assessment that has been found to be predictive of response to surgical therapy. [615]

In 2005, Gearhart et al studied 20 women, 29 to 84 years of age (mean age 50 years), with severe fecal incontinence and large (>or=50%) sphincter defects on ultrasound. All underwent an overlapping sphincter repair following anal manometry (mean resting pressure, mean squeeze pressure, anal canal length, compliance) and pudendal nerve terminal motor latency (PNTML) testing but none of these parameters was able to predict outcome following sphincteroplasty. [616]

In 2006, Glasgow et al showed that mean resting pressure measured preoperatively in 45 patients undergoing perineal proctectomy for rectal prolapse was not predictive of continence postoperatively. [617]

In 2007, Toyonaga et al showed that maximum resting pressure was not predictive of developing postoperative incontinence following fistulotomy for intersphincteric fistula-in-ano in a prospective study of 148 patients. [608]

In 2007, Pascual et al found that resting anal pressure was unable to predict success of pharmacological treatment of anal fissure in 124 patients. [618]

f) Comparison of measurement of resting pressure with digital examination

In 1989, Hallan et al compared digital examination and manometric evaluation in 66 patients and controls. There was good correlation between digital basal score and maximum basal pressure. The sensitivities and specificities of each assessment were similar in separating incontinent from continent individuals and they concluded that digital estimation was equally as good as assessment of anal sphincter function as anal canal manometry. [619]

In 1993, Siproudhis et al evaluated 50 patients (38 females and 12 males; mean age, 44.7 +/- 15 years) who complained of defaecatory difficulties to determine the accuracy of the clinical examination in diagnosing and quantifying pelvicrectal abnormalities. Each parameter was then compared with the features of anorectal manometry and evacuation proctography performed by two independent observers. When compared with anal manometry, digital assessment was able to quantify resting and squeeze pressures and length of the anal canal with excellent correlation and good global agreement as well as predicting a short or hypotonic anal canal. [620]

In 1994, Herbst and Teleky showed that digital rectal examination preceding measurement of maximum resting pressure in 84 incontinent individuals and 14 controls caused unpredictable results, especially in patients with lower maximum resting pressures, and concluded that this practice should strictly be avoided. [621]

In 1998, Buch et al compared digital and manometric assessment of anal sphincter function in 191 patients who were divided into three groups: control, obstructive defaecation and faecal incontinence. A significant correlation was established between the digital and manometric tone assessments, both at rest and at squeeze. Digital assessment was found to be more sensitive but less specific than manometry in differentiating between faecal continence and incontinence. They concluded that digital examination is not an adequate substitute for anorectal manometry, but is a reasonable option where manometry is unavailable [622]

In 2005, Jones et al studied 40 consecutive patients (21 male) with chronic anal fissure. Twenty-two had normal maximum resting pressure on anal manometry and a further 3 had low pressures on anal manometry. On digital assessment, only five patients were evaluated as having no anal hypertonia. Digital assessment of anal tone correctly identified 14 of 15 patients with high manometric maximum resting pressure (STV, 93%), yet detected only 4 of 25 patients with normal or low pressures (SPT, 16%). The PPV of clinical assessment of anal tone was 40% and the NPV, 80%. Therefore, digital examination poorly correlated with manometric findings. [623]

In 2007, Dobben et al prospectively compared digital rectal examination with anal manometry and endoanal ultrasonography in 312 patients with faecal incontinence; 90% were females. Regarding resting pressure, they found that absent, decreased and normal resting pressures at rectal examination correlated to some extent with mean (+SD) resting pressures of 41.3 (+20), 43.8 (+20) and 61.6 (+23) mm Hg (p<0.001) respectively. They concluded that digital rectal examination can give accurate information about internal anal sphincter function. [624]

Conclusions (evidence level 3)

• Measurement of resting pressure in the anal canal is a parameter produced by devices of different type and size. There is no standardisation regarding how the measurement is made nor is there any universal agreement as to what unit of pressure should be used.

• In many hands the measurement is reproducible and sensitive to change following intervention.

• However, it is not of sufficient sensitivity and specificity to distinguish individuals with normal anal continence from those with anal incontinence.
There is little evidence that it has any prognostic power regarding the outcome of intervention.

It gives a more sensitive indication of anal tone than digital examination

**Recommendation (grade C)**

- That this parameter continues to be used clinically in those situations where an objective measure of resting tone will help in the management of a patient with faecal incontinence.
- That consideration is given to some degree of standardisation in the measurement of this parameter.

### 3. HIGH PRESSURE ZONE AND ANAL CANAL LENGTH

The lower GI tract analogue of the “functional urethral length” is the “functional anal canal length” or “length of the high pressure zone (HPZ)”. Rink et al defined this as the length of the anal canal which exerts at least 50% of the maximum resting pressure. [625] However, there is not universal agreement regarding this definition.

In 2006, Liu et al measured the HPZ in 17 asymptomatic nulliparous women and found it to be 39 (±1) mm in length. [626]. In 1989, Pedersen et al measured the physiological variation in this parameter in 78 healthy volunteers and found the maximum variation to be 10 mm with a 95% confidence interval of 4 mm. [589] Although they found higher resting and squeeze pressures in males, there was no gender difference in the length of the high pressure zone.

Although some workers have measured this parameter, it has not generally proved to be of any more value than the resting pressure.

However, in 1999, Yamana et al did show that, amongst other parameters, a longer preoperative HPZ was associated with better defaecatory function six months after low anterior resection for rectal cancer in 32 patients. [627]

Also in 1999, Hool et al carried out a retrospective review of the manometric data of 51 patients having a sphincter repair. Following data entry into a logistic regression model, postoperative anal canal length was highly significant in predicting postoperative continence. [628]

Again in 1999, Osterberg et al compared the length of the high pressure zone in 156 patients with faecal incontinence (mean age 63 yr; 139 women, 17 men) and 25 healthy controls (mean age 54 yr; 20 women, five men) using a perfused catheter with a station pull-through technique. Although the high pressure zone was longer in the continent group, there was not sufficient sensitivity and specificity to consider it as a diagnostic test. [593]

In 1991, Ekhardt and Elmer looked at the reproducibility of sphincter pressure and length on three different days in 10 male and 10 female healthy subjects with the use of a pneumohydraulic capillary perfusion system. There was complete agreement between both observers in the analysis of sphincter length but anal sphincter length varied greatly on different days. [573]

In 2007, Toyonaga et al showed that the length of the high pressure zone significantly decreased following fistulotomy for intersphincteric fistula-in-ano in a prospective study of 148 patients but it was not predictive of developing postoperative incontinence. [608]

In 2008, Rink et al showed in 61 patients having restorative proctocolectomy for ulcerative colitis that the HPZ at rest using vector manometry (see later) only had a sensitivity of 63.6% and a sensitivity of 59.1% for predicting incontinence after the procedure. [625]

**Conclusions (evidence level 3/4)**

- Measurement of manometric sphincter length in the anal canal is an unstandardised measurement which has been considered by relatively few investigators.
- It is not of sufficient sensitivity and specificity to distinguish individuals with normal anal continence from those with anal incontinence.
- There is little evidence that it has any prognostic power regarding the outcome of intervention.

**Recommendation (grade C)**

- That the manometric length of the anal sphincter is not a clinically useful parameter.

### 4. PRESSURE ON VOLUNTARY CONTRACTION

Measurement of the maximum pressure in the anal canal on voluntary contraction is taken to be a measure of external anal sphincter function. Careful observation of the patient during this manoeuvre is essential to ensure that the patient has understood what is required and is using the appropriate muscle group (which is seen as an upward and inward movement of the anal region). Many patients will inappropriately use their gluteal muscles during this manoeuvre; others will tend to “bear down” instead of “squeezing”. Achieving the correct manoeuvre, whilst remaining fairly still, is essential for a valid measurement. Nevertheless, it is also important to appreciate that even when the patient carries out the correct manoeuvre, there can be movement of the catheter; resulting in an erroneous
Pressure reading. In essence, whilst the measurement of resting pressure within the anal canal is a fairly robust measure, the accurate measurement of pressure during voluntary contraction is beset by practical difficulties.

Pressure during voluntary contraction can be measured relative to atmospheric pressure and relative to rectal pressure. It can also be measured relative to the resting pressure at the corresponding location along the anal canal. Different terms have been used to describe pressure on voluntary contraction such as ‘maximal squeeze pressure’, ‘incremental squeeze pressure’, ‘maximal voluntary squeeze’, ‘maximum squeeze pressure’ and ‘maximum voluntary contraction pressure’. It can be measured in units of cm H$_2$O, mm Hg or kPa. There is no universal standard for these measurements.

**a) Reproducibility of squeeze pressure**

In 1989, Rogers et al studied 16 subjects (mean (s.d.) age 50.7 (12.8) years, three men) on two separate occasions by two experienced investigators in random order. No significant differences were found between the results obtained by the two investigators in the measurements of squeeze pressure. [569]

In 1991, Ekhardt and Elmer looked at the reproducibility of sphincter pressure and length on three different days in 10 male and 10 female healthy subjects with the use of a pneumohydraulic capillary perfusion system. There was complete agreement between both observers in the analysis of squeeze pressure. The squeeze pressures on different days correlated significantly (p<0.01) with each other regardless of whether the studies were performed in the prepared or unprepared bowel. [572]

In 1992, Goke et al demonstrated in 12 healthy volunteers that the intraindividual day-to-day variability of maximal squeeze pressure was 17.3% (which was considered to be relatively low). [573]

In a small study of 6 healthy women in 1994, Schnegg et al showed that pressure on contraction was not markedly affected by the menstrual cycle. [571]

In 1997, Ryhammer et al showed in 58 healthy females that the mean difference for maximum anal squeeze pressure was -1 (95% confidence interval: -6.5 - 4.5) cm H$_2$O. They concluded that there was no systematic variation in the repeated measurements however, the nonsystematic variation was generally large. [575]

In 1998, Freys et al showed that in 10 healthy volunteers, maximum squeeze pressure was not reproducible on occasions 4 hours apart and four days apart. [570]

In contrast, Bharucha assessed the intra-individual day-to-day reproducibility of squeeze anal pressures in 19 healthy subjects in 2004 and judged that they were highly reproducible on the basis of a value of r $\geq$0.7. [574]

**b) Normal values of pressure on voluntary contraction**

Although there are some publications containing normal values for anal manometry, these are only specific for the type of manometer being used and how the manometric parameters were recorded. Therefore they cannot be universally applied.

Often they just include a small number of subjects (e.g. a recent determination of the normal ranges for manometry and balloon expulsion and rectal sensation determined in Thai men and women comprised 17 men and 13 women). [576] The mean squeeze pressure in this group of healthy Thai adults was 170.3 mm Hg (1SD, 81.7 mm Hg). However, the measurements of squeeze pressure were greater in men than in women.

In 1987 McHugh and Diamant, using a multilumen continuously perfused catheter and a mechanized rapid pull-through technique described the resting and squeeze pressures in 143 incontinent patients and a control population of 157 healthy subjects. [577] In the control population, maximum squeeze pressures were significantly lower in females compared to men at virtually all ages. In women, parity did not correlate with maximum squeeze pressure but aging showed a consistent reduction in maximum squeeze pressure. In men there was no change in maximum squeeze pressure with age. The normal values for maximum squeeze pressure are summarised in table 11 and shows that maximum squeeze pressure decreases with age in females but not males. Parity does not affect the maximum squeeze pressure.

In 1992, Cali measured pressures in 20 males, 21 nulliparous females and 18 multiparous females. The squeeze pressures were greater in the males compared to both the female groups. [578]

In 2007, Chaliha et al reported that 95% of squeeze pressures in 286 healthy women in the third trimester of their first pregnancy were between 50-163 mm Hg. 12 weeks after delivery 161 of these women returned for re-evaluation and 95% of these resting pressures were between 43–156 mm Hg (with similar values between those who had bowel problems and those who did not). [579].

In 1994 Sultan et al reported the normal values of squeeze pressure for 93 nulliparous women and 21 healthy men. [580]

In 1994 Benninga et al carried out some studies of squeeze pressure in 13 healthy children. [581]

In 1991, Felt-Bersma et al produced normal values of squeeze pressure for 40 men and 40 women aged 20-87 with a perfused catheter system. The mean
maximum squeeze pressure for the men was 183 mm Hg (1SD 73 mm Hg) and for the women was 102 mm Hg (1SD 36 mm Hg). There was a significant difference between the sexes (p<0.001) and squeeze pressure decreased significantly with age (p<0.001) in both men and women. [582]

In 1986 Gibbons et al studied squeeze pressure in 14 normal males and 11 normal females using probes of between 0.4 and 3 cm in diameter. The larger the probe, the higher the squeeze pressure. [583]

Normal values of squeeze pressure were tabulated in a 1999 review of anorectal testing techniques. [584] These are reproduced in Table 11 along with a set of more recent data.

c) Sensitivity and specificity of squeeze pressure

The previous consultation noted that although squeeze pressure was lower in faecally incontinent patients, there was poor sensitivity to distinguish between continent and incontinent individuals [577, 591].

In 1987, McHugh and Diamant showed that although maximum squeeze pressure was lower in 143 incontinent patients compared to a control population of 157 healthy subjects, 39% of females and 44% of males fell within the "normal" range. [577]

In a study of anal manometry on 350 patients, 178 of whom had fecal incontinence and 80 control subjects, Felt-Bersma et al showed in 1990 that incontinent patients had lower anal sphincter pressures during squeeze compared to continent individuals. Although differentiation between incontinent and continent patients was not possible with a single test because there was complete overlap, they found that maximum squeeze pressure had a better sensitivity and specificity for identifying faecal incontinence than resting pressure. [629]

In 1995, Penninckx et al compared "conventional" anal manometry in 27 control subjects (M:8, F:19; mean age: 47 yr) and in 40 incontinent patients (M:5, F:35; mean age: 49 yr). Discriminatory values of ≥ 92 mmHg for squeeze pressure could identify continent patients with 96%, and incontinent patients with 88% accuracy. [592]

In 1999, Osterberg et al compared maximum squeeze pressure in 156 patients with faecal incontinence (mean age 63 yr; 139 women, 17 men) and 25 healthy controls (mean age 54 yr; 20 women, five men) using a perfused catheter with a station pull-through technique. Although maximum squeeze pressure was higher in the continent group, there was not sufficient sensitivity and specificity to consider it as a diagnostic test. [593]

d) Pressure on voluntary contraction’s sensitivity to change

In 1991, Sainio et al studied 28 patients who underwent transabdominal repair of rectal prolapse. In the 22 patients who were incontinent prior to the procedure, they demonstrated an increase in voluntary contraction pressure in those who achieved continence after the procedure. [588]

In 1993, Kushwaha et al showed that incremental squeeze pressure decreased 6 months after radiotherapy of the prostate and bladder [599].

In 2003, Norton et al showed in a randomised study to assess the effect of biofeedback, that squeeze pressures improved in 171 patients with faecal incontinence; irregardless of what conservative therapy they received. These improvements were largely maintained 1 year after finishing treatment. [601]

Table 11. Normal values of maximum squeeze pressures in the anal canal

<table>
<thead>
<tr>
<th>Technique</th>
<th>Women Age (years)</th>
<th>n</th>
<th>Men Age (years)</th>
<th>n</th>
<th>Year</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Station pull-through</td>
<td>135 (±15)</td>
<td>22</td>
<td>218 (±18)</td>
<td>15</td>
<td>1979</td>
<td>[585]</td>
</tr>
<tr>
<td></td>
<td>159 (±45)</td>
<td>18</td>
<td>238 (±38)</td>
<td>18</td>
<td>1985</td>
<td>[586]</td>
</tr>
<tr>
<td></td>
<td>90 (±9)</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>1991</td>
<td>[587]</td>
</tr>
<tr>
<td></td>
<td>106 (45-216)</td>
<td>286</td>
<td>-</td>
<td>-</td>
<td>2007</td>
<td>[579]</td>
</tr>
<tr>
<td>Slow pull-through</td>
<td>103 (78-190)</td>
<td>35</td>
<td>163 (76-234)</td>
<td>23</td>
<td>1989</td>
<td>[589]</td>
</tr>
<tr>
<td>Rapid pull-through</td>
<td>179 (±55)</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>1984</td>
<td>[590]</td>
</tr>
<tr>
<td></td>
<td>159 (±35)</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>1984</td>
<td>[590]</td>
</tr>
<tr>
<td></td>
<td>171 (±40)</td>
<td>20-39</td>
<td>240 (±65)</td>
<td>20-39</td>
<td>27</td>
<td>1987</td>
</tr>
<tr>
<td></td>
<td>132 (±169)</td>
<td>40-69</td>
<td>203 (±45)</td>
<td>40-69</td>
<td>30</td>
<td>1987</td>
</tr>
<tr>
<td></td>
<td>116 (±40)</td>
<td>≥ 70</td>
<td>219 (±32)</td>
<td>≥ 70</td>
<td>3</td>
<td>1987</td>
</tr>
</tbody>
</table>

The values are expressed as means in units of mm Hg with either the SEM or the range in parantheses.
Similarly in 2004, Again in 2004, Martinez-Puente Mdel et al evaluated biofeedback for treating faecal incontinence in 53 patients. Maximum anal squeeze pressure significantly increased after therapy. [604]

In 2004, Yeoh et al showed that in 38 patients who had radiation therapy for localized carcinoma of the prostate showed progressive reductions of anal squeeze pressures up to 2 years following the treatment and this was associated with an increase in bowel frequency, urgency and faecal incontinence. [603]

In 2006, Leung et al showed in 12 children who completed a programme of electrical stimulation and biofeedback exercise of pelvic floor muscle for children with faecal incontinence after surgery for anorectal malformation that there was a significant improvement in faecal soiling 1 year after treatment and a significant increase in anal sphincter squeeze pressure of 29.9 mmHg (p = 0.007). [630]

Also in 2006, Lovegrove et al conducted a meta-analysis of stapled versus hand-sewn IPAA) following restorative proctocolectomy published between 1988 and 2003. This comprised 4183 patients (2699 hand-sewn and 1484 stapled IPAA). Anorectal physiological measurements demonstrated a significant reduction in the squeeze pressure in the hand-sewn IPAA group by 14.4 mm Hg, with the stapled IPAA group having improved nocturnal continence, which was reflected in the higher anal pressure. [607]

In 2005, Singh et al conducted a prospective randomized controlled trial for treatment of postoperative pain in 32 patients undergoing haemorrhoidectomy. Patients were given an inter-sphincteric injection of either placebo or botulinum toxin (150 units). Maximal squeeze pressure was significantly lower in the botulinum toxin group at weeks six and twelve (mean 87.1 mmHg; 95% CI 68.9 - 107.1) compared to the placebo group (mean 185.8 mmHg; 95% CI 134.2 - 237.4) at week twelve (p=0.0014). [631]

Also in 2008, Brisinda et al treated 80 patients with botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Anorectal manometry at 1 month demonstrated a significant reduction in maximum voluntary squeeze pressure. [609]

Again in 2008, Munasinghe et al carried out on audit of biofeedback in 50 patients with faecal incontinence. They showed significant increases in maximal squeeze pressure. [632]

e) Does voluntary squeeze pressure predict outcome of intervention?

As detailed in section 2e, Stadelmaier et al determined the clinical and physiological parameters enabling the prognosis of continence after protective ileostomy closure secondary to rectal resection for rectal cancer. There were no significant correlations between continence and baseline squeeze pressure. [610]

As detailed in section 2e, Prather, in a review in 2004 concluded that pretreatment pressures in the anal canal are not important in predicting response to either biofeedback or surgery. [615]

As detailed in section 2e, Gearhart et al found that mean squeeze pressure was unable to predict outcome following sphincteroplasty in 20 women with severe faecal incontinence. [616]

In 2006, Glasgow et al found in 45 patients that squeeze pressures >60 mm Hg preoperatively were a good indicator of post-operative continence following perineal proctectomy for rectal prolapse. However, abnormalities of pudendal nerve function and mean resting pressures were not predictive of postoperative incontinence. [617]

In 2008, Dobben et al attempted to develop an efficient diagnostic strategy for patients with faecal incontinence to identify subgroups that may benefit from pelvic floor physiotherapy. They studied 281 consecutive patients with faecal incontinence (mean age 59 years), 252 were female. All patients were then offered standardised pelvic floor physiotherapy. A high maximal squeeze pressure by anorectal manometry was associated with a positive treatment outcome but was not a strong predictor. [633]

In the same year, the authors from this study, together with many others, reported on 250 consecutive patients (228 women) who underwent medical history and a standardized series of tests, including physical examination, anal manometry, pudendal nerve latency testing, anal sensitivity testing, rectal capacity measurement, defaecography, endoanal sonography, and endoanal magnetic resonance imaging. Subsequently, patients were referred for pelvic-floor rehabilitation. In addition to the baseline Vaizey score, three elements from medical history were significantly associated with a poor result (presence of passive incontinence, thin stool consistency, primary repair of a rupture after vaginal delivery at childbed). The predictive value was significantly but marginally improved by adding the following test results: perineal and/or perianal scar tissue (physical examination), and maximal squeeze pressure. They concluded that anorectal physiology studies have a limited role in predicting success of pelvic-floor rehabilitation in patients with fecal incontinence. [634]

f) Comparison of measurement of pressure on voluntary contraction with digital examination

In 1989, Hallan et al compared digital examination and manometric evaluation in 66 patients and controls. There were good correlations between digital squeeze score and maximum squeeze pressure. The sensitivities and specificities of each assessment were similar in separating incontinent from continent individuals and they concluded that digital estimation was equally as good as assessment of anal sphincter function as anal canal manometry. [619]
In 1991, Kaushal and Goldner carried out a digital and manometric determination of maximal anal squeeze pressure in 27 patients. Subjective digital assessment showed that three patients had absent squeeze pressure (grade 0); two patients had markedly reduced (grade +1); six patients had reduced (grade +2); and the remaining 16 patients had normal maximal squeeze pressure (grade +3). Simultaneous objective anal sphincter pressure measurements, when compared with these subjective values, revealed a correlation coefficient of 0.97 (p < 0.05). They concluded that the clinician can reliably use the digital rectal examination to voluntary anal sphincter contraction strength. [635]

However, Eckardt and Kanzler in 1993 showed considerable differences between the two methods of assessing voluntary anal contraction. [636]

In the same year Siproudhis et al evaluated 50 patients (38 females and 12 males; mean age, 44.7 ± 15 years) who complained of defecatory difficulties to determine the accuracy of the clinical examination in diagnosing and quantifying pelvic rectal abnormalities (as detailed in section 2f). They found that digital assessment was able to quantify squeeze pressures with excellent correlation and good global agreement. [620]

As detailed in section 2f, Buch et al compared digital and manometric assessment of anal sphincter function in 191 patients who were divided into three groups: control, obstructive defaecation and faecal incontinence. They concluded that digital examination is not an adequate substitute for anorectal manometry, but is a reasonable option where manometry is unavailable [622]

In 2007, Dobben et al prospectively compared digital rectal examination with anal manometry and endoanal ultrasonography in 312 patients with faecal incontinence; 90% were females. Regarding squeeze pressure, they found that absent, decreased and normal squeeze pressures at rectal examination correlated to some extent with mean (±SD) incremental squeeze pressures of 20.6 (±20), 38.4 (±31) and 62.4 (±34) mm Hg (p<0.001) respectively. They concluded that digital rectal examination can give accurate information about external anal sphincter function [624]

g) Endurance and fatigability

Apart from measuring pressure at the height of a maximal contraction, some workers have assessed the voluntary sphincter squeeze endurance with mixed results.

The consensus statement of 1999 defined ‘sphincter endurance’ as the length of time the patient can maintain a squeeze pressure above the resting pressure. [637]

In 1993, Chiarioni et al studied anorectal sensorimotor function in 16 patients with liquid stool incontinence and severe urgency (10 with diarrhoea) unresponsive to conventional medical treatment, and in 16 healthy volunteers. The only significant difference found between incontinent patients and controls was a reduction in squeeze duration. Fourteen patients were selected to receive biofeedback treatment. Treatment was associated with a substantial improvement in incontinence in 12 patients and with a significant decrease in urgency (p < 0.05). Bowel frequency was not significantly influenced. Most patients showed a persistent improvement in anal motor function. Functional parameters were not predictive of outcome of treatment. [638]

In 1996, Rao et al showed that biofeedback therapy improved duration of squeeze in 19 patients with faecal incontinence. [639]

In a retrospective study in 1998, Marcello et al examined the records of 26 healthy volunteers, 33 patients with anal seepage, 75 patients with gross incontinence and 49 patients with severe constipation. For these patients they had calculated both fatigue rate (which is the slope of a linear regression line fitted to the declining pressure when the patient is instructed to contract for 40 seconds) and also the fatigue rate index (which is the projected time in minutes, from this linear regression line, for pressure to reach resting pressure). They showed that fatigue rate index was much shorter in the faecally incontinent group compared to the patients with severe constipation. [640]

In 1998, Mitrani et al showed that squeeze duration on manometry was better in 7 men with idiopathic faecal incontinence compared to 24 women with faecal incontinence of a similar age. [641]

In 1999, Rao et al showed that squeeze duration on manometry was better in healthy men compared to healthy women. [642]

Telford et al in 2004 showed differences in fatigue rate index between 42 continent patients and 20 continent controls. Fatigue rate and maximum squeeze pressure were not different between the two groups. [643]

In the same year, Martinez-Puente Mdel et al showed that maximum duration of anal squeeze improved following biofeedback therapy in 53 patients with faecal incontinence and this was matched by an improvement in both incontinence scores as well as the patient’s subjective satisfaction. [604]

Work by Saad suggested that duration of squeeze might be a better distinguisher between normal and abnormal rather than resting or squeeze pressures. [644] However, Bilali and Pfeifer in 2005 [645] have more recently suggested that such measurements are not clinically useful in distinguishing normal from abnormal. However, they compared 96 faecal incon-
Conclusions (evidence level 3)

- Measurement of pressure in the anal canal on voluntary contraction is a parameter produced by devices of different type and size. There is no standardisation regarding how the measurement is made nor is there any universal agreement as to what unit of pressure should be used.
- There is no conclusive evidence to show that the measurement is reproducible.
- In many hands the measurement is sensitive to change following intervention.
- However, most workers agree that it does not have sufficient sensitivity and specificity to distinguish individuals with normal anal continence from those with anal incontinence.
- There is little evidence that it has any prognostic power regarding the outcome of intervention.
- It gives a more sensitive indication of anal pressure on voluntary contraction than digital examination.
- There have been a few studies which have investigated the endurance or fatigability of the external anal sphincter on voluntary contraction. There is no consensus as to its ability to distinguish individuals with normal anal continence from those with anal incontinence. There is some evidence that it is sensitive to change following intervention.

Recommendation (grade C)

- That measuring pressure changes on voluntary contraction of the external anal sphincter continues to be used clinically in those situations where such an objective measure will help in the management of a patient with faecal incontinence.
- That consideration is given to some degree of standardisation in the measurement of this parameter.
- That further investigation is made of the clinical value of measuring the endurance of the external anal sphincter and, if appropriate, the optimum way of measuring it.

5. VECTOR MANOMETRY

Pressures, both at rest and on contraction, can be measured radially within the anal canal and symmetry indices calculated to quantify the degree of asymmetry of pressures around the anal canal. Vector volumes can also be calculated from these pressures along the anal canal. These measurements do not have a sound scientific basis to them because they are not measuring true sphincter pressures (because pressure is a scalar quantity which cannot be different across the diameter of the anal canal). Rather, they are detecting directionally dependent forces which are artefactual and vary considerably with the stiffness and position of the catheter.

In 1992, Ho and Goh compared conventional anal manometry with computerised three-dimensional vector volume analysis in 25 people with normal faecal control and 22 patients with idiopathic faecal incontinence. The conventional parameters of mean resting and maximum voluntary contraction pressures did not differ significantly between normal and incontinent subjects. The computer calculated vector volumes and pressure symmetries (both at rest and during contraction) were not significantly different between the two groups. They concluded that the vector volume calculations gave little additional objective information to the conventional indices to discriminate milder degrees of idiopathic faecal incontinence. [647]

In 1993, Williams et al studied the effect of lateral sphincterotomy on internal anal sphincter function in patients with chronic anal fissure. They showed that lateral sphincterotomy produces a decrease in anal canal resting pressure and produces a significant increase in manometric asymmetry of the resting anal canal by creating a detectable segmental defect. [648]

In 1994, Yang and Wexner assessed anal pressure vectography (APV) in 50 consecutive patients with faecal incontinence and compared it with anal manometry, anal sphincter electromyography, and anal ultrasonography. Fifty consecutive patients with faecal incontinence were evaluated. APV showed significantly higher mean maximal resting and mean maximal squeeze pressures than conventional manometry. Thirty eight patients had isolated decreased EMG activity in a single quadrant. However, only five of the 38 patients (13.2%) had the same defect localised by APV. Twenty seven patients had anal sphincter defects on ultrasound examination but only 3 of the 27 patients (11.1%) had the same defects localised by APV. The authors concluded that APV has no apparent advantages, so its use cannot be supported because it had poor correlation with other anorectal physiological tests, including anal manometry, anal sphincter EMG, and anal ultrasonography. [649]
In 1997, Sentovich et al evaluated how well anorectal manometry and transanal ultrasonography diagnose anal sphincter injury. Computerised manometry analysis (mean maximum resting and squeeze pressures, sphincter length, and vector symmetry) and transanal ultrasonography were performed in 20 asymptomatic nulliparous women and 20 asymptomatic parous women, and the results were compared with those obtained in 31 incontinent women who subsequently underwent sphincteroplasty and, thus, had operatively verified anal sphincter injury. Decreased anal sphincter length and vector symmetry were found in only 42% of women with known anal sphincter injury. [650]

In 1999, Zbar et al compared conventional water-perfused and vector volume anal manometry in female patients with neurogenic fecal incontinence and chronic anal fissure and in healthy female volunteers. There was a statistically significant relationship between parameters measured by conventional manometry and those variables derived from vector volume manometry at rest and squeeze. [651]

In 2000, Fynes et al tried to determine the role of anal vector manometry in the assessment of postpartum anal sphincter injury and to establish the most suitable method of anal vector volume analysis for identifying significant external anal sphincter (EAS) injury in an at-risk parous population. They recruited 101 consecutive women with a history of instrumental or traumatic vaginal delivery and performed anal ultrasonography and anal vector manometry. Seventeen women had significant EAS disruption identified by anal ultrasonography. Anal vector symmetry index (VSI), determined by analysis of mean maximum squeeze pressure, yielded 100% sensitivity for significant EAS disruption, with a positive predictive value of 61%. They concluded that anal vector manometry complements endoanal ultrasonography and that VSI, determined by means of the squeeze pressure profile, correlates best with significant EAS disruption identified at anal ultrasonography. [652] However, it is difficult to see how vector manometry complements ultrasonography on the basis of this study; the figures suggest that 11 patients who had a defect on ultrasound would have been judged not to have a defect on VSI.

In 2002, Nazir et al used transanal ultrasonography and vector volume manometry to determine whether a correlation exists between anal incontinence, occult sphincter injuries, anal manometry values, and delivery variables in primiparous women after their first vaginal delivery. Nineteen of the 86 women studied experienced flatus incontinence postpartum. After 12 months, only one-third of the women were still incontinent. Fourteen women (19%) showed anal sphincter injuries on ultrasound but these were not associated with vector volume manometry values at 5 months. Vector volume manometry values were not associated with flatus incontinence at 5 months, but were reduced in women who had flatus incontinence at 12 months after labour. [653]

In 2002, Damon et al studied anal sphincter defects detected by ultrasonography, in a population of fecal incontinent parous females without previous anorectal surgery. From 100 consecutive incontinent patients, 61 females with at least one previous vaginal delivery and no past anorectal surgery were studied. Anal vector manometry was performed to measure anal pressures at rest and during voluntary squeeze, and the anal asymmetry index. Twenty-three had a normal sphincter (38 percent), and 38 (62 percent) had a defect detected by ultrasonography: 20 isolated defects of the external sphincter and 18 combined defects of the internal and external sphincters. Combined defects were significantly larger. The radial size of the defects was positively correlated with the severity of clinical symptoms. Anal pressure asymmetry index was significantly increased in the group with combined defects compared with the two other groups. An index of 25 percent or greater had a very high (100 percent) negative predictive value for the presence of a defect larger than 90 degrees. They concluded that anal vector manometry may be a useful tool to confirm the relation between echographic anal sphincter lesions and fecal incontinence. [654]

In 2003, Damon et al assessed the impact of rectal prolapse on anal pressure asymmetry in patients with anal incontinence. 44 patients, (42 women, mean age: 64 (11) years), complaining of anal incontinence, underwent anal vector manometry, endo-anal ultrasonography (to assess sphincter defects) and pelvic viscerogram (for the diagnosis of rectal prolapse). Resting and squeeze anal pressures, and anal asymmetry index at rest and during voluntary squeeze were determined by vector manometry. Patients with rectal prolapse had a significantly higher anal sphincter asymmetry index at rest, whether patients with anal sphincter defects were included in the analysis or not. Among patients without rectal prolapse, a higher anal sphincter asymmetry index during squeezing was found in patients with anal sphincter defects. They concluded that in anal incontinent patients, anal asymmetry index may be increased in case of anal sphincter defect and/or rectal prolapse. In the absence of anal sphincter defect at ultrasonography, an increased anal asymmetry index at rest may point to the presence of a rectal prolapse. [655]

In 2008, Rink et al studied in 61 patients at a median of 86 months after restorative proctocolectomy for ulcerative colitis using 3-dimensional vector manometry. The specificity and sensitivity of the vector volume at rest of the HPZ for the prediction of incontinence was 63.6% and 59.1%, respectively. The corresponding values were 67% and 68%, respectively, for radial asymmetry at rest. They
concluded that a strong anal sphincter at rest and a consistent radial distribution of the sphincter pressure are the most reliable indicators of continence after restorative proctocolectomy obtained by vector manometry but their clinical usefulness is limited. [625].

Conclusions (evidence level 3)

- Measurement of pressure in the anal canal by vector manometry is, at best, comparable to other methods of anal manometry.
- Measuring asymmetry by vector manometry is not as sensitive as endoanal ultrasound in detecting sphincter deficiencies.

Recommendation (grade C)

- Although vector manometry can be used to measure pressures in the anal canal for clinical purposes, it should not be used for diagnosing sphincter deficiencies where there is access to endoanal ultrasound.

6. RECTAL SENSITIVITY BY BALLOON DISTENSION

Some workers assess the response of the rectum to distension by a water-filled or air-filled balloon without manometry to assess the threshold volume for sensation (onset of sensation), sensation of desire to defaecate and maximum tolerated volume (urgency of defaecation). Whilst there are differences between different patient groups [656, 657] there is no validation or standardisation of the technique and no real literature on its sensitivity or specificity. Intuitively, values must depend on the size of the balloon, the rate of inflation and the substance with which it is inflated.

In 1978, Farthing and Lennard-Jones showed that the maximum volume of air tolerated within a rectal balloon was less in colitic patients than in normal subjects. Smaller volumes were tolerated by patients with a spontaneously bleeding mucosa than by those with less severe inflammation. Severe urgency of defaecation with incontinence was experienced by about half those with spontaneous mucosal haemorrhage but was infrequent among other colitics. [656]

In 1989, Fergusson et al compared the subjective response to rectal balloon sensation in 37 healthy subjects, 54 patients with idiopathic faecal incontinence, and 36 with complete rectal prolapse and incontinence. There was no significant difference for any parameter of rectal balloon sensation between patients with idiopathic faecal incontinence. Patients with complete rectal prolapse and incontinence differed only in onset of sensation. They concluded that the appreciation of rectal distension is maintained in idiopathic faecal incontinence. [658]

In 1990, Sun et al studied ramp distention of the rectum with water and air at randomised rates of 10, 20, 50, and 100 mL/min and during intermittent rapid distension with air in 12 normal male subjects. There were no significant differences between the results of ramp inflation with water or with air, and the repeated infusion of the same medium yielded reproducible results. However, they showed that the rectal sensory and anorectal motor responses to distension depend on the rate and pattern of distension. They concluded that results from different laboratories cannot be compared directly unless the pattern and rate of distension are the same. [659]

In 1991, Felt-Bersma et al showed, by rectal balloon distension in 80 mainly healthy volunteers (40 men and 40 women aged 20-87, mean 45 years) that the volume of rectal perception increased with age and should be taken into account when interpreting the measurement. [582]

In 1995, Hoffmann et al retrospectively evaluated anal manometric studies on 170 patients with varying degrees of faecal incontinence. They were divided into three groups based on presenting complaints: complete incontinence (incontinence of gas and liquid and solid stool), partial incontinence (incontinence of gas and liquid stool), and seepage and soiling (incontinence of small amounts of liquid and solid stool without immediate awareness). Amongst other parameters, the minimum rectal sensory volume, and minimum volume at which reflex relaxation first occurs, were compared with those of 35 control group subjects with normal faecal continence. The minimum rectal sensory volume was greater in all incontinent groups than in controls. Sensory volume of the seepage and soiling group was significantly greater than that of the complete incontinence and partial incontinence groups. The difference between sensory volume and the volume producing reflex relaxation was greatest in the seepage and soiling group and differed from that of the partial incontinence and control groups. They concluded that the findings suggest that the mechanism of incontinence is different in seepage and soiling patients and involves a ‘dyssynergy’ of rectal sensation and anal relaxation. [660]

In 1998, Rasmussen et al compared ‘standard’ anal manometry parameters with rectal compliance measurements in 36 patients with faecal incontinence and in 22 control subjects. Patients with faecal incontinence had lower rectal volumes than controls at constant defecation desire (median 138 mL and 181 mL, p < 0.05) and at maximal tolerable volume (median 185 mL and 217 mL, p < 0.05). They concluded that patients with faecal incontinence have a lower rectal volume tolerability than control subjects with normal anal function. [595]

In 2003, Chang et al in a randomised study treated 22 patients who had functional constipation with
impaired rectal sensation. Twelve were treated with electrical stimulation therapy and 10 with biofeedback therapy. Overall symptoms of patients significantly improved after each therapy in both groups but rectal sensory threshold volumes for desire and urge to defecate and maximal tolerated volume improved significantly only in the electrical stimulation therapy group. [661]

However, this test may have some relevance to faecal seepage because Rao et al in 2004 confirmed some of the conclusions of Hoffman et al [660] showed there was a link between impaired threshold for first rectal sensation and faecal seepage in a prospective study of 25 patients with faecal seepage, where their results were compared with 26 faecal incontinence patients and 43 healthy controls. [662]

Also in 2004 Chang et al, following the earlier work of 2003, reported the case of a 25-year-old female patient who complained of intractable constipation for ten years. She had impaired rectal sensation and was treated by electric stimulation therapy for the purpose of improving impaired rectal sensory function. After 14 sessions of electric stimulation therapy, her constipated symptoms improved dramatically. Furthermore, the desire and urge threshold volumes were decreased. [663]

In 2004, Shafik et al investigated the hypothesis that sympathetic skin response can be used as a tool for objective assessment of rectal sensation. The response was recorded in 24 healthy male volunteers using a surface electrode applied to the skin of the palmar surface of the subject’s hand and a reference electrode to the dorsum of the same hand. The EMG activity of the pelvic floor muscles was registered by a surface electrode fixed to the perineal skin and a rectal balloon was filled in increments of 10 mL of saline. Skin and pelvic floor responses occurred with every rectal sensation and corresponded with the volunteers’ subjective perception. The authors concluded that that they had identified a novel approach whereby skin response from the hand could act as a surrogate for measuring rectal sensation by balloon distension. However they acknowledged that further studies were required to investigate the role of this reflex in defaecation and sympathetic disorders. [664]

In 2005, Milone and DiBaise showed in 10 healthy volunteers that sildenafil increases rectal volumes to first sensation, desire to defecate and maximal tolerable volume. [665]

In 2007, De Ocampo et al examined sensory and motor responses of the anorectum during rectal distension in 23 healthy subjects by placing a six-sensor probe in the anorectum and utilising graded rectal balloon distensions. Studies were repeated in six subjects. In 4 subjects (17 percent) the senso-motor (anal contractile) response first occurred synchronously with a sensation of fullness (Group 1) and in 19 (83 percent) with a desire to defecate (Group 2). Mean balloon volume for inducing the sensorimotor response in Groups 1 and 2 were 80 ± 14 mL and 96 ± 26 mL and were not significantly different. Repeat studies showed good reproducibility (intraclass correlation coefficient = 0.9; p < 0.05). They concluded that a desire to defecate is associated with a unique, consistent, and reproducible anal contractile response: the sensorimotor response. This response could play an integral role in regulating anorectal sensation and function. [666]

Conclusions (evidence level 3)

- Measurement of rectal sensitivity to balloon distension is age and technique dependent.
- It is sensitive to change following intervention
- Faecally incontinent patients may have some degree of rectal hypersensitivity.
- There is a link between impaired first rectal sensation and faecal seepage.

Recommendation (grade C)

- The committee recommends that rectal sensitivity to balloon distension continues to be used in the assessment of the anorectum for clinical purposes.
- However, further investigation is required to explore the full potential of measuring this parameter in the patient with anal incontinence by standardising the technique.

7. ANAL AND RECTAL MUCOSAL SENSITIVITY TESTING BY ELECTRICAL STIMULATION

In 1986, Roe et al described a new technique for quantifying anal sensation utilising mucosal electrosensitivity and described the findings in 97 patients. Normal subjects (n = 20) have a sensory threshold varying from 2 to 7.3 mA; being most acute in the region of the anal valves. Sensory awareness also extends into the upper anal canal. Patients with faecal incontinence (n = 17) have a sensory deficit whilst patients with haemorrhoids have less sensitive mucosa displaced into the upper anal canal. Patients with acute fissure-in-ano (n = 10) have lower thresholds of sensation at the site of the fissure and slow transit constipation patients (n = 22) have normal anal sensation. They concluded that the technique is reproducible and should prove useful in the investigation of anorectal disorders. [667]

In 1988, Rogers et al utilised the same technique to compare, amongst other parameters, mucosal electrosensitivity in 11 patients with idiopathic faecal incontinence and nine normal controls. [668] Electrical
stimulation was by a constant current generator delivering square wave pulses of 0.1 ms and delivered at a rate of 5 pulses per second. Two platinum electrodes mounted on a probe delivered these pulses to the mucosa and the current was increased in steps of 0.1 mA until the patient experienced a tingling sensation. They showed that there was a sensory deficit in the anal canal in patients with faecal incontinence compared with controls. For example, the median threshold current was 10.1 mA in the mid anal canal of those with faecal incontinence compared to 3.7 mA for those with normal faecal control.

In 1995, Gee et al studied 16 subjects (mean (s.d.) age 50.7 (12.8) years, three men) on two separate occasions using two experienced investigators in random order. Amongst other tests, they carried out electrophysiological assessments of anorectal motor and sensory function. No significant differences were found between the results obtained by the two investigators in the measurements of the thresholds of mucosal electrosensitivity. They concluded that the standard tests of anorectal sensorimotor function are repeatable by different investigators. [569]

In 1990, Kamm and Lennard-Jones compared rectal sensation assessed by balloon distension and rectal mucosal electrosensitivity using a bipolar ring electrode. The methods were compared in 13 healthy control women and 26 women with severe idiopathic constipation. Balloon distension in the rectum revealed an elevated sensory threshold (16.9 ± 4.4 vs. 30.4 ± 3.1 mL air, controls vs. patients, p = 0.018) and the volume required to elicit a call to stool (61.1 ± 9.1 vs. 97.5 ± 6.4, p = 0.003) in subjects with severe constipation. The maximum tolerated volume was similar in the two groups. Rectal mucosal electrosensitivity testing demonstrated an elevated sensory threshold in the constipated subjects (16.3 ±3.0 vs. 27.4 ± 2.1 mA, p = 0.005). They concluded that electrical testing avoided the variables inherent in balloon distention and was well tolerated, accurately quantifiable, and reproducible. The raised threshold to electrosensory mucosal testing suggests the presence of a rectal sensory neuropathy in patients with severe idiopathic constipation. [669]

In 1995, Ho and Goh compared the accuracy and sensitivity of annular and unilateral electrodes in assessing patients with haemorrhoids, perineal descent, incontinence, constipation, or after low anterior resection (107 subjects). They found that in normal controls (n = 19), annular thresholds ranged from 0.5 to 2.7 mA and unilateral thresholds from 0.6 to 2.6 mA. In prolapsed hemorrhoids, unilateral was more sensitive than annular electrode in detecting deficits at the upper (p < 0.0001), mid (p < 0.005), and lower (p < 0.0005) anus. Patients with perineal descent had a sensory deficit in the upper anal canal, detected more consistently by unilateral electrode (p > 0.05). No significant abnormalities were found in neuropathic incontinence, after anterior resection and in patients with chronic constipation. Repeated measurements of the unilateral electroscopic technique were found to be consistent (r = 0.8878; p < 0.001). They concluded that by being more sensitive than the annular technique, the unilateral electrode method may become, with refinement, a useful test for quantifying anal sensation. [671]

In 1996, Meagher et al assessed the validity of tests of rectal mucosal electrosensitivity by studying 68 patients in three groups (group 1: 50 patients undergoing assessment in the anorectal physiology unit, group 2: 10 patients with coloanal or ileoanal anastomosis, group 3: 8 patients with a stoma). In addition the electrosensitivity was measured in groups 1 and 2 by placing the electrode, mounted on a catheter with a central wire, against the anterior, posterior, right and left rectal or neorectal walls. To assess the influence on this test of loss of mucosal contact due to faeces, a further 8 cases with a normal rectum had electrosensitivity evaluated with and without a layer of water soaked gauze around the electrode to stimulate faeces and prevent the electrode from making contact with the rectal mucosa. There was marked variance in the sensitivity of the different regions of rectal wall tested. In group 1 patients the mean sensitivities were: central 36.6 mA, anterior 27.4 mA, posterior 37.9 mA, right 22.3 mA and left 25.6 mA. This circumferential variation suggests that the pelvic floor rather than rectal mucosa was being stimulated. All patients in group 2 had recordable sensitivities, and the mean sensitivity threshold was significantly higher than group 1 patients in the central (p = 0.03), right (p = 0.03) and left (p = 0.007) positions. In group 3 the sensitivity was greater within the stoma at the level of the abdominal wall muscle than intra-abdominally or subcutaneously, again suggesting an extra-colonic origin of the sensation. The sensitivity threshold was significantly greater with the electrode wrapped in gauze (p < 0.01), and loss of mucosal contact was not detected by the EMG machine. They concluded that it is uncertain what is being measured during rectal mucosal electrosensitivity testing. It does not appear to measure mucosal sensitivity, and is probably influenced by the presence of faeces. [672]

In 1997, Felt-Bersma et al undertook a study to determine the anal sensitivity in controls and in different
patient groups and to establish which factors determine anal sensitivity. Anal sensitivity was assessed in 387 patients with different anorectal diseases and in 36 controls by means of a catheter with two electrodes placed in the anal canal. A constant current (square wave stimuli 100 microsec, pulses per second) was increased stepwise from 1 to 20 mA until the threshold sensation was reached. Controls had a threshold sensation of 3.4 ± 1.7 mA and this was significantly increased in patients with faecal incontinence, soiling, hemorrhoids, mucosal prolapse, constipation, anal scars, anal surgery, and sphincter defects; patients with faecal incontinence had the highest mucosal electrosensitivity (MES) of 6.7 ± 4.3 mA. They concluded that anal sensitivity is diminished in all patients with anorectal diseases except for anal fissures and proctitis but it has limited clinical value and should be used in conjunction with other tests in a research setting. [673]

In 1998, Poen et al investigated the long-term clinical and anorectal functional results 5 years after primary repair of a third-degree obstetrical perineal rupture. In 40 of the 117 women who responded to a postal questionnaire and attended for investigation, anal mucosal electrosensitivity was increased at 4.7(1.7) mA compared to the values in normal controls of 2.5(0.8) mA. However, the risk of incontinence was only related to the presence of a combined sphincter defect or subsequent vaginal delivery. [674]

In 1999, Yamana et al studied 32 patients who underwent low anterior resection for rectal cancer. Anorectal physiological studies were performed preoperatively and six months postoperatively. In univariate regression analyses, a longer preoperative high pressure zone and a more sensitive anal mucosa were associated with better postoperative defecatory function. Using multiple regression analysis, in which age, gender, the level of anastomosis, and preoperative physiologic parameters were examined as independent variables, a longer preoperative high pressure zone, a larger preoperative maximum tolerable volume, and lower sensory threshold of the anal canal were associated with better postoperative defecatory function. Postoperative function score was found to be predictable using the following formula: 1.47 + 0.496 x high pressure zone (cm) + 0.007 x maximum tolerable volume (ml) - 0.247 x sensory threshold (mA) of the anal canal.

Hence, they concluded that early postoperative defecatory function after low anterior resection is predictable from preoperative high pressure zone, maximum tolerable volume, and anal mucosal electrosensitivity. [627]

In 2005, Broens and Penninckx assessed the effect of age and sex on the rectal filling sensation and anal electrosensitivity and explored the relation between anal electrosensitivity and the parameters of the rectal filling sensation. Tests were carried out in 19 control subjects; 10 were younger than 60 years and 9 were older than that. Altogether, there were 11 men and 8 women. They showed that anal electrosensitivity did not differ between the two age groups but women had a significantly lower electrosensitivity 4 and 5 cm from the anal verge than men.

The rectal filling sensation did not differ between sexes. However, in the older age group, the rectal volumes required to induce filling sensations were smaller than those observed in the younger age. Anal electrosensitivity at different anal levels did not correlate with the rectal volume or pressure parameters of successive rectal filling sensations. They concluded that rectal sensation did not correlate with anal electrosensitivity, probably because the receptors are not stimulated by the type of anal stimulation used or because different receptors are involved. Hence, the rectal filling sensation test cannot be replaced by the simpler anal electro-sensitivity test. [675]

In 2007, Tomita and Igarashi examined the significance of the anal canal sensitivity contribution to soiling in 40 patients a mean of 103.6 months following ileostomy closure after ileal J pouch-anal anastomosis for ulcerative colitis. They studied 26 patients without soiling, 14 patients with soiling and compared them with a group of 28 healthy controls. They showed that there was significantly lower sensitivity in the proximal and middle anal canal in ileal J pouch-anal anastomosis patients with soiling. [676]

Conclusions (evidence level 3)

- Measurement of anal mucosal sensitivity testing by electrical stimulation is reproducible by different operators. There is no clear indication whether the measurement is affected by gender or age.

- Measurement of rectal mucosal sensitivity testing by electrical stimulation has been found to be reproducible by some workers but others have not found this and have demonstrated to some extent that the presence of faeces in the rectum affects the result.

- There are differences in the sensitivities between some patient groups and controls.

- Anal mucosal sensitivity is one of the factors that may help predict early postoperative defecatory function after low anterior resection.

Recommendation (grade C)

- Anal and rectal mucosal sensitivity testing by electrical stimulation has limited proven clinical value and it use should be currently restricted to research.
In 2001, Altomare et al studied the long term effects of stapled haemorrhoidectomy; particularly with regard to some concern about the risk of injury to the internal anal sphincter. Internal anal sphincter function and morphology, and anal canal sensitivity were studied prospectively in 20 patients (11 women) with stage III haemorrhoids. All underwent preoperative anorectal manometry, rectoanal inhibitory reflex testing and three-dimensional transanal ultrasonography. A test of anal sensation was administered to evaluate ability to discriminate between air and warm water. All the investigations were repeated 6 months after the operation. The maximal resting pressure, the maximal squeeze pressure, the rectoanal inhibitory reflex and the width of the internal anal sphincter did not change after operation. However, the ability of the anal mucosa to discriminate air from warm water improved in five patients. The authors concluded that stapled haemorrhoidectomy can improve anal sensation in patients with preoperative sensory impairment. [680]

Also in 2001, Salvioli et al quantified anal perception of temperature and light touch in 22 unselected patients with faecal incontinence (21 F, 33-75 yr). Control values were obtained from two groups of 11 (seven F, 32-53 yr), and 32 (18 F, 19-44 yr) volunteers. Most of the patients had low sphincteric pressures and ultrasonic abnormalities. Temperature perception was impaired in incontinent patients, to a greater extent in the proximal anal canal and in patients with passive, as opposed to urgency, incontinence. Intraluminal pressures for sensations of rectal distension were lower in incontinent patients (p = 0.02). Artificial stools elicited sensations of rectal filling at lower volumes than did a barostat bag, and in patients with urgency, as opposed to passive, incontinence. Therefore, they found that although temperature sensation is impaired, the perception of rectal distension is not always reduced in faecal incontinence. Artificial stool tended to induce sensations at lower volumes than did balloon inflation. They concluded that altered sensory mechanisms may contribute to the pathophysiology of faecal incontinence. [681]

In 2003, Chan et al used a thermal probe in the rectum to assess rectal sensation as an alternative to either balloon distension or electrical testing. This was carried out in 31 healthy subjects and compared with other anorectal physiological measurements. The median rectal heat threshold was similar in males (median, 47 C; range, 44-50 C) compared with females (median, 45 C; range, 43-50 C). There was a high degree of repeatability with rectal heat and balloon distension thresholds, but not electrostimulation thresholds. A strong correlation was found between rectal heat thresholds and defecatory desire and maximum tolerable volumes measured with balloon distension. The authors concluded that heat stimulation is a simple technique that has a high degree of repeatability and may be an objective assessment of sensory function in the rectum. [682]

In 1988, Miller et al used this technique to determine the thermal sensitivity in the anal canal in 20 continent patients with haemorrhoids and to compare the results with 40 control subjects and 22 patients with idiopathic faecal incontinence. Anal manometry was performed and sensation to mucosal electrostimulation and temperature change in the lower, middle, and upper zones of the anal canal assessed. Thermal sensation was impaired in the hemorrhoid group as compared with controls, but not to the same degree as in idiopathic faecal incontinence. There was some correlation between the two tests of sensation and the reproducibility of thermal sensory thresholds was reasonable (correlation coefficient of 0.82). They concluded that patients with hemorrhoids have a mild anal sensory deficit, but continence in this group is likely to be augmented by other factors. [678]

In 1996, Solana et al compared anorectal sensitivity to electrical and thermal stimuli in 21 healthy controls (11 females and 10 males; mean age 51.8 ±11 years, range 33-67) and 19 patients (18 females and 1 male; mean age 48 ±15 years, range 20-71) with obstructed defaecation. In the controls the electrical sensitivity threshold was minimal in the mid anal canal, where sensory receptor presence is greater. Sensitivity was significantly higher in the upper and lower anal canal regions and much higher in the rectum. A similar sensory profile was recorded in the patients with obstructed defaecation, though with significantly higher thresholds at all points with respect to the controls. The thermal stimulus thresholds in the lower and middle anal canal were significantly smaller than in the upper canal region and rectum, and the thresholds were again higher among the patients with obstructed defaecation than among the controls. In all cases the thresholds for heat were lower than for cold stimuli. They concluded that patients with obstructed defaecation had sensory deterioration at all points studied in the anal canal and rectum. Sensory pudendal neuropathy was found to be associated with the pudendal motor neuropathy. [679]
Conclusions (evidence level 3/4)

- Different patient groups have different responses to thermal testing of the anal canal and rectum.
- The reproducibility of the measurement is unknown regarding thermal testing of the anal canal but appears to be reproducible in the rectum (in the one study that looked at this)
- Intervention may alter the response of the anal canal to thermal testing.

Recommendation (grade C/D)

- Thermal testing of the anal canal and rectum has no proven clinical value and it use should be restricted to research.

9. SALINE RETENTION TESTS

The saline continence/retention test assesses the ability of the lower GI tract to retain fluid in the rectum. It is used as an outcome measure following treatment [683-686] but there is a paucity of data regarding what is normal.

The saline continence test measures the ability to retain 1500 ml of saline infused in the rectum, via a tube at a rapid rate of 60 ml/min whilst the patient is seated on a commode. The time and volume of first leak as well as the total volume leaked can be measured. [585]

In 1982, Leigh and Tumberg evaluated 76 patients with diarrhea due to a variety of causes. Using a saline retention test, they found that all but 7 of 42 continent subjects could retain more than 500 ml before leaking, whereas 19 of 22 frequently incontinent subjects leaked after infusion of less than 500 ml. They proposed that the saline-infusion test was a simple method of measuring this disturbance of anorectal function. [687]

In 1988, Allen et al compared the ability to retain rectally infused saline in three groups of subjects: 14 patients complaining of faecal incontinence, 14 age- and sex-matched continent patients, and 14 sex-matched younger normal controls. An additional group of unmatched normals and incontinent patients demonstrated significant differences in their ability to retain rectally infused saline. The patients leaked sooner and retained less; however, the performance of the normals was considerably reduced from that reported in previous studies. [688]

In 1989, Penninkcx et al described a balloon-retaining test which consists of progressive filling of a compliant intrarectal balloon in a patient in the sitting position. The pressure inside the balloon is monitored and the patient is asked to retain the balloon as long as possible and to report first, constant, and maximal tolerable sensation levels. They claimed that this test is a more realistic approach to the evaluation of faecal continence than the rectal saline infusion test and proposed that it permits objective evaluation of the effect of different treatments in incontinent patients. [689]

Also in 1989, Yoshioka et al performed posterior abdominal rectopexy in 12 patients with a full-thickness rectal prolapse of whom 9 had faecal incontinence. The prolapse was successfully controlled in all cases and six of nine patients were rendered continent. They found that delayed leakage during the saline infusion test preoperatively helped predict the return of continence. [690]

In 1990, Felt-Bersma et al carried out the saline-infusion test in 350 patients, 178 of whom had faecal incontinence and 172 of whom were continent. Compared with continent patients, incontinent patients leaked earlier and more with the saline infusion test. However, differentiation between incontinent and continent patients was not possible because there was considerable overlap. [629]

In 1995, Penninkcx et al carried out the rectal saline infusion test and the balloon-retaining test in 27 control subjects (M:8, F:19; mean age: 47 yr) and in 40 incontinent patients (M:5, F:35; mean age: 49 yr). The uncontrollable evacuation of a balloon, progressively filled with water at 60 ml/min, before the maximum tolerable sensation level was reached, was related to the degree of clinical incontinence. The balloon-retaining test proved to be superior to the rectal saline infusion test for the determination of the severity of incontinence. The saline infusion test, however, was found to be more adequate to identify minor defects of continence. [592]

Conclusions (evidence level 3/4)

- Different patient groups have different abilities to retain saline or a fluid-filled balloon in the rectum.
- Although continent individuals have better retention than incontinent patients there is considerable overlap between the two groups
- The reproducibility of the measurement is unknown
- It may help predict the return to continence of some patient groups post-operatively

Recommendation (grade C/D)

- Saline retention and balloon retention tests have limited clinical value and it use should be restricted to research.

10. RECTAL COMPLIANCE

Isometric and isobaric distension of the rectum to assess its compliance (the ratio of changes in volume to changes in pressure) are options available for
testing of the faecally incontinent (although more commonly used for those with constipation).

In isometric assessment, compliance of the rectum is assessed in a manner similar to cystometry whereby a rectal balloon is filled with water up to a specified volume and the pressure change inside the balloon from the start to the end point enable compliance to be calculated (after correcting for the compliance of the balloon).

In the isobaric assessment of compliance, a barostat (a device used to maintain constant pressure in a closed system) is connected to a thin, infinitely compliant bag which is inflated in the rectum in a variety of ways; often ‘stepwise’ and ‘ramp’ are used. The volumes at various pressures and levels of rectal sensation can be measured.

Measurement of rectal compliance has been used in both paediatric [691, 692] and adolescent [693] constipated subjects. It has also been used in adults with constipation. [694] It has also been used in the investigation of subjects with irritable bowel syndrome (IBS) [695], ulcerative colitis [696] and obstructed defaecation. [697]

There is little data to assess its sensitivity in detecting the faecal incontinent from healthy subjects.

In 1986, Varma and Smith showed that in 15 patients, the proctometrogram (a method of measuring rectal distensibility by continuous controlled fluid inflation with a balloon) was reproducible. [698]

In 1990, Rasmussen et al studied rectal compliance in 31 patients with faecal incontinence, 8 patients with constipation, and 16 control subjects. Patients with faecal incontinence experienced a constant defaecation desire at a lower rectal volume and also had a lower maximal tolerable volume and a lower rectal compliance than control subjects (median 126 vs 155 mL, 170 vs 220 mL, and 9 vs 15 mL/mm Hg, respectively; p < 0.05). Constipated patients had a higher constant defaecation desire volume and maximal tolerable volume than controls (median, 266 mL and 300 mL; p < 0.05). There were no differences in the parameters between patients with idiopathic faecal incontinence and patients with incontinence of traumatic origin, indicating that a poorly compliant rectum in patients with faecal incontinence may be secondary to anal incontinence due to the lack of normal reservoir function. [699]

In 1992, Sorensen et al measured the volume of air inflated in a latex balloon placed in the rectum and the corresponding pressures in 48 subjects (24 men and 24 women) at three points: (1) earliest defaecation desire; (2) constant defaecation desire; and (3) maximum tolerable volume. The rectal pressures in all three cases were higher in men than in women. Woman aged over 60 years had higher rectal compliance than men in the same age group, while no difference was found between men and women below the age of 60 years. Day-to-day variation of the measurements was tested in ten subjects. Reproducibility was good only for maximum tolerable volume. Reproducibility of rectal compliance decreased with increasing values for this parameter. They concluded that maximum tolerable volume is a reproducible parameter and suitable for clinical use in evaluation of patients with faecal incontinence or constipation. [700]

In 1997, Whitehead and Delvaux presented a standardisation of barostat procedures for testing muscle tone and sensory thresholds in the GI tract. [701]

In 1998, Hammer et al examined the reproducibility of repeated assessments of sensory perception, basal tone, and compliance and/or elastance of the rectum during distension. They studied 5 healthy volunteers and found that repeated distensions evoked reproducible responses of sensation and compliance and/or elastance on a single day, providing a conditioning distension preceded them. They also found that day-to-day variability was also sufficiently small to allow valid comparisons to be made on different days in healthy persons. [702]

In 1998, Rasmussen et al studied whether anorectal pressure gradients discriminated better than standard anal manometry between patients with faecal incontinence and subjects with normal anal function. Anorectal pressure gradients were measured during rectal compliance measurements in 36 patients with faecal incontinence and in 22 control subjects. With standard anal manometry, 75% of patients with faecal incontinence had maximal resting pressure within the normal range, and 39% had maximum squeeze pressure within the normal range. Anorectal pressure gradients did not discriminate better between faecal incontinence and normal anal function, since, depending on the parameters used, 61%-100% of the incontinent patients had anorectal pressure gradients within the normal range. They concluded that measurements of anorectal pressure gradients offer no advantage over standard anal manometry when comparing patients with faecal incontinence to controls. [595]

In 2000, Felt-Bersma et al measured the rectal compliance in 974 consecutive patients and compared them with 24 controls. Rectal compliance measurement was performed by filling a latex rectal balloon with water at a rate of 60 ml per minute. Volume and pressure at three sensitivity thresholds were recorded for analysis: first sensation, urge, and maximal toleration. At maximal toleration, the rectal compliance (volume/pressure) was calculated. They did not see any effect of age or gender in either controls or patients. They concluded that rectal compliance measurement
with a latex balloon is easily feasible and some patient groups showed an abnormal rectal visceral sensitivity and compliance. However, there was an overlap with controls. [703]

In 2001, Krogh et al noted that pressure-volume measurement during distention with a compliant balloon is the most commonly used method for computation of rectal compliance. However, they stated that intraindividual and interindividual variations are apparently large, restricting the usefulness of the method. Therefore, they compared the in vivo reproducibility of pressure-volume measurement during distention with a compliant balloon and pressure-volume measurement during rectal distention by a large, noncompliant bag, and rectal impedance planimetry. They also carried out an in vitro study of their reproducibility and validity. For the in vivo study, 10 healthy volunteers (6 men) aged 21-59 years were randomised to either rectal pressure-volume measurement with a compliant balloon or rectal impedance planimetry. After a one-hour rest, the other procedure was performed. After two weeks, both procedures were again performed in the same order. During rectal impedance planimetry the volume of the bag used (maximum volume 450 ml; secured at both ends to the probe) was continuously registered, measuring pressure-volume relations during rectal distention by a large, noncompliant bag. They found that in vivo reproducibility for pressure-volume measurement with a large, noncompliant bag and rectal impedance planimetry was significantly better than for pressure-volume measurement with a compliant balloon. No statistically significant difference was found between pressure-volume measurement with a large, noncompliant bag and rectal impedance planimetry. In vitro reproducibility was studied using polyvinyl chloride tubes with known cross-sectional areas. The reproducibility of pressure-volume measurement with a large, noncompliant bag and rectal impedance planimetry was good, but some elongation occurred, reducing the validity of pressure-volume measurement with a compliant balloon. Coiling and elongation of the balloon within the lumen were major sources of error for pressure-volume measurement with a compliant balloon. They concluded that in vivo and in vitro reproducibility of methods used for measurement of rectal compliance can be improved by restricting the effects of elongation within the lumen either by using a large-volume, noncompliant bag or by rectal impedance planimetry. However, pressure-volume measurement will to some degree depend on the properties of the balloons or bags. [704]

In 2001, Herman et al showed, using a rectal barostat that transanal endoscopic microsurgery in 33 patients with small, mobile rectal tumors, rectal compliance significantly changed 3 weeks after surgery and remained low at 6 months. There was a control group of 20 healthy volunteers. [612]

In 2005, Cremonini et al demonstrated that isobaric testing is fairly reproducible in healthy volunteers. The 34 participants had rectal barostat assessments carried out three times, at 2 centres. The results from the 2 centres differed minimally and the authors concluded that pressure threshold for pain and sensory ratings at 36-48 mmHg of distension are reproducible. [705]

In 2005, Siproudhis et al showed that rectal compliance was altered in some patients with faecal incontinence. They investigated 148 patients (12 men, 136 female) with incontinence to liquid and/or solid stools. Pain during isovolumic rectal distension at a level of 100 mL or less was experienced in 21 subjects. They showed that, as defined by isobaric distensions, incontinent patients with this low maximal tolerable volume more frequently had a poorly compliant rectum when compared with those with a higher maximal tolerable volume. Unsurprisingly, incontinent patients with low maximal tolerable volume more frequently had a hypersensitive rectum when compared with those with normal or high maximal tolerable volume. However, only four of 21 incontinent subjects with low maximal tolerable volume had an isolated hypersensitive rectum. They concluded that both sensitivity and compliance are altered in patients with low maximal tolerable volume but a more extensive study of the role of sensory and compliance aspects of subjects with incontinence is warranted. [706]

In 2006, Fox et al validated a barostat measurement of rectal capacity. Slow staircase (0-40 mm Hg) and rapid phasic (12-40 mm Hg) barostatic distentions were performed on two separate days in 41 healthy, continent subjects, filling sensations were assessed by visual analog score. Correction for rectal capacity measured at 40 mm Hg reduced the “normal range” of compliance measurements. Compared with unadjusted volume measurements, normalised rectal volume (percentage filling relative to rectal capacity) improved the description of rectal sensation visual analogue score. They concluded that barostat measurements of rectal capacity at 40 mm Hg are highly reproducible and not affected by distention protocol. Correction for rectal capacity provides an assessment of rectal wall stiffness independent of rectal geometry and improves the association of barostat volume measurements with rectal sensitivity and continence. [707]

In 2008, de Nardi et al studied 10 patients with third-degree and fourth-degree haemorrhoids who underwent stapled haemorrhoidopexy. One week before and six months after surgery, they underwent three different rectal distensions (pressure-controlled stepwise, volume-controlled stepwise, and ramp) controlled by an electronic barostat. They showed that rectal distensibility and volume thresholds for sensations decrease after stapled haemorrhoidopexy and persist for at least six months after surgery. [708]
The American Gastroenterological Association concluded in 1999 that measurement of rectal compliance, by whatever means, had no established clinical value. [584]. They stated that although the measurement appears to be reproducible in some patients and is sensitive to change in some patients, there is overlap of values between abnormal and controls and it has no role in the prediction of outcome. Therefore, its clinical value has still not been demonstrated. Papers published since 1999 do not appear to have substantially challenged this view.

A recent report from the German Societies of Neurogastroenterology (committee for proctology), Abdominal Surgery (coloproctology working group), and Coloproctology concluded that if compliance measurements have to be carried out, they are best done with a ‘static’ system measuring the pressure change on instilling 100 mL of fluid in the rectal balloon rather than using a barostat. [709]

Conclusions (evidence level 2)

- Measurement of rectal compliance is fairly reproducible to some extent; particularly at the maximum tolerable volume.
- There are differences in rectal compliance between some patient groups and controls. However there is a fair degree of overlap and there is no proven clinical benefit from carrying out this measurement.
- There is some evidence that rectal compliance is altered by intervention.

Recommendation (grade B)

- Measurement of rectal compliance has limited clinical value and its use should be restricted to research.

11. NEUROPHYSIOLOGICAL TESTING

There are some electrophysiological tests employed in faecal incontinence. The techniques and their limitations are described in the chapter relating to imaging, neurophysiology and other tests and there has been a recent review paper [710]. However, it is worth briefly mentioning a few points here.

a) Pudendal nerve motor latency

Pudendal nerve terminal motor latency (PNTML) testing has been applied in lower GI tract dysfunction since its development in 1984 [711]. An intrarectal device electrically stimulates the pudendal nerve where it angulates around the ischial spine in the pelvis and the latency is the measurement of the time taken for the electrical impulses to travel down the nerve and cause the external anal sphincter to contract. The initial work by Kiff and Swash showed that patients with faecal incontinence had a slowing of electrical conduction along the pudendal nerves compared to those with normal faecal control.

Whilst initially it was used to investigate the aetiology of faecal incontinence, it has since been used prognostically to predict likely success from various operative procedures such as post anal repair, procedures for rectal prolapse and sphincteroplasty. However there are different opinions regarding its use in this way. For example, Gilliland et al demonstrated that it has good prognostic value in predicting success following sphincteroplasty [712] whilst Chen et al in the same year demonstrated it has no prognostic ability in this respect [713].

These differences in conclusions probably reflect the fact that this is an inherently insensitive test (see chapter on imaging, Neurophysiology and other Tests) which is operator dependent and it is probably for limitations such as these that the American Gastroenterological Association in 1999 could not recommend its use in faecal incontinence [584]. Nevertheless some workers still regard it is a useful test and even spend time considering how best to teach the technique to trainees [714]. It continues to be widely used, particularly in a research setting [715, 716] when trying to understand the effects of therapeutic intervention.

Initial work showed some correlation between PNTML and external anal sphincter function as assessed by manometry. [717] However, several workers have more recently demonstrated that pudendal nerve terminal motor latency does not correlate with the function of the external anal sphincter [718-720], even when considering patients with intact sphincters on endoanal ultrasound.

Bilateral neuropathy has been shown to correlate with poor resting pressure in the anal canal but not with squeeze pressures [721]

Chemoradiation prior to restorative proctectomy for rectal cancer appears to have a significant risk of prolonging nerve latencies [722]

Fistula and haemorrhoid surgery do not appear to affect pudendal nerve latencies (although a mean of 2.4 ms in both groups tends to suggest that either these patients are already compromised or the technique of measurement is not ideal) [723]

Even recently its value in predicting success from sacral nerve stimulation has been assessed although it has not been found to have any predictive value [724]

Obtaining the same measurement by intravaginal stimulation appears to produce equivalent results to intrarectal stimulation [725]

Although most nerve latency assessments are carried out with a digital device, other workers have reported good results using an externally manipulated device which causes less discomfort to the patient. [726, 727]
Recently, the whole compound muscle action potential (CMAP) from the external anal sphincter (produced by stimulating the pudendal nerve) has been studied [728]. Initial results show some differences between nerve latency and the other parameters of the CMAP (the amplitude of the response, the duration of the response and the area under the curve). However, these differences may prove to be of no real clinical significance and the CMAP may have no real advantage over PNTML.

Pudendal nerve latency testing has also been used in studying perineal neuralgia although the measurements have not been of much use in detecting the problem, clinical evaluation has been shown to be superior [729].

- **NORMAL VALUES OF PNTML**

Normal values of PNTML have been published but vary widely. Pradal-Prat et al describe average values of 5.52 ± 1.9 ms on the right and 5.74 ± 1.6 ms on the left in male subjects and 6.16 ± 1.8 on the right and 6.42 ± 1.96 on the left in female subjects. [730]

Lefaucheur reported values of between 1.8 to 5.6 ms (mean ± SD 2.94 ± 0.8 ms) using a St Mark's electrode and a range of 2.2 to 5.4 ms (3.7 ± 0.9 ms) using an externally manipulated device [727].

Many workers use the threshold values of between 2.2 ms and 2.4 ms, reported by Ricciardi [721] with 2.2ms being reported by Hill et al [719]; derived from the previous work of Smith et al [731] and Allen et al [726].

Tetzschner reported normal values for mean PNTML of 1.91 ms (2 SD, 0.52 ms) in women and 1.74 ms (2 SD, 0.33 ms) in men [732]. Allen et al reported a mean value of 1.9 ms (1 SD, 0.2ms) in the immediate post-partum period and 8 weeks post-natally in over 50 women having their first child. [726]

Smith et al reported a mean value of 1.6 ms (1 SD, 0.2 ms) in 28 nulliparous women and 1.7 ms (1 SD, 0.2 ms) in 14 parous women with normal urinary control. Women with USI had a mean value of 1.9 ms (1 SD, 0.2 ms); 42 women with both USI and genito-urinary prolapse had a mean value of 1.9 ms (1 SD, 0.3 ms), whilst continent women with genito-urinary prolapse had a mean value of 2.1 (1SD, 0.3 ms). [731]

- **REPEATABILITY OF PNTML**

There is some evidence to suggest that PNTML has both good intraobserver and interobserver reproducibility [732].

**Conclusions (evidence level 2/3)**

- The substantially different published ‘cut-off’ values discriminating normal from abnormal demonstrate that the measurement is operator dependent and may often not be carried out in an optimal fashion.
- There is no conclusive evidence that it is predictive of success following intervention.
- Patients with incontinence have may have longer latencies than continent individuals but there is considerable overlap between the groups.

**Recommendation (grade B/C)**

- Measurement of pudendal nerve motor latency has no proven clinical value.
- There may be merit in continuing to use it as a research tool provided that it is carried out in a well-controlled, optimal manner. Although it is an inherently insensitive measure of neuropathy, patients with genuinely markedly prolonged values of latency could have a different response to therapy compared to those who do not.

**b) Needle electromyography**

Needle EMG of the external anal sphincter has been used for many years to help understand the aetiology of faecal incontinence. Both single fibre [733] and concentric needle techniques [734] have been used and continue to be used in a research setting[735, 736]. In a clinical setting, concentric needle EMG has been used to map the integrity of the external anal sphincter but the advent of endoanal ultrasound, which is a more comfortable procedure, has largely made this application of EMG obsolete [737]. The current sole clinical application for concentric needle EMG is in the investigation of possible anismus (see later) where it is considered to be more sensitive than defaecography.

**c) Strength-duration tests**

The strength-duration test is an electrophysiological test of superficial muscle which predates EMG. It can determine muscle denervation directly by putting a surface electrode over the muscle, applying square waves of diminishing pulse width and determining at each pulse width the current required to elicit a twitch from the muscle. Normally innervated muscle and denervated muscle have different shaped curves when the current required to elicit a twitch is plotted against the pulse width. Denervated muscle is less excitable and requires more current to elicit a response. This technique has recently been applied to the external anal sphincter and distinguishes people with normal faecal control from those with faecal incontinence, especially when combined with manometry [738]. Work has confirmed that this technique is measuring properties of the sphincter [739] and the optimum position for stimulating the muscle has been
d) Endoanal ultrasound

Perhaps one of the universal investigations relating to faecal incontinence, along with manometry, is that of endoanal ultrasound to image the sphincters. The usefulness of this is discussed in the chapter on Imaging, Neurophysiology and other Tests.

V. TESTS RELATING TO SECONDARY INCONTINENCE

1. RECTOANAL INHIBITORY REFLEX

In the normal, healthy individual, the internal sphincter relaxes in response to rectal distension. [547, 742] In some individuals, there can be a lack of the nervous connections between the upper GI tract and the internal sphincter (e.g. Hirschsprung’s Disease) [743-745]. Usually this is congenital and occurs in infants but there are rare occasions when it can manifest itself in the adult. [746]

The relaxation of the internal sphincter in response to rectal distension can be simply be assessed by inflating a balloon in the rectum and measuring pressure in the anal canal – a decrease in pressure indicating the presence of the rectoanal inhibitory reflex (RAIR).

Technically, the reflex can be difficult to elicit if the anal canal has poor resting pressure.

Whilst biopsy is the gold standard investigation for Hirschsprung’s Disease, there is evidence that looking for the RAIR is just as sensitive [747] and is an effective screening test before biopsy is considered to provide the definitive diagnosis. [857]

In 2007, Kawahara et al described a micromanometry sleeve technique for assessing the RAIR in newborn infants. They claim that the technique has very good sensitivity. [748]

A systematic review in 2006, compiled from the results of the testing of 933 infants, confirms that manometry and rectal suction biopsy are the most accurate tests in the diagnostic workup of Hirschsprung disease. [749]

Assessment of the RAIR has not been confined to infants. In 1998, Deen et al used it to assess 30 patients with diabetes and compare it with the data from 22 age- and sex-matched healthy controls. Twelve of the diabetics had impaired continence for gas (n = 12) and liquid faeces (n = 3). None of the controls had incontinence. They classified the RAIR into three categories: normal, present, abnormal (requiring more distension than normal to elicit a response). They found that the RAIR was present in eight, abnormal in five (one incontinent) and absent in 17 (11 incontinent) diabetics, while it was present in 18 and abnormal in four controls (p = 0.031). They concluded that the RAIR was impaired in significantly more patients with diabetes than controls and that it was either impaired or absent in all diabetic patients with incontinence. [750]

In 2007, Shafik et al [751] noted that the RAIR was elicited with a lower volume of rectal distension in a large proportion of women who suffer from the inadvertent passage of flatus during intercourse compared to women without this problem.

There is also evidence that the RAIR can be altered by therapy:

In 2002, Sunic-Omejc et al treated 49 children with chronic idiopathic constipation; 24 were allocated to conventional and 25 to biofeedback therapy. Amongst other factors, the volume to elicit the RAIR became significantly higher in the group who had had biofeedback therapy (and this group had a better symptomatic response to therapy compared to the group treated with conventional therapy). [752]

In 2003, Saigusa et al retrospectively reviewed the records of 100 patients who had ARPS before and after restorative proctocolectomy with ileal pouch-anal anastomosis for mucosal ulcerative colitis. The rectoanal inhibitory reflex was noted in 96 patients before surgery, but it was found in only 53 (53 percent) after ileostomy closure. Incontinence status data was available in only 62 of the 100 patients (32 RAIR-positive; 30 RAIR-negative). There were significant differences relative to the incidence of nocturnal soiling (12/30 (40%) 23/32 (72%), p = 0.0012) favouring the presence of the rectoanal inhibitory reflex. They concluded that preservation of the rectoanal inhibitory reflex correlated with a decrease in the incidence of nocturnal soiling after double-stapled ileoanal reservoir construction. [753]

In 2004, Sangkhathat et al showed that the RAIR was present in 94% of cases without constipation and 12.5% of cases with constipation following anoplasty in 24 infants aged less than 3 years. They concluded that RAIR plays an important role in emptying function and, as far as possible, this function should be preserved during reconstruction. [754]

Conclusion (evidence level 1/2)

- Assessment of the rectoanal inhibitory reflex in infants is a valuable tool in screening for Hirschsprung’s Disease.

Conclusions (level 3)

- The rectoanal inhibitory reflex may be different in different patient groups and can be modified by intervention.
Recommendation (grade A/B)

- Assessment of the rectoanal inhibitory reflex by manometry is clinically valuable in screening for Hirschsprung’s Disease.

Recommendation (grade C)

- Assessment of the rectoanal inhibitory reflex in any other patient group is of no proven clinical value.

2. ANISMUS

When a patient attempts to defaecate by initiating a Valsalva manoeuvre, puborectalis and the external sphincter should relax. In some patients, the muscles tighten up and this is termed anismus.

Its presence can be detected by EMG of the muscles using surface electrodes or needle electrodes. Evacuation proctography is also used to detect anismus but the results do not always correlate with EMG and evacuation proctography may be a less sensitive indicator of anismus. [755, 756]

Difficulty evacuating a rectal balloon (see next section) is also used as a marker for anismus but again, this does not always correlate with EMG. [755, 756]

A further option to detect anismus is by measuring pressure in the anal canal when the patient performs a Valsalva manoeuvre. [757] If a water-perfused system is used, this may stimulate abnormal muscle activity and overdiagnose anismus. [758] Movement of the pressure sensor during straining is another confounding factor in this assessment and it is not particularly sensitive.

In 2007, Murad-Regadas et al used a different imaging approach to determine anismus. They showed that on anal endosonography, changes in the ano-rectal angle on straining correlated with the presence or absence of anismus as determined by anal manometry [759]

Therefore, it can be seen that there several different methods to test for the presence or absence of a paradoxical contraction of puborectalis and the external anal sphincter on straining. However, measurements by the different techniques are not always in agreement and, whilst it is tempting to consider that needle EMG may be the most sensitive indicator of anismus, there is no real evidence to substantiate such a claim. Perhaps the presence of anismus, detected by one of the methods above, is best confirmed with a positive finding on one of the other tests. This sensible approach was suggested by Park et al in 1996. [760]

The other consideration relating to this topic is that it is difficult to know what the clinical significance of the finding of anismus is. Although there are individuals with defaecatory difficulty who have the finding of anismus, there appear to be many patients who have no difficulty with evacuation who also show evidence of anismus. [756, 761, 762]

Nevertheless, if anismus is treated by biofeedback or botulinum toxin, some patients will show relief of their symptoms and a measurable normalisation of muscle function on straining. [763, 764]

Conclusions (evidence level 3)

- Anismus, the paradoxical contraction of puborectalis and the external anal sphincter on straining, can be detected by various techniques. The techniques all have different sensitivities to detect this phenomenon but there is no evidence to demonstrate which is the best.
- Although anismus can be found in patients with difficult defaecation, it is present in many who do not have such problems. Therefore its clinical significance is uncertain.
- Treatment of anismus can result in normalisation of muscle function and defaecation difficulty in some patients

Recommendation (grade C)

- Techniques to detect anismus may have some validity and lead to the effective treatment of some patients with difficult defaecation.
- The clinical significance of anismus needs more verification and the optimum technique to detect it needs to be determined

3. RECTAL COOLING TEST

In 2007, Shafik et al carried out measurement of rectal pressure with saline at 30°C and then at 4°C. They found that the iced fluid increased rectal tone in healthy controls and constipated patients with anismus while it had no effect in the other patients with consipation. They postulated that the lack of increase of rectal tone may be secondary to rectal inertia. They concluded from this preliminary study that this test might be useful in subdividing constipated patients into those who have rectal inertia and those who have anismus. [765] There have been no further reports on this measurement.
4. BALLOON EXPULSION TESTS

The test determines the ease with which a balloon in the rectum can be expelled. It is alleged to help determine the cause and management of difficult defaecation [766] and study the effects of treatment [767, 768]. However the lack of standardisation coupled with the often unphysiological position a patient has to adopt for defaecation is a current limitation of tests of this sort.

5. AXIAL FORCES

In 2006, Bharucha et al studied the dynamics of defaecation. They measured axial rectoanal forces with an intrarectal sphere or a latex balloon fixed at 8, 6, or 4 cm from the anal verge and connected to axial force and displacement transducers. [769] Rectoanal forces and rectal pressures within the latex balloon were measured at rest and during squeeze, simulated evacuation, and a Valsalva manoeuvre.

The measurements were carried out in 12 asymptomatic women and 12 women with symptoms of difficult defaecation. Anal resting and squeeze pressures were also assessed by manometry and were similar in control patients and symptomatic patients.

At rest, axial rectoanal forces were directed inward and increased as the device approached the anal verge. Control patients augmented this inward force when they squeezed and exerted an outward force during simulated expulsion and a Valsalva maneuver.

The force change during these manoeuvres was also affected by device location and was highest at 4 cm from the verge. In the patients with difficult defaecation, the force at rest and the change in force during all manoeuvres was lower than in control patients.

The rectal pressure during a Valsalva maneuver was also lower in those with difficult defaecation compared to control patients, suggestive of impaired propulsion. They concluded that the women with defecatory symptoms had weaker axial forces not only during expulsion but also during a Valsalva manoeuvre and when they contracted their pelvic floor muscles, suggestive of generalized pelvic floor weakness.

This is an interesting development but the sample size is much too small to determine whether this test has any clinical or research potential. There have been no further publications relating to this measurement.

VI. PUBLISHED RECOMMENDATIONS/GUIDELINES REGARDING PRACTICE OF ANORECTAL PHYSIOLOGY STUDIES

To date, there has been no universal standardisation of the tests, the terminology or the units of pressure employed in anorectal physiology studies. In 2007, there were some recommendations regarding manometry (including sensory testing and compliance measurement) published in German [709]. 8 years prior to that, there were recommendations published by the American Gastroenterological Association [584] and even earlier in 1989, a British working party made some recommendations relating to these measures [770]. None have been universally adopted.

In 2002, Azpiroz et al stated that tests for which there is consensus regarding their clinical utility include 1) resting anal canal pressure, 2) anal canal squeeze pressure (peak pressure and duration), 3) the rectoanal inhibitory reflex elicited by balloon distension of the rectum, 4) anal canal pressure in response to a cough, 5) anal canal pressure in response to defaecatory manoeuvres, 6) simulated defecation by means of balloon or radiopaque contrast, 7) compliance of the rectum in response to balloon distension, and 8) sensory thresholds in response to balloon distension. However, they acknowledged that the clinical utility of all anorectal manometric tests is limited by the relative absence of 1) standardisation of test protocols and 2) normative data from a large number of healthy individuals. They also stated that the interpretation of these diagnostic tests is also complicated by the fact that patients are able to compensate for deficits in specific physiological mechanisms maintaining continence and defaecation by utilising other biological and behavioral mechanisms. [771]

In 2004, Kouraklis and Andromanakos discussed evaluating patients with anorectal incontinence. They discussed the investigations used to evaluate anorectal physiology including anorectal manometry, anal endosonography, nerve stimulation techniques, electromyography, defaecography, endoluminal magnetic resonance imaging, the saline continence test, and the balloon-retaining test. They concluded that, although all of these tests are important, the most useful for patients with incontinence are anal manometry, anal endosonography, and the pudendal nerve terminal motor latency test, because they can identify anatomical or physiological abnormalities for which there may be effective treatments. [772]

In 2004, Bharucha discussed outcome measures for faecal incontinence. Whilst acknowledging that there is no standardisation for anal manometry, he expressed the opinion that, providing careful attention was paid to techniques, that there was sufficient
reproducibility for anal pressures, rectal compliance and sensation to enable them to be used as outcome measures. He outlined problems with surface EMG and pudendal nerve terminal motor latency assessment which prevents them from being considered as an outcome measures. He thought that needle EMG was a more reliable measure than surface EMG but did not pass an opinion as to whether there was evidence for it being a good outcome measure; he expressed the view that it may help identify people who would respond to therapy such as sphincter repair or sacral nerve stimulation. [773]

In 2005, Prott et al acknowledged that there were conflicting recommendations from consensus groups with regard to the assessment of resting anal sphincter pressure. In 54 patients suffering with constipation or faecal incontinence, they evaluated and compared the performance of stationary, stationary pull-through and slow pull-through techniques for evaluating resting anal sphincter pressures. Although the measurements from each technique highly correlated with each other, they concluded that resting anal sphincter pressure varies according to the specific technique employed and made a plea that standardised anal sphincter testing should be established to enable inter-laboratory comparisons. [774]

In 2005, Ortolani et al stated that anorectal manometry is the basic investigation for the study of anorectal function. However, they stated that lack of a standard execution technique and of any common definition of the manometric parameters constitutes a major limitation. They proposed a standard technique for performing manometry which would enable manometry to be performed in less than 30 minutes and yield approximately 10 parameters which are easily identified and interpreted. [775] However, there does not appear to be any subsequent publications using this proposal.

In 2007, Deutekom et al studied a consecutive series of 162 patients with faecal incontinence. They found that the hypothesised associations between urgency and passive incontinence and functional and anatomical impairment of the anorectum were less clear-cut than previously assumed. They concluded that patients presenting with faecal incontinence should undergo physiological investigation. [551]

In 2007 a consensus conference on faecal incontinence formed part of the programme at the International Conference on Faecal Incontinence (Bari, Italy). [776] The expert participants discussed the place of endoanal ultrasound, PNTML assessment, anal manometry, EMG and rectal sensitivity testing by balloon distension in the assessment of a patient with faecal incontinence. Most thought that endoanal ultrasound was the most useful investigation in helping to determine treatment and some carry it out on every patient they see with faecal incontinence. There was also a strong opinion that assessment of rectal sensation was important. At best, the other tests were carried out on an individual basis, some carrying out PNTML assessment in order to counsel patients regarding the outcome of a sphincter repair. Interestingly, one expert carried out anal manometry and PNTML assessment not because he needed it but because “there’s no journal that will accept a paper from me when I haven’t done it!”

In 2008, Thekkinkattil et al again acknowledged that that there is no standardisation of investigations, and treatment outcomes are variable for patients with faecal incontinence. They also pointed out the lack of a pretreatment classification of incontinence. They proposed that patients could be divided into four groups: traumatic incontinence, neuropathic faecal incontinence, combined faecal incontinence and idiopathic faecal incontinence (according to manometric variables and demographics). Their hope is that such a classification system will enable comparison and interpretation of the outcomes of different studies and also help in the selection of patients for appropriate treatments. [777]
There have been old [778] and more recent reviews of these tests[779]

1. The only test under the umbrella of anorectal physiology studies that appears to have proven clinical value is determining the presence or absence of the RAIR in newborn infants.

2. There have not been any major studies setting out normal ranges for the parameters measured in ARPS. Therefore, the sensitivity of the measures to distinguish normal from abnormal is largely unknown.

3. This situation is compounded by the great variety in techniques of testing, size and types of catheter for manometry, the lack of standardisation of other techniques of testing the lower GI tract, the lack of standardisation of terminology and even simple issues such as to whether particular tests require an empty or full rectum.

4. A minor point but there is no universal unit of pressure adopted for anal manometry which does not help comparisons of the results from different centres.

5. Many studies have shown changes in the measured parameters as a result of treatment but, without there often being a control arm, the significance and relevance is unknown.

6. There is some evidence to suggest that some of the tests under the umbrella of ARPS can help in determining patient management.

### Recommendations

The committee recognises that anorectal physiology studies are helpful in objectifying the function of the anorectum and aiding the diagnosis of the cause of faecal incontinence. There is some evidence that some of the tests can help determine patient management.

However, the committee recommends that urgent consideration needs to be given to standardising the tests and terminology. This will then help to better determine the reproducibility, reliability and prognostic value of the tests. It should then also be possible to generate a universally useful set of normative data.

### Grades of recommendation

- Grade A
- Grade B
- Grade C
- Grade D
- Investigational

<table>
<thead>
<tr>
<th>Tests</th>
<th>ADULT</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal manometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>resting pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>squeeze pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rectal sensitivity (balloon distension)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAIR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurophysiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNTML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surface EMG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>needle EMG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>static</td>
<td></td>
<td></td>
</tr>
<tr>
<td>barostat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anal rectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>balloon expulsion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### H. ACKNOWLEDGEMENTS

The authors of this chapter wish to acknowledge the following other contributors to “urodynamics” and “dynamic testing” in the three previous consultations: JE Batista, SB Bauer, M Craggs, N Diamant, DJ Griffiths, P Hilton, Y Homma, G Kramer, S Kulseng-Hanson, LLiao, G Lose, HPalmotag, W Schäfer, MWF Stöhrer, N Yoshimura. We have built on the solid foundation that they have helped to establish.

Thanks are also expressed to Bärbel Junginger who translated and summarised the guidelines of the
German Societies of Neurogastroenterology (committee for proctology), Abdominal Surgery (coloproctology working group), and Coloproctology.

Finally, thanks to the members of the committees for Conservative and Surgical treatment of Faecal Incontinence, especially Prof Chris Norton, for their comments on an early draft of the section on anorectal physiology studies.

REFERENCES


188. Harvey, M.A. and E. Versi, Predictive value of clinical evaluation of stress urinary incontinence: a summary of


190. AHCPR. 1992, Rockville.


633. Dobben, A.C., et al., [Limited predictive value of diagnostic tests for outcomes following pelvic floor physiotherapy in...


519


Committee 7 A

Clinical Neurophysiological Tests

Co-Chairman

D. VODUSEK (Slovenia)

Members

G. AMARENCO (France),
S. PODNAR (Slovenia)
## CONTENTS

### I. INTRODUCTION
- 1. CLASSIFICATION OF CLINICAL NEUROPHYSIOLOGICAL TESTS
- 2. BIOLOGICAL CORRELATES OF ELECTROPHYSIOLOGICAL TESTS
- 3. GENERAL METHODOLOGICAL CONSIDERATIONS

### II. CLINICAL NEUROPHYSIOLOGICAL TESTS
- 1. SOMATIC MOTOR SYSTEM TESTS
- 2. SENSORY SYSTEM TESTS
- 3. SACRAL REFLEXES
- 4. AUTONOMIC FUNCTION TESTS

### III. EVIDENCED BASED USE OF NEUROPHYSIOLOGICAL TESTS
- 1. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN EVALUATION OF INDIVIDUAL PATIENTS
- 2. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN RESEARCH

### IV. RECOMMENDATIONS
- 1. RECOMMENDATION FOR CLINICAL NEUROPHYSIOLOGICAL TESTING
- 2. RECOMMENDATION FOR TECHNICAL STANDARDS
- 3. RESEARCH RECOMMENDATIONS

## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR</td>
<td>bulbocavernosus reflex</td>
</tr>
<tr>
<td>CMAP</td>
<td>compound muscle action potential</td>
</tr>
<tr>
<td>CMCT</td>
<td>central motor conduction time</td>
</tr>
<tr>
<td>CNEMG</td>
<td>concentric needle electromyography</td>
</tr>
<tr>
<td>EAS</td>
<td>external anal sphincter</td>
</tr>
<tr>
<td>ED</td>
<td>erectile dysfunction</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>GSI</td>
<td>genuine stress incontinence</td>
</tr>
<tr>
<td>IP</td>
<td>interference pattern</td>
</tr>
<tr>
<td>MEP</td>
<td>motor evoked potential</td>
</tr>
<tr>
<td>MSA</td>
<td>multiple system atrophy</td>
</tr>
<tr>
<td>MU</td>
<td>motor unit</td>
</tr>
<tr>
<td>MU</td>
<td>motor unit potential</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>PNTML</td>
<td>pudendal nerve terminal motor latency</td>
</tr>
<tr>
<td>QST</td>
<td>quantitative sensory testing</td>
</tr>
<tr>
<td>SEP</td>
<td>somatosensory evoked potential</td>
</tr>
<tr>
<td>SFEMG</td>
<td>single fibre electromyography</td>
</tr>
<tr>
<td>SSR</td>
<td>sympathetic skin responses</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>T/A</td>
<td>turns/amplitude</td>
</tr>
</tbody>
</table>
Neurophysiological investigations of muscles and nerves in the perineum and pelvis originated over 60 years ago, and have evolved with the developments in general clinical neurophysiology. The data from these investigations can assist clinicians in diagnosing neurological disease or injury, and are applicable in research. Compared to neurophysiological testing of the limbs and trunk, pelvic neurophysiological testing is relatively limited because of the restrictions imposed by pelvic neuroanatomy.

This text details the investigations, their applications and limitations, enabling investigators and clinicians to make a well informed decision about using these tests. The present text is based on the previous chapter on clinical neurophysiology prepared for the International Consultations on Incontinence [1], which has been updated by a literature search in Medline using key words incontinence, clinical neurophysiology, electro-myography, reflex, evoked potentials.

1. CLASSIFICATION OF CLINICAL NEUROPHYSIOLOGICAL TESTS

Although different types of tests may be included under the term “neurophysiological”, it is particularly the electrophysiological tests that shall be discussed in the present text.

Electrophysiological tests are an extension of the clinical examination, and a functional anatomic approach to classification makes most sense. For the purpose of this categorisation, the nervous system is divided into the somatic and the autonomic nervous systems. The somatic nervous system provides motor innervation to the skeletal muscles, and sensory innervation from skin and muscle spindles. The autonomic nervous system provides motor innervation to the viscera and other end-organs not under voluntary control (e.g., sweat glands). Its sensory fibres are referred to as visceral afferents. Both systems have central pathways (neurons participating in spinal cord and supraspinal control) and peripheral nerves (those going to and from end-organs).

Thus, electrophysiological tests can be divided into:

a) somatic motor system tests (EMG, terminal motor latency measurements/ motor nerve conduction studies, and motor evoked potentials (MEP));
b) somatosensory system tests (sensory neurography, somatosensory evoked potentials (SEP));
c) reflexes;
d) the autonomic nervous system tests (for sympathetic or parasympathetic fibres).

Electrophysiological tests may also be categorized “technically” into those which “just” record some bioelectrical activity (for instance: electromyography), and those which record some biological response to stimulation (these may be subsumed under the term “conduction tests”).

2. BIOLOGICAL CORRELATES OF ELECTROPHYSIOLOGICAL TESTS

a) Conduction Tests: Nerve Conduction, Evoked Potential and Reflex Studies

The electrophysiological responses obtained on stimulation are compound action potentials and relate to populations of biological units (neurons, axons, motor units, muscle fibres, etc.). Latency and amplitude are commonly measured parameters of responses during neurophysiological testing. If the onset of the potential is measured, the latency of a compound potential represents the fastest conduction through a particular neural channel. As a general rule, latency measurements are not markedly affected by technical factors, but provide little information about the loss of biological units (e.g., motor neurons or axons).

The amplitude of the compound potential correlates with the number of activated biological units. In theory, the amplitudes are the more relevant physiological parameter, as they reflect the functional or structural loss of biological units. Unfortunately, amplitudes are also strongly influenced by many poorly controllable technical factors. Measurements of latencies and amplitudes of evoked potentials and reflex responses, including sympathetic skin responses, relate not only to conduction in peripheral and central neural pathways, but also to trans-synaptic transmission.
b) Electromyography (EMG)

Knowledge of the structure and function of the motor unit (Figure 1) is fundamental to understanding the application of EMG. Motor neurons, which innervate striated muscle, lie in the anterior horn of the spinal cord and are called “lower motor neurons”. (Neurons that innervate the sphincters lie in Onuf’s nucleus in the sacral spinal cord; they are somewhat smaller than those innervating skeletal limb and trunk muscles).

Within the muscle, the motor axon branches to innervate a certain number of muscle fibres, which are scattered throughout the muscle. All muscle fibres innervated by one lower motor neuron are activated simultaneously; all these constituents together are called “motor unit”. The innervation of muscle fibres is such that it is unlikely that muscle fibres that are part of the same motor unit will be adjacent to one another.

It is difficult to estimate the number of muscle fibres innervated by a single axon (i.e., the "innervation ratio") or the number of motor units supplying a muscle, by clinically available neurophysiological techniques.

3. GENERAL METHODOLOGICAL CONSIDERATIONS

To date, there are no universally accepted standards for conducting individual uro-genital-anal neurophysiological tests, but the variations of testing in different laboratories are minor.

There are technical standards on equipment safety; standardisation of concentric needle EMG and penilo/clitoro-cavernosal testing has been proposed.

a) Equipment

Clinical neurophysiological tests are conducted with complex electronic instruments and various devices that come into contact with the patient. Though this equipment is mostly standard, some specially constructed electrodes or stimulating devices have been devised to conform to uro-genital-anal anatomy.

As long as the standards of electrical safety are adhered to, the risk to patients is negligible.

The common form of neurophysiological testing is electrophysiological. Surface electrodes, which are applied to skin or mucosal surfaces, or needle electrodes are used for electrical stimulation and to record bioelectrical activity. The important neurophysiological difference between surface and needle electrodes is their selectivity, and the practical difference is their invasiveness. The choice and application of electrodes is guided by the need for selective recording or stimulation. Less commonly, special devices are used for magnetic and mechanical stimulation.

Stimulation Parameters. The electrical stimulus should be specified and characterised both in technical (e.g., rectangular pulse, 0.2 ms, 15 mA) and physiological terms (e.g., 3-times sensory threshold). A stimulus with defined technical parameters may have variable biological effects because of the variable influences of electrode condition, contact, tissue conductivity etc. Supramaximal stimulation is preferred to elicit a compound muscle action potential (CMAP) or sensory nerve action potential. Supramaximal stimuli yield responses with the largest amplitude and shortest latency, and are the least variable and most reproducible. The sites at which stimulation electrodes are applied should be described using anatomical terms.

b) Recording

1. APPARATUS SETTINGS

For recording, the apparatus settings (gain, sweep speed) have to be adapted to the known range of amplitudes, latencies, and duration of the response and it has to be appropriately displayed for analysis. Particularly important is the frequency setting of filters: for surface electrode recordings it is typically 2 Hz – 1 kHz; for concentric needle EMG recordings, it is 5 Hz – 10 kHz.

Placement of electrodes on the scalp for evoked potential recordings is defined according to the 10-20 International EEG System.

2. REPRODUCIBILITY AND RELIABILITY

Any potential elicited by stimulation should be reproducible; therefore, as a rule, at least two consecutive recording procedures need to be performed. To improve the signal-to-noise ratio some small amplitude responses need to be averaged. Therefore, many repetitions of stimulation/recording need to be done (typically 100-200). Even such an averaged recording needs to be repeated at least twice. CMAPs (i.e., M-waves), MEP, sacral reflexes and sympathetic skin responses (SSR) are recognisable after single stimuli. However, as a rule, several responses are recorded to demonstrate reproducibility. In contrast, other responses (e.g., SSR) show marked fatigability with stimulus repetition.

526
3. **Waveform Analysis**

For a particular stimulation procedure, the shape, latency, and amplitude of the recorded potentials are analysed. Morphologically, a particular response (or part of it) needs to be recognised as present or absent. The shape of potentials is important to accurately determine the latency and amplitude of the response. The onset of the response (for M-waves, MEP and sacral reflex testing) or the individual peaks of the potentials (for SEP) are used to determine the latency. The amplitudes are analysed relative to the baseline or “peak to peak”.

**II. CLINICAL NEUROPHYSIOLOGICAL TESTS**

1. **SOMATIC MOTOR SYSTEM TESTS**

   a) **Electromyography (EMG)**

   The term "EMG" is often used for several different procedures, the common denominator of which is the recording of bioelectrical activity from muscle. The term applies particularly to recordings from striated muscles.

   EMG is used a) “just” to record muscle activity (as for instance in combined sphincter EMG and pressure-flow study) and b) to differentiate between normal, denervated, reinervated, and myopathic muscle. For a) see below - “Kinesiological EMG”.

   Although EMG abnormalities are detected as a result of a host of different lesions and diseases, there are in principle only two standard manifestations which can occur: a) disease of the muscle fibres themselves (“myogenic” changes), and b) changes in their innervation (“neuropathic” changes). "Myogenic changes may result from muscle disease, probably also from direct trauma (e.g., the anal sphincter tear during vaginal delivery). Neurogenic changes may be attributable to injury at any level along the lower motor neuron supplying the external anal sphincter, extending from the motor neuron body, sacral nerve roots to the small branches within the external sphincter. In the pelvic floor muscles, only neurogenic changes are well recognised and routinely evaluated.

   The EMG signal may be further used to indicate that muscle has been activated through its motor nerve, either by stimulation applied to motor pathways (M-wave, MEP) or to sensory pathways (reflex response).

   b) **Concentric needle EMG (CNEMG)**

   The examination is conducted with a single use, disposable electrode. The commonly used amplifier filter settings for CNEMG are 5 Hz – 10 kHz, and need to be defined if MUP parameters are to be measured, as are filter settings employed during data acquisition.

   The concentric needle electrode consists of a central insulated platinum wire inserted through a steel cannula and the tip ground to give an elliptical area which can record spike or near activity from about 20 muscle fibres [2]. The number of motor units recorded therefore depends both upon the local arrangement of motor units within the muscle fascicle and the level of contraction of the muscle.

   CNEMG can provide information on a) insertion activity, b) abnormal spontaneous activity (Figure 2), c) MUPs, and d) interference pattern (IP).

   In normal muscle, needle movement elicits a short burst of “insertion activity,” which is due to mechanical stimulation of excitable muscle cell membranes. This is recorded at a gain setting of 50 µV per division (sweep speed 5 – 10 ms/division), which is also used to record spontaneous activity. Absence of insertion activity with appropriately placed needle electrode usually means a complete denervation atrophy of the examined muscle.
The amount of recruitable motor units during voluntary and reflex activation can also be estimated. Normally, MUPs should intermingle to produce an “interference” pattern on the oscilloscope during muscle contraction, and during a strong cough. In addition, the number of continuously active MUPs during relaxation [3], MUP variability as well as MUP recruitment on reflex and voluntary activation can be observed [4].

MUPs (and occasionally encountered end-plate activity) are recordable in normal resting sphincter muscles in a relaxed subject. This is in contrast to limb muscles where relaxation is associated with “electrical silence” by EMG. In addition to continuously firing motor units, new MUPs are recruited voluntarily and reflexly in the sphincters. It has been shown that the two MUP populations differ in their characteristics: reflexly or voluntarily activated “high-threshold MUPs” being larger than continuously active “low-threshold MUPs”. As a consequence, standardised level of activity at which a template based multi-MUP analysis obtains 3-5 MUPs on a single muscle site was suggested [5]. In partially denervated sphincter muscle there is – by definition – a loss of motor units (MUs). This can be estimated during relaxation by counting the number of continuously firing low-threshold MUPs. In patients with cauda equina or conus medullaris lesions, fewer MUPs fire continuously during relaxation [6], probably due to partial axonal loss. The main obstacle to qualified assessment of reduced number of activated MUs and activation of MUs at increased firing rates (as occurs in limb muscles) is a lack of concomitant measurement of level of contraction of the examined muscle (this can be readily assessed when studying limb muscles).

There are two approaches to analysing the bioelectrical activity of motor units: either analysis of individual motor unit potentials (MUPs), or analysis of the overall activity of intermingled MUPs. (This is the so called “interference pattern” – IP. Exploring different sites of the activated muscle with a needle electrode provides “samples” of intermingled motor unit potentials (IP epochs), which can be analysed).

Generally three different techniques of MUP analysis (manual-MUP, single-MUP and multi-MUP) and 1 technique of IP analysis (turn/amplitude – T/A) are available on advanced EMG systems [6].

It is easy to grasp the “motor unit potential analysis”, as it is simply a measurement (by different methods) of the “parameters” of single individual MUPs (ie. its amplitude, duration, number of phases...). The changes in MUP parameters furthermore are “direct” results of understandable physiological changes, and are thus “meaningful” to the interpreter.

The changes in IP parameters are, however, less readily grasped. These are: numbers of turns per second (any peak or trough of the signal where the activity changes by more than 100 µV); amplitude/turn (change in volts between two turns); number of short segments (parts of signal that has “sharp” activity) percent activity (percent of epoch with sharp activity); envelope (peak to trough amplitude exceeded by 1% of peaks/troughs). These parameters relate both to MUP parameters and to the activation level of the muscle. Recorded data are log transformed and linear regression lines are created. Amplitude/turn, and number of turns/second data from normal subjects can be used to create upper and lower boundaries (95 % confidence intervals) for assembly of future data from individual patients. Individual data create a scatter plot (“cloud”) which compares to the normative boundaries (Figure 3). It has been asserted that this approach does not require a standardized muscle contraction, but the shape of the “cloud” is dependent on the strength of muscle contraction. Therefore it has been suggested to standardize the method by measuring pressure exerted by the contracting sphincter [7].

Both the template based multi-MUP analysis of MUP and T/A analysis of IP are fast (5-10 and 2-3 minutes per muscle, respectively), easy to apply, and, technically, represent clinically useful techniques.

i) CNEMG Findings due to denervation and reinervation

After complete denervation, all motor unit activity ceases. In a denervated muscle, complete "electrical silence" is noted in the first days after such an event. The diagnosis of complete denervation is confirmed by the absence of muscle response during electrical stimulation. Because motor axons take days to degenerate after injury, this proof is not available for up to 5-7 days after a denervation injury. However, it is rarely necessary to demonstrate complete denervation in the acute stage because the clinical condition is usually obvious. Denervated muscle fibres become hyperexcitable and start to fire spontaneously giving rise to abnormal spontaneous activity, but these may take up to three weeks to appear. The "insertion activity" becomes prolonged and short biphasic spikes (fibrillation potentials) and biphasic potentials with prominent positive deflections (positive sharp waves) appear (Figure 2). Thus, concentric needle EMG (CNEMG) correlates of denervation are pathologically prolonged insertion activity and pathological spontaneous activity. Completely denervated muscle may be reinnervated by axonal regrowth from the proximal nerve stump with few muscle fibres constituting "nascent" motor units. These are short, bi- and triphasic, soon becoming polyphasic, serrated and with prolonged duration. In partially denervated muscle, collateral reinnervation takes place. Surviving motor axons will sprout and grow out to reinnervate those muscle fibres that have lost their nerve supply. This results in a change in the arrangement of muscle fibres within the unit. Whereas in healthy muscle, it is unusual for two adjacent muscle fibres to be part...
of the same motor unit, following reinnervation, several muscle fibres belonging to the same motor unit come to be adjacent to one another. CNEMG correlates are changes in MUPs (duration, amplitude, number of phases, turns, etc). Early in the process of reinnervation, the newly outgrown motor sprouts are thin. Therefore, they conduct slowly such that the time taken for excitatory impulses to spread through the axonal tree is abnormally prolonged. Moreover, the neuromuscular transmission is unstable due to immaturity of the motor end-plates. The CNEMG correlate is instability of long-duration complex potentials.

In partially denervated muscle, some MUPs remain and mingle eventually with abnormal spontaneous activity. Changes due to collateral reinnervation are reflected by: prolongation of the wave form of the MUP (Figure 3) which may have small, late components ("satellite potentials"). MUPs show "instability" due to insecure transmission in newly formed axon sprouts and end-plates. This "instability of potentials" (meaning both "jitter" and "blocking" of individual components in a complex potential) is not routinely assessed during sphincter EMG. Nonetheless, it can be a helpful parameter, and may be evaluated not only by SFEMG, as originally described [8], but also by CNEMG, if a low frequency cut-off filter of 0.5 (up to 2) kHz is used along with a trigger – delay unit. In skeletal muscle, the diameter of reinnervating axonal sprouts and conduction velocity increase with time, thereby improving synchrony of activation in the reinnervated motor unit. Thus MUP amplitude increases while MUP duration reverts towards normal. However, in degenerative neurological diseases (such as multiple system atrophy), long duration motor units are a prominent feature of anal sphincter reinnervation [9]. It is important to note that in patients with more severe neurogenic lesions, reinnervation may be inefficient resulting in MUP with parameters below confidence limits describing size (area, duration) [10].

The changes in MUP parameters (along with changed number of MUPs and changes in activation frequency of MUPs) will be reflected also in IP parameters.

Abnormalities of parameters evaluated by needle EMG are in principle non-specific, i.e. most abnormalities can occur both in neuropathic or myopathic conditions. It is the overall clinical picture that dictates interpretation of results.

**ii) CNEMG of the External Anal Sphincter**

The external anal sphincter (EAS) is the most practical indicator muscle for sacral myotomes because it is easy to access, has enough muscle bulk for exact EMG analysis, and its examination is not too uncomfortable.

The needle electrode is inserted into the subcutaneous EAS muscle about 1 cm from the anal orifice, to a depth of a 3-6 mm under the non-keratinised epithelium. For the deeper part of the EAS muscle 1-3 cm deep insertions are made at the anal orifice, at an angle of about 30° to the anal canal axis [5]. In most patients only examination of the subcutaneous EAS muscle is necessary. Separate examinations of the left and right EAS muscles are recommended. The needle is inserted into the middle of the anterior and posterior halves of each side ("quadrants") of the EAS muscle. After insertion in two positions on each side the electrode is turned backwards and forwards in a systematic manner. At least 4 sites in each of the subcutaneous and/or the deeper EAS muscle are thus analysed [5, 11].

Use of quantitative MUP and IP analyses of the EAS is further facilitated by the availability of normative values [11] that can be introduced into the EMG systems' software. It has been shown that normative data are not significantly affected by age, gender [11], number of uncomplicated vaginal deliveries [12], mild chronic constipation [12], and the part of EAS muscle (i.e. subcutaneous or deeper) examined [12].

Intramuscular electrode insertion into other perineal muscles and pelvic floor muscles is not standardized and is described in textbooks and primary literature.

**3. Single fibre EMG (SFEMG)**

The SFEMG electrode has similar external proportions to a concentric needle electrode, but with a smaller recording surface. It will pick up activity from within a hemispherical muscle volume 300 µm in diameter, much smaller than the volume of 2-3 mm diameter from which a concentric needle electrode records [2]. Because of the arrangement of muscle fibres in a normal motor unit, a SFEMG needle will record only 1-3 single muscle fibres from the same motor unit.

The SFEMG parameter that reflects motor unit morphology is fibre density, which is defined as the mean number of muscle fibres belonging to an individual motor unit per detection site. To assemble this data, recordings from 20 different intramuscular detection sites are necessary [8].

SFEMG recording needles are very expensive, and disposable needles are not available.

**4. Kinesiological EMG**

Kinesiological EMG is used to assess patterns of individual muscle activity/inactivity during defined manoeuvres (Figure 4), typically during urodynamics.
Figure 3: Consecutive firings of motor unit potential (MUP) and its average (left and right, respectively) as obtained from the external anal sphincter (EAS) muscle of 59-year-old woman by multi-MUP analysis. Note that multi-MUP analysis does not preclude inclusion of late components into MUP duration measurement; this is possible by manual correction of duration cursor (see arrow).
As such, the specific interpretation of electrical activity within a muscle is based on its presence or absence, rather than the type of activity. Technical issues will be dealt here; the relevance for diagnostics will be discussed in the Chapter on dynamic testing.

**Figure 4 :** Kinesiological EMG recording from the urethral sphincter muscle of a healthy 53 years old continent female. Recruitment of motor units on reflex manoeuvres and on a command to contract is shown; regular continuous activity of motor units represents "tonic activity". (Recorded with concentric needle electrode).

When using surface electrodes there are problems related to validity of signal (e.g., artefacts, contamination from other muscles). With intramuscular electrodes, the procedure is more invasive, and there are questions as to whether the whole muscle in large pelvic floor muscles is properly represented by the sampled muscle portions. Intramuscular electrodes should ideally be fine wire electrodes, as they do not dislodge, and no pain is induced with muscle contraction.

The kinesiological sphincter EMG recordings in health show continuous activity of MUPs at rest. It can be recorded in many but not all detection sites of the levator ani muscle. The urethral and anal sphincter as well as the other pelvic floor musculature (e.g. pubococcygeal) can be voluntarily activated typically for less than 1 minute [13]. Timely activation of the levator ani muscle has been demonstrated to be an important aspect of stable bladder neck support; its activation precedes activity of other muscles in the cough reflex [14].

Sphincter activity during voiding is characterised by the cessation of all EMG activity prior to detrusor contraction. Pathologic incoordination of the detrusor and sphincter is called detrusor sphincter dyssynergia.

5. **CLINICAL APPLICATION OF EMG**

**i) Neurogenic Conditions**

Trauma, surgery, and neurological disease have all been implicated in denervation of pelvic floor and perineal muscles and pelvic organs.

Following a cauda equina or a conus medullaris lesion, the MUP of pelvic floor and perineal muscles are prolonged and polyphasic, of increased amplitude, area, number of turns [6]. Surgical dissections can also affect the innervation of the sphincter and lead to loss of motor units and reinnervation of those surviving [15]. After pelvic trauma, gross changes of denervation and reinnervation may be detected in pelvic floor muscles. The bulbocavernous muscle is particularly useful in suspected recent minor partial denervation as it lacks on-going activity of low-threshold MU during relaxation. (In women the muscle is thin).

Neuropathic changes can also be recorded in sphincter muscles of patients with multiple system atrophy (MSA) [16]. MSA is a progressive neurodegenerative disease, which can be mistaken for Parkinson’s disease (PD). Urinary incontinence and erectile dysfunction occur, often some years before the onset of obvious neurological features [17]. Sphincter EMG has been used to distinguish MSA from Parkinson’s disease. EMG is probably not helpful to distinguish MSA from the later stages of Parkinson’s disease and from progressive supranuclear palsy. Extensive discussion on the subject can be found elsewhere [18].

In patients with acute idiopathic autonomic neuropathy and lower urinary tract (LUT) dysfunction the EMG of external sphincter muscles was reported as normal [19].

**ii) “Changes in Primary Muscle Disease**

In skeletal muscle, the “typical” features of a myopathy are small, low amplitude polyphasic units recruited at mild effort. There are few reports of pelvic floor muscle EMG in generalised myopathy. In a nulliparous woman with limb-girdle muscular dystrophy, histology revealed involvement of pelvic floor muscles, but concentric needle EMG of the urethral sphincter was normal [20]. Myopathic EMG changes were observed in the puborectalis and the EAS in patients with myotonic dystrophy (21), but not in another group of patients with myopathy [22].

**iii) Stress Incontinence**

Pelvic floor muscle denervation has been implicated in the pathophysiology of USI [23]. EMG techniques have been used to identify sphincter injury after childbirth and to evaluate women with USI. Stress incontinence and genitourinary prolapse were associated with partial denervation of the pelvic floor [24]. The changes were most marked in women who were incontinent after delivery, who had a prolonged second stage of labour, and had given birth to heavier babies.

Myogenic histological changes in pelvic floor muscles after vaginal delivery were also reported [25], with some EMG support by another group [26]. Myopathic EMG changes (i.e. short, small MUPs) may, however, be a consequence of deficient reinnervation [27]. There were claims urethral sphincter EMG can assist in selecting the type of surgery for patients with intrinsic sphincter deficiency [25].
Although CNEMG of the urethral sphincter seems the logical choice in patients with urinary incontinence of possibly neurogenic origin, only a small amount of pathological muscle tissue remains in many incontinent parous women which makes EMG of the muscle impractical [15]. CNEMG findings generally will not affect therapeutic considerations [28].

iv) "Idiopathic" Faecal Incontinence

"Idiopathic" faecal incontinence refers to patients in whom this symptom is not attributable to an underlying disorder, but has been often implied that it is a neurogenic condition. Vaginal delivery is proven to cause structural sphincter defects; it may cause outright sphincter denervation in rare cases, but its more widespread implication in causing "idiopathic" incontinence is controversial.

CNEMG may be helpful in selected patients with faecal incontinence if a specific neurogenic condition (e.g., trauma or disease affecting the conus, sacral roots, sacral plexus or pudendal nerves) is suspected on clinical grounds.

v) Idiopathic Urinary Retention in Women

In young women with urinary retention (or obstructed voiding) complex repetitive discharges in profuse amounts in the external urethral sphincter against a background of firing motor units have been described, suggesting that these findings are of pathogenic and diagnostic significance. The external urethral sphincter was reported to be hypertrophic. A percentage of these women were hirsute and had polycystic ovaries [29, 30].

Repetitive discharges are, however, prone to develop in chronically partially denervated sphincters, and are present even in a proportion of asymptomatic women [31]. The distinguishing feature of the spontaneous EMG activity defining the particular pathology in women with retention seems to be its abundance, but the issue remains in dispute.

vi) EMG in Urodynamic and Functional Anorectal Studies

In health, voiding is characterised by cessation of motor unit firing in the urethral sphincter prior to detrusor contraction, as can be demonstrated by recording of “kinesiological EMG”. Bladder-sphincter coordination is impaired with lesions between the lower sacral segments and the upper pons. Consequently, sphincter activity is not inhibited, and often increases before detrusor contraction (i.e., 'detrusor-sphincter dyssynergia'). On the basis of the temporal relationship between urethral sphincter and detrusor contractions, three types of dyssynergia have been described [32].

There are other clinical situations that mimic detrusor sphincter dyssynergia. Sphincter contraction or at least failure of relaxation during involuntary detrusor contractions can be seen in patients with Parkinson's disease. The pelvic floor muscle contractions of the so-called non-neurogenic voiding dyssynergia may be a learned abnormal behaviour [33], and are a feature of dysfunctional voiding [30].

The pubococcygeus in the healthy female reveals similar activity patterns to the urethral and anal sphincters at most detection sites: continuous activity at rest, often some increase of activity during bladder filling, and reflex increases in activity during any activation manoeuvre performed by the subject such as talking, deep breathing, coughing. The pubococcygeus relaxes during voiding; the muscles on either side act in unison [13]. In stress-incontinent patients, the patterns of activation and the co-ordination between the two sides can be lost [34]. A delay in muscle activation on coughing has also been demonstrated, as compared to continent women [14]. Little is known about the complex activity patterns of different pelvic floor muscles (the urethral sphincter, urethrovaginal sphincter, anal sphincter muscle, different parts of the levator ani) during different manoeuvres. It is generally assumed that they all act in a co-ordinated fashion functionally as one muscle. However there are demonstrable differences between the intra- and peri-urethral sphincter in healthy females [35] and in activation of the levator ani and the urethral sphincter [36]. Co-ordinated behaviour is frequently lost in abnormal conditions.

Kinesiological needle EMG analysis of the urethra with the patient at rest and coughing may predict the outcome after certain types of incontinence surgery [37].

Current concepts suggest that defecation requires increased rectal pressure co-ordinated with relaxation of the anal sphincters and pelvic floor muscles. Pelvic floor relaxation allows opening of the anorectal angle and perineal descent, facilitating faecal expulsion. During defecation puborectalis activity is as a rule inhibited, but was unchanged in 9 % and increased in 25% of healthy subjects [38]. Thus, while "paradoxical" puborectalis contraction during defecation is used to diagnose pelvic floor dyssynergia in patients with typical symptoms, this finding may be a variation of the normal.

d) Pudendal nerve conduction tests

Measurement of motor conduction velocity is routinely used to evaluate limb motor nerves, distinguishing between a demyelinating and axonal neuropathy. To make the measurement requires access to the nerve at two well-separated points and measurement of the distance between them, a requirement that cannot be met in the pelvis. Another way to evaluate peripheral motor nerve function is the measurement of the) motor latency of a muscle response, requiring only a single
stimulation site. The muscle response is the compound muscle action potential (CMAP) or M-wave. Because in limb nerves the site of stimulation to obtain only the motor latency (without measuring the actual conduction velocity) is as a rule placed distally on the nerve, it is also called the (distal or terminal) latency. For the pudendal nerve the site of stimulation may be more or less “distally”, but the term distal or terminal has – in accordance to general clinical neurophysiology – become generally used. Distal motor latency can be measured by recording with a concentric needle electrode from the bulbocavernosus, the EAS and the urethral sphincter muscles in response to bipolar surface stimulation placed in the perianal/perineal region, or with selective needle stimulation of the pudendal nerve (branches) in the perineum. The most widely employed technique to obtain pudendal nerve terminal motor latency (PNTML) relies on stimulation with a special surface electrode assembly fixed on a gloved index finger, known as the St Mark’s stimulator [39]. It consists of a bipolar stimulating electrode on the tip of the gloved finger with the recording electrode pair placed proximally on the base of the finger. The finger is inserted into the rectum or vagina and stimulation is applied close to the ischial spine. If a catheter-mounted electrode is used for recording, EMG responses from the striated muscle of the urethral sphincter can be obtained. Experts differ in their estimation of validity of this test. A prospective evaluation of anorectal physiologic tests in 90 patients with faecal incontinence did not find that PNTML results changed treatment decisions [40]. Indeed, the American Gastroenterological Association statement indicated that “PNTML cannot be recommended for evaluation of patients with faecal incontinence” [41].

c) Anterior sacral root (cauda equina) stimulation

Anterior root stimulation has been used to study conduction of the sacral nerve roots. Electrical stimulation with needle electrodes at vertebral laminae Th12-L1 elicit M-waves in the bulbocavernousus and EAS muscle [42].

Transcutaneous stimulation of deeply situated nervous tissue became possible with development of special electrical and magnetic stimulators. When applied over the spine, these stimulators activate the roots as they exit the vertebral canal. Needle EMG rather than non-selective surface electrodes should be used to record pelvic floor and particularly sphincter responses to electrical or magnetic stimulation of the cauda equina. These stimuli non-selectively depolarise underlying neural structures, thereby activating several muscles innervated by lumbosacral segments [43].

Invasive percutaneous stimulation of individual roots in sacral foramina is used to identify patients with lower urinary and anorectal dysfunction who are likely to benefit from long-term stimulation, e.g. with the Interstim (Medtronic, Inc., Minneapolis, USA). Electrical stimulation of nerve roots at the level of the appropriate sacral foramina results in observable muscle contraction in the foot and perineum. These responses can be identified as MEP or reflex responses on the basis of their latency.

In conclusion, demonstrating the presence of a perineal MEP on stimulation over lumbosacral spine may occasionally be helpful in patients without voluntarily activated muscles. It also identifies the particular nerve root before introducing therapeutic electrical stimulation. However, the clinical value of the test has yet to be established and there are no sensitivity and specificity data on test results in individual patients.

d) Motor evoked potentials

Using magnetic or electric stimulation, it is possible to depolarise the motor cortex and record a response from the pelvic floor. Magnetic cortical stimulation is better tolerated than electrical stimulation, which has been abandoned in awake subjects, but may be useful for intraoperative monitoring.

By performing the stimulation at two different sites (brain and spinal roots), it is possible to record three different conduction times: a total conduction time, a peripheral conduction time, and a central conduction time (Figure 5). The total conduction time corresponds to the transit time from brain to target muscle. The peripheral conduction time is the transit time from sacral roots to the muscle. The central conduction time is obtained by subtracting the peripheral conduction time from the total conduction time. The total conduction time can be measured both at rest and during a facilitation procedure. MEPs from the EAS, the urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle have been reported, but normative values have only been obtained (for transcranial magnetic stimulation) for the urethral sphincter and the puborectal muscle in adult women [44]. The necessity to use concentric needle EMG for recording has been reconfirmed [45]. Substantially longer central conduction times have been found in patients with multiple sclerosis and spinal cord lesions as compared to healthy controls [46]. However all patients in this study had clinically recognisable cord disease.

Conceptually, MEP may help to differentiate between involvement of motor and sensory pathways. However, the clinical utility of these measurements is not established. MEP have opened an avenue of research on excitability of motor cortex. It has been demonstrated that in comparison to the motor area for hand muscles the anal sphincter motor cortex has less intracortical inhibition [47].

2. SENSORY SYSTEM TESTS

There are several methods of sensory testing for the perineum, the genitourinary and anorectal tract. Clinical
testing includes perineal and external genital skin sensation for light touch and pinprick, and sensation of bladder filling during cystometry. Anorectal sensory testing can be clinically assessed through rating of applied stimuli. More objective sensory testing can be performed with quantitative sensory testing (QST), which assesses sensory perception. For evaluation of the integrity of sensory pathways sensory neurography, and somatosensory evoked potentials (SEP) can be used.

**a) Sensory Measurements During Cystometry**

During routine cystometry bladder sensation is assessed by recording first sensation of bladder filling, first desire to void and strong desire to void.

Bladder and urethral sensory thresholds have also been measured using electrical stimulation [48], and mechanical traction on the bladder trigone [49]. There is no established clinical use for any of these tests other than simple reporting of sensation during cystometry.

**b) Assessment of Anorectal Sensation**

Rectal sensation is assessed by progressively distending a balloon manually or by a barostat while measuring thresholds for first perception, desire to defecate, and severe discomfort. The intensity of perception during rectal distension can be recorded by a visual analogue scale during phasic distensions of graded intensity [50]. The rate and pattern of distension affect rectal perception and internal sphincter relaxation [51].

Anal sensation can be assessed by determining the perception threshold to an electrical stimulus or temperature change in the anal canal. Electrical testing does not activate mucosal receptors. Anal sensitivity to temperature change has been reported reduced in faecal incontinence [52].

**c) Quantitative Sensory Testing**

Quantitative sensory testing (QST) of the urogenital system should provide more objective and reproducible data than routine clinical testing. QST sensory modalities applied to the evaluation of urogenital function include vibration [53], temperature [54], and electrical current [55]. There is no commonly accepted, detailed, standardised test, and the specificity and sensitivity of the tests are not known. The relationship of cutaneous quantitative sensory tests to bladder and urethral sensation and function is unknown. The physiological, psychophysiological and methodological issues and controversies will not be addressed in this chapter.

**d) Sensory Neurography**

Nerve conduction velocities of the dorsal nerve of the penis can be calculated by placing a pair of stimulating electrodes across the glans and a pair of recording electrodes across the base of penis. A nerve action potential can be recorded with amplitude of about 10 \( \mu V \). It can also be recorded by stimulating trans-rectally or transperineally. There is no known association between penile sensory neuropathy and bladder/sphincter dysfunction.

A few studies have recorded activity in sacral roots during electrical stimulation. Intraoperatively, when the sacral roots are exposed, compound sensory action potentials on stimulation of dorsal penile and clitoral nerve may be recorded directly [56]. This helps to preserve roots mediating perineal sensation in spastic children undergoing dorsal rhizotomy, and reduce the incidence of postoperative voiding dysfunction. These tests are limited to their very specific intraoperative indications.

**e) Somatosensory Evoked Potentials (SEP)**

Somatosensory evoked potentials are electric waveforms of biologic origin elicited by stimulation of a sensory nerve (or a sensory innervated skin area
– dermatome). The most commonly performed tests in the urogenitoanal region are pudendal somatosensory evoked potentials (SEP), which assesses conduction in large fibre pathways between the site of nerve stimulation and the parietal sensory cortex. Potentials can also be measured at the spinal level (spinal SEP). Visceral (thin) fibre pathways are assessed by recording SEPs while stimulating the proximal urethra and bladder, although this is technically not depolarization of nerves, but a mesh of afferents.

1. Pudendal Somatosensory Evoked Potentials
   i) Cerebral Pudendal SEP

On electrical stimulation of the dorsal penile/clitoral or perineal nerve, a cerebral SEP can be recorded. (Figure 6) This SEP is as a rule of highest amplitude at the central recording site (Cz - 2 cm : Fz of the International 10-20 EEG System) and is highly reproducible. The first positive peak at about 40 ms (called P40) is usually clearly defined in healthy subjects using a stimulus 2-4 times stronger than the sensory threshold [57]. The presence and amplitude of subsequent negative and positive waves are quite variable between subjects. Classically described pudendal SEP techniques stimulate both dorsal penile/clitoral nerves, thus reducing the sensitivity of the test. However, techniques of pudendal SEP that isolate each dorsal penile/clitoral nerve may be more sensitive for identifying pathology [58].

Pudendal SEPs have been advocated in patients with neurogenic bladder dysfunction, e.g. in multiple sclerosis [59]. However, even in patients with multiple sclerosis and bladder symptoms, the tibial cerebral SEP was more often abnormal than the pudendal SEP. The combination of an abnormal pudendal SEP with a normal tibial SEP suggests isolated conus involvement [60]. The pudendal SEP was less useful than neurological examination for identifying neurological disease in patients with urogenital symptoms [61]. Following spinal cord injury, tibial and pudendal SEPs may be of some value for predicting recovery in bladder control [62]. Cerebral SEP during penile/clitoral stimulation may be useful for intraoperative monitoring. Pudendal SEP were used to study the mechanism of sacral neuromodulation [63].

3. Sacral Reflexes
   a) Sacral Reflex on Electrical Stimulation

Electrical stimulation of the dorsal penile or clitoral nerve elicits (somato-somatic) sacral reflexes in perineal muscles with a typical latency approx. 33 ms, traditionally called the bulbocavernosus reflex (Figure 6). Stimulation of the perianal skin, bladder neck or proximal urethra elicits sacral reflexes with latencies above 50 ms. This latency is longer compared to responses conveyed by the pudendal nerve, suggesting that the afferent limb for these responses involves visceral afferent fibres accompanying the pelvic nerves, which are thinly myelinated and have a slower conduction velocity than the thicker pudendal afferents. With visceral denervation (e.g. following radical hysterectomy) the viscerosomatic reflexes (from both bladder and urethral stimulation) may be lost while the bulbocavernosus (penilo-clitorocavernosus) reflex is preserved. Loss of bladder-urethral reflex with preservation of bladder-anal reflex has been described with urethral afferent injury after recurrent urethral surgeries [64].

Figure 6: SEPs (traces on the left) and sacral reflexes (traces on the right) in a healthy woman. Cerebral SEPs are recorded from Cz - 2 cm; sacral reflexes from the anal sphincter. The dorsal clitoral nerve is being stimulated with rectangular electrical pulses at 2 Hz. Stimulation and recording is performed with surface electrodes. The cerebral SEP and sacral reflex are recorded simultaneously. In the upper row the stimulation is just above sensory threshold, in the middle row the stimulation is 1.5, and in the lower row at 2-times sensory threshold (pulse duration 0.2 ms; two consecutive averages of 128 responses are superimposed).
The longer latency anal reflex (the contraction of the EAS on stimulation of the perianal region) is quite variable thus limiting its usefulness as a diagnostic tool.

On perianal stimulation, a short latency response can also be recorded, as a result of depolarisation of motor branches to the EAS, possibly involving antidromic travelling of the depolarisation, with "returning" of the depolarisation orthodromically to the sphincter at a branching point of the motor axon.

EMG recording of the sacral reflex has been shown to be more reliable than the clinically assessed response (e.g. observing and palpating the contraction) in males and particularly in females [65]. In men with cauda equina lesions penilo-cavernous reflex could not be elicited in 64%, 47% and 47% of patients on single electrical, double electrical, and mechanical stimulation, respectively. Measurement of the reflex latency increased the sensitivity to record abnormalities for 17%, 36%, and 34%, respectively. Furthermore, it has been shown that sacral reflex measurement increase sensitivity of quantitative EMG of the EAS muscles from 73% to 81-83% using the different stimulation techniques mentioned [66].

Sacral reflex testing has been studied extensively and is used in many laboratories in everyday practice to demonstrate objectively the integrity of the S2-S4 reflex arc. The sacral reflex evoked on dorsal penile or clitoral nerve stimulation (the bulbocavernosus or penilo-clitoro-cavernosus reflex) was shown to be a complex response, often forming two components. The first component with a typical latency of about 33 ms, is the response that has been most often called the bulbocavernous reflex. It is stable, does not habituate, and has other attributes of an oligosynaptic reflex response [67]. The second component has latency similar to the sacral reflexes evoked by stimulation perianally or from the proximal urethra, and is not always demonstrable as a discreet response. In those subjects in whom the first reflex component is difficult to elicit, stimulation strength should be increased, but preferably double electrical stimuli should be used. A complete reflex arc lesion should not be inferred absence of a response if only single pulse is used for stimulation.

During voiding sacral reflexes are un-elicitable but in presence of spinal cord lesions such as myelodysplasia this normal suppression is lost.

Sacral reflex responses recorded with needle or wire electrodes can be analysed separately for each side from the EAS or bulbocavernous muscle. Using unilateral dorsal penile nerve blocks, the existence of two unilateral BCR arcs has been demonstrated. Thus by detection from the left and right bulbocavernosus (and also the EAS) muscles separate testing of right and left reflex arcs can be performed. Some authors reported that the sensitivity of the test can be increased by use of the inter-side latency difference (normative limits: < 3 ms), but this finding could not be confirmed by others (normative limits: < 7.2 ms) [68]. In cases of unilateral (sacral plexopathy, pudendal neuropathy) or asymmetrical lesions (cauda equina), a healthy reflex arc may obscure a pathological one on clinical elicitation, but not on neurophysiologic measurements of the sacral reflexes.

As described above, penilo-cavernosus reflexes were absent in 47-64%, and delayed in additional 17-19% of patients with conus/cauda lesions. Of these patients 47% were incontinent for urine and 47% for faeces. However, a reflex with a normal latency does not exclude the possibility of an axonal lesion in its reflex arc, as demonstrated by pathologic quantitative EMG of the EAS in 79-86% of patients with conus/cauda lesions [66]. Furthermore, much delayed sacral reflex responses are compatible with normal bladder and sexual function as found in patients with hereditary motor and sensory demyelinating neuropathy.

Sacral reflex recording is suggested as a complementary test to CNEMG examination of pelvic floor muscles in patients with suspected peripheral nervous lesions [4]. In addition to latency, a number of other parameters can also be measured using electrical, but not mechanical stimulation.

These are the sensory threshold (i.e., the stimulus strength (mA) at which subjects feels stimulation), reflex threshold (i.e., the stimulus strength (mA) at which the reproducible penilo/clitoro-cavernosus reflex appears on the screen), and stimulation strength (i.e., the stimulation intensity (mA) at which the response latency does not shorten and amplitude does not increase in spite of increasing the stimulus strength). Although for men normative data for these parameters is available (68), their utility in clinical situation remains unclear.

Continuous intraoperative recording of sacral reflex responses on penis/clitoris stimulation is feasible if double pulses or a train of stimuli are used [69].

b) Sacral Reflex on Mechanical Stimulation

Mechanical stimulation has been used to elicite BCR in both sexes and found to be a robust technique. Either a standard reflex hammer or a customised electromechanical hammer can be used. Such stimulation is painless and can be used in children. The latency of the BCR elicited mechanically is comparable to the electrically elicited reflex in the same patients, but depends on the electromechanical device used.

4. AUTONOMIC FUNCTION TESTS

Most uro-neurophysiological methods discussed so far assess myelinated fibres, but not the autonomic nervous system, especially the parasympathetic component, which is most relevant for pelvic organ functions. Methods for evaluating the autonomic nerves
innervating the pelvic viscera are not available. Cystometry indirectly evaluates the parasympathetic innervation to the bladder. However, from a clinical neurophysiological point of view direct electrophysiological testing would be desirable.

a) Tests in Generalised Autonomic Neuropathy

Cardiovascular autonomic function tests are useful for identifying generalised autonomic dysfunction in patients with bladder or gastrointestinal motility disturbances.

In cases when a general involvement of thin fibres is expected, an indirect way to examine autonomic fibres is to assess thin sensory fibre function. Thin visceral sensory fibres are tested by stimulating the proximal urethra or bladder, and by recording sacral reflex responses or cerebral SEP.

b) Smooth Muscle Electromyography

Technical problems have so far limited smooth muscle electromyography of the detrusor muscle, and of genital smooth muscle. There is no evidence to prove the clinical utility of these tests in the evaluation of urinary tract function.

c) Sympathetic Skin Response (SSR)

The sympathetic nervous system mediates sweat gland activity in the skin. Changes in sweat gland activity lead to changes in skin resistance. On noxious stimulation (such as a sudden noise, electrical pulse, etc.) a potential shift can be recorded with surface electrodes from the skin of the palms and the soles, and has been reported to be a useful parameter in assessment of neuropathy involving non-myelinated nerve fibres. The response, known as the SSR, can also be recorded from perineal skin and the penis.

The SSR is a reflex, which consists of myelinated sensory fibres, a complex central integrative mechanism and a sympathetic efferent limb with postganglionic nonmyelinated C fibres. SSR is the only electrophysiological method directly testing sympathetic fibres. Limited literature exists regarding the relationship between SSR results and bladder dysfunction. A correlation has been shown between the absence of the SSR response in the foot and bladder neck dyssynergia following spinal cord injury [62]. Recording from the perineal assesses sympathetic nerve function within the thoracolumbar cord [70].

Only complete absence of response can be regarded as abnormal. Its utility in evaluating bladder and urethral dysfunction is not established.

Evidence-based medicine is founded on the assessment of evidence for and against the efficacy of particular types of therapeutic intervention. Clinical neurophysiology testing should thus demonstrate evidence that testing improves outcome (through treatment choice and patient selection), which would provide a strong basis for its use. However, testing and therapeutic intervention are different concepts, and neurophysiological testing has another important objective, which is not applicable to interventions and lies outside the scope of evidence-based medicine. It is to generate knowledge about the situation to be treated in a given patient, so that the practitioner can formulate rational treatment options based on knowledge rather than do so blindfold; that is, he or she can practice "knowledge-based medicine".

To judge the importance of this second objective different criteria are needed. Particularly in the referral setting, the physician is confronted with complicated cases in whom the underlying pathophysiology is quite uncertain, and what is required is to identify all the factors that may be contributing. Neurophysiology is helpful in assessment of neurogenic dysfunction because it contributes to "knowledge-based medicine", whether or not there is narrowly-defined "evidence" that it improves outcomes.

Of course, it remains true that we should seek evidence of the conventional kind for and against testing. Any test should be subjected to three questions:

1. Does the test have good technical performance?
2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

Clinical diagnosis requires that measures obtained in individual patients be compared to population norms with the intent of determining whether they are "normal" or "abnormal". Data can be classified as "abnormal" only with the understanding that they are compared to a sample from the normal population. Predictive statements are made possible by the use of tolerance limits. For most clinical neurophysiological tests, one-tailed tolerance limits are recommended. For any given limit of normality, there is a certain probability
of falsely interpreting values (obtaining false-positives or false-negatives). Further confounding these issues is the practice of applying multiple criteria of abnormality. But ultimately, the adequacy of any given normal limit in discriminating between normal and abnormal must be supported by appropriate clinical or clinico-pathological correlations; for uroneurophysiological techniques, such data are scarce.

1. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN EVALUATION OF INDIVIDUAL PATIENTS

Whenever pathophysiology is uncertain or unpredictable, and especially if irreversible treatment is necessary or contemplated, it seems logical to gather quantitative knowledge of the dysfunction in order to make a rational treatment choice. In most patient groups with neurogenic incontinence, the pathophysiology is unpredictable and comprehensive urodynamic evaluation is essential in order to practice knowledge-based medicine. In selected patients from these groups, clinical neurophysiological testing will clarify issues related to the neural control of lower urinary tract, relevant for understanding pathophysiology. Most patients, however, will not require a precise definition of the neurological lesion.

As is generally true for electrophysiological tests, uroneurophysiological examinations are particularly useful for substantiating the clinical diagnosis of a peripheral nerve lesion. The potential usefulness of testing in an individual patient needs to be analysed in the overall clinical setting. The indications for testing are guided primarily by expert opinion, not on definitely established criteria derived from controlled studies.

In the incontinent patient without other signs or symptoms of a neurological condition, neurophysiological testing is generally unnecessary. In patients with stress/urge, or mixed urinary incontinence electrophysiological testing is as a rule non-contributory [28].

2. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN RESEARCH

Uro-neurophysiological techniques have been most often applied in research, for instance to elucidate the innervation of pelvic floor muscles; to study the physiology of contraction of sphincter muscle, to describe activation patterns of pelvic floor muscles. Suggestions of increased efficacy of sacral neurostimulation with the use of neurophysiologic tests have been made [71]. As understanding pathophysiology and neural control is essential in the application of more sophisticated therapeutic methods, such as electrical stimulation techniques, there seems to be a continuing place for clinical neurophysiology in research on neurogenic urinary and anorectal dysfunction and their therapy.

IV. RECOMMENDATIONS

1. RECOMMENDATION FOR CLINICAL NEUROPHYSIOLOGICAL TESTING

The information gained by clinical examination and urodynamic testing may be enhanced by uroneurophysiological tests in selected patient groups with suspected neurogenic urinary incontinence with lesions within the nervous reflex arcs of sacral segments 2 - 5. Concentric needle EMG to diagnose denervation and reinervation of pelvic floor and perineal muscles, and sacral reflex testing to assess the continuity of the sacral reflex arc, are the recommended tests.

Level of evidence: 2b
Level of recommendation: B

2. RECOMMENDATION FOR TECHNICAL STANDARDS

3. RESEARCH RECOMMENDATIONS

Clinical neurophysiological methods should be further used to better define the neural control in lower urinary tract function, demonstrating both the nervous system's "hardware" (integrity of anatomy) as well as "software" (level of activity, excitation thresholds) for co-ordinated urinary storage and voiding, in physiological and in pathological conditions. In particular, there is the opportunity to better define neurophysiological changes induced by therapeutic electrostimulation.

There is the challenge to develop tests to assess directly the sacral parasympathetic system.
REFERENCES


Committee 7 B

Imaging and Other Investigations

Chairman
A. TUBARO (Italy)

Members
W. ARTIBANI (Italy),
C. BARTRAM (U.K),
J. DELANCEY (USA),
V. KHULLAR (U.K),
M. VIERHOUT (The Netherlands)

Consultants
M. DE GENNARO (Italy),
K. KLUIVERS (The Netherlands)
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>three dimensional</td>
</tr>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>ACG</td>
<td>anterior cingulate gyrus</td>
</tr>
<tr>
<td>ADH</td>
<td>anti diuretic hormone</td>
</tr>
<tr>
<td>ARJ</td>
<td>anorectal junction</td>
</tr>
<tr>
<td>ATT</td>
<td>alpha-1 antitrypsin</td>
</tr>
<tr>
<td>BBI</td>
<td>bladder base insufficiency</td>
</tr>
<tr>
<td>BCR</td>
<td>bulbocavernous reflex</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BOO</td>
<td>bladder outlet obstruction</td>
</tr>
<tr>
<td>BWT</td>
<td>bladder wall thickness</td>
</tr>
<tr>
<td>CCC</td>
<td>concordance correlation coefficient</td>
</tr>
<tr>
<td>CMAP</td>
<td>compound muscle action potential</td>
</tr>
<tr>
<td>CMCT</td>
<td>central motor conduction time</td>
</tr>
<tr>
<td>CNEMG</td>
<td>concentric needle electromyography</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DO</td>
<td>detrusor overactivity</td>
</tr>
<tr>
<td>EAS</td>
<td>external anal sphincter</td>
</tr>
<tr>
<td>EAUS</td>
<td>endoanal ultrasound ultrasound sonography</td>
</tr>
<tr>
<td>ED</td>
<td>erectile dysfunction</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>FOV</td>
<td>field of view</td>
</tr>
<tr>
<td>HASTE</td>
<td>single-shot turbo spin echo</td>
</tr>
<tr>
<td>HOXA</td>
<td>Homebox A</td>
</tr>
<tr>
<td>IAS</td>
<td>internal anal sphincter</td>
</tr>
<tr>
<td>ICTP</td>
<td>carboxy-terminal telopeptide of type I collagen</td>
</tr>
<tr>
<td>IIQ-7</td>
<td>incontinence impact questionnaire</td>
</tr>
<tr>
<td>IP</td>
<td>interference pattern</td>
</tr>
<tr>
<td>ISD</td>
<td>intrinsic sphincter deficiency</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urography</td>
</tr>
<tr>
<td>LLM</td>
<td>longitudinal layer muscle</td>
</tr>
<tr>
<td>LMR</td>
<td>longitudinal muscle of the rectum</td>
</tr>
<tr>
<td>LUT</td>
<td>lower urinary tract</td>
</tr>
<tr>
<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MCC</td>
<td>maximum cystometric capacity</td>
</tr>
<tr>
<td>MEP</td>
<td>motor evoked potential</td>
</tr>
<tr>
<td>MMPS</td>
<td>matrix metalloproteinases</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MSA</td>
<td>multiple system atrophy</td>
</tr>
<tr>
<td>MU</td>
<td>motor unit</td>
</tr>
<tr>
<td>MUP</td>
<td>motor unit potential</td>
</tr>
<tr>
<td>PA</td>
<td>puboanalis</td>
</tr>
<tr>
<td>PAG</td>
<td>periaqueductal grey</td>
</tr>
<tr>
<td>PCL</td>
<td>pubococygeal line</td>
</tr>
<tr>
<td>PDI</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFMT</td>
<td>pelvic floor muscle training</td>
</tr>
<tr>
<td>PGPI</td>
<td>patient global perception of improvement</td>
</tr>
<tr>
<td>PICP</td>
<td>propeptide of type I procollagen</td>
</tr>
<tr>
<td>PIINP</td>
<td>amino-terminal propeptide of procollagen III</td>
</tr>
<tr>
<td>PIVS</td>
<td>posterior intravaginal singlusty</td>
</tr>
<tr>
<td>PMC</td>
<td>pontine micturition centre</td>
</tr>
<tr>
<td>POP-Q</td>
<td>pelvic organ prolapse quantification</td>
</tr>
<tr>
<td>PNTML</td>
<td>pudendal nerve terminal motor latency</td>
</tr>
<tr>
<td>PUV</td>
<td>posterior urethrovesical (angle)</td>
</tr>
<tr>
<td>PVR</td>
<td>post-void residual</td>
</tr>
<tr>
<td>QST</td>
<td>quantitative sensory testing</td>
</tr>
<tr>
<td>SCP</td>
<td>sacrocolpopexy</td>
</tr>
<tr>
<td>SEP</td>
<td>somatosensory evoked potential</td>
</tr>
<tr>
<td>SERMS</td>
<td>selective estrogen-receptor modulators</td>
</tr>
<tr>
<td>SFEMG</td>
<td>single fibre electromyography</td>
</tr>
<tr>
<td>SII</td>
<td>symptom impact index</td>
</tr>
<tr>
<td>SMA</td>
<td>supplementary motor area</td>
</tr>
<tr>
<td>SO</td>
<td>symphysis orifice (distance)</td>
</tr>
<tr>
<td>SSF</td>
<td>sacrospinous fixation</td>
</tr>
<tr>
<td>SSFSE</td>
<td>single-shot fast spin echo</td>
</tr>
<tr>
<td>SSII</td>
<td>symptom severity index</td>
</tr>
<tr>
<td>SSR</td>
<td>sympathetic skin responses</td>
</tr>
<tr>
<td>STARD</td>
<td>Standards for Reporting of Diagnostic Accuracy</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>T/A</td>
<td>turns/amplitude</td>
</tr>
<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>TGF-ß</td>
<td>transforming growth factor-ß</td>
</tr>
<tr>
<td>TIMP</td>
<td>tissue inhibitor of metalloproteinases</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>UAR</td>
<td>urethral axis at rest</td>
</tr>
<tr>
<td>UAS</td>
<td>urethral axis during straining</td>
</tr>
<tr>
<td>UEBW</td>
<td>ultrasound estimated bladder weight</td>
</tr>
<tr>
<td>UP</td>
<td>urethropelvic (angle)</td>
</tr>
<tr>
<td>UPP</td>
<td>urethral pressure profile</td>
</tr>
<tr>
<td>USI</td>
<td>urodynamic stress incontinence</td>
</tr>
<tr>
<td>USS</td>
<td>ultrasonography</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>VCCU</td>
<td>voiding colpo cystourethrography</td>
</tr>
<tr>
<td>VUCG</td>
<td>voiding urethrocystogram</td>
</tr>
<tr>
<td>WA</td>
<td>white American</td>
</tr>
</tbody>
</table>
A. INTRODUCTION

The Committee reviewed the evidence provided in the 2005 edition and updated the chapter with data from the peer-review literature published in the last 4 years. The chapter covers different issues including: imaging, neurophysiological testing, and other investigations (laboratory tests, tissue analysis and Pad test) with reference to paediatric and adult population, male and female subjects, neurogenic and non-neurogenic patients.

Imaging: the Medline database was searched using the following keywords: imaging, urinary incontinence, continence, anal incontinence and faecal incontinence; the search has been limited to period from 2004 to 2008. Neurophysiology: clinical neurophysiology, conventional urodynamics, neuourology, urinary dysfunction. Other investigations: keywords including urinary incontinence, continence, pad test, urinalysis, urine culture, tissue analysis were used. Members of the committee were allocated the different topics of the chapter based on their specific expertise in the field. All committee members reviewed the chapter draft, recommendations were collegially discussed on at the occasion of the ICI meeting in Paris (July 2008), the final draft was then edited first by the Committee Chair and then by the book Editors. As far as imaging is concerned, the chapter is structure based on anatomical issues: upper, lower urinary tract, bowel, central nervous system, and imaging technique: X-rays, ultrasonography, Magnetic Resonance Imaging. Imaging techniques were analysed taking into considerations the technique and its standardisation, intraobserver and interobserver variability, diagnostic accuracy, cost/benefit ratio and clinical benefit.

Levels of evidence and grades of recommendations were provided according to the guidelines of the ICUD summarised elsewhere in this book. Areas of future research were identified. The application of the ICUD guidelines to diagnostic issues such as those dealt with in this chapter is not without problems as they were developed for the evaluation of formal clinical trials.

Proper design, implementation and reporting of studies on diagnostic accuracy are essential to improve their quality and make evaluation of research easier. Most of the issues discussed in the present chapter fall within the remits of diagnostic tests and the evaluation of diagnostic accuracy as regulated by the Standards for Reporting of Diagnostic Accuracy (STARD) initiative provides a checklist and flow diagram that are essential to achieve transparent reporting [1]. The highly dynamic world of diagnostic tests requires a rigorous evaluation process to prevent premature dissemination of tests of unproven clinical value. Studies in this particular area provide additional information on patient health status that are important for managing the underlying condition or disorder such as pelvic organ prolapse, urinary or faecal incontinence. Evaluation of diagnostic accuracy can not be separated from analysis of the clinical benefit, in the absence of which diagnostic tests (laboratory and imaging tests, history, physical examination or pathology) can not be recommended.

Imaging studies should follow the suggestions of the STARD initiative and they differ substantially from clinical trials. The aim of clinical studies of diagnostic tests should in fact aim to provide information regarding the diagnostic accuracy of the proposed test. Imaging studies represent per se a unique category because of the known issues involving interrater variability in the interpretation of radiological pictures and the variability in imaging techniques (although this mainly applies to ultrasonography and endoscopy only). Consequently, the criteria proposed by the Agency for Health Care Policy and Research endorsed by the Oxford Centre for Evidence Based Medicine for evaluating levels of evidence and for deriving grades of recommendation do not apply as, for example, randomization is not a issue and consequently, levels of evidence 1 and 2 can not be found in the peer-review literature and grades of recommendation A and B rarely occur. Furthermore recommendation for imaging studies is not just related to the quality of the published manuscripts but on the presence or absence of clinical benefit for the patient category of interest. Imaging is currently used in the field of urinary and anal incontinence or pelvic organ prolapse to evaluate
parameters with proven positive or negative predictive value for patient management or to investigate the prognostic value of novel parameters. Imaging can be used to reduce the diagnostic burden providing information on parameters with known safety or prognostic value (eg: ultrasound imaging of post void residual) or to investigate new parameters that can not be investigated in any other way (eg: bladder wall thickness).

A few considerations on the levels of evidence in imaging studies may be instrumental in reading this chapter and are summarized herewith.

Imaging of parameters with known prognostic value (e.g. PVR)

• The first issue is to prove that imaging studies image what they are supposed to image. Although the issue may be trivial in case of PVR imaging or anal sphincter imaging, the issue is relevant in other areas (eg: enterocele imaging) and should be solved using imaging in cadavers or other approaches such as intraoperative confirmation of the observed condition.

• When the imaging is quantitative, accuracy versus the gold standard technique should be provided. When the imaging is qualitative (e.g. presence or absence of vaginal vault prolapse) the diagnostic value should be provided (sensibility sensitivity, specificity, positive and negative predictive value, accuracy, interrater and intrarater variability).

• Once validity has been proven, one can assume that the predictive value of the imaging study is equal to that observed for the parameter measured with the gold standard. The same applies to its value for patient management.

Imaging of parameters with unknown prognostic value (e.g. MRI of the pelvic floor)

• When the imaging in qualitative (eg: intact versus damaged levator ani), once validity is proven, the diagnostic value should be investigated providing sensitivity, specificity, positive and negative predictive value, accuracy, interrater and intrarater variability in cadavers or patients undergoing surgery.

• Once validity is proved, the prognostic value for patient management should be investigated.

• Extramural confirmation of the proposed imaging study is required ideally for both validity and prognostic value or at least for the latter parameter (we can assume that confirmation of the prognostic value is obtained, validity of the imaging technique can be inferred).

A proposal for new levels of evidence and grades of recommendations for imaging studies is provided elsewhere in this book.

REFERENCES


B. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

B1. IMAGING OF THE UPPER URINARY TRACT

Urinary incontinence is defined as the complaint of any involuntary leakage of urine, it can be urethral or extrourethral. This latter condition either results from congenital anomalies such as ectopic ureters (inserting in the female distal urethra or vagina), iatrogenic or traumatic conditions such as fistula. In some patients, lower urinary tract dysfunction causing urinary incontinence, might compromise the transport of urine from the kidneys to the bladder resulting in hydronephrosis and renal failure. The relationship between high bladder storage pressure and renal deterioration was first identified in myelodysplastic children and then considered to apply in all neurogenic patients [1]. In male patients, chronic retention of urine can be associated with urinary incontinence and lead to chronic renal failure. In females, severe urogenital prolapse may cause angulation of the pelvic ureter by the uterine arteries leading to hydronephrosis in up to 30-40% of patients [2] (Figure 1 a,b).

I. INDICATIONS

Generally speaking, there is no need for upper tract imaging in cases of urinary incontinence unless any of the previously described conditions is suspected or diagnosed. Patients with extraurethral incontinence may also benefit from upper urinary tract imaging.

The objectives for upper tract imaging in the incontinent patient are as follows:

1. Evaluation of the upper urinary tract when the presence of an ectopic ureter or ureterovaginal fistula are suspected.

2. Evaluation of the kidneys whenever urinary incontinence is related to bladder dysfunction with high storage pressures (e.g. in neurogenic voiding dysfunction, chronic retention with overflow or low compliance bladders).

3. Exclusion of hydronephrosis in cases of urinary incontinence associated with severe uterine prolapse (Figure 2 a,b,c,d).
Figure 1a. Procidentia uteri

Figure 1b. IVU: bilateral hydrenephrosis. Left kidney is in sacral ectopia.

Figure 2a. MRI: complete urogenital prolapse

Figure 2b. MRI: ureteral dilation

Figure 2c. MRI: ureteral dilation

Figure 2d. MRI bilateral hydrenephrosis
II. TECHNIQUES

Upper tract imaging modalities include intravenous ultrasonography (USS), intra-venous urography (IVU), computer-terized tomography (CT scan), MRI, and isotope scanning. No data as to specificity, sensitivity, predictive value or reproducibility in connection with the diagnosis and management of urinary incontinence are available. The use of the different imaging modalities also depend on availability, expertise, and local management policies. Generally speaking, low cost and low risk techniques such as USS should be preferred. Unless otherwise described, the following considerations regarding the different imaging modalities are based on expert opinion.

1. ULTRASONOGRAPHY

Ultrasonography is the gold standard technique for primary imaging of the upper urinary tract because of the relatively low cost of the equipment and therefore of the examination, its large wide availability, the lack of any exposure to ionising radiation. Renal USS is independent on kidney function, provides a good evaluation of renal anatomy including malformations, kidney size, cortex/medulla index, hydronephrosis. Concurrent kidney disorders such as urinary lithiasis and neoplasms can also be diagnosed. In patients with lower urinary tract dysfunction (LUTD), the detection of hydronephrosis is of importance and it can be related to either vesico-ureteral reflux or obstruction. Although, no correlation exists between the degree of dilatation and the severity of obstruction, the grade of hydronephrosis is correlated with the extent of cortical damage [3]. Measurement of the resistive index in the interlobar and arciform arteries of the kidney has been proposed for the diagnosis of urinary obstruction but this is rarely used in the evaluation of the incontinent patient [4]. Whenever hydronephrosis is diagnosed on USS, other imaging modalities are often used to evaluate renal function, the degree of obstruction or vesico-ureteral reflux. USS is an ideal technique to follow the degree of hydronephrosis over time or the response to treatment.

2. INTRAVENOUS UROGRAPHY

Intravenous urography or intravenous pyelography (IVU) is the original radiographic examination of the upper urinary tract which allows evaluation of upper urinary tract anatomy and function. Successful examination is dependent upon adequate renal capacity to concentrate urine and the examination is currently contraindicated when creatinine levels exceed 2.0 mg/dL [5]. A number of different conditions such as renal dysfunction, obstruction, congenital anomalies, fistula, stones and tumors may be detected. IVU is the appropriate first study in cases of extraurethral incontinence. When ectopic ureter is suspected (although this condition can also be responsible of for urethral incontinence), delayed films and tomography are important because the renal unit or moiety associated with an ectopic ureter is often poorly functioning. In fact, IVU is sometimes unable to detect a small, malfunctioning moiety associated with a duplication and ectopic ureter or a poorly functioning or abnormally located kidney with a single ectopic system [6-8]. In such cases where the diagnosis of ectopia is still suspected after IVU, another imaging modality such as CT, MRI (Figure 3 a,b) or isotope scanning should be considered [9-11]. IVU is the appropriate first imaging study when ureterovaginal fistula is suspected, usually after pelvic surgery. Typically, one sees ureteropelvicocaliectasis proximal to the level of the fistula. This finding has been reported in 84-92% of cases [12, 13]. Sometimes extravasation can be seen. Confirmation of the presence of the fistula, its size and exact location is often obtained with retrograde ureteropyelography.

3. COMPUTERIZED TOMOGRAPHY

High quality information of the upper urinary tract anatomy can be obtained using multislice CT and 3D reconstruction software. Differently from IVU which only acquires images in the antero-posterior straight or oblique CT acquires images in the transverse plane. Pictures can then be reconstructed in 2D along any plane or in 3D whenever required. CT scan can be used irrespective of renal function when no iodinated contrast media are used. Whenever hydronephrosis is found, urine can be used to delineate the collecting system avoiding the use of contrast medium.

Intravenous contrast medium can be required to highlight specific anatomic characteristics. CT scan is often used after a first line evaluation is performed using USS and constitutes a valid test if no better alternative to IVU and it is usually no more expensive. Several authors have reported the use of CT scan to detect ectopic ureter, in cases where the diagnosis is suspected, despite a normal IVU and ultrasound (14). In these cases the small size and poor function of the ectopic moiety make diagnosis difficult by IVU.

4. MAGNETIC RESONANCE IMAGING

MRI shares some of the advantages of CT over IVU in the evaluation of the upper urinary tracts. Furthermore acquisition can be performed along any plane and pictures can then be presented in a 2D or 3D fashion. The paramagnetic contrast medium is free of allergic reaction risk although its use in the upper urinary tract remains dependent upon renal function and concerns about its nephrotoxicity have been recently raised [15]. The development of the uro-MRI technique has gained an increasing role for the technology in the evaluation of hydronephrosis and urinary tract anomalies in as an alternative to IVU. MRI usefulness in the diagnosis of ectopic ureter has recently been described [16-18].
5. ISOTOPES

Isotopes are used primarily to examine morphological and functional characteristics of the upper urinary tract. Isotope scanning can be used to identify the location of a small kidney which is otherwise difficult to image with radiological techniques.

Renography is used to examine the differential function of the two kidneys, to identify disorders of urine transit and to quantify obstruction of the upper urinary tract. There are many physiological factors and technical pitfalls that can influence the outcome including the choice of radionucleotide, timing of diuretic injection, state of hydration and diuresis, fullness or back pressure from the bladder, variable renal function and compliance of the collecting system [19, 20]. Diuresis renography with bladder drainage is recommended when obstructive uropathy is suspected [21]. Renal scintigraphy may be useful in the evaluation of ectopic ureters associated with hypoplastic kidneys [22].

CONCLUSIONS AND RECOMMENDATIONS

Imaging of the upper urinary tract is NOT indicated in the evaluation of non-neurogenic stress, urge or mixed urinary incontinence. [Level of Evidence 3, Grade of Recommendation C]

Imaging of the upper urinary tract is indicated in cases of:

a) neurogenic urinary incontinence with high risk of renal damage (due to high detrusor pressure, e.g. myelodysplasia, spinal cord injury, and low compliance bladders) [Level of Evidence 3, Grade of Recommendation C]

b) chronic retention with incontinence [Level of Evidence 3, Grade of Recommendation C]

c) untreated severe urogenital prolapse [Level of Evidence 3, Grade of Recommendation C]

d) suspicion of extra-urethral urinary incontinence by upper tract anomaly [Level of Evidence 3, Grade of Recommendation C]

The choice of the imaging techniques and their sequence depend on the clinical question and their availability. The least invasive techniques should be preferred and should precede the more invasive, also taking into consideration cost effectiveness. [Level of Evidence 3, Grade of Recommendation C]

SUGGESTED RESEARCH AREAS

- Prevalence of upper tract deterioration in various urinary incontinence populations
- Natural history of upper tract damage
- Relation between upper tract dilation, renal damage and bladder function
REFERENCES


B2. IMAGING OF THE LOWER URINARY TRACT

Imaging of the lower urinary tract (LUT) has a long tradition in the management of urinary incontinence, particularly in female patients. The techniques have changed, over the decades from static to dynamic imaging, from qualitative to quantitative information. Although some of the techniques are now more than 50 years old, their standardisation is insufficient and their clinical value often unclear. Most of the possible imaging modalities remain “investigational” as their impact on the management of urinary incontinence has not been established yet.

Voiding cystourethrogram (VUCG) was the mainstay of imaging studies in urinary incontinence until recently when US evaluation of the lower urinary tract through the pelvic window became prevalent because of its immediacy, low cost and availability.

While CT never gained acceptance because of the exposure of ionising radiations, MRI took the lead as the most promising imaging modality and a number of papers have been published over the years riding the wave of technological development.

In males the purpose of voiding cystourethography has been mainly to locate infravesical obstruction although it may play a role in the management of post-prostatectomy incontinence [1]. In children the diagnosis and classification of reflux and diagnosis of posterior urethral valves have been the primary goals [2]. The severity of the vesicoureteric reflux on one side determines the development of contralateral reflux and indicates a poorer resolution rate for the reflux [3].

Positive-pressure urethrography has been designed only for the diagnosis of female urethral diverticula, it was shown to be more sensitive than voiding cystourethrography [4-6] although MRI is the gold standard to diagnose diverticula and assess their anatomical relation to the surrounding structures [7, 8].
I. X-RAY IMAGING

The rationale for imaging studies of the lower urinary tract in this field derives from the supposed relation of morphology and function and particularly the causative role of urethral hypermobility in stress urinary incontinence. Investigation into cohorts of continent and incontinent patients failed to provide evidence to support the hypothesis and some imaging techniques have been abandoned. The same applies to outcome research in urinary incontinence where restoration of normal anatomy does not necessarily lead to cure of the condition. A renewed interest derived from the availability of USS which took imaging out of the radiology suite and moved it into the urological and gynaecological outpatient clinics opening new opportunities for clinical research in this field. The interest in MRI derives from the specific characteristics of this imaging modality which allowed both fast acquisition in the dynamic range and accurate evaluation of tissue characteristics together with the possibility to investigate the whole pelvis as one functional unit.

1. FEMALE CYSTOURETHROGRAPHY

X-ray imaging of the urinary bladder and urethra has been used to assess the female urinary tract in women suffering urinary incontinence to evaluate urethral/bladder neck hypermobility and to assess associated conditions such as urethral obstruction, vesico-urethral reflux, diverticula, fistula, stones and tumours. In males the purpose of voiding cystourethrography has been mainly to locate infravesical obstruction [1, 9]. The diagnosis and classification of reflux and diagnosis of posterior urethral valves in children have been the primary goals [2]. In a study comparing cystourethrography with direct radionuclide voiding cystography and voiding urosonography with contrast medium were compared. Voiding sonography and direct radionuclide voiding cystography were shown to be the most sensitive [10].

2. BACKGROUND

History and methodology of cystourethrography in females had been reviewed by Olesen [6]. The technique is now over 70 years old. Voiding cystourethrography with lateral projection was first done by Mikulicz-Radecki in 1931 [11]. The use of a metallic bead to identify the urethra was introduced by Stevens and Smith in 1937, and in 1956 Ardran, Simmons and Stewart reported on a cinematographic technique with contrast media also in the vagina and rectum [12, 13]. In an attempt to combine qualitative and quantitative information as to the function of the lower urinary tract, the combined used of fluoroscopy and pressure-flow recordings was proposed during the sixties and seventies [14-18].

3. METHODOLOGY (PROJECTION, POSITIONING AND EXPOSURES)

Bladder neck displacement is best viewed and quantified in true lateral projection although image quality is sometimes poor because of the increased body mass and the overlap of bony structures with the bladder neck area. Consequently, oblique projections are sometimes used notwithstanding the lack of quantitative information. Achieving a quasi-physiological voiding in a radiology suite is difficult because of the inevitable impact of the environment. The use of a sitting position is recommended for micturition studies as voiding while standing or lying will increase the embarrassment and thereby the bias of the examination [11]. Especially in patients with large body mass index, imaging of female urethra in a true lateral projection is difficult, it necessitates high radiation doses as the central x-ray beam must penetrate the trocanteric regions and further because the urethrovesical junction is sometimes is overshadowed by the lateral parts of the bladder. A significant improvement in this area has been brought about by digital imaging which allows the subtraction of the bony structures (Figure 4). The position and mobility of the urethrovesical junction as well as urine leakage are supposed to be influenced by the filling volume as has been demonstrated on ultrasonography and leak point pressure measurements [19, 20]. However, in voiding cystourethrography the bladder is filled to capacity. Addition of a urethral bead chain or catheter and vaginal contrast to improve the visualisation of the urethra, bladder neck and trigone has been abandoned. Contrast in the rectum is not necessary for urinary incontinence purposes. Exposures at rest should be supplemented with provocative manoeuvres to test bladder neck mobility by contracting and relaxing the pelvic floor (e.g.: coughing, straining, and squeezing). Whenever possible, pictures while the patient is voiding the bladder should be obtained. It is important to consider that coughing and straining result in a different effect on the pelvic floor. Straining might be associated with relaxation or contraction of the pelvic floor, and the imaging can change accordingly.

During coughing there is a reflex contraction of the pelvic floor, but coughs are of short duration and difficult to catch on spot films. Bladder suspension defects were diagnosed at rest in 49% of 420 examinations, while coughing and micturition disclosed a further number of 20% and 4% respectively [11]. Squeezing can demonstrate pelvic floor awareness and contraction [21].

4. COMBINED IMAGING AND URODYNAMICS

Videourodynamics has been by some regarded as the “gold standard” in the evaluation of lower urinary tract dysfunction [21]. Reproducibility of the combined examination has not been assessed and further the
radiation dose has to be considered [13, 18, 22-24]. One study has attempted to compare videourodynamic with saline cystometry [21]. Independent observers carried out the two procedures with 75 women having the saline cystometry first and a further 75 women had videourodynamic first. The degree of bladder descent noted on screening was greater than on clinical examination. Nineteen women had trabeculation and a further 11 women had bladder or urethral diverticula, urethral stenosis and vesicoureteric reflux [1, 9, 12]. Only seven of the eleven women could have been predicted by a selective imaging policy based on history alone which would image 43% of the 150 women. This suggests that a selective policy of screening will unnecessarily expose patients to radiation while not using the optimal technique for investigation for all patients who need the test. Nevertheless simultaneous videomonitoring along with tracings of pressure and urine flow rate are important means to be sure that the exposures are made at appropriate moments so that the radiographs can be representative of the various functional states [11, 16, 25, 26].

Patients with Parkinson’s disease and multiple system atrophy are best evaluated by videourodynamic and sphincter motor unit potential analyses to identify characteristic features of these conditions including: external sphincter denervation, neurogenic sphincter motor unit potentials, open sphincter denervation bladder neck at rest and detrusor-external sphincter dyssnergia [27].

Neurogenic patients show severe bladder trabeculation with diverticula and pseudodiverticula, pelviureteric reflux, widening bladder neck and proximal urethra; narrowing at the level of the membranous urethra and the bladder neck can suggest the presence of neurogenic dysfunction of the lower urinary tract (occult spinal dysraphism, non-neurogenic neurogenic bladder) even in the absence of neurogenic symptoms and signs [28-30]. Urodynamic parameters in children do not discriminate between those with or without vesicoureteral reflux thus videourodynamic studies have been considered essential. Additionally children with non-neurogenic voiding dysfunction are found to have a number of abnormalities with videourodynamic [31, 32]. Indications for videourodynamic include previous continence and vaginal surgery, neurological disorders and suspicion of urethral diverticula.

5. NORMAL AND DEFECTIVE BLADDER SUPPORT

The whole issue about the clinical value of cystourethrogram is about the pathophysiology of defective bladder support in the pathophysiology of stress urinary incontinence in female patients and the relation between the surgical correction of such a defect and cure. The concept of urethral hypermobility was inherent to the classification of stress urinary incontinence and the concept that an impaired transmission of abdominal pressure to female urethra could be responsible for the observed leakage. Little remains about the concept of urethral hypermobility in a modern view of female stress urinary incontinence and this contributed to the gradual abandoning of cystourethrogram in the evaluation of a standard patient.

The normal resting bladder has a smooth surface although bladder trabeculation is often seen in elderly lady women and not necessarily related to any pathological condition. The internal urethral orifice is located just above a horizontal line through the lowermost part of the symphysis in a coronal projection. The urethra is straight and runs anteriorly and caudally toward the external meatus.

On coughing and straining, relaxation of the pelvic floor results in downward movement of the bladder...
neck, which can be associated with a backward movement of the bladder neck resulting in a change in urethral axis. Squeezing (and sometimes also straining) results in contraction of the pelvic floor muscle with a cranial movement of the bladder neck Figure 5a. During voiding (Figure 5b) the bladder base is usually lowered about 1 cm, the angle between the urethra and the trigone is straightened, making a funnelled appearance of the proximal urethra and the bladder base, the bladder contour is rounded and a fine sawtooth irregularity of the mucosa becomes visible above the trigone.

Angles and distances between the urethra, bladder base and symphysis pubis have been assessed radiologically. The following parameters have been assessed for reliability:

1. The posterior urethrovesical angle (PUV) is defined by lines along the posterior urethra and the trigone [33]. Cut off values were usually 115° or more [34, 35];

2. The urethral inclination is between the proximal urethral axis and the vertical plane, which is a plane outside the patient and, therefore, the angle also varies with pelvic inclination. In Green type I and type II descent the angle is less or more than 45° respectively [35];

3. The urethropelvic (UP) angle is measured during voiding as the anterior angle between a line through the middle of the internal urethral orifice and the urethral knee and a line through the posterior surface of the symphysis through the lowermost part of the obturator foramen closest to the film. In normals the mean UP is about 95° and the cut off point for bladder descent are values below 70° [11];

4. Symphysis orifice (SO) distance is measured at rest as the distance on a horizontal line from the symphysis to the internal urethral orifice. Normal values are 31 ± 6 mm (mean ± SD) and values less than 20 mm are the cut off points for descen t [11];

5. The urethral axis at rest (UAR) and during straining (UAS) (Figure 6)

Funnelling of the proximal urethra and flatness of the bladder base (both anterior and posterior to the internal urethral orifice) and the most dependent portion of the bladder base (the urethrovesical junction or a point posterior to that) are important qualitative parameters estimated on straining films [34].

Anterior bladder suspension defects or bladder base insufficiency (BBI) (Figure 7) is defined as SO < 20 mm with a normally positioned vagina at rest, during coughing or micturition and/or funneling of the bladder base at rest or with coughing. The insufficiency can be graded 1-3, which corresponds to Green's type I descent [11, 36]. The supportive defect is supposed to be in the fascial and ligamentous system and their abnormal detachments (eg., paravaginal defects).

Posterior bladder suspension defects (Figure 8) are defined as a posterior-inferior bladder displacement and a UP of less than 70° [11]. It corresponds to Green's type II [37]. Sometimes (Figure 9) only the trigone and posterior part of the bladder is involved. The supportive defect is supposed to be in the muscular pelvic floor, that is, the pubo-vesical part of the pubococcygeus muscle or in paravaginal detachment.

Interestingly, when UAR and UAS were examined in a group of 76 continent women and correlated with age, a perfect linear regression was noted between UAR and age (R^2= 0.28). Patients with stress urinary incontinence were found to have an average UAR value of 25° with a mean UAS of 43° leading to a threshold value of hypermobility of about 20°. When standing cystourethrograms were repeated 3 to 6 months after surgery for stress urinary incontinence, UAR and UAS values were found to be close to normal suggesting a relation between the correction of the defective bladder support and cure [37]. A more structured definition of cystocele (ranked by height in centimetres) was also obtained, adding to the

Figure 5 : Female Cysto-urethrography 1a: normal appearance on coughing, straining and squeezing b: normal appearance on voiding
Figure 6: Example of standing, lateral views on VCUG with 125 mL of contrast within the bladder. (A) Preoperative UAR. (B) Preoperative UAS. (C) Postoperative UAR. (D) Postoperative UAS. The urethral angle is calculated from a reference line drawn through the inferior portion of the pubic symphysis.
emerging data that the reliability of the pelvic organ prolapse quantification (POP-Q) system (POP-Q) increases when measurements are performed in a more upright position [37].

6. REPRODUCIBILITY

The observer variation has been evaluated in four university uro-gynecological units (Table 1) [21, 34, 38, 39]. The inter-observer agreement was 43-79% and the intra-observer agreement was 53-99%. These figures are in the same range as has been found for other diagnostic tests [40].

Accuracy for the diagnosis of stress incontinence and post-operative results

Evaluation of accuracy is the mainstay in the evaluation of a diagnostic technique. One has to consider that sensitivity and specificity depend on intrinsic factors such as reproducibility (as measured by intraobserver and interobserver variation) and extrinsic ones such as the characteristic of the patient cohort used for to assess accuracy.

The accuracy of the previously mentioned radiological criteria have been measured by comparing imaging data with the ‘so called’ index-test which in this case was a clinical diagnosis of urodynamic stress incontinence and expressed as specificity and sensitivity or as predictive values. Unfortunately the diagnosis of stress urinary incontinence is controversial and might be based on subjective criteria, urodynamic tests, or measurement of leakage. Even radiological criteria have been included in the diagnosis.

Reproducibility (e.g. test-re-test agreement) has not been measured, but intra- and inter-observer variation has been calculated and also adjusted for expected chance agreement (kappa coefficient). The predictive values and the kappa coefficient are supposed to depend on the prevalence, and therefore, comparison between different materials are difficult [40].

No consensus has been reached in the peer-review literature as to the lack of discriminant value of cystourethography between stress incontinence and continence, the majority of published papers are consistently negative although new promising data have been published [35, 37, 41-43]. The specificity of 5 radiological parameters on static bead chain cystourethography was 44-76% and the sensitivity 53-100% [43, 44]. Neither was the degree of stress incontinence correlated to the type or degree of suspension defects [21, 38, 45]. The positive and negative predictive values for a bladder suspension defect were 0.70 (95% C.I.: 0.62-0.78) and 0.52 (95% C.I. 0.41-0.63) respectively on voiding colposcystourethography [36, 46]. In a later publication on 159 women, positive and negative predictive values of 0.56 and 0.74 were obtained [43]. Evaluation of the urethral angle at rest and during stress in controls and in patients with stress urinary incontinence and various grades of anterior vaginal prolapse show a significant relation between UAR and aging (from 2.4° ± 14.9° in the third decade to 29° ± 9.2° in the 9th decade; \( r^2= 0.28 \)). In patients with SUI, UAR and UAS decreased from 25.7° ± 13.6° and 42.6° ± 15.9° to 16.6° ± 14.7° and 23.8° ± 17.5°, respectively; the observed change were found to be statistically
significant. A similarly significant difference was found in patients with moderate to grade 3 cystocele and urethral hypermobility (at least 5 cm descent of the bladder base below the inferior ramus of the pubic symphysis on the lateral view of a standing VUCG): UAR and UAS decreased from 48.1° ± 16.5° and 64.4° ± 16.8° to 22.3° ± 26.9° and 29.8° ± 22.8°, respectively.

Comparison of a randomly selected control cohort (aged-matched) with patients suffering SUI showed a significant difference of UAR and UAS at diagnosis while similar values were found after surgery (Figure 9). This was similar to patients with grade 3 cystocele in whom both UAR and UAS were significantly different from controls at baseline while showed similar values in the postoperative follow-up.

Measurement of the cystocele height (LATH), obtained as the distance between the inferior border of the pubic symphysis and the inferior edge of the cystocele in controls and patients with mild and severe cystocele showed a significant difference between the two cohorts (16.63 ± 10.9 mm versus 27.4 ± 12.3 mm versus 73.4 ± 15.6 mm, respectively). Following formal cystocele repair, a significant change of LATH values was found in patient with mild and severe cystocele (from 27.4 ± 12.3 mm to 13.9 ± 18.0 mm and from 73.4 ± 15.6 mm to 25.4 ± 24.6 mm, respectively [p<0.001]).

These are the first data supporting the used of standing VCUG as an outcome measured, previous peer-review

Table 1. Inter- and intra-observer variation (agreement) on cystourethrography in females with urinary incontinence.

<table>
<thead>
<tr>
<th>Type of examination, patients and observers</th>
<th>Inter-observer variation</th>
<th>Intra-observer variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bead-chain [1] stress &amp; urge incontinence</td>
<td>45.8-80.7 %</td>
<td></td>
</tr>
<tr>
<td>n°92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 observers on 5 landmarks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCCU [2] stress incontinence n° 52</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>1 observer on type of descent</td>
<td>95% c.l. 65-89</td>
<td></td>
</tr>
<tr>
<td>VCCU [3] stress incontinence n° 29</td>
<td>70%</td>
<td>53%</td>
</tr>
<tr>
<td>2 observers on type of descent</td>
<td>95% c.l. 75-89</td>
<td>95% c.l. 27-78</td>
</tr>
<tr>
<td>VCCU [4] n° 93 stress &amp; urge incontinence</td>
<td>43-60%</td>
<td>72-99%</td>
</tr>
<tr>
<td>incontinence</td>
<td>Kappa 57-98%</td>
<td>Kappa 20-39%</td>
</tr>
<tr>
<td>6 observers on type of descent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCUG [5] Stress incontinence n° 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 observers on urethral angle shift from</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest to straining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r = 0.83 (p=0.001) for</td>
<td>UAR</td>
<td></td>
</tr>
<tr>
<td>r = 0.82 (p=0.002) for UAS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1: static bead-chain cystourethrography with straining [34]. The 5 landmarks were the posterior urethrovessical angle, urethral inclination, funnelling of the proximal urethra, flatness of the bladder base and most dependent position of the bladder base;

2: voiding colpo-cystourethrography (VCCU) at rest and with coughing, straining, micturition and squeezing; one observer against original diagnosis (that is, normal appearance or anterior, posterior or combined suspension defects) made by a few senior radiologists [20];

3: voiding colpo-cystourethrography at rest and with coughing, straining, squeezing and micturition. Possible diagnoses were: normal appearance or anterior, posterior or combined descent respectively [39].

4: voiding colpo-cystourethrography at rest, coughing, with holding and voiding. Possible diagnoses were: normal appearance and anterior or posterior descent respectively [38];

5: standing voiding cystourethrography, urethral angle was measured at rest (UAR) and during straining (UAS) [37].

Figure 9 : Mean 6 95% confidence interval for UAR (squares) and UAS (circles) before and after surgical correction compared with age-matched controls. Difference from “before” to “after” was significant for both surgical groups; difference between “after” and “control” was not significant.
papers suggested the inability of the technique to distinguish postoperative failures from success [11, 21, 40, 42, 44, 47-50].

7. COMPARISON OF CYSTOURETHROGRAPHY AND ULTRASONOGRAPHY

The development of USS techniques for the evaluation of the lower urinary tract raised the question of the relationship of X-ray versus USS imaging. Static bead chain cystourethrography has been compared with transrectal and perineal ultrasonography and voiding colpo-cystourethrography has been compared with perineal ultrasonography [44, 45, 51, 52]. The findings correlated well regarding bladder neck position and mobility, PUV, urethral inclination, SO distance and rotation angle.

Specificity, sensitivity and interobserver agreement were also comparable for the two methods. All the authors seem to prefer the sonographic modality because the imaging study can be performed at the same time as the physical examination. This has also been the case in men with neuromuscular dysfunction [9]. Simple and extensive funneling is more easily imaged in upright patients during cystourethrography than in the supine position frequently used for ultrasound studies [28].

8. COMPARISON OF CYSTOURETHROGRAPHY AND MRI

The introduction of MRI in the assessment of the LUT required an adequate comparison of this technique with standard X-ray imaging. The comparison of cystourethrography and colpo-cystourethrography with dynamic MRI showed comparable data on bladder neck position and cystocele extension [53, 54]. Although there is an obvious concern about the fact that dynamic MRI is usually performed with the patient lying in a dorsal lithotomy position, comparison of standing and lying colposcystourethrography did not show any significant difference [54].

CONCLUSIONS

The role of cystourethrography in the evaluation of female urinary incontinence remains to be established although preliminary evidence is now available that the measurement of urethral angle and cystocele height might have some clinical utility in the management of patients with urinary incontinence and genital prolapse who are scheduled for surgery. Defective bladder support can be diagnosed on voiding cystourethrography with a reliability comparable with other diagnostic tests.

Dependent on local facilities the method might be considered if the choice of a surgical procedure is based on type and degree of supporting tissue deficiencies and possibly if new procedures are evaluated for the ability to restore this deficiency. The method can not yet be recommended for the diagnosis or classification of urinary incontinence.

RECOMMENDATIONS

- Cystourethrography is NOT indicated in primary uncomplicated stress, urge or mixed female urinary incontinence [Level of Evidence 3, Grade of Recommendation C].
- Cystourethrography may be a reasonable option in the preoperative evaluation of complicated or recurrent female urinary incontinence [Level of Evidence 3, Grade of Recommendation C].

SUGGESTED RESEARCH AREAS

- Standardization of technique, parameters and interpretation of cystourethrography.
- Possible value of cystourethrography in the evaluation of pelvic floor dysfunction (correlation of imaging to pelvic floor physical examination and to clinical outcome following therapy)

REFERENCES

52. Dietz HP, Wilson PD. Anatomical assessment of the bladder outlet and proximal urethra using ultrasound and videocy-
1. BACKGROUND

X-ray imaging has been used for decades in the evaluation of the lower urinary tract; the contrast agents are used to visualize the bladder and a bead chain can help to outline female urethra. Dynamic cystograms, were used to classify female urinary incontinence, the technique was gradually abandoned for its poor accuracy in diagnosing the condition, its little impact on patient management and poor correlation with treatment outcome [1].

Ultrasonography has been used in the evaluation of urinary incontinence as early as 1980 [2]. In the late eighties and nineties of the previous millennium, the quality of ultrasonography greatly improved as well as its availability. Various new developments, such as the use of contrast medium, colour Doppler, 360 degree transducers and three-dimensional imaging have been introduced and have been instrumental to a more widespread use of ultrasonography in the evaluation of pelvic floor disorders.

A number of studies have reported good correlations between ultrasonography and x-ray in the evaluation of urinary incontinence [3-10]. In particular, the position of the bladder neck at rest and during Valsalva manoeuvre has frequently been compared, and all authors agree on a good correlation. Some authors even found a better accuracy for the ultrasonographic method [6], especially in obese women [3]. Ultrasonography is cheaper than X-ray imaging, it is often preferred by physicians because the imaging studies can be performed in their own office as part of the physical examination and it is also more acceptable to patients because of the lack of for radiation exposure.

2. TYPES OF ULTRASONOGRAPHY

Different imaging windows have been used, such as abdominal, transvaginal, transrectal, perineal and transurethral. Synonyms for perineal access are transperineal, introital, labial or translabial access. Abdominal ultrasonography is general not considered to be helpful in pelvic floor imaging because of the acoustic shadow caused by the pubic bones. All types of access have the potential risk of interference with the existing anatomy. With vaginal ultrasonography this risk is probably highest [11], although this has also been denied [12]. Most recent studies report on perineal ultrasonography that allows the visualization of all three compartments in one image.

The development of three-dimensional ultrasonographic systems has brought a new dimension to pelvic floor imaging. Three-dimensional ultrasonography was first described for the female urethra in 1999 [13]; the three-dimensional image can either be evaluated as a separate entity on the screen, or in combination with each of the two-dimensional planes from which it is derived (Figure 1). These three two-dimensional planes are the sagittal, coronal and axial. Three-dimensional images are built up as a rendered image of a self defined region of interest, major advantages over 2D imaging include the possibility to review the acquired images from any investigator and the ability to analyse the acquired volume through any plane (likewise CT scans or MRI) (Figure 2) so that, for example, the levator ani muscle can be easily visualised. Four-dimensional imaging, i.e. real-time three-dimensional imaging, incorporates the enormous improvement in speed of three-dimensional systems over the last few years and it makes three-dimensional assessment of the dynamic relation of the pelvic organs on Valsalva manoeuvre and pelvic floor contraction possible.

2. STANDARDISATION

No consensus has been reached as to the standardisation of image orientation. Some prefer orientation with cranial structures above (Figure 3a) [14] whereas others prefer presentation of the cranial parts below (Figure 3b) [15]. All authors agree that the symphysis pubis, and its inferior border in particular, is a well recognizable and fixed reference point. This point can be used in the evaluation of the various aspects of relevant structures at rest and during dynamic imaging. In general, ultrasonographic studies are performed in the supine position (Figure 4). Small differences between the supine and standing position of the patient have been documented, although these differences disappeared during a Valsalva manoeuvre [16]. Only a few studies have been performed in the standing position [17]. There is no clear consensus on the amount of bladder filling, some authors prefer significant bladder filling, others prefer a nearly empty bladder because an empty bladder seems to descend more on Valsalva manoeuvre compared with a full bladder [18, 19]. Attempts to standardize Valsalva manoeuvre, ideally with intra-abdominal pressure measurements, has not been widely accepted [20]. In a recent study [17], a peak flow meter has been used, where women were asked to “huff” maximally and to reach the same force during a number of “huffs”. It has been shown that the mobility of the bladder neck differs between coughing and Valsalva manoeuvre [21]. Co-activation of the pelvic floor muscles during Valsalva manoeuvre has been
Figure 1: Perineal midsagittal two-dimensional view and three-dimensional rendered image. Normal anatomy.

Figure 2: Perineal midsagittal two-dimensional view. Normal anatomy of the levator ani muscle.

Figure 3a: Perineal midsagittal two-dimensional ultrasound view on three compartments and horizontal reference line according to Dietz.

Figure 3b: Perineal midsagittal two-dimensional ultrasound view on three compartments and reference lines according to Tunn and Schaer. A= horizontal reference line B= central line of the symphysis as reference line for bladder neck descent.
documented and is one of the reasons for the lack of standardization [21].

4. THE URETHRA AND BLADDER NECK

When collagen fibres and muscle fibres are located parallel to the ultrasound beam, the structure becomes hypoechoic. These same structures will become hyperechoic, however, when the fibres are located perpendicular to the beam. On two-dimensional ultrasonography, this may result in variable images of the urethra, since the echogeneity of the structures depends on the position of the transducer in relation to the urethra. This may produce confusing images, especially in the dynamic process of pelvic floor contraction and Valsalva manoeuvre. In the midsagittal plane on perineal ultrasonography, and with normal anatomical position of the urethra at rest, the internal sphincter and inner mucosal layer of the urethra will appear hypoechoic (Figure 1), these structures cannot be distinguished from each other on ultrasonography. In the midsagittal plane and with normal anatomical position of the urethra at rest, the striated external sphincter or rhabdosphincter will appear hyperechoic, and can hardly be distinguished from the surrounding structures. It will, however, be easily visible as a hyperechoic circular structure in the axial plane as seen on three-dimensional ultrasonography. The rhabdosphincter has been found to be thinner dorsally [13], and both ventrally and dorsally [22] by various authors and more difficult to distinguish from the internal sphincter ventrally and dorsally compared with laterally [23].

With the use of ultrasonography, thickness and length of the urethral sphincter muscle can be measured and urethral volume calculated [15, 23, 24]. Some make use of intra-urethral ultrasonography for this purpose, [25] others use two- or three-dimensional ultrasonography of the urethra [13, 22, 26, 27]. Comparison of transvaginal and transrectal approach showed a lower degree of urethral compression with the latter approach [22, 28]. Ultrasound measurement of female urethra has been found to be reproducible [13, 27]. Sphincter volume may differ significantly when 2D or 3D imaging is used [27]. Urethral volumes, measured by 3D ultrasonography, were positively correlated with the actual volumes in cadavers [26]. A significant and positive correlation between rhabdosphincter volumes and symptoms and signs of urinary incontinence has been reported [13]; correlations with the urethral pressure profile (UPP) have been found [23, 24, 26, 29] but these data could not be reproduced [30]. Ultrasonography imaging during micturition has been explored with the aid of a remote control systems [31].

The use of intra-urethral ultrasonography with rotating probes (360°) has been proposed by various authors although no particular advantages over perineal US could be identified [25, 32-35].

The advantage of preoperative and intraoperative three-dimensional ultrasound scanning in women with urethral diverticula has been outlined by Yang et al. [36, 37].

5. BLADDER NECK

The bladder neck and proximal urethra are easily visible on all types of ultrasonography without the need for catherization (Figure 1). Measurements are usually taken at rest, during straining (Valsalva manoeuvre), and sometimes during a cough and squeeze. The position and movements are measured in relation to the lower margin of the symphysis pubis. The difference between rest and strain is referred to as the bladder neck descent (the distance between the bladder neck and a horizontal line through the lower end of the symphysis pubis) (Figure 5). On Valsalva manoeuvre the bladder neck rotates in a posterior and inferior direction under the symphysis pubis. The axis of the urethra in relation to a vertical or horizontal line can be measured in degrees and provide the degrees of urethral rotation ((hyper) mobility). Other parameters are the posterior urethrovesical angle and the anterior urethrovesical angle.

A number of studies have validated the use of ultrasonography in the assessment of the position and mobility of the bladder neck and proximal urethra. Good results for this validity testing have been reported although the clinical value of such measurements is still elusive [5, 12, 38-40]. Normal values of bladder neck mobility have not been defined, since there is a great range in mobility even in young nulliparous women. In one study amongst nulliparous continent women of approximately 20 years of age, the bladder neck descent varied between 1mm and 40mm [41]. Others [38] found an average descent of 15 mm on Valsalva manoeuvre and 8 mm on a cough. Brandt et al. have found an average bladder neck descent of...
only 5 mm in 16 year old girls [42]. Racial differences have been demonstrated, with white women having a greater bladder neck mobility compared with black women [43]. Genetic determination of bladder neck mobility has been suggested [44].

Numerous studies have found greater bladder neck mobility in parous compared with nulliparous women [12, 30, 45-47]. Bladder neck hypermobility, however defined, is considered to be related to stress urinary incontinence [15, 30]. A large number of studies have correlated ultrasonographic findings with urodynamic parameters [47-56]). Specificity and sensitivity of ultrasonography for the diagnosis of stress incontinence were 83 and 68% in one study [50] and 92 and 96% in another study [57].

One research group has specifically investigated simultaneous perineal ultrasonography and urethrometry. They were able to demonstrate that the variations in urethral pressure were caused by the activity of the urethral sphincter as well the pelvic floor muscles [58]. The contractions from the urethral sphincter are always fast contractions. Some studies have used ultrasonography in an attempt to optimize patient management, but despite the abundant literature on the use of ultrasonography in the work up in women with urinary incontinence, disappointedly, a clinical advantage in terms of patient outcome has not been studied up till now [59, 60].

Urethral funnelling can be observed on ultrasonography (Figure 6) particularly with the use of contrast agents. It is a typical finding in women with stress urinary incontinence but can be seen in asymptomatic women as well [61-63]. In a study on stress incontinent women, funnelling was found to be present in nearly all women [62, 64]. Urinary incontinence can be demonstrated by the use of colour Doppler of the urethra [65, 66]. Colour Doppler has, furthermore, been used to visualize the perirectal vasculature and differences have been described between continent and incontinent women [67, 68] and before and after estrogen supplementation in postmenopausal women. Doppler velocimetry has recently been used in a study on the vascularisation of the levator ani muscles and a correlation has been found between the absence of an end-diastolic shift and the presence of stress urinary incontinence [69].

6. DETERMINATION OF THE POST VOID RESIDUAL URINE AND BLADDER WALL THICKNESS

Ultrasonography is the gold standard technique for measuring bladder volume and post-void residual urine [70-74]. Ultrasonographic data have been compared with residual volumes obtained by in-and-out catheterization under ultrasound control and were found satisfactory. However, Khan et al. have challenged the methodology of these studies and have found deficiencies in all reports on the topic [75]. A simple formula often used is \[ \text{Volume (ml)} = \text{Height} \times \text{Width} \times \text{Depth} \times 0.7 \] in which the factor 0.7 is the correction for the non circular shape of the bladder.

Automated ultrasound systems for measuring bladder volume and post-void residual have been developed and found to be more accurate than standard ultrasound measurements, furthermore they can be safely used by health care providers with no training in ultrasound imaging and by the nursing staff [76]. These machines are widely used and are, in general, experienced as reliable enough for clinical use, however, in case of ascites [77] or an ovarian cyst [78] for example, the estimated urinary volumes can be
incorrect. Recently the normal values for the post void residual urinary volumes in asymptomatic women have been presented; in 60 year old women, the median residual volume was 19 ml, and 95% of women had a post void residual volume of less than 100 ml [71].

Ultrasound measurement of bladder wall thickness (BWT) and ultrasound estimated bladder weight (UEBW).

Ultrasound measurement of BWT was first proposed as a non-invasive method for diagnosing infravesical obstruction in children [79]. More recently, BWT has been used to predict the outcome of children with primary nocturnal enuresis [79-81]. BWT has also been proposed as a risk factor for upper urinary tract deterioration in children with myelodysplasia [82]. Measurement of BWT was also proposed to diagnose bladder dysfunction (DO and detrusor hypocontractility versus normal detrusor function) in children with urinary tract infection [83, 84]. Additional parameters such as the bladder wall thickness index (length x width x depth of the bladder at full bladder/average BWT) were proposed and a nomogram for the paediatric population provided [85].

In the adult population, higher BWT values have been measured in men than in women. Thickness may certainly differ depending the measurement technique; values of 3.3 ± 1.1 mm and 3.0 ± 1.0 mm, respectively were reported by Hackenberg and co-workers [86]. Oelke confirmed a significant difference between male and female detrusor thickness (1.4 versus 1.2 mm, respectively) [87]. A small increase of detrusor hypertrophy with age has been reported in both genders [86].

In men, measurement of bladder wall thickness proved to be the most sensitive parameter (outperforming uroflowmetry) to diagnose BOO in patients suffering LUTS [88, 89].

Transvaginal ultrasound was first proposed in 1994 for the measurement of BWT in women with bladder volume of less than 20 ml. A significant difference was shown in patients with DO and USI (6.7 ± 0.6 versus 3.5 ± 0.6 mm, respectively). Low intraobserver and interobserver variability were measured: 0.02 mm in both cases with a 95% confidence interval of -0.22 to 0.18 and -0.32 to 0.35 mm, respectively [90].

In 1996, Khullar and co-workers showed how ultrasound measurement of BWT is a sensitive method for diagnosing DO in symptomatic women without bladder outlet obstruction with 94% of women with BWT greater than 5 mm having involuntary detrusor contractions on videocystourethrogramy or ambulatory urodynamics [91]. In 2002, the same group showed no overlap in the 95% confidence intervals of BWT was shown in patients with DO and USI in women with storage symptoms, confirming the potential of this parameter for diagnosing DO [92]. In 2003, a study on ultrasound cystourethrography in women confirmed a significant association between age and intravesical pressure at maximum flow with BWT [93].

Methodological and technical issues in the ultrasound measurement of bladder wall thickness and weight remain open and constitute a major limitation for a more widespread use of these parameters. In 2005 Chalana and co-workers published an early report on automatic measurement of the ultrasound-estimated bladder weight from three-dimensional ultrasound. An average value of 42 ± 6 g was measured in healthy male subjects. A standard deviation of 4 g was seen among measurements performed in the same subject at different bladder
Further research in this area is certainly needed and further improvement in the accuracy of automated systems is eagerly awaited. Although data published in the peer review literature on this subject are quite consistent, two discordant papers were recently published from Australia. Blatt and co-worker showed uniform values of BWT among men and women with non-neurogenic voiding dysfunction suggesting this parameter cannot be used to diagnose storage or voiding dysfunction [95]. A retrospective study on women undergoing translabial ultrasonography suggests a significant association between BWT and DO although a low diagnostic accuracy was shown for the diagnosis of DO which could be due to the fact that translabial ultrasound is unreliable [96].

The association between detrusor hypertrophy and bladder dysfunction (DO and BOO) is a well established fact in Urology. Ultrasound measurement of BWT and UEBW is an interesting alternative approach that may avoid invasive urodynamics in some patients. The development of automated ultrasound systems for measuring UEBW is instrumental to foster further research in this area, particularly in the management of patients with LUTS and in the evaluation of bladder response to pharmacologic treatment.

7. PELVIC FLOOR MUSCLES

Ultrasoundography can be used to assess pelvic floor muscles and their function. Contraction of the pelvic floor results in displacement of pelvic structures that can easily be imaged on ultrasound (Figure 7) such as the cranial lift of the urethra in relation to the symphysis pubis during a maximal squeeze [16, 97] but also the dimensions of the genital hiatus or the posterior ano-rectal angle can serve this purpose [98]. Comparison with traditional measurements of pelvic floor muscle strength has been performed [97], and good correlations with palpation and perineometry have been found [99, 100]. Ultrasonography has been used to evaluate the effects of pelvic floor muscle training. A higher resting position of the bladder neck and a reduction in the rotational excursion of the urethra during Valsalva manoeuvre has been found with training [101]. Another research group has reported that the thickness of pelvic floor muscles increased after training [102]. A number of studies have assessed healthy female volunteers to establish normal values [41, 102], and one study has specifically compared elite athletes with normal volunteers [103]. Measurements of the levator ani muscle, with the use of two-dimensional imaging, has recently been described, and although direct comparisons to three-dimensional ultrasonography are lacking, the acquired data were comparable [104].

Almost half of women are unable to perform an optimal contraction of the pelvic floor muscles. Ultrasonography can be used in pelvic floor training to provide women a visual feedback of their exercise [16, 105]. In one study, 57% of the women who were not able to perform a proper pelvic floor contraction, were able to do so with the help of visual biofeedback of ultrasonography [16]. Whether this form of biofeedback results in better outcomes from pelvic floor physiotherapy is not known. The contraction of the pelvic floor muscle just before and during a cough, “the knack”, can also be visualized [106]. It has been demonstrated that the knack can significantly reduce urethral mobility during a cough.

Figure 7: Perineal midsagittal two-dimensional view at rest and on contraction. Levator contraction with ventro-cranial displacement of the urethra. Measurement of minimal dimension of genital hiatus (from symphysis pubis to levator ani muscle)
Direct measurement of the pelvic floor muscles is possible with the use of two and three-dimensional perineal ultrasonography. An alternative technique makes use of a 360 degree rectal probe intravaginally (Figure 8) [104]. Most studies, however, have used three-dimensional perineal ultrasonography for this purpose [17, 98, 103, 107, 108]. The thickness of the muscles as well as the hiatal area can be measured. Hiatal dimensions and pelvic floor muscle thickness have been extensively validated and have good test-retest and inter observer characteristics [17].

The pelvic floor muscles were found thinner in women with pelvic organ prolapse [15, 104, 109] and with urinary incontinence [110], whereas their genital hiatus was found larger [111]. Well trained women have thicker pelvic floor muscles compared with controls [103], and Chinese women had thinner muscles compared with Caucasian women [108]. In nulliparous Chinese women, the anterior/posterior hiatal diameter was significantly increased in women with a higher body mass index [108].

Pelvic floor biomechanics were investigated with ultrasound using the position of the bladder neck in combination with continuous vaginal pressure measurements [112, 113]. A novel biosensor was used to measure the force as well as the displacement of the pelvic floor during contraction [114]. Another research group has inserted a water filled plastic bag to study the shape of the vagina during contraction [115]. Others [116] have assessed elasticity by means of the correlation of the dynamic dimensions of the hiatal circumferences and direct palpation of the muscles.

8. LEVATOR TRAUMA

Avulsion of the levator ani muscle from the symphysis pubis is known to occur in up to 36% of parous women [59, 117]. The integrity of the attachment of the pelvic floor muscle to the symphysis pubis can be visualised (Figure 2 and 9a). This is best evaluated on a pelvic floor contraction, since detachments are better visualised when the muscle is retracted away from the symphysis, and the potential gap between muscle and bone increases. Another marker of the detachment of the muscle is the loss of the typical H shape of the vagina in the axial plane, with the upper arms of the H hanging aside after detachment (Figure 9a, 9b).

It has been shown that the detachment of the levator ani muscle from the symphysis pubis is associated with pelvic organ prolapse with an odds ratio of six [118] especially of the anterior and central compartment [119]. This is similar to results from MRI studies, where it has been shown that the risk of pelvic organ prolapse further increases when the levator injury goes together with vaginal architectural distortion [120, 121]. Although these defects have recently been identified during labour, it is not known whether there is any reasonable (preventive) treatment for these women [118, 122]. There is an increase of the occurrence of pelvic floor muscle trauma with maternal age at first delivery [123]. There was a strong correlation between the presence of levator muscle avulsion and poorer muscle strength [124]. It has, however, been shown that the correlation between the clinical assessment (palpation of the muscle) and three-dimensional ultrasonographic assessment of muscular defects was only poor [125], as well as the intero-bserver repeatability of the palpation of defects [126]. A quantification method for levator muscle defects on ultrasonography (tomographic ultrasound imaging) (Figure 9a and 9b) has been described [107].

Another parameter, which has been found to be related to the severity of pelvic organ prolapse, was the size of the inner circumference at minimal hiatal dimension of the levator ani muscle on Valsalva manoeuvre [104, 107, 118]. The area of the levator hiatus on Valsalva manoeuvre ranges from 6 to 36 cm² in nulliparous women, with an outlier of almost 50 cm² in a young nulliparous athlete [103, 111]. An area of more than 30 cm², 35 cm² and 40 cm² on Valsalva manoeuvre has been described as mild, moderate and severe ballooning of the genital hiatus respectively (Figure 10) [127]. The assessment of the levator hiatus has been shown to be a reproducible measurement [17, 117], whereas the reproducibility was less for muscle...
Figure 9a: Tomographic ultrasound imaging (TUI) in oblique axial plane. Normal attachment of the levator ani muscle.

Figure 9b: Tomographic ultrasound imaging (TUI) in oblique axial plane. Both-sided avulsion of the levator ani muscle from the symphysis pubis.
diameter measurements [17, 98, 111]. Comparisons of the hiatal diameters and hiatal area as measured by three-dimensional ultrasonography and MRI revealed good correlations, especially for the measurements at rest. The correlation for hiatal diameter at Valsalva manoeuvre was lower, which is most likely due to the difficulty to reach the correct plane of the levator ani muscle on MRI [128].

The presence and clinical relevance of paravaginal defects represent a controversial issue amongst urogynaecologists, and there is a lack of scientific proof for the concept. In a study by Reisinger et al., an echogenic layer in the lower anterior vagina, which was thought to be a part of the endopelvic fascia, could be identified reproducibly in nulliparous and parous women by transrectal three-dimensional ultrasonography [129]. According to more recent insights, however, previously described paravaginal defects with loss of the H-shape of the vagina in the axial plane on three-dimensional ultrasonography [124, 130, 131] are likely to represent the detachment of the levator ani muscle from the symphysis pubis [132].

9. PELVIC ORGAN PROLAPSE

In cases of mild and moderate pelvic organ prolapse, perineal ultrasonography can be used, for the investigation of the prolapse. Ultrasonography should, however, only be used in addition to the patients history and clinical examination. In cases of severe pelvic organ prolapse, ultrasonographic assessment is impracticable due to transducer dislocation by the prolapse.

The ultrasonographic imaging of the anterior compartment (i.e. bladder, bladder neck and urethra) is the easiest to perform, and the majority of scientific studies deal with this compartment (Figure 11). Correlations with clinical examination [133, 134] are also highest for this compartment. Reproducibility of ultrasonographic imaging of prolapse in the anterior compartment were shown to be good [133]. This reproducibility has not been studied for the other two compartments until now.

In studies amongst 83 and 117 women with the uterus in situ, the uterus could be visualized on perineal ultrasonography in 82% and 97% of cases, respectively (Figure 12) [134, 135].

A number of studies have focused on the posterior compartment [136-144]). The distinction between enterocele (Figure 13) and rectocele (Figure 14) is known to be difficult on clinical assessment. In these cases, two-dimensional ultrasonographic imaging in the midsagittal plane can be helpful. The ultrasonographic visualisation of an enterocele has been confirmed with defecography as well as intraoperative findings [136]. It has not been shown, until now, however, whether this extra ultrasonographic investigation indeed leads to superior clinical outcomes of prolapse surgery.

In a study on ultrasonography of the posterior compartment a differentiation between true rectocele, enterocele and perineal hypermobility has been made [139]. Intussusception can also be visualised on ultrasonography [145]. The true rectoceles were diagnosed in case of a sharp discontinuity of the rectovaginal septum, with herniation of the rectal wall through this discontinuity and with a depth of at least 10 mm (Figure 15). Perineal hypermobility and an enterocele was seen as a descent of the rectovaginal septum or abdominal content on Valsalva manoeuvre respectively, below a horizontal line through the inferior margin of the symphysis pubis (see below for more information on these measurements). Ultrasonographic staging was significantly correlated with clinical staging and the presence of symptoms of obstructed defecation [15, 140]. In one third of the patients with clinically diagnosed rectocele, however, no ultrasonographic abnormality could be found. As far as interrater reliability was concerned, two expert ultrasonographists have reached moderate to good interrater reliability for the detection of a rectovaginal septum defect, descent of rectal ampulla, and the depth and width of a rectocele [139].

In one study, rectocele and perineal hypermobility were present in nulliparous women in 12 and 13% respectively the significance of these findings has not yet been determined [141].

The posterior anorectal angle, which is the angle between the anal canal and the posterior rectal wall, can be measured at rest and under dynamic circumstances such as straining and squeezing. A number of studies have compared these findings with defecography and found in general a good correlation [143, 144, 146].

10. QUANTITATIVE ASSESSMENT OF PELVIC ORGAN PROLAPSE

In the quantitative assessment of prolapse in the various compartments, a reference line, such as the hymen in POPQ, is needed. For ultrasonography, a horizontal line drawn from the inferior margin of the symphysis pubis is the most widely used reference line for the purpose (Figure 3a). A disadvantage of this line is that only one fixed point through which the reference line is drawn is available, and the horizontal line may thus change with the rotation of a handheld transducer. The effect of rotation is obviously increasing with the distance from the fixed point, and consequently is greatest in the posterior compartment [134]. Although this problem has been overcome in research settings with the use of motion tracking systems, at the moment this is not a realistic option for routine use in clinical practice [147]. For quantitative assessment of rectoceles, the depths of the rectocele as measured
Figure 10: Perineal three-dimensional rendered image. Ballooning of the genital hiatus.

Figure 11: Perineal midsagittal [left upper], coronal [right upper] and axial [left lower] two-dimensional view and three-dimensional rendered image [right lower]. Cystocele.
Figure 12: Perineal midsagittal two-dimensional view. Cystocele and descending uterus. (S= symphysis pubis; B= bladder; U= Uterus; C= cervix.)

Figure 13: Perineal midsagittal two-dimensional view and three-dimensional rendered image. Enterocoele.
(S= symphysis pubis; B= bladder; E= enterocoele; R= rectum; A= anal canal.)

Figure 14: Perineal midsagittal two-dimensional view. Measurement of the depth of the rectocele, perpendicular to a straight line through the anterior border of the anal sphincter complex, i.e. 14 mm.
in relation to a line through the anterior anal canal, may be more useful as compared with the descent in relation to the horizontal reference line [148].

Since pelvic organ prolapse can be visualised well with the use of ultrasonography, it raises the question whether this assessment modality is superior to others, such as clinical examination. In a recent study on the relationship between prolapse symptoms and the most dependent point of the prolapse on POPQ and on ultrasonographic assessment, POPQ performed better in the prediction of prolapse symptoms with increasing stages of prolapse [148]. In a previous study, where only women with a single compartment prolapse were studied, the area under the receiver operating curve was, however, as good as 0.86 and 0.82 for the anterior and posterior compartment respectively [149]. In both studies the cut-off value for symptomatic prolapse averaged 15 mm below the horizontal reference line through the symphysis pubis.

As far as dynamic MRI and X-ray defecography are concerned, there are only a few studies available as yet, on comparisons with ultrasonography. For enterocele detection in women with obstructed defecation, perineal ultrasonography has been compared with X-ray defecography, but not with the clinical findings [143]. In the women in whom enterocele had been detected by either method, the enterocele was detected by both ultrasonography and X-ray in 71% of women. In this study, perineal ultrasonography showed more severe stages of enterocele compared with X-ray defecography. In another recent study from a different research group, X-ray defecography has been compared with perineal ultrasonography using a vaginal probe in women with impairment of the posterior pelvic floor. Good to excellent concordance has been found for the assessment of the anorectal angle, rectocele and intussusception. The authors claimed, however, that rectoceles with a depth less then 20 mm could not be detected on ultrasonography [138], which is discordant with most other publications on the topic and as well as the authors’ experience.

11. ULTRASONOGRAPHY IN RELATION TO PREGNANCY AND DELIVERY

Vaginal childbirth is commonly accepted as the major risk factor for the development of pelvic organ prolapse later in life. In nulligravid women, however, a wide variation in pelvic organ descent has been shown for all three compartments [114, 135, 150-152]. In a study on 169 women who underwent ultrasonography during and after pregnancy, a significant increase in pelvic organ mobility (downwards displacement) has been found in all three compartments [153]. The increase in mobility was significantly correlated with the length of second stage of labour and the mode of delivery. The highest mobility was found in women who underwent an operative vaginal delivery, but no association was found with the length of gestation at delivery, with the length of the first stage of labour, and with birth weight, although birth weight reached borderline significance. In a similar study, focussing on the posterior compartment in 52 nulliparous pregnant women, 8 women developed de novo true rectoceles, and the descent of the rectovaginal septum increased with 22 mm for the entire group, which was statistically significant [154]. On the other hand, in a study amongst 207 women, of whom half of the women had a clinically diagnosed rectocele, no relation has been found with (vaginal) parity, and only a weak correlation has been found with age for a posterior vaginal wall prolapse as assessed with ultrasonography [139]. This suggests that the effect of vaginal parity on pelvic organ descent, is most evident in the anterior and central compartment, and may have
another pathophysiology compared with the posterior compartment [153]. Concerning bladder neck descent, it has been shown that the first delivery caused the most marked changes compared with the subsequent deliveries, with the most marked changes with forceps delivery [155].

Another interesting point of view came from two different research groups, who have reported that an increased antenatal ultrasonographic bladder neck descent was associated with normal vaginal delivery [156, 157]. Furthermore, vaginal delivery was strongly associated with a larger, and more distensible antenatal levator hiatus [156]. The underlying reason remains hypothetical, but more antenatal laxity of the structures may allow for a smoother delivery. Women with increased bladder neck mobility, however, also have a increased risk of de novo urinary incontinence post partum [20].

Avulsion of the levator ani muscle from the symphysis pubis, as outline above, is typically found in vaginally parous women only (Figure 9b) [117, 119, 158]. It has, furthermore, been shown that a higher maternal age at first vaginal delivery is strongly related to an increased risk of these avulsions [117, 158]. These avulsions are again associated with an increased risk of urinary incontinence and more severe stages of prolapse later in life.

12. PELVIC FLOOR SURGERY

Ultrasonography has been used during anti-incontinence surgery with the aim of obtaining optimal results from surgery, for example during Burch colposuspension [159, 160]. On an individual basis, the bladder neck was lifted between 1 mm and 10 mm. The authors have obtained excellent results with a 94% continence rate after 1 year, but unfortunately no control group was incorporated in the study.

13. SLINGS AND MESHES

Monofilament meshes, for example polypropylene meshes, are easier to visualise on ultrasonography compared with multifilament meshes, such as IVS [161]. Ultrasonography has been widely used to localize the exact position of tension free midurethral tapes (Figure 15) [156, 162-165]. The tape is generally easily visible as an hyperechogenic structure under the urethra and is easy to recognize, which is in contrast with the poor visualisation on MRI [166]. Exact midurethral position of the tape is not essential for proper function [167]. Despite the fact that the tape was located in the midurethra in only two-third of cases, this had no relation to postoperative continence status [168]. During Valsalva manoeuvre, the tape moves in a semicircle movement around the inferior margin of the symphysis pubis [169]. This results in a position closer to the symphysis, which consequently leads to a certain degree of mechanical compression during Valsalva manoeuvre. Another mechanism of action is kinking of the urethra around the tape [170]. A number of studies have studied transobturator tape and compared these with retropubic tapes [161, 171-174]. Two studies could not detect any differences between the two types of tape [161, 174], whereas in the other two studies [171, 173], subtle differences with no apparent clinical consequences were found. No study has found a clear correlation between cure of stress incontinence or post-operative voiding troubles and the position of the tape.

Recently, ultrasonographic localization of polypropylene mesh as used in prolapse surgery has been described (Figure 16 and 17) [175]. These meshes are usually easily visible on ultrasonography. It appears that the ultrasonographic appearance of the mesh is significantly shorter than the size at implantation. It is unclear whether this is due to shrinkage of the mesh or represents difficulties in visualizing the full extent of the implanted mesh.

Perineal ultrasonography can, furthermore, be helpful in the assessment of recurrences after mesh implantation. The differentiation between recurrent herniation and the detachment of the mesh arms from the pelvic sidewall for example, will aid in the better understanding of the mode of action of these meshes [176].

14. BULKING AGENTS / INJECTABLES

Periurethral bulking agents/injectables, such as microparticulate silicone (Macroplastique), various gels (e.g. Durasphere, Zuidex) and collagen, can be visualized by imaging techniques. For MRI, an overview of appearances of periurethral bulking agents is already available [177]. On ultrasonography, the injectables appear hypoechogenic after injection, and become more hyperechogenic over time due to dehydrogenation. Good intra-observer variability of repeated measurements of periurethral collagen volumes have been found [178].

The location in relation to the bladder neck and a circumferential distribution of collagen injectables around the urethra, as well as the height and volumes of the injected periurethral collagen bumps, were associated with the treatment success of periurethral bulking agents [178-180]. Although the volume range was wide, a collagen volume of 2.8 cc on three-dimensional ultrasonography has been assessed as optimum volume from a continence point of view. Poon et al. have published a decision tree, in which a combination of the patients’ symptoms after collagen injection and the configuration and volume of the periurethral collagen on three-dimensional ultrasonography, assist in the decision for further treatment of women with intrinsic sphincter deficiency [178]. In this algorithm, women with asymmetric deposition and/or low collagen volumes were offered further treatment with injectables.
Ultrasonography has not only been used for follow-up, but also during placement of periurethral injections. Transurethral ultrasonography-guided injection of autologous stem cells has been used in women and men with stress urinary incontinence.

The technique allowed precise injection of the myoblasts directly into the rhabdosphincter, and was more effective in the resolution of incontinence compared with urethroscope guided collagen injectables in the submucosa in a randomized controlled trial [181, 182]. The use of stem cells in the management of urinary incontinence is of great interest although the subject remains controversial and confirmatory studies are eagerly awaited.

REFERENCES


120. Huebner M, Margulies RU, Delancey JO. Pelvic architectural distortion is associated with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Jan 12.


Ng CC, Lee LC, Han WH. Use of three-dimensional ultrasound scan to assess the clinical importance of midurethral placement of the tension-free vaginal tape (TVT) for treatment of incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2005 May-Jun;16(3):220-5.


Shek C, Dietz HP. Transobturator mesh anchoring for the repair of large or recurrent cystocele. . Neurourol Urodyn. 2006;25:554.


III. MRI

1. BACKGROUND

The role of MRI in evaluating pelvic floor disorders continues to evolve. This technique provides unparalleled images of pelvic floor muscles, connective tissue, and organs. In addition to the detailed static picture of the pelvic organ support system anatomy, MRI can also reveal the downward movement of each pelvic compartment during increases in abdominal pressure. Advances in MRI equipment and software have significantly improved image quality and provides ever more detailed pictures of anatomy and function. At present active investigation is ongoing to try to see if and how this imaging might result in a better understanding of these diseases.

One proposed rationale for the use of MRI in the evaluation pelvic floor disorders derives from the observation that although patients might present with symptoms isolated to one of the pelvic compartments, they may have concomitant defects in other compartments and that imaging can provide information to extend what can be determined on physical examination [1]. Furthermore, it has been suggested that surgical failures could result from lack of a thorough preoperative evaluation of the female pelvis and to inadequate diagnosis and staging of pelvic floor dysfunction [2]; accurate diagnosis of the coexisting abnormalities is essential in planning reconstructive and anti-incontinence procedures. Although most diagnoses of pelvic floor prolapse are made on detailed physical exam, some studies have alluded to the poor sensitivity and specificity of the pelvic exam in diagnosing various forms of pelvic floor prolapse [3-5]. Ultrasound and fluoroscopy have been used to improve diagnosis of certain aspects of pelvic floor dysfunction [6,7] and the role of MRI in pelvic floor dysfunction is rapidly changing and new developments may become clinical mainstays if they can demonstrate improved outcome.

MRI provides anatomical detail of the pelvic floor including assessment of bladder neck and urethral mobility, rectocele, cystocele, enterocoele and uterine prolapse, in a single non-invasive study that does not expose the patient to ionizing radiation [8-17]. MRI also provides a multiplanar thorough evaluation of the pelvic contents including the uterus, ovaries, ureters, kidneys, and levator muscles, as well as the urethra, that is unavailable by any other imaging modality [10,12-16,18,19]. MRI provides useful information regarding ureteral obstruction, hydronephrosis, and uterine and ovarian pathology, which is essential in the management of women with pelvic floor disorders. In addition, at this time, MRI is the study of choice for the evaluation of urethral diverticuli.

Proof that MRI has value will eventually need to come from increased operative success rates. It is possible that better documentation of preoperative and postoperative anatomy could allow us to seek reasons for operative failure. Because MRI provides a detailed picture of a woman’s pre-operative anatomy, once operative failures are discovered, it would be possible to look back at images from women with successful and unsuccessful operations to seek anatomical explanations for failure. This chapter provides a current view of where we are in evaluating the role of MRI in understanding the cause and treatment of pelvic organ prolapse.

2. METHODOLOGY

a) Conventional MRI

Standard MRI consists of two dimensional image acquisitions. Usually conventional T1 images and spin echo T2 weighted images are obtained and specifically proton density T2 weighted scans provide excellent soft-tissue definition (Figure 1). These static images provide good information on patient anatomy and pathological abnormalities but the long imaging time of conventional MRI hampers its ability to evaluate pelvic organ prolapse and pelvic relaxation. The muscular anatomy of the pelvic floor, as well as the anatomy of the pelvic organs can be visualized with the use of a body coil. The use of an endovaginal coil provides superior information regarding the zonal anatomy of the urethra but it can result in deformity of the normal anatomy [20-21]. Recent improvements in Magnet strength and instrument refinement produce remarkable images.

b) Ultra fast image acquisition and MRI sequences

It is possible to see pelvic organ movement during Valsalva using very fast single-shot MRI sequences allowing excellent visualization of the pelvic floor in women [14,15,22-23]. These sequences images allow a series of images to be obtained approximately once per second, either by acquiring a series of images covering the entire pelvis (static imaging) or repetitively in one plane while the patient is straining (dynamic imaging). The patients are placed in the supine position with legs slightly spread apart, and knees bent and supported by a pillow. There is no need for bowel preparation, premedication, instrumentation or contrast medium. The MRI torso coil is centred at the symphysis pubis. Images are acquired in the sagittal plane using single-shot fast spine echo (SSFSE) or half Fourier acquisition, single shot turbo spin echo (HASTE) sequences. Single, mid sagittal views are obtained during 3 seconds of apnea with the patient relaxed and during various degrees of progressive abdominal straining (Figure 2).

During a typical study two sets of images are obtained. The first set consists of static sagittal and para-sagittal...
images covering the pelvis from left to right sidewall. These images provide information on pelvic anatomy, pathological abnormalities, and are used to select the mid-sagittal plane for the dynamic second set of images. This static sequence also allows for anatomic delineation of the pelvic sidewalls and muscular and fascial components of the pelvic floor [14, 15, 22-23] (Figure 1). The perineal membrane and the levator ani musculature, as well as the anal sphincter anatomy, are also clearly demonstrated [24-25].

The static set consists of 17-20 sequential images independently acquired in a total of about 18 seconds. Static images can be acquired with a SSFSE pulse sequence using 128 x 256 matrix with repetition time (TR) of 4000 ms, echo time (TE) of 22.5 ms, 5 mm slice thickness and field of view (FOV) of 28 cm [15]. Other similar sequences have been described.

The second set of images consists of relaxed and straining mid-sagittal images used to assess the degree of pelvic floor relaxation and organ prolapse (Figure 2 a,b). One series [15, 23] describes the SSFSE parameters as 128 x 256 matrix, TR=3000ms, TE=90ms, FOV=28cm and 5 mm slice thickness. Variations in these parameters have been described and thus the image acquisition sequences have are not standardized yet. Images can then be looped for viewing on a digital station as a cine stack.

c) Three dimensional MRI

Three dimensional (3-D) MRI provides great detail of the bony and muscular pelvic structures (Figure 3). In this technique, static or dynamic images are reconstructed using consecutive planes in the axial, sagittal and coronal dimensions. Anatomic variations of the insertion and path of the pubococcygeus and iliococcygeus muscles can be easily seen. Fielding et al. studied nulliparous continent female volunteers and found that the muscle morphology, signal intensity and volume are relatively uniform [28]. They described an average volume of the levator ani of 46.6 cc, width of the levator hiatus of 41.7 mm and an average posterior urethrovesical angle of 143.5°.

3. NORMAL PELVIC ORGAN SUPPORT

Static, dynamic and three-dimensional MRI studies of normal subjects have improved our understanding of normal pelvic anatomy [24-26]. The use of MRI to image the pelvic floor musculature has also contributed greatly to our understanding of pelvic floor dysfunction [19, 21, 27]. MRI has been used to study the normal female pelvic anatomy, as well as the anatomy of the aging female and the symptomatic patient. It has been shown that in the supine position the female pelvic floor is dome shaped at rest [27, 28]. During voluntary pelvic floor contractions the levator musculature straightens and becomes more horizontal. With bearing down the muscle descends, the pelvic floor becomes basin-shaped, and the width of the genital hiatus widens. Studies are usually done with the patients supine and so the anatomy as it is seen in the standing position is not generally possible. Upright static and dynamic MRI are possible, but are used mostly as a research tool because they are not widely available. Recently, Bø et al [33] evaluated the changes seen with pelvic floor contraction in continent and incontinent women using MRI in an upright sitting position. Although there was no statistical difference between the two groups, the authors demonstrated an inward movement with pelvic floor contraction (average 10.8 mm) and an outward movement with straining (average 19.1 mm). This was also reflected in the bladder neck. Interestingly, the coccyx appeared to move in the cranial direction with contraction and caudally with straining.

4. PELVIC ORGAN PROPLASCE

MRI has proven to be a key assessment for understanding pelvic organ prolapse; a problem that arises from damage to connective tissue, muscles, and nerves that are invisible on standard radiography. With the advent of ultrasound and especially MRI the actual structures involved in the cause of prolapse can be seen and examined. This is possible not only in static scans that reveal morphological details of the pelvic structure, but also in dynamic scans where the movements of the various organs can be studied.

a) Normal Pelvic Floor Functional Anatomy

1. MRI OF THE NORMAL PELVIC ORGAN SUPPORT STRUCTURES

MRI in pelvic organ prolapse requires that the specific structures involved are identified and their normal
variations described (Figure 4). Tan [21] demonstrated that the anatomy of the female pelvic floor with endovaginal MRI. Ten healthy nulliparous volunteers (age, 22-26 years) underwent MRI with an endovaginal coil. Pelvic floor structures such as the pelvic diaphragm and the urogenital diaphragm were well depicted as were urethral supporting structures—the peri-urethral and paraurethral ligaments—were visualized. The zonal anatomy of the urethra was clearly visible. The endovaginal MRI findings in the volunteers correlated with the endovaginal MRI findings and gross anatomy in the cadavers. Chou [30] developed a systematic method for analyzing the normal MRI location and appearance of structural features involved in urethral support. Multiplanar proton density MRI of 50 nulliparous women were made at 0.5 cm intervals. This allowed the presence or absence of urethral support structures in each scan level relative to the arcuate pubic ligament to be evaluated and recorded as the percent likelihood that the structure is seen at that level. Support structures examined included the arcus tendineus fasciae pelvis, the perineal membrane, the pubococcygeal levator ani muscle and its vaginal and bony attachments, and the pubovesical muscle. This systematic magnetic resonance evaluation allows quantification of the normal anatomic location of urethral support structures.

Tunn et al [32] addressed the topic of anatomical variation in the normal pelvic floor. They developed a system to quantify inter-individual variation in the appearance of continence system structures in 20 healthy continent nulliparous women (mean age, 30.1 +/- 5.1 years) with normal pelvic organ support and urodynamics. The ratio of the maximum-to minimum measured values shows that 2- to 3-fold differences occur in distance, area, or volume measures of continence system morphologic features that are detailed in the paper. Umek et al [33] found that in 80 healthy women, the uterosacral ligaments exhibited greater anatomic variation than their name would imply.

It has long been recognized that the pelvic floor is greatly distorted in cadavers where loss of muscle tone and pressures caused during embalming distort pelvic floor topography. Otcenasek et al have recently used MRI of a normal nulliparous woman to establish geometry and then added details from dissection to produce an anatomically based topographically normal
Figure 4: Axial images in 22-year-old (A, D, G, and J), 24-year-old (B, E, H, and K), and 34-year-old (C, F, I, and L) nulliparous women without urogynecologic problems. A-C, Level of cervix (Cx) and ischial spine (IS); uterus (Ut) with bright endometrium is also seen. Paracolpium and parametrium suspend (open tips) vagina and cervix from lateral and posterior pelvic sidewall. Smooth muscle of uterosacral ligament (open tips) is best seen in C. GM, Gluteus maximus muscle. D-F, Level of bladder (B) base. Upper vagina between bladder and rectum (R) and its attachment to pelvic sidewall by vascular and connective tissue mesentery (small arrow) are seen. Levator ani muscle (iliococcygeal part, filled arrowhead) arises from arcus tendineus of levator ani muscle (filled arrow). OI, Obturator internus muscle. G-I, At level of proximal urethra, levator ani muscle (pubovisceralis part, filled arrowhead) arises from pubic bone (open arrow). Pubovesicalis muscle (open arrowhead) is clearly seen in H. Vessels (white gap) are visualized between smooth muscle layer of lateral vaginal wall and levator ani muscle at this level. J-L, At level of middle urethra, pubovesicalis muscle is seen as shown in J (open arrowhead). Vessel layer (white gap) between lateral vaginal wall and levator ani muscle (filled arrowhead) has disappeared; direct connection between vagina and levator ani muscle is seen at this level. Small white gap in levator ani suggests fascia between puborectalis and pubococcygeal muscles (especially in J and L). From Tunn et al. 2001. [31]
3-D model that displays the features of pelvic floor anatomy (Figure 5) [34].

2. LEVATOR ANI MUSCLE FUNCTIONAL ANATOMY

Recent work has extended our understanding of normal levator ani muscle anatomy. Guo and Li [35] studied MRI and CT images obtained at rest in 22 male and female volunteers and 10 cadavers. They described levator shape by dividing it into a transverse portion and a vertical portion. The anterior transverse portion was found to be basin-shaped; the middle transverse portion was funnel-shaped, while the posterior transverse portion was dome-shaped. The puborectalis was found to be a u-shaped muscle outside the vertical portion. Detailed information about the specific levator ani muscle subdivisions has also been studied. Margulies et al [36] have used detailed MRI images to visualize the specific origins and insertions of the five Terminologia Anatomica-listed levator ani components: pubovisceral (pubovaginal, puboperineal, and puboanal), puborectal and ilioococcygeal portions of the levator ani muscles in 80 nulliparous women with normal pelvic support.

In the axial plane, the puborectal muscle can be seen lateral to the pubovisceral muscle and decussating dorsal to the rectum. The course of the puboperineal muscle near the perineal body is seen best in the axial plane. The coronal view is perpendicular to the fibre direction of the puborectal and pubovisceral muscles and shows them as “clusters” of muscle on either side of the vagina. The sagittal plane consistently demonstrates the puborectal muscle passing dorsal to the rectum to form a sling that can consistently be seen as a “bump.” This plane is also parallel to the pubovisceral muscle fibre direction and shows the puboperineal muscle. Ultrasound has also been useful in evaluating levator ani muscle morphology. Similarities and differences between MRI and 3-D ultrasound have been studied recently [37] in a group of 27 nulliparous asymptomatic young women. Levator hiatal dimensions were measured and were data acquired at rest, on maximum Valsalva and maximum pelvic floor contraction. Interobserver repeatability was fair to excellent for all parameters measured with both methods. Moderate-to-substantial agreement between methods was shown for all tested parameters (intraclass correlation coefficients 0.587-0.783). There was a systematic but non-significant difference between methods, in that measurements on Valsalva tended to be larger for MRI, and the poorest agreement

Figure 5: Left lateral view from above the female pelvis. The vagina, endopelvic fascia, and levator ani muscle are cut in the sagittal plane. Urethra, urinary bladder, and rectum have been removed. OIM, obturator internus muscle; PCF, pubocervical fascia; ATLA, arcus tendineus levator ani; LA, levator ani muscle; ATFP, arcus tendineus fasciae pelvis; PS, pubic symphysis; VW, vaginal wall; RVF, rectovaginal fascia; ATFR, arcus tendineus fasciae rectovaginalis; PM, perineal membrane; PB, perineal body; EAS, external anal sphincter; SC, space of Courtney; ACR, anococcygeal raphe; ACL, anococcygeal ligament; PM, piriformis muscle; CL, cardinal ligament; USL, uterosacral ligament; C, cervix of the uterus; CM, coccygeus muscle; Co, coccyx; SP, sacral plexus. Illustration: Ivan Helekal. [34]
(intraclass correlation coefficient 0.587) was found for hialtal area on Valsalva. This demonstrates substantial similarity between the two methods for these assessments (Figures 6-7).

3. Functional MRI

Functional MRI of the brain has recently been used to better understand central control of pelvic floor muscles. Kuhntz-Buschbeck et al [38] used functional MRI to identify cortical and subcortical regions involved in voluntary pelvic floor muscle control. During pelvic muscle contraction they found a strong and consistent recruitment of the supplementary motor area (SMA), with foci of peak activity located in the posterior portion of the SMA, suggesting that this region is specifically involved in voluntary pelvic floor muscle control. Further significant activations were identified bilaterally in the frontal opercula, the right insular cortex and the right supramarginal gyrus.

These may reflect the attentive processing and evaluation of visceral sensations. Weaker signals were detected in the primary motor cortex (M1) and the dorsal pontine tegmentum. Similarly Seseke et al [39] in a study of 11 healthy women found that relaxation and contraction of pelvic floor muscles induced strong activation patterns including frontal cortex, sensory-motor cortex, cerebellum, and basal ganglia. Furthermore, well-localized activations were identified bilaterally in the pontine micturition centere and the periaqueductal gray were identified.

4. Pathophysiology

i) Levator ani muscle defects muscle bulk

Although it has long been known that birth is highly strongly associated with pelvic organ prolapse, proof of a specific injury that occurred at birth and was associated with prolapse later in life had not been found. Recent MRI studies have demonstrated that the type of LA injury seen after vaginal birth is highly strongly associated with pelvic organ prolapse. In [40] a case-control study with group matching for age, race, and hysterectomy status 151 women with prolapse (cases) were compared to 135 controls with normal support (controls). Magnetic resonance imaging was used to grade muscle defects on each side from 1 to 3 (with 0 designating normal muscle (Figure 8).

Defect severity for a woman was then classified by adding the scores for the two sides together to make a score from 0 to 6. These were then classified as “major” (4 to 6), “minor” (1 to 3), or no defects (0) in the levator ani muscles. Cases (n=151) were more likely to have major levator ani defects than controls (55% compared with 16%), but equally likely to have minor defects (16% compared with 22%) as seen in Figure 9. These defects had functional consequences. Women with defects generated less vaginal closure force during a pelvic muscle contraction than women without defects (2.0 Newtons compared with 3.1 Newtons) and women with prolapse also generated less vaginal closure force during pelvic muscle contraction than controls (2.0 Newtons compared with 3.2 Newtons), whereas the genital hiatus was 50% longer in cases than controls (4.7 +/- 1.4 cm compared with 3.1 +/- 1.0 cm). This confirmed earlier uncontrolled observations made with ultrasound [41] of urogynecologic patients with ultrasound. This added new information concerning specific muscle defects to previous studies of muscle bulk. It is important to distinguish between muscle thickness and muscle damage. A woman with a normally thin but intact muscle may have less muscle substance than a woman with naturally bulky muscles who has a defect that has involved 25% of her muscle bulk. The issue of muscle damage is relevant to seeing who is injured while that of muscle bulk, with the capability of the muscle to close the hiatus. Loss of muscle bulk in women with pelvic floor dysfunction was studied by Hoyte et al [42]. They studied two- and 3-dimensional MRI comparison of levator ani structure, volume, and integrity in women with prolapse and stress incontinence to identify imaging markers for urodynamic stress incontinence and pelvic organ prolapse by using MRI and reconstructed 3-dimensional models. Thirty women were examined; 10 with prolapse, 10 with urodynamic stress incontinence, and 10 asymptomatic volunteers. Manual segmentation and surface modelling was applied to build 3-dimensional models of the organs. Mean 3-dimensional parameters in the 3 groups showed levator volumes of 32.2, 23.3, and 18.4 cm (P <0.005); hiatus widths of 25.7, 34.7, and 40.3 mm (P <0.005); left levator sling muscle gaps of 15.6, 20.3, and 23.8 mm (P =0.03), right levator sling muscle gaps of 15.6, 22.5, and 30.8 mm, (P =0.003), and levator shape (90%, 40%, and 20% dome shaped; P <0.005). This studies show that MRI can be used to demonstrate both 2-dimensional magnetic resonance images and 3-dimensional models yield findings that differ among asymptomatic subjects compared with those with urodynamic stress incontinence and prolapse. Later in a similar design, they used a novel thickness mapping [43] to studied MRI datasets from 30 women who were studied: 10 asymptomatic, 10 with urodynamic stress incontinence, and 10 with pelvic organ prolapse. They found thicker, bulkier anterior portions of the levators in asymptomatic women, compared with women with prolapse or urodynamic stress incontinence while the more posterior portions of the muscle were not affected.

Hsu and colleagues quantified levator ani muscle cross-sectional area as a function of prolapse and muscle defect status [44]. They selected thirty women with prolapse and 30 women with normal pelvic support. For each of the two groups, 10 women were selected from three categories of levator defect
Figure 6: Three-dimensional model of levator ani subdivisions including the pubic bone and pelvic viscera. This model was created by using the magnetic resonance images shown in Figures 2, 3, and 4. The pubovaginal, puboperineal, and puboanal muscles are all combined into a single structure, the pubovisceral muscle. Inferior, left 3-quarter view. B. The same model without the pubic bone. PB, pubic bone; V, vagina; U, uterus; Ur, urethra; B, bladder; IC, iliococcygeus muscle; PR, puborectal muscle; PVi, pubovisceral muscle; EAS, external anal sphincter [36].

Figure 7: Axial scan of 25-year-old nullipara showing subdivisions of the levator. Level of scan in centimeters relative to the arcuate pubic ligament (A) is indicated in lower left corner with positive numbers cranial to the ligament and negative numbers caudal. Additional abbreviations: PP, puboperineal muscle; PVa, pubovaginal attachment; PA, puboanal muscle; OI, obturator internus muscle; STP, superficial transverse perineal muscle; R, rectum. White arrows indicate puborectal muscle progression [36].
severity: none, minor, and major identified on supine magnetic resonance scans. They calculated muscle cross-sections perpendicular to the muscle fibre direction of the pubic portion of the levator ani muscle based on 3-D reconstructions made from proton-density MRI. The ventral component of the levator muscle of women with major defects had a 36% smaller cross-sectional area, and women with minor defects had a 29% smaller cross-sectional area compared with the women with no defects (P < 0.001). In the dorsal component, there were significant differences in cross-sectional area according to defect status (P = 0.03); women with major levator defects had the largest cross-sectional area compared with the other defect groups. For each defect severity category (none, minor, major), there were no significant differences in cross-sectional area between women with and those without prolapse. This indicates that women with visible levator ani defects on magnetic resonance imaging have less muscle ventrally compared with women with intact muscles. Women with major levator ani defects had larger cross-sectional areas in the dorsal component than women with minor or no defects indicating that compensatory hypertrophy may occur in this area.

ii) Identifying the injury zone within the levator ani muscle most often involved by injury

The specific anatomical location of these injuries has been studied in several ways. Otcenasek and colleagues [45] created two 3D computer models of the female pelvic floor, one of a healthy nulliparous woman and the other of a woman with bilateral puborectal muscle avulsion after vaginal delivery based on magnet resonance imaging examinations. They found that the damage affected the pubic origin of the muscle and that this structurally altered the support to the whole endopelvic fascia and destabilized both the anterior and the posterior vaginal walls. Margulies [46] extended these findings by examining a unique set of 14 women who had significant muscle on one side that allows normal muscle and damaged muscle to be compared in the same individual. This allowed the anatomical connections affected by defects the pubovisceral portion of the muscle to be studied using 3-D reconstructions of the levator ani muscles the normal side in each woman could be compared with the side with muscle damage. It was shown that the injury involved the muscle’s origin from the posterior pubic bone. The insertion points of the missing muscle involved its connections with the vaginal wall, perineal body, and the space between the internal and external anal sphincter. It was accompanied by distortion of the surrounding connective tissue with lateral spilling of the vagina towards the obturator internus muscle in 50% of women. The defect was right sided in 71% of patients. In a separate study quantifying the amount of muscle lost in these types of injury, Chen [47] found that the average difference between the normal side and the defective side was up to 81% at locations...
nearest the pubic origin. Almost all of the volume difference (13.7%, P=0.0004) was attributable to a reduction in the pubic portion (24.6%), not the iliococcygeal portion of the muscle (Figure 10).

iii) Changes in the hiatus size and levator plate angle with prolapse

The levator ani muscles constant activity closes the genital hiatus. In addition to evaluating defect status and muscle bulk, MRI has revealed changes in the levator hiatus and angle of the levator plate (that midline portion of the muscle between the anus and the coccyx) whose angle is presumed to be influenced by muscle action. Hsu and colleagues [48] studied 68 women with pelvic organ prolapse and 74 normal controls. During Valsalva, controls had a mean levator plate angle of 44.3 degrees. Cases had 9.1 degrees (21%) more caudally directed levator plate angle compared to controls (53.4 degrees vs. 44.3 degrees), 15% larger levator hiatus length (7.8 cm vs 6.8 cm), and 24% more caudal perineal body location (6.8 cm vs 5.5 cm).

Increases in levator plate angle were correlated with increased levator hiatus length (r = 0.42) and perineal body location (r = .51). Ansquer and colleagues [49] sought to see if hiatus dimensions parameters varied with the degree of prolapse present in 40 patients referred for evaluation prior to genital prolapse surgery. They found that greater bladder neck descent at straining was correlated with the larger levator plate angle at rest, hiatus length at rest and at straining. Uterine cervix descent at straining was correlated with increased hiatus length and width at straining, and greater levator plate angle (p=0.007) at straining. Paradoxically anterior rectal bulging at straining was inversely correlated with the hiatus width at rest (p = 0.04).

Perineal descent and localized outward bulging of the during Valsalva was evaluated by Gearhart and colleagues [50]. In this study, dynamic magnetic resonance imaging of symptomatic patients with pelvic floor prolapse demonstrated unsuspected levator ani hernias. Eighty consecutive patients with pelvic organ prolapse, faecal and/or urinary incontinence, or chronic constipation were evaluated. Twelve patients (15 percent) were found to have unilateral (n = 8) or bilateral (n = 4) levator ani hernias on dynamic magnetic resonance imaging. No one specific symptom was directly associated with the presence of a levator ani hernia. Perineal descent on physical examination was associated with the finding of a levator ani hernia in nine patients. At present, the clinical implications of these hernias remain to be determined.

b) MRI of pelvic floor after vaginal delivery

Vaginal birth increases the likelihood that a woman will develop pelvic organ prolapse by 8 fold after 2 deliveries and 12 fold after 4 [51]. There are changes observed in the levator ani and pelvic floor musculature immediately after delivery that appear to change over time. Boreham [52] evaluated the normal visibility of the levator in postterm nulliparas using 3-dimensional (3-D) magnetic resonance. They studied 84 nulliparas and found that LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in the 92%. Mean LA volume was 13.5 (3.7) cm³. Interestingly there was a positive association between LA volume and higher fetal station increasing BMI. Tunn evaluated the changes that occur after delivery studying patients on postpartum day 1 and compared the MRI images to those obtained at 1, 2, and 6 weeks and 6 months after delivery [53]. They evaluated levator muscle signal intensity, muscle topography, muscle thickness and pelvic floor descent. There was increased muscle signal intensity on T2 weighted images at 1 day postpartum but the signal intensity approached normal by 6 months. The area of the urogenital and levator hiatus decreased significantly by 2 weeks postpartum. There was no statistically significant difference seen in muscle thickness over time. More recent studies have added further information to these investigations. Lienemann [54] studied 26 primiparous women after vaginal delivery and had a control group of 41 healthy asymptomatic nulliparous volunteers. They found thinning of the puborectal muscle in the study group (0.6 cm vs. 0.8 cm) and increased descent of the bladder, vaginal fornix, and anorectal junction in the study group during straining.

The relationship between delivery method and levator anatomy, has been studied. Baytur et al evaluated pelvic floor anatomy seen in MRI scans and muscle function after childbirth in young women who were recruited into 3 groups: 1. elective, prelabour caesarean delivery (n =12); 2. vaginal delivery (n = 15); and 3 age-matched nulliparas as controls (n = 13) [55]. Descent of the bladder and cervix on straining was greater in the subjects who delivered vaginally than in the caesarean delivery and nulliparous groups. There was a positive and significant correlation between the duration of labour and the area of the levator sling and also between birth weight and the descent of the cervix on straining.

In a study that evaluated changes in the levator ani muscles among primiparous women, DeLancey [56] studied 80 nulliparous asymptomatic women, 160 vaginally primiparous women half of whom had new stress incontinence after their first birth. A visible defect in the levator ani muscle was identified in 32 primiparous. Twenty-nine of these 32 defects were in the pubovisceral portion of the levator and three were in the iliococcygeal portion. Both unilateral and bilateral defects were found. None of the nulliparous women showed these abnormalities. In a further study of this cohort they [57] evaluated obstetric factors associated
with development of levator ani injury after first vaginal birth. There were increased odds ratios for levator defect were found: forceps use 14.7, anal sphincter rupture 8.1 and episiotomy 3.1 but not vacuum delivery 0.9 or oxytocin use 0.8. Women with levator injury were 3.5 years older and had a 78-minute longer second stage of labour. Differences in gestational age, birth weight, and head circumference were not statistically significant. The traumatic nature of these lesions has been supported by Dietz [58] who has reported the specific findings in a woman at vaginal delivery with a visible tear who had persistent evidence of muscle injury at 6 months on imaging. Excellent prospective information about damage is also available from 3-D ultrasound although this imaging modality is outside the topic covered by this chapter [59].

Danneker [60] studied women who experienced spontaneous vaginal delivery (n = 26) and compared them with women delivering by vacuum extraction (n = 49) and a control group that consisted of healthy nulliparous volunteers (n = 20). Significant differences for individual POPQ component measurements were noted for points Aa and Ba, TVL, and GH (spontaneous delivery versus control) and in addition for Ap, Bp, and D (vacuum extraction versus control). Significant differences for MRI measurements were observed for the position of bladder base, bladder neck, posterior fornix of the vagina, anorectal junction, hiatus perimeter and depth of rectocele.

Branham and colleagues [61] assessed postpartum changes in the levator ani muscle related these changes to obstetric events in 45 primiparous women and 25 nulliparous women comparing their status at 6 weeks to that at 6 months after delivery. The occurrence of muscle abnormality at any of the 4 sites (pubovisceral or iliococcygeal; left and right) was considered as abnormal. In those subjects recovering to normal magnetic resonance by 6 months an average of nearly 60% increase in right puborectalis muscle thickness compared with that seen at 6 weeks indicated the extent of the injury. Subjects with injury to both the “puborectalis” and iliococcygeus at 6 weeks did not recover to normal at 6 months, whereas those with injury only to the puborectalis tended to have normal magnetic resonance images at 6 months.
Younger white primiparous women had a better recovery at 6 months than older white women.

5. MRI AND BIOMECHANICAL INVESTIGATION OF THE PELVIC FLOOR

Dynamic MRI has allowed specific mechanistic hypotheses to be tested. Summers and colleagues [62] evaluated whether the degree of anterior compartment (bladder) and apical compartment (cervix) prolapse are correlated with maximal Valsalva. They studied 153 women with a complete spectrum of pelvic support loss from normal support to stage 4 prolapse using dynamic magnetic resonance scans taken during Valsalva. They found that there was a strong correlation ($r^2 = 0.53$) between prolapse of the how far the bladder base and of uterine cervix were below normal with was $r^2 = 0.53$ indicating that slightly over half of the observed variation was explained by apical support. Further analysis in the same patients to evaluate what other factors might be associated with cystocele size [63]. Anterior vaginal wall length, location of distal end of the vaginal wall and the curvature of the anterior wall were measured during maximal Valsalva. Vaginal length was the strongest secondary factor determining 30% of the variation after apical descent was taken into account. This finding that a longer vaginal wall was associated with increasing cystocele size was unexpected, but seems consistent with clinical observations.

MRI has also allowed anatomically based biomechanical models to be constructed. Simulations performed with these models have demonstrated important interactions between muscle and connective tissue in providing for anterior vaginal wall support [64]. MRI has also been used as a basis for biomechanical analysis by allowing construction of finite element analysis [65,66] and has allowed for capture of 3D shape variation of the levator ani during straining for studying dynamic shape changes of 3D structures where complete volumetric imaging is prohibited by the inherent temporal resolution of the scanning technique [67]. Research is just beginning on evaluating changes that can be seen in the vaginal wall and support tissues. Hsu et al. for example used axial magnetic resonance imaging to test the null hypothesis that no difference exists in apparent vaginal thickness between women with and those without prolapse [68]. They found that vaginal thickness is similar in women with and those without pelvic organ prolapse. However, the vaginal perimeter and cross-sectional areas are 11% and 20% larger in prolapse patients respectively. These techniques should provide objective evidence of changes in the tissues involved in pelvic organ support.

a) Racial differences in pelvic dimensions

There has been interest in racial differences in the occurrence of pelvic floor dysfunction. Several groups have evaluated differences in the bony pelvis and the levator ani muscles between women from different races [69-71]. In a study by Handa et al, 59 women with pelvic floor disorders were compared with 39 women without pelvic floor disorders. After controlling statistically for age, race, and parity, a wider transverse diameter (odds ratio 3.4) and a shorter obstetrical conjugate (odds ratio 0.2) were found to be associated with pelvic floor dysfunction. Hoyte and colleagues compared pelvic morphology between asymptomatic African-American and white nulliparas in 3-D reconstructions from resting supine T2-weighted MRI images in 12 African-American (AA) and 10 white American (WA) women without pelvic floor dysfunction [70]. They found that levator ani volume was significantly greater in the AA compared to the WA group (mean = 26.8 vs. 19.8 cm$^3$, $P = .002$). The levator-symphysis gap was smaller in the AA (left-18.2, right-18.8 mm) versus the WA group (22.4, 22.6 mm, $P = .003$, .048) on the left and right. Significant differences were also seen in bladder neck position, urethral angle, and the pubic arch angle. In another study Downing et al compared levator and obturator thickness between asymptomatic black and white nulliparas using three-dimensional (3D) MRI colour mapping [71]. Using 3D color-mapped MRI of pelvic muscles in 22 similar nulliparas black (n=12) and white (n=10) women they found that levator thickness was significantly greater in blacks bilaterally yet obturator internus muscle thicknesses were similar. Hnda et al used static and dynamic MRI to compare dimensions of the bony pelvis and soft tissue structures in a sample of African-American and white women [72]. They included 104 primiparous women with an obstetric anal sphincter tear, 94 who delivered vaginally without a recognized anal sphincter tear and 36 who underwent caesarean delivery without labour. They found that the pelvic inlet was wider among 178 white women than 56 African-American women (10.7+/-.0.7 cm compared with 10.0+/-.0.7 cm, $P<0.001$). The outlet was also wider (mean intertuberosity diameter 12.3+/-.1.0 cm compared with 11.8+/-.0.9 cm, $P<0.001$). There were no significant differences between racial groups in interspinous diameter, angle of the subpubic arch, anteroposterior conjugate, levator thickness, or levator hiatus. A broader group of races was studied by Rizk et al who studied dynamic pelvic floor and bony pelvic morphologic condition with MRI in asymptomatic multiethnic nulliparous young volunteers from 5 ethnic groups (n=11 x 5 volunteers: Emirati, other Arab, Filipino, Indian/Pakistani, and European/white volunteers), with the white volunteers as the reference group [73]. The white volunteers were significantly taller ($P<0.0001$) than the other women. Their levator hiatus was significantly longer than the Emirati women ($P=0.03$) and wider than the Filipino women ($P=.04$). The bladder neck descent on straining was also
significantly greater than the other groups (P <0.00001). The white women also had the longest transverse diameter of the pelvic inlet (P=0.002). Their sagittal outlet diameter was significantly longer than the Emirati and Arab women (P=0.02), and their interspinous diameter was significantly longer than the Arab women (P=0.002).

1. MRI FOR CLINICAL EVALUATION OF PROLAPSE

There is growing experience with evaluating in the interpretation of MRI images of pelvic organ prolapse the type and size of prolapse visible in MRI. Several ways in which this might enhance patient care and treatment outcome are under investigation.

2. ENTEROCELE

Enterocoele can be seen during MRI [74,70]. In the past enterocoeles were usually only appreciated on radiographic examination after repeated straining after evacuation and usually required opacification of the vagina in order to demonstrate the insinuation of small bowel loops between the rectum and vagina [75]. MRI has proven to be a much simpler and less invasive technique for the evaluation of enterocoeles. Gousse et al. compared physical examination, intraoperative findings and MRI images in women with and without prolapse [15]. The investigators found that when compared to intraoperative findings, MRI had a sensitivity of 87%, specificity of 80%, and positive predictive value of 91%. MRI was significantly superior in detecting enterocoele when compared to physical examinations. The images are obtained with the patient supine in the relaxed and straining state (Figure 11). Neither instrumentation nor invasive procedures are required. Similarly, Lienemann et al., using MRI with opacification of organs with ultrasound gel, showed that MRI had a much higher sensitivity for detection of enterocoeles when compared to physical exam and dynamic cystoproctography [76]. Whether or not this technique alters clinical outcome remains to be seen.

b) CYSTOCELE

High-grade cystoceles, as other forms of prolapse, usually do not occur in isolation and represent a spectrum of pelvic floor dysfunction [1, 3, 14]. When a large vaginal mass is present differentiating between a high-grade cystocele, an enterocoele, vaginal vault prolapse or high rectocoele by physical examination alone can be challenging for those inexperienced with physical examination of prolapse [3-5]. Gousse et al. found that, repair of only the cystocele without attention to the rest of the pelvic floor predisposes patients not only to increased incidence of urinary incontinence, but also to an increased incidence of enterocoele, rectocoele, and/or uterine prolapse postoperatively [15]. In the same study, MRI had a sensitivity of 100%, specificity of 83%, and positive predictive value of 97% when evaluating for cystocele compared to intraoperative findings.

In addition, urethral hypermobility and post-void urine residual can be documented, as well as evaluation of ureteral obstruction and other pelvic abnormalities. Gousse et al. also found that MRI was able to diagnose other type of pelvic pathology besides prolapse in 55 of 100 patients studied, including 3 with bilateral hydrourereteronephrosis. Figures 12 a, b show an MRI of two patients with grade 2 and 3 cystocele, respectively.

Other uses of MRI can also be helpful in documenting the status of pelvic organ support as part of a program to assess operative efficacy [77,78] and differentiating such problems as Müllerian remnant cysts from cystocele [79].

c) RECTOCELE

Rectoceles have been considered to exist in up to 80% of asymptomatic patients with pelvic floor dysfunction [13]. The diagnosis is usually made by physical exam, the reported sensitivity of pelvic examination for diagnosis of rectocoele ranges from 31% to 80% [3-4, 6, 80,81]. This is usually secondary to organ competition for space in the vagina when accompanied by other significant prolapse [7]. In addition, it is often difficult to reliably distinguish an
enterocele from a high rectocele. Figure 13 shows a rectocele diagnosed by dynamic MRI. A rectocele is easily seen when filled with gas, fluid, or gel. Although highly specific, when no rectal or vaginal opacification is used, MRI can miss up to 24% or rectoceles [15].

When rectal opacification is used during MRI, a correct diagnosis of rectocele can be made in 100% of patients studied when compared to intraoperative findings [18]. It therefore appears that in order to increase MRI's ability to diagnose rectocele, rectal opacification is necessary. This is usually accomplished by introducing sonographic transmission gel or gadolinium into the rectum prior to MRI scanning. In complex situations such as rectal intussusception [82] by distinguishing mucosal from full-thickness descent MRI can provide important information. MRI defecography also shows movements of the whole pelvic floor.

In this study, 30% of the patients studied were found to have associated abnormal anterior and/or middle pelvic organ descent that would not necessarily be seen in traditional evacuation proctography (unless opacification of vaginal, bladder and intestine are carried out).

What remains unclear is the relationship between anatomical findings and functional problems. The diagnosis of an anatomical abnormality does not mandate surgery. Simply identifying a woman has having a rectocele on an imaging study based on the location of the intestinal lumen to a reference line does not mean that correction of the rectocele will cure defecation problems. Rectocele surgery is not without complications and the risk of dyspareunia after posterior colporrhaphy is real. Attention should be paid to make sure that symptoms are truly depending on stool trapping and the condition must be shown on imaging.

d) Uterine Prolapse

Although uterine prolapse is easily diagnosed on physical examination MRI is an excellent modality to permanently record the structural relationships with the bladder and rectum present in patients with uterine prolapse (Figure 14). In addition to depicting the position of the uterus and adjacent organs, it has the ancillary benefits that evaluates not only uterine size, position, orientation (retroversion) and pathology (fibroids, tumours, Nabothian cysts, etc.), but also ovarian pathology (cyst or mass) which is essential information in may sometimes prove useful if these problems have not been picked up on physical examination is helpful information in determining if a vaginal of abdominal hysterectomy is indicated. In addition, MRI provides information on the presence or absence of cystocele, rectocele, urethral hyper-mobility and urethral diverticula, and evaluates for ureteral obstruction [9-10, 13-15, 83]. Gousse et al. reported a sensitivity of 83%, a specificity of 100% and a positive predictive value of 100% when comparing dynamic MRI to intraoperative findings. These numbers were similar when compared to physical examination alone [15]. More importantly, MRI was able to clearly define the other compartments of the pelvic floor and diagnose uterine and/or ovarian disorders in 30 of 100 patients evaluated [15].

e) Grading of pelvic floor relaxation

A number of studies have described reference values for grading organ prolapse [14-15, 17]. In order to evaluate pelvic organ descent, certain anatomical landmarks are used. The pubococcygeal line (PCL) marks the distance from the pubis to the coccyx and serves as a fixed anatomical reference. In the nomenclature used by Comiter et al. [14], Gousse et al. [15], and Barbaric [23], the width of the levator hiatus is measured as the distance from the pubis to the pubococcygeus muscle (H-line). The hiatus is
formed by the puborectalis muscle and encompasses urethra, vagina, and rectum. The M-line depicts the relaxation of the muscular pelvic floor by measuring the descent of the levator plate from the pubococcygeal line. Using these three simple measurements, an MRI classification for degree of organ has been described [14, 23]. In the normal population, during straining, the hiatus (H-line) is less than 6 cm long and does not descend (M-line) more than 2 cm below the PCL line. The upper urethra, urethrovesical junction, bladder, upper vagina, uterus, small bowel, sigmoid colon, mesenteric fat and rectum are all above the H-line. As the pelvic floor descends, so do the organs above it. The grading system for prolapse of any pelvic organ is based on 2 cm increments below the H-line, the degree of rectocele, enterocele, cystocele, and uterine descent can be graded in a 0 to 3 scale as follows: 0=none, 1=minimal, 2=moderate, and 3=severe (Table 2). Other similar systems have been described [17] and therefore there is a need for standardization of nomenclature and grading of organ prolapse using MRI. Singh et al [84] assessed a new technique of grading pelvic organ prolapse by using dynamic MRI with the clinical staging proposed by the POP-Q system [85]. In a cross-sectional study, 20 patients with pelvic organ prolapse underwent dynamic MRI and clinical staging along with 10 women with normal support. A new reference line, the mid-pubic line, was drawn on the magnetic resonance image to correspond to the hymenal ring marker used in the clinical staging. The proposed staging by MRI showed good correlation with the clinical staging (kappa = 0.61). As this more closely approximates the location of the clinically used hymenal ring, the mid-pubic line was a useful reference line for grading prolapse on magnetic resonance imaging.

Torricelli [74] also used MRI to evaluate functional disorders of the female pelvic floor. Healthy volunteers and 30 patients with clinically suspected pelvic floor deficiency, with or without pelvic organ prolapse, were evaluated both at rest and during Valsalva’s manoeuvre. In the group of symptomatic women, MRI confirmed the pelvic examination findings in all cases; In 7 cases MRI detected additional alterations (4 cases of uterine prolapse and 3 of enterocele) that had been missed at clinical evaluation. Whether or not these would have been noted at the time of surgical repair or not remains to cannot be determined.

Figure 13: Resting (a) and straining (b) midline sagittal section showing a rectocele that traps intestinal contents.

Figure 14: Pelvic Floor MRI: Uterine Prolapse
Deval [85] compared dynamic MRI with physical examination as an alternative to dynamic cysto-proctography for the evaluation of pelvic floor prolapse. Pubococcygeal line and puborectalis muscle were the references points. The grading system is based on the degree of organ prolapse through the hiatus and the degree of puborectalis descent and hiatal enlargement. They also used the mid pubic line drawn on the magnetic resonance image to correspond to the hymeneal ring marker used in clinical staging. Intra-operative findings were considered the gold standard against which physical examination, dynamic colpocysto-defecography and MRI were compared. Using these criteria the sensitivity, specificity and positive predictive value of MRI were 70%, 100%, 100% for cystocele; 42%, 81%, 60% for vaginal vault or uterine prolapse; 100%, 83%, 75% for enterocele; 87%, 72% and 66% for rectocele.

More recently Etlik [86] studied 46 patients who were known to have pelvic prolapses from their vaginal examination and thirty women who underwent vaginal examination and shown not to have pelvic prolapse served as a control group. Physical examination and MRI findings were very concordant in the diagnosis of pelvic prolapse and statistical correlations in the stages of prolapse between both of the methods were significant for anterior and middle compartment (P<0.01), as well as for posterior compartment (P<0.05).

6. ASSESSING TREATMENT OUTCOME

a) Pelvic Organ Prolapse operations:

Various studies have looked at the anatomic changes seen after surgical procedures in order to better understand how surgical therapies affect pelvic support and structures. Lineman et al. [87] evaluated women after abdominal sacrocolpopexy. The authors found that functional cine MRI identified the exact sacral fixation points after the procedure and easily identified the axis of the vagina and the exact position of the synthetic material used for the repairs. Goodrich et al. used MRI to provide a dynamic analysis and evaluation of patients before and after surgical repair to evaluate structures involved in pelvic support [42]. Similar studies will be needed in order to better evaluate the structures important for pelvic support and, continence as well as the effects of surgical interventions. Sze [88] used MRI to study vaginal configuration on MRI after abdominal sacro-colpopexy and sacrospinous ligament suspension. This study was able to demonstrate the differences in the geometry of these two operations and should prove helpful in establishing outcome variables for different surgical procedures. Similarly Rane [89] used MRI to compare the vaginal configuration on MRI following transvaginal sacrospinous fixation (SSF), posterior intravaginal slingplasty (PIVS) (intracoccygeal sacropexy) and sacrocolpopexy (SCP) and was able to demonstrate significant improvements in the restoration of vaginal configuration were achieved in patients and differences between the procedures in final anatomy.

Boukerrou [90] used MRI scans to compare outcomes of 1) abdominal (Sacral cervicopexy), 2) vaginal hysterectomy with paravaginal repair, sacrospinous suspension and posterior colporrhaphy and 3) sacrospinous suspension and posterior repair without paravaginal suspension demonstrating objective effectiveness provided by these three techniques. The correction provided by the vaginal route resulted in a return of the bladder and the vaginal apex to their normal positions, which clearly demonstrates the short-term effectiveness of these surgical suspensions. In addition they confirmed that vaginal shortening and postoperative change in vaginal orientation were not present postoperatively.

Relationship between assessment of surgical correction studied with MRI and symptoms have been studied reported. Gufler [91] studied 15 patients with uterovaginal prolapse and 15 asymptomatic female volunteers comparing preoperative evaluations with those determined two to four months after surgery. Of the seven patients who had symptoms postoperatively, only two had abnormal findings on physical examination but MRI showed pathologic findings in five of the seven patients. Huebner et al. assessed symptomatic changes after anterior levatorplasty with morphologic changes visualized by magnetic resonance defecography [92]. They were able to demonstrate that anterior levatorplasty improved quality of life in patients with symptomatic rectocele and that correction of rectocele is accurately documented by magnetic resonance defecography, however only moderate correlation between morphologic and clinical improvements was observed.

### Table 2. Grading of hiatal enlargement, pelvic organ prolapse and pelvic floor descent using MRI

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hiatal enlargement</th>
<th>Pelvic Organ Prolapse</th>
<th>Pelvic floor descent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Less than 6 cm</td>
<td>Organ above H line</td>
<td>0-2 cm</td>
</tr>
<tr>
<td>1</td>
<td>6-8 cm</td>
<td>0-2 cm below H line</td>
<td>2-4 cm</td>
</tr>
<tr>
<td>2</td>
<td>8-10 cm</td>
<td>2-4 cm below H line</td>
<td>4-6 cm</td>
</tr>
<tr>
<td>3</td>
<td>10 cm or more</td>
<td>4 cm or more below H line</td>
<td>cm or more</td>
</tr>
</tbody>
</table>
b) Pelvic Floor Muscle Exercises

Studies have also been conducted concerning the effects of pelvic floor muscle training on the pelvic floor [93] demonstrating reduced levator ani surface area and volume encircled by the levator ani muscle at rest and during contraction. The fact that muscle morphology might be affected by training was investigated by comparing elite athletes to normal women, finding significant differences in the cross-sectional area and width of the pelvic floor muscles, measured in the line of the anal canal between athletic group and the controls [94]. These types of studies are being facilitated by improved techniques of aligning contracted and non-contracted muscle [95]. Assessment of techniques to evaluate structure and function has recently been reviewed [96].

7. COMPARISON OF MRI WITH OTHER EXAMINATIONS AND ASSESSMENT OF RELIABILITY

In the evaluation of incontinence and simple low-grade cystoceles, the studies of choice in the past have been the voiding cystourethrogram (VCUG) and urodynamics. VCUG is useful in determining the severity of cystocele, evaluating for urethral hypermobility, and SUI, and documenting PVR [6]. In addition to the above information, the evaluation of high-grade cystoceles should also provide information on concomitant pelvic floor prolapse and the presence or absence of urinary retention and ureteral obstruction [9-10, 13-15, 83]. Gufler et al. compared chain cystourethrography with dynamic MRI [83]. The authors found that with pelvic straining the measurements of bladder neck descent, angle of the urethra and the posterior urethrovaginal angle, were not significantly different. This was not the case with perineal contraction, where the difference between the measurements was more marked. In the diagnosis of cystocele, MRI had a high degree of correlation to lateral cystourethrography with a Spearman correlation coefficient of 0.95 [83].

Until recently, dynamic contrast roentography and multiphasic fluoroscopic cystocolpoproctography were considered the best radiological studies for detecting organ prolapse. These studies rely on the opacification with contrast material of the bladder, vagina, small bowel, and rectum with all organs opacified together or in phases with each organ opacified individually prior to each straining phase [4, 89, 92,93]. These studies fail to detect up to 20 percent of all enteroceles [93, 97-99]. Therefore, MRI has proven to be a much simpler and less invasive technique for the evaluation of enteroceles. In addition, MRI is able to differentiate the enteroceles according to their contents (small bowel, large bowel, rectosigmoidocele or mesenteric fat). MRI is also an excellent study to differentiate high rectoceles from enteroceles, thus allowing adequate surgical planning and safer planes of dissection [14, 15, 18, 76]. Although a recent study found that multiphasic MRI with opacification of organs and multiphasic fluoroscopic cystocolpoproctography had similar detection rates for enterocele [97], excellent images can be obtained from dynamic MRI without giving the patient oral contrast for opacification of the small bowel or giving rectal contrast. Thus the minimal added information obtained by contrast administration does not seem to warrant the invasiveness of organ opacification at this time [15, 75, 98].

In the evaluation of rectoceles, evacuation proctography has been used to diagnose enteroceles, rectoceles, perineal descent and rectal intussusception. Dynamic contrast roentography or fluoroscopic cystocolpoproctography have also been used [4. 80,81, 97,100] to diagnosed rectoceles. The disadvantages of these techniques are the inability to visualize the soft tissue planes comprising the pelvic floor, their invasiveness, and their use of significant levels of ionizing radiation. Without the use of rectal opacification, MRI appears to be a poor choice for the evaluation of rectoceles missing up to 25% of such defects. When rectal opacification is used during MRI, Tunn et al. showed that a correct diagnosis of rectocele can made in 100% of patients studied when compared to intraoperative findings [18]. Other investigators have also shown that triphasic dynamic MRI and triphasic fluoroscopic cystocolpoproctography have similar detection rates for rectocele [97]. Recently, upright dynamic MRI defecating proctography has been reported [101]. Although these studies might prove to be more sensitive in detecting anorectal anomalies, their utility seems to be more pronounced in patients with disorders of defecation include anismus, intussusception, and others, and may be too invasive to justify their routine use in the evaluation of rectocele.

Kaufman [102] evaluated dynamic pelvic magnetic resonance imaging and dynamic cystocolpoproctography in the surgical management of females with complex pelvic floor disorders. Twenty-two patients were identified from a Pelvic Floor Disorders Centre database who had symptoms of complex pelvic organ prolapse and underwent dynamic MRI, dynamic cystocolpoproctography, and subsequent multidisciplinary review and operative repair. Physical examination, dynamic MRI, and dynamic cystocolpoproctography were concordant for rectocele, enterocele, cystocele, and perineal descent in only 41 percent of patients. Dynamic imaging lead to changes in the initial operative plan for 41 percent of patients. Dynamic MRI was the only modality that identified levator ani hernias. Dynamic cystocol-poproctography identified sigmoidoceles and internal rectal prolapse more often than physical examination or dynamic MRI. Whether this type of imaging creates measurably better outcomes remains to be seen. Singh et al [103] showed was reasonably good correlation between
clinical staging and MRI staging (Kappa = 0.61) with the mid pubic line being used as a surrogate for the hymenal ring. In addition, specific features such as the levator-vaginal angle the area of the genital hiatus could be assessed quantitatively on magnetic resonance images. Torricelli [74] studied ten healthy volunteers and 30 patients with suspected pelvic floor deficiency with and without pelvic organ prolapse. They compared MRI findings with findings on pelvic examination. They found good concordance between physical examination and MRI with four cases of uterine prolapse and three cases of enterocele seen on MRI that had not been suspected on pelvic examination. Whether these would have been detected at the time of surgery was not discussed. In a study looking at the diagnostic characteristics of pelvic floor imaging, Deval [104] compared intraoperative findings as a gold standard for MRI based diagnosis. Using these criteria, they found that the sensitivity, specificity, and positive predictive value of MRI were 7%, 100%, 100% for cystoceles; 42%, 81%, 60% for vaginal vault and positive predictive value of MRI were 7%, 100%, 75% for enteroceles; 87%, 72%, 66% for rectocele. Although all of these measurements are somewhat subjective, these figures show that it is possible to quantify the individual elements of pelvic floor dysfunction. in reasonable parameters.

**RECOMMENDATIONS**

1. MRI is not yet indicated in the routine evaluation of patients with [uncomplicated primary] pelvic organ prolapse; however data concerning the causes of prolapse are rapidly accumulating and this may change soon. It can provide useful information concerning complex prolapses and can be used in difficult cases. [Level of evidence 3, Grade of Recommendation C]

**SUGGESTED RESEARCH AREAS**

1. Studies that identify specific defects in the connective tissue and the muscles of the pelvic floor that correlate these findings with the clinical presentation in prolapse are needed.
2. Additional studies comparing MRI of healthy volunteers and patients with pelvic organ prolapse are needed to better evaluated the anatomic changes involved in pelvic floor prolapse.
3. Quality control in MRI, including: what maneuversmanoeuvres are required to produce a maximal prolapse during MRI, standardisation of bowel conditions, degree of bladder filling, pushing instructions, etc.)

**REFERENCES**


I. POST-VOID RESIDUAL

Post-void residual urine (PVR) is defined as "the volume of urine left in the bladder at the end of micturition [1]. Evaluation of PVR prevalence in women with symptomatic pelvic floor dysfunction suggests that 81% have a post-void residual of 30 ml or less [2]. This is not significantly different from asymptomatic perimenopausal and postmenopausal women in whom 15% of subjects had a PVR greater than 50 ml [3]. If symptoms can not predict elevated PVR, a urogenital prolapse beyond the hymen seems to be associated with incomplete bladder emptying [4]. Among patients with symptoms of overactive bladder, age older than 55 years, prior previous incontinence surgery, history of multiple sclerosis and vaginal prolapse stage 2 or greater, were found to be independent predictors of elevated PVR [5]. Similar data were obtained by Fitzgerald in patients with urgency incontinence, the presence of pelvic organ prolapse ≥stage 2, symptoms of voiding difficulty and absence of stress incontinence symptoms predicted 82% of patients with elevated PVR [6]. Higher prevalence of post-void residual was found in patients with stress urinary incontinence with 35.5% of women had a PVR >50 ml suggesting they have some degree of voiding dysfunction [7]. Although elevated PVR and bacteriuria are common among elderly residents in nursing homes, no association between the two was observed in a Swedish study [8]. Analysis of elderly patients with urinary incontinence failed to identify any significant association between PVR and any other clinical or urodynamic parameter [9]. Sanders and co-workers addressed the issue of the real need for measuring flow rates and post-void residual urine in women with urinary incontinence. Analysis of 408 women suggest a 4% incidence of PVR of 200 ml or greater and a 6% rate of PVR of 149 ml or greater. The authors calculated that only 1.5% of patients (6 of 408) had their management modified because of the results of free uroflowmetry and PVR measurement. In their opinion, these data do not justify the inclusion of these tests in the “minimal care” programme for assessing primary, uncomplicated, urinary incontinence in female patients [10].
PVR can be measured at the time of endoscopy, were reduced to 14% with a mean difference of 85 ml. However, education of the nurses, inaccurate assessments were found to be inaccurate [16]. After further residual volume of 76 ml in those measurements that a mean difference between the initial and the actual patients evaluated by full-time urological nurses with Millard showed inaccuracies in 26% of 515 male diverticula and vesicoureteric reflux [15]. Stoller and suprapubic pressure), especially in cases of bladder instructed as to the procedures and techniques to assure complete emptying (moving the catheter in and out slowly, twisting it, suctioning with syringe, suprapubic pressure), especially in cases of bladder diverticula and vesicoureteric reflex [15]. Stoller and Millard showed inaccuracies in 26% of 515 male patients evaluated by full-time urological nurses with a mean difference between the initial and the actual residual volume of 76 ml in those measurements that were found to be inaccurate [16]. After further education of the nurses, inaccurate assessments were reduced to 14% with a mean difference of 85 ml. PVR can be measured at the time of endoscopy, provided there is a blinded insertion of the instrument to avoid irrigation fluid inflow. Both invasive means are usually performed with some kind of local anaesthesia and carry a small the risk of urethral damage and urinary infection.

Before the era of ultrasonography, PVR was measured non-invasively by the phenolsulfonphthaleine excretion test or with isotopes [17, 18].

In 1967, Holmes described the use of ultrasonography in the evaluation of bladder volume and this technique rapidly gained widespread acceptance as a satisfactory level of accuracy was demonstrated [19, 20]. Using either three diameters (length, height, width) or the surface area in the transverse image and the length obtained in the longitudinal image, various volume formulae for a spherical or an ellipsoid body are utilised to estimate the bladder volume (Table 3). Twenty-one different formulae have been proposed over the years making assumptions about bladder shape which have often been questioned [21]. Comparison of values of bladder volumes obtained using different formulas did not result in any significant difference amongst the various calculations [22]. At present, no single formula can be indicated as the one best volume calculation formula. Several studies report a sufficient accuracy in the ultrasound estimation of PVR [20, 21, 23-26]. False negative results are rare with PVR less than 20 ml [27]. Recently portable scanners were introduced, with automatic measurement of bladder volume. In a prospective comparison of one hundred measurements of PVR by portable ultrasound with measurements by catheterisation, the mean absolute error of the scanner was 52 ml [28]. For volumes below 200 ml and 100 ml, the error was 36 ml and 24 ml respectively. More recent studies suggest a good level of accuracy in both female and paediatric populations [29, 30]. Residual urine is usually referred as an absolute value, but it can be measured also as a percentage of bladder capacity.

The intra-individual variability of PVR is high from day to day and even within a 24 hours period. This was reported in men with BPH by Birch et al. and by Bruskevitz et al. [31, 32]. Griffiths et al. examined the variability of PVR among 14 geriatric patients (mean age 77 years), measured by ultrasound at three times [32].

### 2. MEASURING PVR

The measurement of PVR can be performed by invasive and noninvasive means. Invasive methods include: in-and-out catheterisation and endoscopy. Noninvasive means are transabdominal ultrasonography with real-time ultrasound or fully automated systems, and radioisotope studies. In-and-out catheterization has been considered for some time, the gold standard for the measurement of PVR. Nevertheless the method is subject to inaccuracies, if the person performing the catheterization is not fully instructed as to the procedures and techniques to assure complete emptying (moving the catheter in and out slowly, twisting it, suctioning with syringe, suprapubic pressure), especially in cases of bladder diverticula and vesicoureteric reflex [15]. Stoller and Millard showed inaccuracies in 26% of 515 male patients evaluated by full-time urological nurses with a mean difference between the initial and the actual residual volume of 76 ml in those measurements that were found to be inaccurate [16]. After further education of the nurses, inaccurate assessments were reduced to 14% with a mean difference of 85 ml. PVR can be measured at the time of endoscopy, provided there is a blinded insertion of the instrument to avoid irrigation fluid inflow. Both invasive means are usually performed with some kind of local anaesthesia and carry a small the risk of urethral damage and urinary infection.

Before the era of ultrasonography, PVR was measured non-invasively by the phenolsulfonphthaleine excretion test or with isotopes [17, 18].

In 1967, Holmes described the use of ultrasonography in the evaluation of bladder volume and this technique rapidly gained widespread acceptance as a satisfactory level of accuracy was demonstrated [19, 20]. Using either three diameters (length, height, width) or the surface area in the transverse image and the length obtained in the longitudinal image, various volume formulae for a spherical or an ellipsoid body are utilised to estimate the bladder volume (Table 3). Twenty-one different formulae have been proposed over the years making assumptions about bladder shape which have often been questioned [21]. Comparison of values of bladder volumes obtained using different formulas did not result in any significant difference amongst the various calculations [22]. At present, no single formula can be indicated as the one best volume calculation formula. Several studies report a sufficient accuracy in the ultrasound estimation of PVR [20, 21, 23-26]. False negative results are rare with PVR less than 20 ml [27]. Recently portable scanners were introduced, with automatic measurement of bladder volume. In a prospective comparison of one hundred measurements of PVR by portable ultrasound with measurements by catheterisation, the mean absolute error of the scanner was 52 ml [28]. For volumes below 200 ml and 100 ml, the error was 36 ml and 24 ml respectively. More recent studies suggest a good level of accuracy in both female and paediatric populations [29, 30]. Residual urine is usually referred as an absolute value, but it can be measured also as a percentage of bladder capacity.

The intra-individual variability of PVR is high from day to day and even within a 24 hours period. This was reported in men with BPH by Birch et al. and by Bruskevitz et al. [31, 32]. Griffiths et al. examined the variability of PVR among 14 geriatric patients (mean age 77 years), measured by ultrasound at three times [32].

### Table 3. Comparison of different formulae to assess PVR by transabdominal ultrasound in 30 men with BPH scanned three times [32].

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Method</th>
<th>Standard error</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakenberg et al [40]</td>
<td>625 x H x W x (D1+D2)/2</td>
<td>17.5</td>
<td>34.3</td>
</tr>
<tr>
<td>Poston et al [41]</td>
<td>7 x H x W x D1</td>
<td>20.0</td>
<td>39.2</td>
</tr>
<tr>
<td>Hartnell et al [42]</td>
<td>625 x H x W x D1</td>
<td>17.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Rageth and Langer [43]</td>
<td>Nomogram based on areas</td>
<td>15.0</td>
<td>29.4</td>
</tr>
</tbody>
</table>

Modified from the Proceedings of the 4th International Consultation on Benign Prostatic Hyperplasia p. 205
different times of day on each of two visits separated by 2-4 weeks [33]. Within-patient variability was large (SD 128 ml) because of a large systematic variation with time of day, with greatest volumes in early morning. The inherent random variability of the measurement was much smaller (SD 44 ml). Several factors can influence PVR variability: voiding in unfamiliar surroundings, voiding on command with a partially filled or overfilled bladder, the interval between voiding and the estimation of residual (it should be as short as possible), the presence of vesicoureteric reflux or bladder diverticula. Several studies reported the questionable value of PVR as an important outcome prognosticator in male patients with benign prostatic enlargement and benign prostatic obstruction [34-39]. The cause of PVR is probably multifactorial, and no consensus exists on the relation of PVR, bladder outlet obstruction and detrusor contractility.

CONCLUSIONS

The knowledge as to the pathophysiology of PVR remains unclear. In patients with urinary incontinence, no consensus exists as to its value as a safety parameter and particularly its relation with upper tract dilatation, bacteriuria and urinary infection. The intra-individual variability of PVR has been investigated mainly in male patients with bladder outlet obstruction but little information is available as to its variability in patients with urinary incontinence.

Ultrasound is the recommended method for assessing PVR because it is the least invasive and it is sufficiently accurate for clinical purposes yet is the most expensive. In-and-out catheterization is invasive and can be inaccurate even if carefully performed.

The general opinion is that PVR measurement forms an integral part of the study of urinary incontinence, as a safety parameter to exclude a voiding dysfunction associated with incontinence.

RECOMMENDATIONS

1. Residual urine measurement is recommended in the initial assessment of urinary incontinence as a safety parameter and in the evaluation of treatment outcome (Level of evidence 3- Grade of recommendation C)

2. The determination should be performed utilising realtime sonography or portable scanner or in and-out catheterisation (Level of evidence 3- Grade of recommendation C).

3. Due to intra-individual variability, in cases where significant PVR is detected by the first measurement, several measurements should be performed (Level of evidence 3- Grade of recommendation C)

4. The modality of measurement should be indicated

SUGGESTED RESEARCH AREAS

1. Pathophysiology of PVR in male and female populations with UI;

2. Diurnal variation of residual urine in patients with UI;

3. Determination of the cut off value of significant residual urine in different patient populations with UI

4. Residual urine as a prognostic indicator of outcome in the treatment of incontinence

REFERENCES


37. el Din KE, Klemenny LA, de Wildt MJ, Rosier PF, Debruyne FM, de la Rosette JJ. The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol. 1996 Sep;156(3):1020-5.


II. OPEN BLADDER NECK AND PROXIMAL URETHRA AT REST

An open bladder neck and proximal urethra at rest is usually an unexpected observation of voiding cystourethrograph or pelvic floor ultrasonography and its significance remains doubtful [1]. A 21% prevalence in nulliparous asymptomatic women has been reported [2]. In the non-neurogenic population there is no pathophysiological correlation between such this and urinary incontinence. Digges and co-workers reported a prevalence of 1:3 amongst females suffering LUTS. An open bladder neck at rest is not pathognomonic of sphincter incompetence although it is associated with USI [3]. In patients with stress incontinence, but also in asymptomatic women [4], funneling of the internal urethral meatus may be observed on Valsalva (Fig. 5) and sometimes even at rest; funneling is often associated with leakage. However, funneling may also be observed in urgency incontinence and cannot be used to prove USI. Marked funneling has been shown to be associated with poor urethral closure pressures [5, 6].

Reports in the peer reviewed literature suggest that the open bladder neck and proximal urethra at rest, during the storage phase, can be observed during cystography, videourodynamic or bladder ultrasound, both in patients with and without neurological disease and is interpreted as a sign of internal sphincter denervation as occurs in 53% of patients with MSA [7]. Distal spinal cord injury has been associated with an open smooth sphincter area, but whether this is due to sympathetic or parasympathetic decentralisation or defunctionalisation has never been settled [8]. Relative incompetence of the smooth sphincter area may also result from interruption of the peripheral reflex arc very similar to the dysfunction observed in the distal spinal cord injury. Twenty-one out of 54 patients with spinal stenosis were found to have an open bladder neck at rest [9]. In a review of 550 patients [10], 29 out of 33 patients with an open bladder neck had neurological disease. Although the association was more commonly seen in patients with thoracic, lumbar and sacral lesions, the difference when compared to cervical and supraspinal lesions was not significant. Damage of sympathetic innervation to the bladder was also frequently observed in patients undergoing major pelvic surgery, such as, abdominal perineal resection of the rectum. Patients with myelodysplasia had an inordinately high incidence of open bladder neck (10 out of 18 patients; versus 19 out of 290 having different neurological disorders).

Patients with sacral agenesis are included in the larger category of myelodysplastic patients and suffer from an open bladder neck with an underactive bladder. Shy-Drager syndrome is a Parkinson-like status with peripheral autonomic dysfunction. Neurogenic detrusor overactivity is usually found in association with an open bladder neck at rest and a denervated external sphincter [11]. Peripheral sympathetic injury results in an open bladder neck and proximal urethra from a compromised alpha-adrenergic innervation to the smooth muscle fibres of the bladder neck and proximal urethra [12]. Although it can occur as an isolated injury it is usually associated with partial detrusor denervation and preservation of sphincter EMG activity. The loss of bladder neck closure suggests an autonomic neural deficit. The site and nature of the requisite deficit is unclear. Most of the authors agree on the importance of the sympathetic system in maintaining the integrity of the bladder neck [13-16] although the possible role of parasympathetic innervation has been proposed by others [17, 18]. An open bladder neck at rest in children or in women without neurological disease can represent a different disorder, either related to a congenital anomaly or secondary to an anatomical pelvic floor defect. Stanton and Williams [19] described an abnormality in girls with both diurnal incontinence and bed-wetting, based primarily on micturating cystourethrogram, in which the bladder neck was wide open at rest. Murray et al [20] reported the “wide bladder neck anomaly” in 24.5% of the girls [35] and 9.3% of the boys [10] out of 251 children (143 girls and 108 boys) undergoing videourodynamic measurements. The assessment of non-neurogenic bladder dysfunction (mainly diurnal incontinence). The authors considered the anomaly congenital and made the hypothesis that wide bladder neck anomaly in girls may provide a basis for the development of USI in later life.

Open bladder neck is a key point in defining type III stress incontinence according to the classification of Blaivas and Olsson [21]. The classification is based on history, imaging, and urodynamics, and distinguishes five diagnostic categories of stress incontinence. Incontinence type III is diagnosed by the presence of an open bladder neck and proximal urethra at rest in the absence of any detrusor contraction suggesting an intrinsic sphincter deficiency. The proximal urethra no longer functions as a sphincter. There is obvious urinary leakage that may be gravitational in nature or associated with minimal increase in intravesical pressure. In pelvic fracture with membranous urethral distraction defects, when cystography (and/or cystoscopy) reveals an open bladder neck before urethroplasty, the probability of postoperative urinary incontinence may be significant, although the necessity of a simultaneous (or sequential) bladder neck reconstruction in controversial [22-24]. Skala and co-workers suggest that an open bladder neck at rest is associated with an increased risk of postoperative complications and failure after open colposuspension [25]. Further research in this area is required to confirm these data.

In conclusion, the diagnosis of open bladder neck at rest does not seem to be helpful to diagnose the underlying cause of urinary incontinence.
RECOMMENDATIONS

When observing an open bladder neck and proximal urethra at rest in male patients, during the storage phase, whatever imaging technique is used, it may be worthwhile to evaluate the possibility of an underlying autonomic neural deficit. (Level of Evidence 3, Grade of Recommendation C)

SUGGESTED RESEARCH AREAS

1. The relation of open bladder neck and proximal urethra at rest to the different neurogenic disorder
2. Longitudinal study of wide bladder neck and proximal urethra at rest in asymptomatic women
3. Evaluate the prognostic value of the open bladder neck and proximal urethra at rest

REFERENCES

The prevalence of urethral diverticula ranges between 1 and 6% with rates up to 10% in among symptomatic women from tertiary referral centres [1, 2]. The suspicion of a urethral diverticulum stems from LUTS or urethral masses on physical examination. Urethral masses include leiomyoma, vaginal cysts, malignancy, ectopic ureter, granuloma and urethral diverticula. The first case of female urethral diverticulum was reported in 1805 [3]. Since the report from Davis and Cian in 1956 [4] using positive-pressure urethrography (PPU), the diagnosis has become much more common even though, despite increased clinical awareness, this pathology continues to be frequently overlooked. Urinary incontinence is often associated with a urethral diverticulum. Incontinence may be a sequel to urine loss from the diverticulum itself with stress manoeuvres, USI or urgency incontinence [5]. Aldridge et al. [6] reported urethral diverticula in 1.4% of patients with stress urinary incontinence. The presenting symptoms of a urethral diverticulum have classically been described as the three Ds (Dysuria, postvoid dribbling, and Dyspareunia). Since most patients present with nonspecific lower urinary tract symptoms, and the pathognomonic presentation (postvoid dribbling, urethral pain, tender periurethral mass and expression of pus form the urethra) is very uncommon, these patients undergo extensive evaluation and treatment before a correct diagnosis is established [7, 8]. The diagnosis of a urethral diverticulum may be achieved by physical examination, voiding cystourethrography, positive-pressure (double-balloon) urethrography, urethroscopy, endovacitary (transurethral or transvaginal) or transperineal ultrasound sonography, urethral pressure profile or MRI. Positive pressure urethrography is usually accomplished using a double balloon catheter according to the method described by Davis and Cian [4]. Two different models exist: the Davis-TeLinde and the Tratner catheter. Positive-pressure urethro-graphy (and voiding urethrography) may result in a false negative study when the inflammation of the diverticulum neck prevents contrast medium to flow into the diverticulum cavity.

The accuracy of a diagnostic test may depend upon the characteristics of the study population and conflicting data are often reported in the peer-review literature. Blaivas et al report a diagnostic accuracy of VCUG of 97% in a series of 66 patients and similar results (95%) were obtained by Ganabathi et al. [7, 9]. Less favourable results were reported by others. Comparison of VCUG versus PPU in the diagnosis of urethral diverticula showed a clear superiority of the latter with good consistency among different studies [10, 11]. In some patients, VCUG only delineated the lower part of the diverticulum [12]. Ultrasound sonography and MRI should be theoretically free of such false negative imaging. Chancellor et al. [13] described the use of intraoperative intraluminal echographic evaluation which may be of help in dissecting the diverticulum and achieving complete excision without damaging the bladder neck and urethra. A number of studies have shown that MRI is a superior imaging modality to both voiding cystourethrography and positive-pressure urethrography and can be considered, if available, the imaging of choice when the diagnosis of urethral diverticulum is suspected [14-19] (Figure 28 a,b). MRI is superior to VCUG or double-balloon urethrography, particularly in diagnosing diverticula with narrow, noncommunicating necks [15, 16]. MRI proved to be superior to X-ray studies because diverticula can go undiagnosed on voiding cystourethrogram, furthermore size and complexity of the diverticulum is better defined on MRI [17]. Endoluminal MRI is considered to be of particular importance in the diagnosis of circumferential urethral diverticulum, a condition that is relatively rare but the diagnosis may increase with the increased use of this imaging technique. Proper evaluation of diverticular anatomy is essential in planning reconstructive surgery [1, 20]. MRI also proved to be useful in diagnosing inflammation and tumour of the diverticulum [21, 22]. Endoluminal MRI with either a vaginal or rectal coil, may provide even better image quality than simple MRI [18]. A comparison of MRI versus urethrography and urethroscopy, in a group of 20 women with urethral diverticulum, reported a 69 and 77 per cent accuracy of the two latter imaging studies versus MRI [14]. When surgical findings were compared to MRI, urethrography and urethroscopy, the diagnostic ability of the three methods was 70, 55 and 55 per cent, respectively. Diverticula ostia could not be identified by MRI study not withstanding the use of contrast material. Neitlich et al. [15] reported in a series of 19 patients that MRI (using a fast spin echo T2-weighted pulse sequence and a dedicated pelvic multicoil) had a higher sensitivity for detecting urethral diverticula and a higher negative predictive rate in comparison with double balloon urethrography. Blander et al. [17], comparing MRI and VGUG in 27 patients with urethral diverticula, found that endoluminal (endorectal or endovaginal) MRI was extremely accurate in determining the size and extent of urethral diverticula compared to VCUG; the related information can be critical when planning surgical approach, dissection and reconstruction. In conclusion, review of the peer reviewed literature suggests that positive pressure urethrography is still a valuable tool to diagnose female urethra diverticula not withstanding both ultrasound sonography and particularly MRI can represent valuable alternatives with a significantly higher diagnostic accuracy. In males, both VCUG and ultrasonography can be successfully used to diagnose syringocele (cystic dilatation of the Cowper’s gland), congenital and acquired diverticula [23].
RECOMMENDATIONS

In cases of female urinary incontinence if a urethral diverticulum is suspected, appropriate imaging (positive pressure urethrography, voiding cystourethrography, urethroscopy, ultrasound, MRI) is recommended. (The choice of the type of imaging depends on their availability. Data show a higher accuracy of MRI.) (Level of Evidence 3 – Grade of Recommendation C)

AREAS FOR RESEARCH

Properly conducted prospective studies are needed to compare the accuracy of ultrasonography and MRI in the diagnosis and staging of female and male diverticula

REFERENCES

IV. IMAGING OF THE NERVOUS SYSTEM IN URINARY INCONTINENCE

1. LUMBOSACRAL SPINE X-RAYS

No significant update can be provided compared to the previous report of the 2005 [1]. In children with lower urinary tract dysfunction and urinary incontinence, the presence of a spinal dysraphism must be ruled out. Although in most of the cases abnormalities of the gluteosacral region and/or legs and foot are clearly visible, antero-posterior and lateral films of the lumbosacral spine have to be evaluated in order to identify vertebral anomalies. Sacral agenesis involves the congenital absence of part or all of two or more sacral vertebrae. In the absence of two or more sacral vertebrae a neurogenic bladder is the rule usually found. Spina bifida occulta has a variable significance. Simple failure to fuse the laminae of the fourth and fifth lumbar vertebrae is unlikely to be important, but if the spinal canal is noticeably widened, there may be cord involvement (diastematomyelia, tethered cord syndrome).

RECOMMENDATIONS

In patients with suspected congenital neurogenic incontinence, with or without abnormalities of neurologic physical examination, lumbo-sacral spine anteroposterior and lateral radiological evaluation (or MRI) is indicated. (Level Evidence 3, Grade of Recommendation C)

2. CT, MRI, SPECT and PET

Numerous papers refer to rare neurological conditions presenting with different symptoms including urinary incontinence in which CT scan, MRI, SPECT, and PET imaging were carried out to identifying the underlying CNS disease. These references have little impact on the daily practice although can be helpful in occasional difficult cases.

With regards to the clinical diagnostic use of CT or MRI, a few papers evaluated the role of fetal MRI imaging. Fetal MRI has higher contrast resolution than prenatal sonography and allows better identification of normal and abnormal tissue. Moreover, MRI can diagnose some abnormalities such as cerebral malformations and destructive lesions which can be occult on prenatal sonography, where the more anterior cerebral hemisphere cannot be properly evaluated due to reverberations by the overlying structures [2]. Common indications for fetal MRI include the evaluation of all the sonographically diagnosed abnormalities of ventriculi, corpus callosum, or posterior fossa, as well as all those fetuses at increased risk for brain abnormalities, such as in families with a history of a prior child or fetus with anomalies, genetic disorders, complications of monochorionic twinning, and maternal illness (such as maternal infection or major cardiac event). Moreover, with recent advances in fetal surgical techniques, fetal MRI is being increasingly used before surgical intervention [3]. The results of fetal MRI, whether verifying absence of abnormality, confirming sonographically detected abnormalities, or discovering additional abnormalities that were not apparent by sonography, have been shown to affect clinical decision-making during pregnancy, both by physicians and parents, resulting in changes in pregnancy management in nearly half of cases [2]. With regards to myelomeningocele, prenatal ultrasound can easily identify the absence of posterior elements of the vertebral bodies at affected levels and extension of the subarachnoid space posteriorly through the bony spina bifida, as well as the frequently associated presence of small posterior fossa alteration and haerniation of cerebellar tissue into the cervical subarachnoid, which define the Chiari II malformation. However, fetal MRI can be a helpful adjunct when sonography analysis is limited, such as in cases of large maternal body habitus, oligohy-dramnios, low position of the fetal head, or when the fetal spine is positioned posteriorly with respect to the mother. Moreover, fetal MRI can be very useful to detect additional associated anomalies, such as callosal agenesis or hypogenesis, periventricular nodular heterotopia, cerebellar dysplasia, syringo-hydromyelia, and diastematomyelia [3]. If fetal surgery will be shown to improve long-term outcome, fetal MRI will surely become a routine examination for affected fetuses.

MRI is also recommended in children with anorectal abnormalities as abnormalities of the spine and of the spinal cord are diagnosed in 42 to 46% of cases and in about 50% of cases the spinal cord is involved [1]. Wraige et Borzyskowski suggested that spinal cord imaging should be considered in children in whom day-time wetting is associated with impaired bladder sensation or poor bladder emptying even in the absence of clinical or radiological suspicion of lumbosacral spine abnormalities. Four out 10 children with these symptoms had a spinal cord defect diagnosed on MRI [4].

MRI imaging of the lumbar spine is now the gold standard for evaluating children with spina bifida and adults in which an occult form of spina bifida is suspected. A potential technical update might be the use of intrathecal contrast medium to perform cisternography and ventriculography contrast-enhanced MRI. Munoz et al., evaluated a series of 10 patients with complex cerebrospinal fluid diseases, where other imaging techniques had been unclear or inconclusive, performing MRI with intrathecal administration of gadopentate dimeglumine. In 8 out of the 10 patients, imaging findings influenced or changed the clinical decision-making program and the surgical planning [5].
Sharma et al. recently evaluated with MRI the surgical outcome in patients with spinal dysraphism. Specifically, MRI spectroscopy was used to evaluated the composition of cerebro-spinal fluid before and after surgery. Before surgery, high levels of lactate, alanine, acetate, glycerophosphate, and choline were observed in the cerebrospinal fluid of patients with spinal dysraphism, while these levels normalized postoperatively to those observed in control subjects. However, in those patients where cord re tethering occurred, increased concentrations of lactate and alanine were found, suggesting that MRI spectroscopy might be a promising tool in the assessment of surgical outcomes in patients with spinal dysraphism [6].

Several papers refer to the use of CNS imaging in clinical research of dysfunction and pathophysiology. Positron emission tomography (PET) and functional MRI studies provided information on specific brain structures involved in micturitions in humans. During micturitions an increase in regional blood flow was shown in the dorsomedial part of the pons close to the fourth ventricle, in the pontine micturitions centercentre (PMC), in the mesencephalic periaqueductal grey (PAG) area, as well as in the hypothalamus including the preoptical area [1].

A couple of significant original studies were have been published since the last International Consultation on Incontinence on the role of functional MRI in stress and urge urinary incontinence. Specifically, previous brain imaging studies showed that during pelvic floor muscle contraction there was activity in the superior medial precentral gyrus, anterior cingulate cortex (ACC), cerebellum, supplementary motor cortex (SMA) and the thalamus [7, 8]. Similarly, during anal sphincter contractions multifocal cerebral activity was shown in the primary and secondary sensory/motor cortices, the insula as well as the cingulate gyrus, prefrontal cortex, and the parietooccipital region [9]. Di Gangi Herms et al. evaluated the neuroplastic changes of cortical representation of pelvic floor motor functions induced with pelvic floor muscle training (PFMT) by biofeedback in patients with SUI [10]. Specifically, the authors used functional MRI to evaluate 10 patients with stress urinary incontinence SUI before and after a 12-week PFMT with EMG-biofeedback program. In the MRI performed before the beginning of PFMT, the authors identified significant brain activation in superior lateral and medial precentral gyrus and the superior lateral postcentral gyrus, in the SMA, the left premotor area, and in the left and middle cerebellum, as well as in the insula as well as in the ACC. In the MRI film after PFMT, less brain areas were activated, mainly the superior lateral and medial precentral gyrus, superior lateral post-central gyrus and the insula. In other words, after PFMT it was identified a more focused activation in the primary motor (superior lateral and superior medial precentral gyrus) and somatosensory areas, which is consistent with automatization automation of the relearned skillful behavior [10]. PFMT with biofeedback may improve muscular strength therefore enhancing support of the urethra and also optimize central muscular control of the pelvic floor, modulate bladder sensation, and reflect the emotional neutralization related to symptom reduction.

With regards to urge urinary incontinence, Tadic et al. reported a small study, which used functional MRI to investigate 11 patients with urge urinary incontinence and 10 healthy controls. Specifically, the connections of the right insula (RI) and anterior cingulate gyrus (ACG) to other cortical area were evaluated, based on the assumption that the two areas were among the most important regions of the supraspinal neuronal network controlling the bladder. In normal subjects, there were significant positive effective connections with many of the regions involved in supraspinal bladder control, including left insula and frontotemporal and parietal regions, thalamus, putamen and claustrum, posterior cortex, cerebellum, pontine micturition centre and mesencephalic periaqueductal grey. Vice versa, in the patients with urgency incontinence, significant negative connections to left parieto-temporal lobes, hippocampus, parahippocampal gyrus and cerebellum were found, with few positive connections [11].

In subjects with normal bladder function, RI and/or ACG have been reconfirmed to have effective connections with many of the brain regions involved in bladder control such as the frontotemporal and sensorimotor regions, thalamus, putamen, cerebellum and midbrain, as well as to the posterior cortex, a region which may have a role in the control of bladder function. Vice versa, in the patients with urgency incontinence, the connections were shifted to an alternative complex of brain regions, such as left parieto-temporal lobes, parahippocampal gyrus and parts of cerebellum, which might represent expression of the recruitment of accessory pathways in order to control urgency and the voiding reflex as well as the emotional charge due to the abnormal sensation of urgency [11]. On the whole the data of these recently published studies have improved our knowledge of nervous functional anatomy related to vesicourethral function and dysfunction but, to date, have no clear clinical relevance.

In conclusion, central nervous system imaging is rarely indicated in urinary incontinence. Spinal cord imaging is recommended in cases of children with anorectal malformation and whenever spina bifida occulta is suspected. In the case of clinical neurological signs and/or symptoms suggestive of central nervous lesions, imaging may be indicated along with more specific neurophysiological tests (e.g., signal latency, testing, evoked potential, etc.). Further improvements in the knowledge of the correlation between
morphologic and functional evaluation of the CNS is foreseeable using present CNS functional imaging technology.

**RECOMMENDATIONS**

Neuroimaging should be considered when a nervous system disorder is suspected on the basis of clinical and/or neurophysiologic test findings (Level of Evidence 3 - Grade of Recommendation C)

**REFERENCES**


5. Evaluation of the membranous and prostatic urethra in male patients with post-prostatectomy stress incontinence to appraise possible iatrogenic damage of the external sphincter region. Assessment of bladder outlet in males with urgency incontinence considered to be secondary to bladder outlet obstruction to appraise prostate morphology.

2. EVALUATION OF THE FEMALE BLADDER OUTLET

Robertson described the procedure of dynamic urethroscopy to evaluate the bladder neck [1]. In this procedure a gas urethroscope is used to observe the urethra, bladder neck, and portions of the bladder.
During visualisation manometric recording can be performed. Robertson described the appearance of SUI as a sluggish closure of the bladder neck and the appearance of the overactive bladder as a bladder neck that closes and then opens like the shutter of a camera. This procedure was reported to be extremely useful in patients with urinary incontinence as the bladder neck can then be observed at rest, with straining, and Valsalva manoeuvres. Unfortunately, in Robertson’s original description of this procedure, it was never compared to other standard methods of measuring outlet resistance. Others who advocate the technique of Robertson reported that only 43% of patients with SUI actually had loss of bladder neck support on urethroscopy [2]. Scotti, et al performed a retrospective review of 204 patients who underwent dynamic urethroscopy for the evaluation of USI [3]. Of the 204 patients, 99 had USI. Urethroscopy was found to be an imprecise predictor of USI with a 62% sensitivity, a 74.6% positive predictive value and a specificity of 79.1%. Moreover, there were many equivocal studies. The authors concluded that urodynamic evaluation rather than urethroscopy was a more accurate predictor of stress incontinence. Sand, and associates compared supine urethrocystographic cystometry (dynamic urethroscopy) to the gold standard of multichannel urethrocystometry [4]. They found a sensitivity of only 24.6% and a positive predictive value of only 65.2% in predicting detrusor overactivity.

Horbach and Ostergard tried to predict urethral sphincter insufficiency in women with SUI using urethroscopy [5]. They retrospectively reviewed the records of 263 women who had a diagnosis of USI. They defined ISD as a maximal urethra closure pressure of 20 cm H2O or less with the patient upright. They then divided patients into two groups, those with ISD and those with maximal urethral closure pressures of more than 20 cm H2O. Based on this classification, 132 women, or 50.2%, had evidence of ISD. However, when urethral function was assessed by endoscopy, only six of 132 patients with ISD were found to have an open or partially open proximal urethra and urethrovessical junction at rest during urethrocystoscopy. Clinically, these patients had very low urethral pressures and reported difficulty with continuous leakage of urine. Endoscopy appeared to have little predictive value for ISD as defined by urethral pressure profilometry. Govier et al compared cystoscopic appearance of the female urethral sphincteric mechanism to the videourodynamic studies in 100 consecutive women with complex types of urinary incontinence [6]. Sphincteric dysfunction was classified as minimal, moderate, and severe based on the radiographic appearance of the bladder neck with straining. Urethrocystoscopy underestimated the degree of sphincter deficiency 74% of the time in patients with moderate sphincteric dysfunction and 44% of the time in patients with severe sphincteric dysfunction. The authors concluded that cystoscopy is inadequate to judge the functional integrity of the bladder outlet. Furthermore, cystoscopy alone will underestimate intrinsic sphincter deficiency in a large number of patients.

3. EVALUATION OF THE BLADDER

Is cystoscopy necessary to rule out concomitant bladder pathology in patients with urinary incontinence? Langmade and Oliver reported on 253 patients who were operated on for SUI [7]. They used a simple evaluation that consisted of history, stress tests, and urinalysis alone. They did, however, recommend cystoscopic evaluation if the patient also complained of symptoms of urgency. Although this dogmatic approach was recommended, it was never clearly stated if it made a difference in the treatment or outcome in these patients. Fischer-Rasmussen, et al performed extensive evaluation of women with urinary incontinence [8]. This included cystoscopy in 190 patients. They found cystoscopy to be abnormal in only 12 patients, 8 who had stress incontinence and 4 who had other types of incontinence. Abnormal findings were trabeculated bladder mucosa in five patients, benign bladder papillomas in four, and metaplasia of the trigonal mucosa in two. None of these was considered to be a significant finding. The authors concluded that cystoscopic examination did not contribute to the classification of incontinence in any case. Cardozo and Stanton evaluated 200 patients with SUI and detrusor overactivity [9].

Cystoscopy revealed no abnormalities amongst the 100 patients with USI. Fourteen of the 100 patients with detrusor overactivity had cystoscopic abnormalities, eg trabeculation, injected mucosa, sacculation, a bladder capacity of less than 100 cc. However, in none of these patients was the treatment affected by the results of cystoscopy. In support of these findings, Mundy has stated that there is no direct diagnostic value of endoscopy in a patient with an overactive bladder. It may sometimes be helpful to look for and exclude a cause of hypersensitivity when this is in the differential diagnosis [10]. Dulidulao and colleagues found this necessary only in patients with haematuria [11]. They performed urinalysis, urine cytology, and cystoscopy on 128 women who presented with urgency incontinence and/or storage voiding symptoms. Of these, 68 patients had urgency incontinence, 35 of whom also had microscopic haematuria. One patient with urgency incontinence and haematuria was found to have a transitional cell carcinoma of the bladder. None of the patients with urgency incontinence (or storage symptoms only) and no haematuria were found to have significant cystoscopic findings. This would support the routine use of cystoscopy for patients with urgency incontinence only if haematuria is present.
4. EXTRA-URETHRAL URINARY INCONTINENCE

Endoscopy can be an invaluable tool in the diagnosis and treatment of extraurethral incontinence due to vesico-vaginal fistula and ectopic ureter. With respect to vesico-vaginal fistula, cystoscopy can precisely localize the fistula site in the bladder and help plan surgical correction. Occasionally, a small fistula that is not seen on physical examination or radiographic studies, can only be diagnosed by cystoscopy.

Incontinence due to ectopic ureter in the female is usually diagnosed by radiographic studies. However, the exact location of the ureteral orifice in the urethra or vagina can be identified by cystourethroscopy and/or vaginoscopy. This can be extremely helpful in the planning of corrective surgery.

5. INTRAOPERATIVE LOWER URINARY TRACT EVALUATION

Several authors have studied the value of routine cystoscopy during operative procedures for incontinence and prolapse. The approach may be transurethral [12] or transvesical [13]. The American College of OB/GYN has published a Bulletin on Operative Lower Urinary Tract Injuries [14] in which it is stated “at the conclusion of the procedure, when hemostasis has been ensured, both ureters and the bladder should be inspected to confirm their integrity.” Harris and co-workers [12] reported 9 unsuspected ureteral or bladder injuries during urogynaecological surgery, which included 6 ureteral ligsations, with four of these occurring after Burch cystourethropexy. Burch sutures were also found in the bladder as well as fascial lata from a sling procedure.

6. EVALUATION OF THE MALE BLADDER OUTLET

Urgency incontinence is one of the lower urinary tract symptoms associated with benign prostatic hyperplasia, bladder outlet obstruction, and aging in the male population. Based on the available evidence and world literature, The Fourth International Consultation on BPH made the following recommendation: “Diagnostic endoscopy of the lower urinary tract is an optional test in the standard patient with LUTS because: 1) the outcomes of intervention are unknown, 2) the benefits do not outweigh the harms of the invasive study, 3) the patients’ preferences are expected to be divided. However, endoscopy is recommended as a guideline at the time of surgical treatment to rule out other pathology and to assess the shape and size of the prostate, which may have an impact on the treatment modality chosen” [15]. Several contemporary series have described the value of urodynamics in the diagnosis of post-prostatectomy urinary incontinence [16-20]. However, only one describes the routine use of urethrocystoscopy. In that series 67% of patients had urethral fibrosis confirmed by endoscopy [17]. However, how this finding affected treatment was not discussed. In the study by Leach and Yun treatment of incontinence was based solely on urodynamic findings and was successful in 87% of patients [21]. Anastomotic strictures may be suspected based on uroflow and urodynamic (pressure-flow) studies and can be confirmed by voiding cystourethrogram or videourodynamics as well as by endoscopy. However, if intervention for the stricture is deemed necessary, endoscopy would be a more critical part of the evaluation. Furthermore if surgical treatment of incontinence, such as, an artificial urinary sphincter, is planned it would seem to make good clinical sense to evaluate the urethro-vesical anastomosis with endoscopy prior to surgery.

7. EVALUATION OF URETHRAL SPHINCTER IN POST-PROSTATECTOMY INCONTINENCE

Iatrogenic UI in males usually occurs after prostate surgery for benign and malignant conditions. The pathophysiology of UI following transurethral surgery for BPH includes sphincter damage from extending the resection too distal, particularly in the ventral aspect of the sphincter where muscle fibres are more abundant. Endoscopy in post-TURP incontinence reveals insufficient closure at rest with tissue loss in the ventral aspect of the sphincter area, voluntary muscle recruitment is often good. The pathophysiology of UI in post-radical prostatectomy patients is unclear. Numerous studies investigated the relation between parameters of urethral pressure profile, morphology of the prostate apex and length of the external sphincter area to post-prostatectomy incontinence. Although the results of these studies suggest a relation between sphincter competence and UI, no consensus has been reached yet as to the gold standard test to be performed prior to surgery to assess the individual patient risk of incontinence.

Recently, Gozzi and Rehder suggested that post-radical prostatectomy incontinence may be related to prolapse of the sphincter complex and that repositioning of it by a transobturator sling may be successful. Pre-operative selection of surgical candidates for such intervention include endoscopy of membranous urethra testing whether manual push-up of the centrus tendineus perinei results in recruitment of the sphincter fibres comparable to a voluntary contraction. Contraction of the sphincter muscle upon repositioning in a more cranial position is used as an indication for a transobturator sling with the Gozzi and Rehder technique [22-24]. Further research is required to confirm such an interesting pathophysiological explanation of post-radical prostatectomy incontinence and to support the role of endoscopy in the evaluation of these patients.
RECOMMENDATIONS

- Routine urethro-cystoscopy is NOT indicated in primary female urinary incontinence, when other pathologies are not suspected (Level of Evidence 3, Grade of Recommendation C).
- Endoscopy can be considered (Level of Evidence 3, Grade of Recommendation C):
  - a) in urgency incontinence to rule out other pathologies, especially in case of microscopic haematuria (e.g., bladder tumor, interstitial cystitis, etc)
  - b) in the evaluation of recurrent or iatrogenic cases when surgery is indicated and planned
- Endoscopy is indicated in the evaluation of vesico vaginal fistula and extra-urethral urinary incontinence (Level of Evidence 3, Grade of Recommendation C).
- Endoscopy is indicated intraoperatively in incontinence surgery to evaluate for ureteral or vesical injury (Level of Evidence 3, Grade of Recommendation C).

SUGGESTED RESEARCH AREAS

To relate endoscopic features to diagnosis and outcome of urinary incontinence (mainly urgency incontinence)

REFERENCES

C. IMAGING IN ANAL INCONTINENCE

I. BACKGROUND

Anal incontinence may result from anal sphincter weakness and/or rectal sensory disturbance. Imaging provides highly detailed evidence of changes to sphincter morphology. This started with the development of endoanal ultrasound (EAUS) in 1989, which soon became the gold standard[1] for demonstrating internal and external sphincters tears. Important early findings were the unexpectedly high incidence of occult sphincter damage following vaginal delivery[2], and an association between a history of obstetric trauma with faecal incontinence developing later at menopause. Parks’ original work[3] had focussed on denervation and striated muscle atrophy as the main cause of faecal incontinence. One limitation of EAUS was in measuring the external sphincter thickness, and it was not until MRI with an endocoil for the anal canal was developed that highly detailed images of the striated sphincteric muscle to show thickness and fat replacement were possible, and external sphincter atrophy could be assessed by means other than EMG. Studies of rectal evacuation are performed mainly fluoroscopically, and give only a rough indication that the patient suffers from incontinence. They are used mainly to investigate difficult defaecation and rectal prolapse.

II. INDICATIONS

The role of imaging is largely to place patients into treatment defined groups, so the emphasis may change as new treatments evolve. Endosonography took over from EMG studies as the optimum method to select patients with sphincter disruption for surgical repair, and this remains its main indication. When to investigate for external sphincter atrophy is a more complex question. Endocoil MRI may be indicated prior to sphincter repair if there is any doubt as to the quality of the external sphincter. Biofeedback has become a popular first line treatment, and a recent study suggests that imaging has only a limited role in predicting success[4], which could have a negative impact on the utilization of imaging.

III. IMAGING MODALITIES

1. ENDOANAL ULTRASOUND (EAUS)

Several systems are available, and recently integrated 3D systems are available (B&K Medical, Sandofen 9, 2820 Gentofte, Denmark). US probes designed for transvaginal examination with endfire linear arrays may be used in women to image the sphincters from the perineum. Women should be examined prone with an endoanal system to minimise anatomical distortion.

The standard EAUS image of the anal canal is of 4 layers (Figure 1):

- The subepithelial layer is moderately reflective.
- The internal sphincter is the most obvious landmark and is a well defined low reflective ring. The internal sphincter varies in thickness with age, being <1mm in neonate, 1-2mm in young adults, 2-3 in middle age and >3mm in the elderly.
- The longitudinal layer is a complex structure with a large fibroelastic and muscle component, the latter formed from the puboanal as well as the longitudinal muscle of the rectum (Figure 2).
- The external sphincter is better defined in men than women, where it tends to be less hypechoic. It is distinguished mainly by interface reflections between muscle/fat planes either side (Fig 1). In women the external sphincter is shorter anteriorly than posteriorly, which must not be misinterpreted as a tear. The transverse perinei fuse anterior with the sphincter, whereas in men they remain separate.

With experience the examination can be performed in about 5 minutes and provides an ideal method for a rapid assessment of sphincter integrity and thickness.
2. MRI

Dedicated endoanal coils are no longer available, so that much of the research using these cannot now be transferred into routine practice. However, image quality has improved dramatically with standard external coils, and MRI is particularly useful to show atrophy and tears outside the sphincter, such as the puborectalis [5].

The advantages of MRI are multiplanar imaging and that the difference in signal between fat and striated muscle allows precise measurement of external sphincter (Figure 3) thickness and estimation of fat replacement.

3. EVACUATION PROCTOGRAPHY

The rectum is opacified with 120 mls of a barium paste and the small bowel with a dilute barium suspension given orally about 30mins before. The patient is seated sideways within the fluoroscopic unit on a radiolucent commode. Evacuation of the barium paste is recorded either on video or on cut film at 1 frame/sec using a low dose protocol. At rest the anorectal junction is at the level of the ischial tuberosities and the anal canal closed. Evacuation is rapid (<30sec) and the rectum below the main fold should be emptied completely. During evacuation the anorectal angle widens as the anorectal junction descends and the anal canal opens. At the end of evacuation pelvic floor tone returns and the puborectalis pulls the anorectal junction upwards and forwards back to the resting position. Intra-anal intussusception creates a thick double fold of rectum, which impacts into the anal canal on straining at the end of rectal evacuation. Rectal prolapse represents an extension of this process, with passage of the intussusception through the anal canal and inversion of the rectum (Figure 4a-c).

Dynamic examinations of rectal emptying may also be performed with MRI, though this is technically more difficult and perhaps not worthwhile unless a global view of pelvic floor prolapse is required, although it does eliminate any harmful radiation. A simpler method involves views during only rest and stress. This is useful to show bladder and uterovaginal prolapse as well as pelvic floor descent (Figure 5a-b), but gives limited information as to rectal function.

IV. SPHINCTERIC DISORDERS

1. THE INTERNAL ANAL SPHINCTER

Abnormalities of thickness have to be related to the patient's age. A sphincter less than 2mm thick in a patient more than 50 years of age is indicative of internal sphincter degeneration (Figure 6) and is associated with passive faecal incontinence.

Obstetric trauma to the internal sphincter parallels that of the external sphincter in extent, but should always be in the anterior half, so that any defect between 3 and 9 is due to some other cause.
Figure 4: Evacuation proctogram showing the development of rectal prolapse. Intussusception starts at the end of rectal emptying (a) and rapidly passes through the anal canal (b) to form the external prolapse (c).
Sphincterotomy may be more extensive than was planned, particularly in women, and 3D studies are especially helpful to assess the longitudinal extent of the defect. The length of the sphincter divided relates directly to the risk of incontinence[6]. Dilatation procedures are hazardous and may completely fragment (Fig 7) the internal sphincter.

2. THE EXTERNAL ANAL SPHINCTER

When striated muscle is stretched beyond the limits of its elasticity fibres rupture and heal with granulation tissue and eventually fibrosis. Most chronic tears are seen with scar formation, and present as a uniform area of low reflectivity distorting and obliterating normal anatomical planes (Figure 8). A key to the diagnosis is lack of symmetry with the anterior part of the external sphincter not fusing at 12 o’clock as the probe is moved slowly down the canal. This may also be seen on 3D studies in the coronal plane (Figure 9). Other perineal structures, such as the puboanalis and transverse perineii are frequently torn and distinguishing these tears from external sphincter trauma requires experience, and again may be helped by 3D multiplanar imaging. The distinction is important as tears of the puboanalis or transverse perineii are not associated with a significant fall in squeeze pressure[7], and it is only damage to the external sphincter that results in a significant change.

In healthy young adults a good correlation has been found between measurements of layers thicknesses on endosonography and endocoil MRI, with an Ri of 0.96 for the external sphincter[8].

The outer border of the external sphincter is easier to see on MRI, but fibrosis is not so markedly different in signal from normal muscle, so that the conspicuity of tears may not be as obvious as with endosonography.

Atrophy is a more difficult problem. Determining the thickness of the external sphincter on EAUS depends on visualising its borders from interface reflections between the longitudinal layer on the inside and subadventitial fat on the outer border. As atrophy involves a reduction of muscle fibres and an increase in fat, the outer interface reflection is lost and the thickness of the external sphincter cannot be measured. Such loss of definition of the outer border of the external sphincter on endosonography has a positive predictive value of 71% for atrophy[9]. Using 3D EAUS and a grading system based on definition (Figure 10) and echogenicity of the external sphincter showed a comparable accuracy to endocoil MRI in detecting atrophy [10].

Pelvic floor descent at rest with the patient seated and impaired movement during pelvic floor contraction[11] (measured either on MR or EP) are good indicators of generalised pelvic floor weakness, and if the anal canal is open (Figure 11) this indicates
Figure 7: Endosonography in the mid canal showing gross internal sphincter irregularity, typical of the "fragmented" appearance from trauma after an anal stretch procedure.

Figure 8: Tears of internal and external sphincters (arrows) between 10 and 1 o’clock following a traumatic vaginal delivery.

Figure 9: 3D EAUS of a small tear to the external sphincter (arrow).

Figure 10: EAUS showing a normal internal sphincter, but the external sphincter is not visible as it is echogenic and the interface reflections due to advanced atrophy.
significant sphincter weakness. Most other findings, such as rectal prolapse, are really either secondary or associated with faecal incontinence, and EP is used to investigate these rather than the incontinence.

**V. CONCLUSIONS AND RECOMMENDATIONS**

Claims for superiority of one or other modality for the detection of sphincter tears probably depend largely on individual experience, but the cheapness and speed of endosonography makes this an ideal screening procedure to assess sphincter integrity.

Fluoroscopic studies have little role in faecal incontinence, unless there is an underlying rectal abnormality such as prolapse. Dynamic MRI studies have the added value of demonstrating prolapse in the rest of the pelvis, but apart from the lack of ionising radiation, has no real advantage for studying rectal function.

A leading issue is the significance of occult sphincter tears (diagnosed on endosonography but not apparent clinically) following vaginal delivery. Although these may be detected by careful examination immediately post partum [12], retrospective detection will still require EAUS. A meta-analysis of 717 vaginal deliveries revealed a 26.9% incidence of anal sphincter tears in primiparous, with 8.5% new tears in multiparous women. Overall 29.7% of women with tears were symptomatic, compared to only 3.4% without tears. The probability of faecal incontinence being due to a sphincter tear was 76.8-82.8% [13]. Recent studies confirm the strong relationship between obstetric sphincter damage and faecal incontinence [14,14], and its late onset [15,16]. Subsequent deliveries increase the risk of incontinence particularly if there has been a tear at the first delivery [17]. Tears that involve the internal sphincter increases the severity of incontinence [18].

A sphincter tear at EAUS is therefore an important finding, but how is this used to decide management a little more controversial. Sphincter repair has fallen out of fashion a little following the finding that results deteriorate over a few years [19], although a more recent study [20] suggests a better response.

EAUS therefore remains the first line imaging investigation for faecal incontinence, giving accurate information as to external and/or internal sphincter tears and the likelihood of atrophy. Dynamic studies of rectal evacuation are required only if there is some other problem suspected, such as prolapse. The advantages of using MRI are the lack of ionising radiation and a global view of the pelvic floor. Although imaging gives hard evidence of sphincter damage, this is really only part of a much more complex functional problem, and colorectal abnormalities may be just as important [11] with tears accounting for perhaps only 45% of incontinence [21].

**RECOMMENDATIONS**

- EAUS is the first line imaging investigation for faecal incontinence providing accurate information as to external and/or internal sphincter tears and the likelihood of atrophy. **[Level of Evidence 3, Grade of Recommendation C]**.
- Dynamic imaging of rectal function is required when rectal abnormalities such as prolapse are suspected **[Level of Evidence 3, Grade of Recommendation C]**.
- MRI offers no advantage over other imaging modalities except for the lack of ionising radiation and a global view of the pelvis **[Level of Evidence 3, Grade of Recommendation C]**.

**SUGGESTED RESEARCH AREAS**

MRI has allowed a much clearer understanding of pelvic floor anatomy, and this in turn has enabled the sonographic anatomy to be worked out. However, conflicting views remain when sonographic abnormalities are compared to function. Are clinical symptoms related to the size of a tears [22] or not [23]?
Problems after sphincter repair include:

- understanding the significance of the image soon after surgery [24],
- the value of manometry and imaging in assessing the repair [25],
- confirming that the length of the repair affects outcome [20].

Perhaps the most valuable aspect of MRI imaging is that it gives a global view of the pelvis, capable of confirming that the length of the repair affects outcome [25], and should be the prime area future investigation.

REFERENCES

The use of a perineal electronic nappy using electrical conductivity to estimate the amount of urine leakage was first proposed by James et al.[1, 2]. Accuracy of this technique was, however, questioned by others and the technique was improved [3-8]. Walsh & Milis and Sutherst et al. introduced a more simple approach by estimating leakage by perineal pad weight gain [9, 10]. These tests were not standardised until Bates et al. described a "structured" one hour pad test which was endorsed by the International Continence Society in 1988 [11]. This test, however, was shown to have poor interdepartmental correlation and to be highly dependent on bladder volume [12, 13]. In an attempt to make pad tests more reliable 24 hour and 48 hour pad tests were developed. A more precise estimation of urine loss was shown, but they were more cumbersome. The Pyridium pad test was also proposed for diagnosing urinary incontinence [14].

**I. DEFINITION**

The pad test is a diagnostic method to detect and quantify urine loss based on weight gain of absorbent pads during a test period under standardized conditions.

**INDICATION AND METHODOLOGY**

A pad test allows the detection and quantification of urine loss, but it is not diagnostic of the cause of the incontinence. Several different standards have been developed. Tests can be divided in four groups according to the length of the test: <1h, 1h, 24h and 48 h. (Table 4)

**II. OFFICE-BASED PAD TESTING**

Pad tests up to 2 hours were developed to be performed in outpatient clinics or hospital wards under supervised conditions. Bladder volume is predefined to reduce variability and a structured set of exercise is usually implemented to elicit the occurrence of urine loss.

**1. SHORT PAD-TEST**

* a) Quantification

These tests are based on a fixed bladder volume and a standard set of activities to facilitate the occurrence of urine loss, if any, over a short period of time. Jakobseny et al. found that the 40 minute test with a bladder volume of 75% maximum cystometric capacity and similar activities as a 1-hour ward test produced consistently larger amounts of urine loss than a standard 1-hour ward test [17]. The difference was attributed to significantly larger bladder volumes during performance of physical activity in a 40 minute pad test.

Kinn & Larsson reported no correlation between a short 10 minute test with fixed bladder volume and the degree of incontinence as judged from the symptoms [18].

Hahn & Fall in a 20 minute test with half cystometric capacity showed no false negative results in 50 women with stress urinary incontinence although there was a discrepancy in 12% of patients between the perception of incontinence severity and pad test results [15].

These data suggest that short pad tests are more provocative than activities of daily living.

* b) Reproducibility

The correlation factor (Pitman’s nonparametric permutation test) between two separate 20 minute pad tests up to 2 hours was calculated by Hahn & Fall [15] and Jorgensen et al. [16]. The correlation was highly dependent on the bladder volume and the height of the physical activity.

**Table 4. Types of pad test**

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>Bladder load</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn &amp; Fall [15]</td>
<td>20 min</td>
<td>50% of MCC*</td>
<td>stair climbing, 100 steps, coughing (10x), running (1 min), wash hands (1 min)</td>
</tr>
<tr>
<td>ICS [11]</td>
<td>1h</td>
<td>Drink 500 ml (15 min) before test</td>
<td>walking &amp; stair climbing (30 min), standing up 10x, coughing (10x), running (1 min), bending (5x), wash hands (1 min)</td>
</tr>
<tr>
<td>Jorgensen et al. [16]</td>
<td>24h</td>
<td></td>
<td>Everyday activities</td>
</tr>
<tr>
<td>Jakobseny et al. [17]</td>
<td>48h</td>
<td></td>
<td>Everyday activities</td>
</tr>
</tbody>
</table>

*Maximum Cystometric Capacity
tests was 0.94 (p<0.001) [15]. Kinn and Kinn & Larsson showed that the 10 minute test with a fixed pre-test bladder volume of 75% of maximal capacity was moderately reproducible (r=0.74) [18]. Using a 1 minute pad test, a standardised bladder volume of 300ml and standardised physical activity mean differences of leakage was 8.5 ml and coefficient of repeatability was 33.6 ml [19].

2. ONE-HOUR TEST

The use of a one-hour pad test has been investigated thoroughly for validity, reproducibility and sensitivity to change.

a) Quantification

Jakobseny et al. reported that a one hour test detected less leakage at 3 g compared to a 40 minute (7 g) and a 48 hour pad test (37 g) [17]. In the elderly a one-hour ward test did not demonstrate incontinence in 66% of those complaining of incontinence compared to 90% with a 24 in-patient monitoring of urine leakage [20]. A one hour pad test was found to reflect everyday incontinence in only 48% of the patients in comparison to 81% in a 48 hour test and 77% in a 40 minute test. Jorgensen et al. noted that 90% completed the test and 69% had test results which correlated with daily leakage [16]. Lose et al. found a poor to moderate correlation of the modified one-hour test (200-300 ml in the bladder) with a history of stress urinary incontinence (n=31) [21]. Mouritsen et al. showed that a 1-hour ward pad test did not detect grade I stress incontinence in 46%, grade II in 27% and grade III in 66% [22]. Third & Gerstenberg compared a 1-hour ward pad test to a 24-hour home pad test and found that a 1-hour pad test had a 36% false-negative rate as compared to a 24-hour home pad test [23].

b) Reproducibility

Klarskov & Hald demonstrated in 3 consecutive 1-hour pad tests, a correlation coefficient of 0.75 and 0.97 depending on the activity regimen [24]. The test, however, was quite demanding and a lot of patients did not complete the full testing. Christensen et al. compared a one-hour pad test in two different urological and one Obstetrics & Gynecological departments (20 women) [13]. The test results in two urological departments did not differ with an average pad gain of 24g and 21 g (p>0.1). However, pad test results between the departments of urology and gynecology differed significantly, with average pad weight gain 9 g and 24 g respectively (p<0.05).

Lose and co-workers showed a significant variation between 1-hour ward test and retest in 18 patients (correlation coefficient 0.68) [12]. In 50% of patients the leakage volume was variable due to differing bladder volume. When the results of the 1-hour pad test were corrected for urine volume, the correlation coefficient value increased to 0.96. Simons et al found the reproducibility of the standard 1 hour pad test to be poor [25].

c) Validity

Walsh & Mills in the elderly and Holm-Bentzen et al. in patients with an AMS artificial sphincter showed that the one hour pad test did not correlate with subjective patient satisfaction but this may due to other lower urinary tract symptoms [9, 26].

c) Bladder volume

Jorgensen et al showed test-retest correlation was improved when the bladder volume was taken into account and the correlation value (r) raised from 0.68 to 0.93 [16]. Fantl et al used a one hour test with the bladder filled to capacity had a test-retest correlation of 0.97 which was improved if the fluid loss was expressed as a percentage of bladder volume [27]. Lose et al. using a 1-hour pad test with standardised bladder volume of 50% of maximal cystometric capacity (MCC) showed in 25 women a test retest correlation of 0.97 but the intertest variation was up to 24g [28]. Jakobsen et al. compared a 1-hour pad test with a bladder filled to 50% and 75% of maximal cystometric capacity and found that the final bladder volume was equal in both groups showing the importance of diuresis even with equal starting bladder capacities [29]. The amount of leakage in both groups was the same. Simons et al. found the volume in the bladder after a standard 1 hour pad test varies by ~44 to +66g in a test-retest situation [25]. The fluid volume in the bladder appears to be critical in making the pad test reproducible and increasing the sensitivity of the test for detecting leakage.

Aslan et al compared a 1 hour pad test loss with the symptom impact index (SII) and the symptom severity index (SSI) [30]. Only the SSI showed a relationship between the severity of the score and the pad test loss. The 1 hour pad test has also been used in assessing the validity of the Incontinence Impact Questionnaire and the Urogenital Distress Inventory unfortunately both had poor correlations with the pad test [31]. This is to be expected as the questionnaires assess other urinary symptoms than just leakage.

d) Diagnosis

Fluid loss was significantly greater in patients with detrusor overactivity in comparison to urodynamic stress incontinence [27, 32]. The reverse finding was reported by Matharu and co-workers [33]. There is high variability in patients with detrusor overactivity making the test impractical as a diagnostic tool.

e) Sensitivity to change

The 1 hour pad test has been shown to be useful in detecting significant improvements after pelvic floor exercises for men suffering urinary incontinence after radical prostatectomy [34]. Ward et al. found the
standard 1 hour pad test to show significant reductions in loss after tension free vaginal tape procedures from 18 g (IQR 6-37) and Burch colposuspension from 16 g (IQR 6-38) both decreasing to 0 g (IQR 0) [35]. The 1 hour pad test has also been tested for the reduction in loss after conservative and surgical therapy [36]. The changes were significant but there was moderate correlation (r = 0.53) with the changes in the St. George Urinary Incontinence Score.

3. 2-HOUR PAD TEST

A test period of 60-120 minutes after a 1 litre fluid load was proposed as the optimal duration for the pad test because of a consistently high bladder volume [37]. Han et al showed, however, that a 1-hour pad test is more practical [38]. In children a 2-hour ward pad test yielded 70% positive results for incontinence [39]. Griffiths et al found only a 10% false negative rate of good at detecting incontinence as a 48-h test [22]. This was better than the results of a 24-h home test. Lose et al. found that a 24h home test performed during daily activities is more sensitive that a 1-hour ward test with standardised bladder volume of 200-300 ml [21]. High fluid intake did not change the results of a 24-h home test, but a low fluid intake reduced a positive test by 56% [42]. Ryhammer et al. showed that 24-h test is superior to subjective self-reported assessment of urinary incontinence [43].

b) Reproducibility

Lose et showed poor correlation in a test-retest study with a variation of more than 100% [21] although Groutz et al. using Lin’s CCC, found 24-h test very reliable instrument [44]. Increasing test duration to 48 and 72 hours slightly improved reliability but decreased patient compliance.

The values for the pad test increase in asymptomatic men and women was reported by Karantanis et al with the median value 0.3g (IQR 0.2 – 0.6; 95th centile 1.3g). It is surprising that the loss is so low and the same for men and women [45].

c) Diagnosis

Matharu et al found women with urodynamic stress incontinence leaked more than women with detrusor overactivity but the amounts were not diagnostic for the individual abnormalities [33]. Pad test loss is unaffected by the degree of hypermobility however there is an increased loss associated with urethral sphincter incompetence diagnosed by a vesical leak point pressure less than 60 cmH2O [46].

d) Validity

Karantanis et al found the 24-hour pad test was poorly correlated in women with USI with incontinence episodes on a 3 day urinary diary (Kendall’s corr coeff b = 0.4) and the ICIQ-SF (r = 0.4) [47]. Singh et al. reported that fewer (52%) women after surgery were willing to complete a 24 hour pad test at follow up [48].

3. 48-HOUR PAD TEST

a) Quantification

Jakobsen et al. showed that 48-hour pad test reflects everyday incontinence in 81% of patients [17]. No statistical analysis data were given. Ekelund et al., found patients own weighing correlate well to control weighing at the clinic in 48-h pad test (r=0.99) [49] (Tables 5&6).

Nygaard and Zmolek in 14 continent women showed a mean pad weight, attributed to sweat for all exercise sessions of 3.19 ± 3.16 g (the Kendall coefficient of concordance of the test-retest reliability was 0.96) but there was a lot of variation between patients [53]. Pyridium staining was not helpful in increasing specificity. Similar results with Pyridium were reported by Wall et al. in a 1-hour ward test [14]. In his study

III. HOME BASED PAD TESTING

These tests were developed to diagnose and measure urine loss in a situation as close as possible to standard daily life of the patient. The longer observation period usually requires a less structured procedure.

1. 12-HOUR PAD TEST

Quantification

Hellstrom et al. demonstrated in 30 children with incontinence a positive 12-hour home pad test in 68%. When a standard fluid load (13 ml/kg) was instituted in 20 children, the frequency of the positive test increased to 80% [39].

2. 24-HOUR PAD TEST

a) Quantification

Lose et al. found a 90% correlation of a 24-hour pad test with history of stress incontinence in 31 women [21]. This was better than the results of a 1-hour test. Thirteen of 31 patients were found to be continent after a 1-hour ward test in comparison to only 3 with a 24-hour home pad test. Mouriøtøen et al. showed that the 24-h home test is well tolerated and is as good at detecting incontinence as a 48-h test [22]. Griffiths et al. found only a 10% false negative rate of a 24-hour pad test in an elderly population [20]. Using non-parametric coefficient of correlation, they found a significant difference between the 1-hour test and the 24 hour test. Lose et al. found that a 24h home test performed during daily activities is more sensitive than a test performed during daily activities is more sensitive that a 1-hour ward test with standardised bladder volume of 200-300 ml [21]. High fluid intake did not change the results of a 24-h home test, but a low fluid intake reduced a positive test by 56% [42]. Ryhammer et al. showed that 24-h test is superior to subjective self-reported assessment of urinary incontinence [43].

b) Reproducibility

Lose et showed poor correlation in a test-retest study with a variation of more than 100% [21] although Groutz et al. using Lin’s CCC, found 24-h test very reliable instrument [44]. Increasing test duration to 48 and 72 hours slightly improved reliability but decreased patient compliance.

The values for the pad test increase in asymptomatic men and women was reported by Karantanis et al with the median value 0.3g (IQR 0.2 – 0.6; 95th centile 1.3g). It is surprising that the loss is so low and the same for men and women [45].

c) Diagnosis

Matharu et al found women with urodynamic stress incontinence leaked more than women with detrusor overactivity but the amounts were not diagnostic for the individual abnormalities [33]. Pad test loss is unaffected by the degree of hypermobility however there is an increased loss associated with urethral sphincter incompetence diagnosed by a vesical leak point pressure less than 60 cmH2O [46].

d) Validity

Karantanis et al found the 24-hour pad test was poorly correlated in women with USI with incontinence episodes on a 3 day urinary diary (Kendall’s corr coeff b = 0.4) and the ICIQ-SF (r = 0.4) [47]. Singh et al. reported that fewer (52%) women after surgery were willing to complete a 24 hour pad test at follow up [48].

3. 48-HOUR PAD TEST

a) Quantification

Jakobsen et al. showed that 48-hour pad test reflects everyday incontinence in 81% of patients [17]. No statistical analysis data were given. Ekelund et al., found patients own weighing correlate well to control weighing at the clinic in 48-h pad test (r=0.99) [49] (Tables 5&6).

Nygaard and Zmolek in 14 continent women showed a mean pad weight, attributed to sweat for all exercise sessions of 3.19 ± 3.16 g (the Kendall coefficient of concordance of the test-retest reliability was 0.96) but there was a lot of variation between patients [53]. Pyridium staining was not helpful in increasing specificity. Similar results with Pyridium were reported by Wall et al. in a 1-hour ward test [14]. In his study
Table 5. Test-retest correlation

<table>
<thead>
<tr>
<th>Author</th>
<th>Test</th>
<th>Correlation coefficient</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klarskov &amp; Hald 1984</td>
<td>1-h</td>
<td>0.96</td>
<td>SUI &amp; UUI</td>
</tr>
<tr>
<td>Lose et al. 1986</td>
<td>1-h</td>
<td>0.68</td>
<td>SUI &amp; MIX</td>
</tr>
<tr>
<td>Fantl et al. 1987</td>
<td>1-h (vol)</td>
<td>0.97</td>
<td>SUI</td>
</tr>
<tr>
<td>Fantl et al. 1987</td>
<td>1-h (vol)</td>
<td>0.84</td>
<td>SUI &amp; UUI</td>
</tr>
<tr>
<td>Lose et al. 1988</td>
<td>45-m (vol)</td>
<td>0.97</td>
<td>SUI &amp; MIX</td>
</tr>
<tr>
<td>Victor et al. 1987</td>
<td>24-h</td>
<td>0.66</td>
<td>SUI</td>
</tr>
<tr>
<td>Lose et al. 1989</td>
<td>24-h</td>
<td>0.82</td>
<td>LUTS</td>
</tr>
<tr>
<td>Mouritsen et al. 1989</td>
<td>24-h</td>
<td>0.87</td>
<td>MIX</td>
</tr>
<tr>
<td>Versi et al. (1996)</td>
<td>24-h</td>
<td>0.9</td>
<td>LUTS</td>
</tr>
<tr>
<td>Groutz et al. (2000)</td>
<td>24-h</td>
<td>0.89</td>
<td>LUTS</td>
</tr>
<tr>
<td>Victor et al. 1987</td>
<td>48-h</td>
<td>0.9</td>
<td>SUI</td>
</tr>
<tr>
<td>Versi et al. (1996)</td>
<td>48-h</td>
<td>0.94</td>
<td>LUTS</td>
</tr>
<tr>
<td>Groutz et al. (2000)</td>
<td>48-h</td>
<td>0.95</td>
<td>LUTS</td>
</tr>
</tbody>
</table>

Table 6. Pad-weight gain (g) in normal women

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>No</th>
<th>Mean (g)</th>
<th>Range (g)</th>
<th>SD</th>
<th>SEM</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn &amp; Fall 1991</td>
<td>20 min</td>
<td>10</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nygaard &amp; Zmolek, 1995</td>
<td>39.5 min</td>
<td>14</td>
<td>3.19</td>
<td>0.1-12.4</td>
<td>3.16</td>
<td></td>
<td>Exercise</td>
</tr>
<tr>
<td>Versi &amp; Cardozo 1986</td>
<td>1h</td>
<td>90</td>
<td>0.39</td>
<td>0.1-1.15</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutherst et al. 1981</td>
<td>1h</td>
<td>50</td>
<td>0.26</td>
<td>0.1-2.1</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walsh &amp; Mills, 1981</td>
<td>2h</td>
<td>6</td>
<td>1.2</td>
<td>0.1-4.0</td>
<td>1.35</td>
<td></td>
<td>Daily activity</td>
</tr>
<tr>
<td>Lose et al. 1989</td>
<td>24h</td>
<td>46</td>
<td>4.0</td>
<td>0.1-10</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jorgensen et al. 1987</td>
<td>24h</td>
<td>23</td>
<td>4.0</td>
<td>0.1-10</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouritsen et al. 1989</td>
<td>24h</td>
<td>25</td>
<td>2.6</td>
<td>0.1-7</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karantinis et al. 2003</td>
<td>24h</td>
<td>120</td>
<td>0.3</td>
<td>0.1-1.3</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Versi et al. 1996</td>
<td>48h</td>
<td>15</td>
<td>7.13</td>
<td>0.3</td>
<td>4.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of the relation between the patient perception of UI and diagnosis of UI and entered the more interesting field of diagnostic accuracy of pad test versus a urodynamic test. Following this line of thought, research has moved away from the evaluation of diagnostic accuracy of pad test versus a urodynamic diagnosis of UI and entered the more interesting field of the relation between the patient perception of UI and pad test.

Franco and co-workers from the St. George Hospital in London, UK tested the correlation between different questionnaires for UI and 1-hour pad test showing that only the ICIQ-SF reached statistical significance with a Kendall’s tb of 0.177 and a P value of 0.037 while no significant correlation was found for a 0 to 10 VAS score, a patient-based 3-point symptom severity scale, Stamey grade, Urogenital Distress Inventory and the Incontinence Impact Questionnaire (IIQ-7) [56]. In another study from Wijma and co-workers, the diagnostic strength of pad test for self-reported symptoms of UI was evaluated during pregnancy and after childbirth and the authors conclude that the diagnostic value of pad testing has no clinical relevance in this setting [57]. A similar analysis, performed in a male population undergoing sling surgery for post-radical prostatectomy incontinence suggests a good correlation between ICIQ-SF and the Patient Global Perception of Improvement (PGPI) with a 24-hour pad test [58].

Studies from the Urinary Incontinence Treatment Network in US investigated the relation between different measures of incontinence severity and showed how pad weight from a 24-hour test had a good correlation with the incontinence episodes frequency derived from a 3-day bladder diary (Spearman correlation coefficient 0.61 but a much lower degree of correlation was found with questionnaires such as the Medical, Epidemiological, and Social Aspect of Aging (r=0.33), the Urogenital Distress Inventory (r=0.17) and the Incontinence Impact Questionnaire (r=0.34) [59].

In the same study, the use of pad testing as a prognostic parameter for treatment outcome was investigated but the 24-hours pad testing showed no prognostic value for treatment failure in a study of Burch colposuspension versus autologous rectus sling [60]. An interesting result was obtained in a predominantly female population of patients receiving neuromodulation for refractory urgency incontinence in which a 24-hour pad test performed after the initial test stimulation was able to predict long term satisfaction of this difficult patient population [61]. In this, as in other studies, the number of pads used per day proved to be an unreliable measure of urinary incontinence [62].

A couple of important methodological issues have been raised concerning the use of pad testing. Khan & Chien eloquently pointed out that test-retest comparison should include methods of blinding and use of an appropriate index of degree of agreement which is the intra-class correlation coefficient. In most of the literature this was not implemented [63]. Kromann-Andersen et al. argued that with considerable inter- and intra-individual variation of urine loss, the correlation of test/retest results may be overestimated and suggested different trials for small, modest and large leakage in large numbers of the patient [64]. This trial has not been carried out.

A recent Health Technology Assessment of pad testing concluded that although high sensitivity and specificity for the diagnosis of UI was reported in some studies, it was difficult to draw any conclusion about the diagnostic accuracy for SUI because of the differences existing in pad test methodology. The number of studies comparing the same pad tests with adequate reporting is insufficient and no formal pooling of published data could be performed [65].

c) Role of the investigation

The test has been standardised by ICS in 1988 for quantification of urine loss and suggested uses for assessment and comparison of treatment outcomes in different centres. Also, the AUA report on Surgical Management of Female Stress Urinary Incontinence includes a pad test (pretreatment evaluation) as a standard of efficiency for clinical trials [66]. The Urodynamic Society included a pad test in a Standards of Efficacy for Evaluation of Treatment Outcomes in Urinary Incontinence [67]. No suggestion was made in the last two reports of which test to use.
• The 1-hour pad test is not very accurate unless a fixed bladder volume is applied
• Set exercises during the test improve test-retest reliability
• The sequence of exercises has little effect on test results
• A pad weight gain $\geq 1$ g suggests a positive 1h test
• A 24 hour test correlates well with symptoms of incontinence
• A 24-hour test has good reproducibility but poorer compliance
• A pad weight gain $\geq 1.3$ g = positive 24 h test
• A test lasting longer than 24 h has little advantage
• A pad test cannot distinguish between urodynamic stress incontinence and detrusor overactivity

**RECOMMENDATIONS**

- The pad test is an optional investigative tool in routine evaluation of urinary incontinence (Level of Evidence 3, Grade of Recommendation C)
- Pad test is a useful outcome measure in clinical trials and research studies. (Level of Evidence 3, Grade of Recommendation C)

The following standards are suggested:

- 20 min-1 h ward test with fixed bladder volume (pad weight gain $\geq 1$ g = positive test) (Level of Evidence 3, Grade of Recommendation C)
- 24 h home pad test during daily activity (pad weight gain $\geq 1.3$ g/24h = positive test) (Level of Evidence 3, Grade of Recommendation C)

**SUGGESTED RESEARCH AREAS**

- Proper validation analysis using the coefficient of variability
- Evaluation of the ability to detect all the spectrum of urinary incontinence (from mild to severe)
- Sensitivity to change in time of incontinence status for 24 hour pad tests
- Validity of pad tests with other measures of incontinence such as urinary diaries and system questionnaires

**REFERENCES**


---

**E. OTHER INVESTIGATIONS**

### I. URINALYSIS

“Urinalysis is a fundamental test that should be performed in all urological patients” [1]. In patients with urinary incontinence, urinalysis is not a diagnostic test for the condition, but it is rather used to screen for haematuria, glucosuria, pyuria and bacteriuria. Even in the absence of controlled studies, there is general expert consensus that the benefits of urinalysis clearly outweigh the costs involved [2]. A positive urinalysis will prompt infection treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. In the evaluation of urinary incontinence in the female, urinalysis is recommended since 60% of women develop urge symptoms at the time of urinary tract infection (UTI). Pyuria was found to be common among incontinent but otherwise asymptomatic, female patients. Pyuria was not necessarily associated with UTI, the significance of sterile pyuria in the elderly population is still unclear [3].

A Norwegian survey of general practitioners' management of female urinary incontinence suggested that urinalysis is the most frequently performed test (73%) and is far more frequent than gynaecological examination (54%) [4]. Another survey suggested that urinalysis is one of the three-part assessment of UI together with patient history and physical examination [5]. The same applies, according to Stricker, for patient selection for collagen implant [6]. A minority of the reviewed papers suggested that urine culture should be carried out together with urinalysis [3, 7].

Urinalysis is also considered of importance in the evaluation of nursing home residents who are incontinent [8], in peri- and postmenopausal women [9], in older women reporting urinary incontinence [10]. Belmin et al., suggested than significant urine samples can even be obtained from disposable diapers in elderly incontinent women [11, 12].

It is recommended that geriatric incontinent patients undergo history, physical examination, tests of lower urinary tract function and urinalysis. The latter test is proposed to rule out the presence of UTI [12]. The clinical relevance of asymptomatic bacteriuria in the elderly is controversial. Although DuBeau and Resnick suggest the use of urinalysis in the diagnostic algorithm to identify asymptomatic bacteriuria in incontinent residents of nursing homes [13], others consider that the condition does not deserve any treatment [11].
The prevalence of renal damage or of biochemical abnormalities in the general population of patients with urinary incontinence is very low, but there are subgroups of patients where the prevalence can be higher (e.g., neurogenic incontinence, overflow incontinence). The routine use of a battery of common chemical and/or hematological tests in patients with urinary incontinence appears to be a prudent rule of good clinical practice in the following situations:

- a) chronic retention with incontinence
- b) neurogenic LUT dysfunction
- c) when surgery is contemplated
- d) when there is a clinical suspicion.

Special tests such as measurement of anti diuretic hormone (ADH) and atrial natriuretic polypeptide have proven useful in research of enuresis in childhood and nocturia in the elderly [1, 2]. Changes in the circadian rhythm of these, and probably also other hormones regulating the renal excretion of water, will in the future contribute to a better understanding of pathophysiology. Synthetic ADH analogues have already come into clinical use for the treatment of nocturnal enuresis. However, the clinical value of these specific tests remains to be established.

**REFERENCES**

III. TISSUE ANALYSIS

Since the last report of the International Consultation on Incontinence in 2005, several papers have been published based on the analysis of sample of tissues coming from patients with stress urinary incontinence (SUI) and/or pelvic organ prolapse aiming at evaluating the molecular bases of these conditions. The main targets of both preclinical and clinical research have been the pelvic floor-supporting tissues and the role of steroid hormones, with some intriguing linkages between the two lines of research.

Pelvic floor-supporting tissues are composed mainly of connective tissue in which fibrous elements such as collagen and elastic fibres and visco-elastic matrix based on proteoglycans are the predominant components of the so called extracellular matrix. Extracellular matrix is a complex network of numerous macromolecules that fulfil a large number of mechanical, chemical and biological functions [1]. While collagens and elastin fibres confer strength and elasticity to tissues, respectively, structural proteoglycans allow tissue cohesiveness. Specifically, collagen is the most prevalent component, with type I fibres usually well organized and associated with ligamentous tissue, while type III collagen is more common in the loose areolar tissue, which makes up the vaginal wall adventitia and surrounds the pelvic organs [2]. According to the molecular weight, indeed, proteoglycans are distinguished into large molecules (aggrecan, versican and perlecan) and small molecules, such as decorin, fibromodulin, biglycan, lumican and chondroadherin [3].

The organized structure of the matrix is due to a clear balance between the production of the different constituents and their breakdown. There are many proteolytic enzymes capable of degrading the elements of the extracellular matrix, falling into three groups: the serine proteases, the cysteine proteases, and matrix metalloproteinases (MMPs) [4].

Several authors evaluated the expression of the different proteins as well as of their precursors and fragments of degradation. With regards to the metabolism of collagen, some studies seem to indicate that women with SUI have a reduced total collagen content in the skin and urogenital tissue [5-7], while other studies reported higher total collagen concentration and higher levels of mRNAs for type I and type III collagen in paraurethral connective tissue [8]. Chen et al., evaluating cultures of fibroblasts taken from endopelvic fascia and skin biopsies in 14 patients with stress urinary incontinence and 12 controls, showed that the overall collagen synthesis and the ratio of type III and type I fibres were not significantly different between fibroblasts obtained from women with or without SUI [4], indicating that alteration in the collagen synthesis might not be involved in SUI. On the other hand, a few studies reported change in the relative percentages of the different fibres, with decreasing in type I and increasing in type III ones [9, 10]. Skorpinski et al., evaluating in DNA obtained from peripheral blood leucocytes the transcription factor Sp1-binding site in the gene encoding a-1 chain of type I collagen, identified G-T polymorphism at the Sp1 binding site of the gene encoding a-1 chain of type I collagen as a possible risk factor for SUI [11], suggesting that alteration of the protein expression might be due to mutations in transcription factors. Again at molecular level, some studies evaluated the cycle regulatory proteins in patients with pelvic organ prolapsed, showing controversial results. Some papers reported reduced expression of proteins such as p53 and p21 which normally cause cycle G1 arrest suggesting an increase in proliferation capacities for fibroblasts derived from human cardinal ligaments of patients with prolapsed [2].

Other authors evaluated markers of collagen degradation. Specifically, Edwall et al. evaluated markers of collagen synthesis and breakdown such as the carboxy-terminal propeptide of type I procollagen (PICP), the carboxy-terminal telopeptide of type I collagen (ICTP), and the amino-terminal propeptide of procollagen III (PIIINP) in urogenital tissue homogenates and peripheral serum from 71 patients with SUI and 31 healthy control women [12].

After adjusting for age, BMI, parity, and hormonal status, the patients with SUI had significantly lower serum concentrations of PICP and significantly lower tissue concentrations of PIIINP and ICTP than the controls, suggesting reducing breakdown in the presence of unchanged synthesis of type I collagen and, regarding type III collagen, a potential reduction in either synthesis or breakdown, the second being considered more probable [12].

These data may lead to the hypothesis that SUI might be associated with impaired degradation of collagen, leading to reduced turnover and accumulation of aging collagen, negatively affecting the strength and elasticity of urogenital tissue. Further studies on transforming growth factor-β (TGF-β) identified the molecular basis of such mechanism, suggesting that overexpression of TGF-β might trigger the accumulation of aging collagen, inhibiting the expression of collagenases and increasing the production of the tissue inhibitor metalloproteinase [13-15]. Moreover, some genes, such as those of the Homebox A (HOXA) family, encoding transcription factors that regulate mammalian embryonic growth and development of the urogenital tract, have been shown to be underexpressed in patients with pelvic organ prolapsed, suggesting a further molecular basis for the alterations in collagens [16].
Other studies were focused on the expression of small proteoglycans. Wen et al. studied mRNA and protein levels of biglycan, decorin, and fibromodulin in vaginal wall tissue from women with SUI and menstrual-cycle matched continent women [1]. Specifically, the authors demonstrated that the mRNA expression of fibromodulin was significantly lower in patients in the proliferative phase compared to controls, while decorin mRNA expression was higher both in the proliferative and secretory phases in the patients with SUI, supporting the hypothesis that the expression of such small proteoglycans was hormonally modulated and may contribute to the altered pelvic floor connective tissues of the women with SUI [1].

Estrogens act interacting with specific receptors which, when activated by the ligand, have conformational change, dimerization and recruitment of co-factors, once translocated into the nucleus, these promote the expression of region of estrogen-responsive genes, called the estrogen response elements, leading to the synthesis of proteins [19]. More recently, selective modulators of estrogens receptors have been identified, that act modulating the activity of the receptors, working as agonists, partial agonists, or antagonists in a tissue-dependent manner [20]. Studies on these molecules supported a new role of estrogens in SUI and pelvic organ prolapsed. Specifically, in a randomized controlled trial testing one of these molecules (levormeloxifene) as osteoporosis treatment, a 3.4-fold increase in the reporting of pelvic organ prolapse and an almost 5-fold increase in the reporting of urinary incontinence have been observed [21]. To explain such effect, the expression of more than 500 proteins have been studied in the rat model, showing that estradiol induced the expression of metalloproteinase 7 and 14, reduced the expression of their inhibitors such as TIMP-3, while selective modulators of estrogens receptors such as raloxifene had minimal effects on metalloproteinase 7, and maintained or restored expression of the mRNA for tissue inhibitor of metalloproteinases-3 (TIMP-3) and other components of the extracellular matrix, such as glypican, and biglycan [19]. Although the role of selective estrogen-receptor modulators (SERMs) in the expression of the component of extracellular matrix has to be further clarified, these findings support the hypothesis that the increased occurrence of urinary incontinence and pelvic organ prolapse observed with estrogen therapy and SERMs such as levormeloxifene may be related to changes in expression of genes regulating collagen turnover that ultimately weaken the normal structural integrity and support for the genitourinary system [19].

To date, all these tissue analyses are not part of the everyday clinical practice but the data of these studies improved are improving our comprehension of the pathophysiology of urinary incontinence and pelvic organ prolapsed.

REFERENCES

Clinical research involving diagnostic accuracy and clinical benefit of imaging studies as other diagnostic tests is particularly difficult. Recommendation of a diagnostic test is based upon the evidence that the outcome of it provides valuable information for patient management and this often involves evaluating the outcome of surgery. Implementation of good clinical research in this area remains difficult and sometimes lack adequate founding. Research in this area is particularly daunting and often relies on academic founding only. We acknowledge that only a few of the imaging techniques and other investigations we reviewed in the current chapter have been properly evaluated with respect to reproducibility, specificity, sensitivity and predictive value in connection with the diagnosis and the management of urinary incontinence. Nevertheless, we acknowledge the great amount of work performed in the last four years and the continuous advancement in this field. The use of imaging and other investigations, described in this chapter, remains mostly based on expert opinion, common sense, availability and local expertise, rather than on evidence based clinical research. The diagnostic tests we considered can be subdivided into safety tests, tests with specific and selected indications, investigational tests.

**Safety tests** - Intended to protect patients’ health, they are indicated in all patients complaining of urinary incontinence. They include urinalysis and measurement of post-voiding residual urine. While a consensus is easily achieved for urinalysis, the clinical benefit and cost-effectiveness of PVR measurement in primary evaluation of urinary incontinence needs to be confirmed in prospective studies.

**Tests with specific and selected indications.** Upper urinary tract imaging (as well as renal function assessment) may be indicated in cases of neurogenic urinary incontinence with risk of renal damage, chronic retention with incontinence, incontinence associated with severe genitourinary prolapse and suspicion of extraurethral incontinence. No other imaging techniques is recommended in the primary evaluation of uncomplicated urinary incontinence and/or pelvic organ prolapse. Cystourethrogram remains a reasonable option only in the preoperative evaluation of complicated and/or recurrent cases. Videourodynamics, is the gold standard in the evaluation of neurogenic incontinence, particularly in the paediatric population, although the clinical benefit of it remains unclear. In female urinary incontinence videourodynamics is not recommended except under specific complex circumstances. MRI remains the gold standard for the diagnosis of urethral diverticula.
although ultrasonography is a good alternative option. Lumbosacral spine X-rays have specific indications in children with suspect neurogenic incontinence without gluteo-sacral stigmata. Imaging of the CNS should be considered when a neurological disorder is suspected on the basis of clinical, imaging and neurophysiological findings. Urethrocystoscopy is indicated in cases of incontinence with microscopic haematuria, in the evaluation of recurrent or iatrogenic cases, in the evaluation of vesico-vaginal fistula and extra-urethral urinary incontinence.

Endoanal ultrasound and endocoil MRI are the gold standard for the evaluation of anal sphincter disorders, dynamic X-ray imaging remain the standard for evaluating rectal prolapse.

**Investigational tests** Pelvic floor ultrasound is widely used as an adjunct to physical examination in patients with urinary incontinence and/or pelvic organ prolapse. Although the technique is rapidly evolving and much progress has been made in clinical research in this field, ultrasonography remains optional as evidence of its clinical benefit is not there yet.

MRI of the pelvic floor is rapidly gaining popularity in the evaluation of enteroceles and in the morphological analysis of pelvic floor muscles although evidence of its clinical benefit is still lacking. Both ultrasonography and MRI are the most rapidly evolving techniques and hold promises for potential future clinical applications.

Research in this area is also performed to improve our understanding of the pathophysiology of continence disorders and pelvic organ prolapse. Functional neuroimaging continues to provide new insight on functional anatomy of CNS related to vesicourethral function and dysfunction. The content of the draft reflects the composition of the Committee which is made of clinicians with a particular interest in a specific area of imaging and neurophysiology. The chapter certainly reveals the enthusiasm the authors poured in clinical research in this area but we believe that the methodology implemented by the Consultation is the best guarantee of a balanced opinion and trustful recommendations. We hope that this chapter will stimulate clinical research in this field and will inspire those involved in the management of continence disorders and pelvic organ prolapse.

Neurophysiological testing should be part of the armamentarium available in the management of neurogenic incontinence and the establishment of good collaboration with neurophysiologists is recommended.
Committee 8

Pharmacological Treatment of Urinary Incontinence

Chairman

*KARL-ERIK ANDERSSON (USA)*

Co-Chairman

*C. R CHAPPLE (U.K)*

Members

*L. CARDOZO (U.K)*,

*F. CRUZ (Portugal)*,

*H. HASHIM (U.K)*,

*M.C. MICHEL (The Netherlands)*,

*C. TANNENBAUM (Canada)*,

*A.J. WEIN (USA)*
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. INTRODUCTION</td>
</tr>
<tr>
<td>I. PUBLICATION SEARCHES</td>
</tr>
<tr>
<td>II. CENTRAL NERVOUS CONTROL</td>
</tr>
<tr>
<td>III. PERIPHERAL NERVOUS CONTROL</td>
</tr>
<tr>
<td>IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS</td>
</tr>
<tr>
<td>V. BLADDER CONTRACTION</td>
</tr>
<tr>
<td>VI. MUSCARINIC RECEPTORS</td>
</tr>
<tr>
<td>B. DRUGS USED FOR TREATMENT OF OVERACTIVE BLADDER SYMPTOMS/DETRUSOR OVERACTIVITY</td>
</tr>
<tr>
<td>I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS</td>
</tr>
<tr>
<td>II. DRUGS ACTING ON MEMBRANE CHANNELS</td>
</tr>
<tr>
<td>III. DRUGS WITH “MIXED” ACTION</td>
</tr>
<tr>
<td>IV. α-ADRENOCEPTOR (AR) ANTAGONISTS</td>
</tr>
<tr>
<td>V. β-ADRENOCEPTOR AGONISTS</td>
</tr>
<tr>
<td>VI. PHOSPHODIESTERASE (PDE) INHIBITORS</td>
</tr>
<tr>
<td>VII. ANTIDEPRESSANTS</td>
</tr>
<tr>
<td>VIII. CYCLOOXYGENASE (COX) INHIBITORS</td>
</tr>
<tr>
<td>IX. TOXINS</td>
</tr>
<tr>
<td>X. OTHER DRUGS</td>
</tr>
<tr>
<td>XI. COMBINATIONS</td>
</tr>
<tr>
<td>XII. FUTURE POSSIBILITIES</td>
</tr>
<tr>
<td>C. DRUGS USED FOR TREATMENT OF STRESS URINARY INCONTINENCE</td>
</tr>
<tr>
<td>I. α-ADRENOCEPTOR AGONISTS</td>
</tr>
<tr>
<td>II. β-ADRENOCEPTOR ANTAGONISTS</td>
</tr>
<tr>
<td>III. β-ADRENOCEPTOR AGONISTS</td>
</tr>
<tr>
<td>IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS</td>
</tr>
<tr>
<td>D. DRUGS USED FOR TREATMENT OF OVERFLOW INCONTINENCE</td>
</tr>
<tr>
<td>E. HORMONAL TREATMENT OF URINARY INCONTINENCE</td>
</tr>
<tr>
<td>I. ESTROGENS</td>
</tr>
<tr>
<td>II. OTHER STEROID HORMONE RECEPTOR LIGANDS</td>
</tr>
<tr>
<td>III. DESMOPRESSIN</td>
</tr>
<tr>
<td>F. CONSIDERATIONS IN THE ELDERLY</td>
</tr>
<tr>
<td>REFERENCES</td>
</tr>
</tbody>
</table>
The function of the lower urinary tract (LUT) is to store and periodically release urine, and is dependent on the activity of smooth and striated muscles in the bladder, urethra, and pelvic floor. The bladder and the urethra constitute a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [Andersson, 1993; de Groat and Yoshimura, 2001; Andersson and Wein, 2004]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance [Wein, 2007].

Many drugs have been tried, but the results are often disappointing, partly due to poor treatment efficacy and/or side effects. The development of pharmacologic treatment of the different forms of urinary incontinence has been slow, but several promising targets and drug principles have been identified [Andersson et al., 2002; 2005; Andersson, 2007; Colli et al., 2007].

In this report, we update the recommendations from the 2004 International Consensus meeting [Andersson et al., 2005]. The most relevant information obtained since the last meeting is reviewed and summarised. Agents specifically used for treatment of urinary tract infections and interstitial cystitis, have not been included. Our clinical drug recommendations are based on evaluations made using a modification of the Oxford system (Table 1). The terminology used is that recommended by the International Continence Society (ICS) [Abrams et al., 2002].

Table 1. ICI assessments 2008: Oxford guidelines (modified)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)</td>
<td>Grade A: Based on level 1 evidence (highly recommended)</td>
</tr>
<tr>
<td>Level 2: RCTs, good quality prospective cohort studies</td>
<td>Grade B: Consistent level 2 or 3 evidence (recommended)</td>
</tr>
<tr>
<td>Level 3: Case-control studies, case series</td>
<td>Grade C: Level 4 studies or &quot;majority evidence&quot; (optional)</td>
</tr>
<tr>
<td>Level 4: Expert opinion</td>
<td>Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended</td>
</tr>
</tbody>
</table>

I. PUBLICATION SEARCHES

The review undertook a comprehensive search of all major literature databases and the abstract books from several major conferences: American Urological Association, ICS, European Association of Urology, International Urogynaecological Association, International Consultation of Incontinence and Societe Internationale d’Urologie. There were no restrictions on the inclusion of publications by language; publications in languages other than English were translated into English.
II. CENTRAL NERVOUS CONTROL

In the adult individual, the normal micturition reflex is mediated by a spinobulbospinal pathway, which passes through relay centers in the brain (Figure 1). In infants, the central pathways seem to be organized as on-off switching circuits, but after the age of four to six years, voiding is initiated voluntarily by the cerebral cortex [de Groat et al., 1999]. Studies in humans and animals have identified areas in the brainstem and diencephalon that are specifically implicated in micturition control, including Barrington’s nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [Griffiths, 2004., Fowler et al., 2008]. These structures directly excite bladder motoneurons and indirectly inhibit urethral sphincter motoneurons via inhibitory interneurons in the medial sacral cord. The periaqueudctal grey (PAG) receives bladder filling information, and the pre-optic area of the hypothalamus is probably involved in the initiation of micturition. According to PET-scan and functional imaging studies in humans, these supraspinal regions are active during micturition [Griffiths, 2004; Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths et al., 2007; Hruz et al., 2008; Mehnert et al., 2008; Tadic et al., 2008].

III. PERIPHERAL NERVOUS CONTROL

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in parasympathetic, sympathetic, somatic, and sensory nerves (Figures 2-4). These nerves are parts of reflex pathways, which either keep the bladder in a relaxed state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of parasympathetic neurones located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 [de Groat et al., 1993]. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide [Andersson and Persson, 1993], although other transmitters might be involved [Bridgewater and Brading, 1993; Hashimoto et al., 1993; Werkström et al., 1995].

Most of the sympathetic innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoraco-lumbar region (T10-L2) of the spinal cord. The axons travel either through the inferior mesenteric ganglia and the hypogastric nerve, or pass through the paravertebral chain and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric and pelvic nerves [Lincoln and Burnstock, 1993].

The predominant effects of the sympathetic innervation of the lower urinary tract are inhibition of the parasympathetic pathways at spinal and ganglion levels (demonstrated in animals), and mediation of contraction of the bladder base and the urethra (shown in animals and man, see Andersson, 1993). However, the adrenergic innervation of the bladder body is believed to inactivate the contractile mechanisms in the detrusor directly. Noradrenaline (norepinephrine) is released in response to electrical stimulation of detrusor tissues in vitro, and the normal response of detrusor tissues to released noradrenaline is relaxation [Andersson, 1993].

Figure 1: Components of the micturition reflex.
Figure 2: Activity in the micturition reflex during storage. The pontine micturition center is inhibited by impulses from the prefrontal cortex, afferent impulses unable to initiate micturition. Activities in the hypogastric and pudendal nerves keep the bladder relaxed and the outflow region contracted.

Figure 3: Activity in the micturition reflex during voluntary voiding. The inhibitory impulses from the prefrontal cortex pontine micturition center are removed and afferent impulses are able to initiate micturition. Activities in the hypogastric and pudendal nerves are inhibited, the outflow region is relaxed, and the bladder is contracted by the activity in the pelvic nerve.

Figure 4: Detrusor overactivity. Despite the inhibitory impulses from the prefrontal to the cortex pontine micturition center the enhanced (?) afferent impulses are able to initiate micturition.
The somatic innervation of the urethral rhabdosphincter and of some perineal muscles (for example compressor urethrae and urethrovaginal sphincter), is provided by the pudendal nerve. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2-S4) in a region called Onuf’s (Onufrowicz’s) nucleus).

Most of the sensory innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia. In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord [Lincoln and Burnstock, 1993]. The most important afferents for the micturition process are myelinated Aδ-fibres and unmyelinated C-fibres travelling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall to the spinal cord. The Aδ-fibres respond to passive distension and active contraction, thus conveying information about bladder filling [Janig and Morrison, 1986]. C-fibres have a high mechanical threshold and respond primarily to chemical irritation of the bladder mucosa [Habler et al., 1990] or cold [Fall et al., 1990]. Following chemical irritation, the C-fibre afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension [Habler et al., 1990]. These fibres are normally inactive and are therefore termed "silent fibres".

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

As pointed out previously, bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding [Wein, 2007]. Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence. Failure to store also occurs if the bladder is overactive, as in the overactive bladder (OAB) syndrome. The prevalence varies with the criteria used for diagnosis, but according to Irwin et al. (2006), using the ICS definition of 2002 [Abrams et al., 2002], the overall prevalence of OAB, based on computer assisted telephone interviews (the EPIC study) was 11.8%; rates were similar in men and women and increased with age [Irwin et al., 2006]. A similar study based on a cross Canada telephone survey found the prevalence of OAB to be 13 % in men and 14.7% in women [Herschorn et al., 2008]. OAB (symptomatic diagnosis) is often assumed to be caused by detrusor overactivity (DO; urodynamic diagnosis), even if this does not always seem to be the case [Hyman et al., 2001; Digesu et al., 2003; Hashim and Abrams, 2004; Aschkenazi et al., 2007].

DO/OAB can occur as a result of sensitization of afferent nerve terminals in the bladder or outlet region, changes of the bladder smooth muscle secondary to denervation, or consequent upon damage to the central nervous system (CNS) inhibitory pathways (Figure 5), as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson’s disease, brain tumors, and spinal cord injury [Ouslander, 2004]. Urinary retention and overflow incontinence can be observed in patients with urethral outlet obstruction (e.g. prostate enlargement), decreased detrusor contractility, or both), neural injury, and/or diseases that damage nerves (e.g. diabetes mellitus), or in those who are taking drugs that depress the neural control of the bladder or bladder smooth muscle directly [Wein, 2007].
V. BLADDER CONTRACTION

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle. Atropine resistance, i.e. contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [Andersson, 1993; Bayliss et al., 1999]. However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused mainly by adenosine triphosphate (ATP) [Andersson, 1993; Bayliss et al., 1999, Andersson and Wein, 2004; Kennedy et al., 2007]. ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G-protein-coupled receptor family (P2Y). Seven P2X subtypes and eight P2Y subtypes have been identified. In several species (rabbit, cat, rat, and human), various studies suggested that multiple purinergic excitatory receptors are present in the bladder [de Groat and Yoshimura, 2001]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that P2X1 receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [de Groat and Yoshimura, 2001]. P2X3 receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves. In P2X3 knockout mice, afferent activity induced by bladder distension was significantly reduced [Cockayne et al., 2000; Ford et al., 2006; Ruggieri et al., 2006]. These data indicate that purinergic receptors are involved in mechanosensory signaling in the nonprimate mammalian bladder.

A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders, and has been reported to occur in hypertrophic bladders [Stjögren et al., 1982], interstitial cystitis [Palea et al., 1993], neurogenic bladders [Wammack et al., 1995], and in the aging bladder [Yoshida et al., 2001]. The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established.

VI. MUSCARINIC RECEPTORS

The neurotransmitter ACh acts on two classes of receptors, the nicotinic and the muscarinic receptors. While the former play a role in the signal transduction between neurones or between neurones and skeletal muscle (e.g. in the distal urethra), the signal transduction between parasympathetic nerves and smooth muscle of the detrusor involves muscarinic receptors [Abrams and Andersson, 2007]. Importantly, the endogenous muscarinic receptor agonist ACh is not necessarily derived only from parasympathetic nerves in the urinary bladder, but can also be formed and released non-neuronally by the urothelium [Bschleiper et al., 2007; Mansfield et al., 2005; Zarghooni et al., 2007]. Five subtypes of muscarinic receptors have been cloned in humans and other mammalian species, which are designated M1-5 [Caulfield and Birdsal 1998]. Based upon structural criteria and shared preferred signal transduction pathways, the subtypes can be grouped into M1, M3 and M5 on the one hand and the subtypes M2 and M4 on the other. The former prototypically couple via pertussis toxin-insensitive Gq proteins to stimulation of a phospholipase C followed by elevation of intracellular calcium and activation of a protein kinase C, whereas the latter prototypically couple via pertussis toxin-sensitive Gt proteins to inhibition of adenyl cyclase and modulation of several ion channels [Caulfield and Birdsal 1998]. While sensitive molecular techniques such as reverse transcriptase polymerase chain reaction can detect mRNA for all five subtypes in the mammalian bladder [Abrams et al., 2006: Hegde, 2006], studies at the protein level, e.g. based upon radioligand binding, have typically detected only M2 and M3 receptors, with the former dominating quantitatively [Abrams et al., 2006: Hegde, 2006]. Functional studies have implicated an involvement of M1 and M4 receptors (alongside with M2 receptors) in the prejunctional regulation of neurotransmitter release in the mammalian bladder, with M1 receptors enhancing and M2 and M4 receptors inhibiting ACh release [Braverman et al., 1998; D’Agostini et al., 1997]. However, most muscarinic receptors in the urinary bladder are located on smooth muscle and urothelial cells.

Apparently, most muscarinic receptors in the bladder are found on the smooth muscle cells of the detrusor. While the detrusor expresses far more M2 than M3 receptors, it appears that detrusor contraction under physiological conditions is largely if not exclusively mediated by the M3 receptor [Hegde et al., 1997; Chess-Williams et al., 2001; Fetscher et al., 2002; Kories et al., 2003; Schneider et al., 2004a, b]. Studies in knock-out mice confirm this conclusion [Matsui et al., 200; 2002; Stengel et al., 2002; Ehler et al., 2007]. Under physiological conditions M2 receptor-selective stimulation causes little contraction [Schneider et al., 2005a], but rather appears to act mainly by inhibiting β-adrenoceptor-mediated detrusor relaxation [Hegde et al., 1997; Ehler et al., 2007; Matsui et al., 2003]. It has been proposed that M2 receptors can also directly elicit bladder contraction under pathological conditions [Braverman et al., 1998; 2002; 2003; 2006; Pontari et al., 2003], but such observations have not
been confirmed by other investigators using distinct methodological approaches [Schneider et al., 2005a; b].

Based upon the prototypical signalling pathway of M₃ receptors [Cauldfield and Birdsall, 1998] and the presence of phospholipase C stimulation by muscarinic agonists in the bladder [Kories et al., 2003; Schneider et al., 2005a] it had originally been believed that muscarinic receptor-mediated contraction is largely mediated by an activation of phospholipase C [Ouslander, 2004]. While some earlier data had supported this concept, it now appears clear that, at least in rat, mice and humans, muscarinic receptor-mediated bladder contraction occurs largely independent of phospholipase C [Schneider et al., 2004; Wegener et al., 2004; Frazier et al., 2007]. Rather, alternative signalling pathways such as opening of L-type calcium channels and activation of a rho-kinase (Figure 6) appear to contribute to muscarinic receptor-mediated bladder contraction in a major way [Frazier et al., 2008].

More recently, muscarinic receptors have also been identified in the urothelium [Chess-Williams, 2002; Kumar et al., 2005]. Similarly to the findings in bladder smooth muscle, the muscarinic receptors in the urothelium mainly belong to the M₂ and M₃ subtype, with the former dominating quantitatively [Mansfield et al., 2005; Bschleiper et al., 2007]. At present the functional role of muscarinic receptors in the urothelium has largely been studied indirectly, i.e. by investigating the effects of urothelium removal or of administration of pharmacological inhibitors. These data indicate that muscarinic stimulation of the urothelium causes release of an as yet unidentified factor which inhibits detrusor contraction [Hawthorn et al., 2000; Wuest et al., 2005; Sadananda et al., 2008]. Some data indicate that muscarinic receptors in the urothelium may partly act by releasing nitric oxide (NO) [Andersson et al., 2008a]. Thus, it appears that muscarinic receptors in the urothelium also contribute to the regulation of overall bladder function but their specific roles in health and disease have not been fully established [Andersson et al., 2008b].

Based upon the involvement of muscarinic receptors in physiological voiding contractions of the bladder, numerous studies have explored whether an overactivity of the muscarinic system may play a causative role in bladder dysfunction. This could involve, e.g., an enhanced expression of such receptors and/or an increased functional responsiveness. In vitro, an increased sensitivity to muscarinic receptor stimulation was found in both idiopathic and neurogenic overactive human detrusors (Stevens et al. 2006). However, according to Michel and Barendrecht [2008] the overall balance of available studies suggests that the muscarinic receptor system is not hyperactive under conditions of DO and, if anything, can be even hypoactive [Michel and Barendrecht, 2008]. This does not exclude a contribution to DO of ACh and muscarinic receptor stimulation during bladder filling (see below). It appears that the contribution of muscarinic mechanisms to the overall regulation of bladder contractility decreases in favour of non-cholinergic mechanisms under pathological conditions [Yoshida et al., 2001; 2008; Rapp et al 2005]. These observations may help to explain the moderate efficacy of muscarinic receptor antagonists relative to placebo in controlled clinical studies [Herbison et al., 2003; Chapple et al., 2005; 2008; Novara et al., 2008; Shamiyan et al., 2008].

![Figure 6](image-url)
It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence, and an abundance of drugs has been used for treatment (Table 2). As underlined by several other subcommittees, drugs may be efficacious in some patients, but they do have side effects, and frequently are not continued indefinitely. Hence it would be worth considering them as an adjunct to conservative therapy.

**I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS**

**Mechanism of action.** Antimuscarinics block, more or less selectively, muscarinic receptors [Abrams and Andersson, 2007]. The common view is that in OAB/DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by ACh, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the lower urinary tract [Andersson, 2004]. Furthermore, antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of ACh, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, but in the dose range used for beneficial effects in OAB/DO, there is little evidence for a significant reduction of the voiding contraction [Finney et al., 2006; Figure 7]. However, there is good experimental evidence that the drugs act during the storage phase by decreasing the activity in afferent nerves (both C- and Aδ-fibres) from the bladder [De Laet et al., 2006; Ijima et al., 2007].

As mentioned previously, muscarinic receptors are found on bladder urothelial cells where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest [Andersson, 2002; Birder and de Groat, 2007], but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues [2004; 2006; 2008] found that there is basal ACh release in human bladder. This release was resistant to tetrodotoxin and much diminished when the urothelium was removed; thus, the released ACh was probably of non-neuronal origin and, at least partly, generated by the urothelium. There is also indirect clinical evidence for release of ACh during bladder filling. Smith and co-workers [1974] found that in patients with recent spinal-cord injury, inhibition of ACh breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and colleagues [2001] inhibited ACh breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78% of the patients with the symptom pattern of overactive bladder, but in no patients without specific complaints suggesting DO. Thus, during the storage phase, ACh and ATP may be released from both neuronal and non-neuronal sources (eg, the urothelium) and directly or indirectly

---

**Figure 7 : Rationale for use of antimuscarinics for treatment of OAB/DO. Blockade of muscarinic receptors at both detrusor and non-detrusor sites may prevent OAB symptoms and DO without depressing the contraction during voiding.**
<table>
<thead>
<tr>
<th>Drugs used in the treatment of OAB/ DO. Assessments according to the Oxford system (modified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimuscarinic drugs</strong></td>
</tr>
<tr>
<td>Tolterodine 1 A</td>
</tr>
<tr>
<td>Trospium 1 A</td>
</tr>
<tr>
<td>Solifenacin 1 A</td>
</tr>
<tr>
<td>Darifenacin 1 A</td>
</tr>
<tr>
<td>Fesoterodine 1 A</td>
</tr>
<tr>
<td>Propantheline 2 B</td>
</tr>
<tr>
<td>Atropine, hyoscyamine 3 C</td>
</tr>
<tr>
<td><strong>Drugs acting on membrane channels</strong></td>
</tr>
<tr>
<td>Calcium antagonists 2 D</td>
</tr>
<tr>
<td>K-Channel openers 2 D</td>
</tr>
<tr>
<td><strong>Drugs with mixed actions</strong></td>
</tr>
<tr>
<td>Oxybutynin 1 A</td>
</tr>
<tr>
<td>Propiverine 1 A</td>
</tr>
<tr>
<td>Flavoxate 2 D</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td>Imipramine 3 C</td>
</tr>
<tr>
<td>Duloxetine 2 C</td>
</tr>
<tr>
<td><strong>Alpha-AR antagonists</strong></td>
</tr>
<tr>
<td>Alfuzosin 3 C</td>
</tr>
<tr>
<td>Doxazosin 3 C</td>
</tr>
<tr>
<td>Prazosin 3 C</td>
</tr>
<tr>
<td>Terazosin 3 C</td>
</tr>
<tr>
<td>Tamsulosin 3 C</td>
</tr>
<tr>
<td><strong>Beta-AR antagonists</strong></td>
</tr>
<tr>
<td>Terbutaline (beta 2) 3 C</td>
</tr>
<tr>
<td>Salbutamol (beta 2) 3 C</td>
</tr>
<tr>
<td>YM-178 (beta 3) 2 B</td>
</tr>
<tr>
<td><strong>PDE-5 Inhibitors+</strong></td>
</tr>
<tr>
<td>(Sildenafil, Tadalafil, Vardenafil) 2 B</td>
</tr>
<tr>
<td><strong>COX-inhibitors</strong></td>
</tr>
<tr>
<td>Indomethacin 2 C</td>
</tr>
<tr>
<td>Flurbiprofen 2 C</td>
</tr>
<tr>
<td><strong>Toxins</strong></td>
</tr>
<tr>
<td>Botulinum toxin (neurogenic)*** 2 A</td>
</tr>
<tr>
<td>Botulinum toxin (idiopathic)*** 3 B</td>
</tr>
<tr>
<td>Capsaicin (neurogenic)*** 2 C</td>
</tr>
<tr>
<td>Resiniferatoxin (neurogenic)*** 2 C</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
</tr>
<tr>
<td>Baclofen* 3 C</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
</tr>
<tr>
<td>Estrogen 2 C</td>
</tr>
<tr>
<td>Desmopressin# 1 A</td>
</tr>
<tr>
<td>*(male LUTS/OAB); * intrathecal; ** intravesical; *** bladder wall; #nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!</td>
</tr>
<tr>
<td><strong>Level of evidence</strong></td>
</tr>
<tr>
<td><strong>Grade of recommendation</strong></td>
</tr>
</tbody>
</table>
(by increasing detrusor smooth muscle tone, Figures 8, 9 and 10) excite afferent nerves in the suburothelium and within the detrusor. These mechanisms may be important in the pathophysiology of OAB/DO and represent possible targets for antimuscarinic drugs.

**Pharmacologic properties.** Generally, antimuscarinics can be divided into tertiary and quaternary amines [Guay, 2003, Abrams and Andersson, 2007]. They differ with regards to lipophilicity, molecular charge, and even molecular size, tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine, are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood brain barrier, but in some cases, such as trospium, darifenacin, and fesoterodine, that is compensated by active transport out of the CNS by the product of the MDR1 gene (P-glycoprotein, see Table 3). Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects [Guay 2003]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, tachycardia, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites [Guay 2003]. The most commonly involved P450 enzymes are CYP2D6, and CYP3A4. The metabolic conversion creates a risk for drug-drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and/or interacting drug. Antimuscarinics secreted by the renal tubules (eg trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism.

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence [Andersson, 2004]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems (Figure 11) may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained if the subtype(s) mediating bladder contraction and those producing the main side effects of antimuscarinic drugs were different. Unfortunately, this does not seem to be the case. One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

Several antimuscarinic drugs are and have been used for treatment of OAB/DO. For some of them, documentation of effects is not based on randomized controlled trials (RCTs) satisfying currently required criteria, and some drugs can be considered as obsolete (e.g., emepronium). Information on these drugs has not been included, but can be found elsewhere [Andersson, 1988; Andersson et al., 1999].

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned. Herbison et al. [2003] stated in a widely discussed article: “Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo.”

**Figure 8 :** The hypothetical role of acetylcholine (ACh) in the generation of DO and OAB. During bladder filling, there is no activity in the parasympathetic outflow from the bladder. However, the myocytes have a spontaneous (myogenic) contractile activity that generates afferent nerve activity (C-fibres and Ad-fibres). In DO bladders, there are areas of “patchy denervation” and ACh in low concentrations is “leaking” from the nerves. This enhances the spontaneous activity and the basal afferent nerve activity (“afferent noise”). This means that the Ad-fibre activity, generated by bladder distension, can initiate the micturition reflex at low degrees of bladder filling. Antimuscarinics in therapeutically recommended doses can inhibit the effects of these low concentrations of acetylcholine, but not of the high concentrations necessary for the generating the voiding contraction (requiring efferent nerve activity). Structural changes in the bladder (e.g., secondary to outflow obstruction) can generate local factors, such as prostaglandins and endothelins, which also can contribute to enhancement of the spontaneous activity.
Figure 9: The hypothetical role of acetylcholine (ACh) in the generation of DO and OAB. During bladder filling, there is no activity in the parasympathetic outflow from the bladder. However, the myocytes have a spontaneous (myogenic) contractile activity that generates afferent nerve activity (C-fibres and Ad-fibres). In DO bladders, there are areas of “patchy denervation” and ACh in low concentrations is “leaking” from the nerves. This enhances the spontaneous activity and the basal afferent nerve activity (“afferent noise”). This means that the Ad-fibre activity, generated by bladder distension, can initiate the micturition reflex at low degrees of bladder filling. Antimuscarinics in therapeutically recommended doses can inhibit the effects of these low concentrations of acetylcholine, but not of the high concentrations necessary for the generating the voiding contraction (requiring efferent nerve activity). Structural changes in the bladder (e.g., secondary to outflow obstruction) can generate local factors, such as prostaglandins and endothelins, which also can contribute to enhancement of the spontaneous activity.

Figure 10: Distension of the bladder and shape-change of the urothelium (U) will generate and release different signaling molecules, including ATP and acetylcholine (ACh), which either directly or by action via the interstitial cells (IC) will initiate activity in the suburothelial afferent nerves. Antimuscarinics may inhibit this ACh-induced activation. GC = glycocalix layer; DRG = dorsal root ganglion.

Figure 11: Important sites of action of antimuscarinics.
The benefits are, however, of limited clinical significance" Large meta-analyses of studies performed with the currently most widely used drugs [Chapple et al., 2005; 2008; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al. [2008] reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references (Figure 12), Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The consequence of this is that none of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment. Reviewing information from more than 12,000 references (Figure 12), Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The benefits are, however, of limited clinical significance" Large meta-analyses of studies performed with the currently most widely used drugs [Chapple et al., 2005; 2008; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al. [2008] reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references (Figure 12), Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The consequence of this is that none of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment for all OAB/DO patients. Optimal treatment should be individualized, implying that the patient’s co-morbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [Chapple et al., 2008].

Below data on the different antimuscarinics are presented. The amount of information for the individual drugs varies, and so does the degree of details from the different studies presented. However, the information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug.

1. ATROPINE SULFATE

Atropine (di-hyoscynamine) is rarely used for treatment of OAB/DO because of its systemic side effects, which preclude its use as an oral treatment. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [Ekström et al., 1992; Glickman et al., 1995; Deaney et al., 1998; Enskat et al., 2001; Fader et al, 2007]. It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO [Fader et al., 2007].

The pharmacologically active antimuscarinic component of atropine is l-hyoscynamine. Although still used, few clinical studies are available to evaluate the antimuscarinic activity of l-hyoscynamine sulfate [Muskat et al., 1996]. For assessment, see Table 2.

2. PROPANTHELINE BROMIDE

Propantheline is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes, which has a low (5 to 10%) and individually varying biological availability. It is metabolized (metabolites inactive) and has a short half-life (less than 2 h) [Beermann et al., 1972]. It is usually given in a dose of 15 to 30 mg 4 times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages are required. Using this approach in 26 patients with detrusor overactivity contractions [Blivas et al., 1980] in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15 mg four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff et al. [1991] comparing the effects of oxybutynin 5 mg three times daily, propantheline 15 mg three times daily, and placebo, in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency and incontinence related to DO (154 patients), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes et al. [1991] found no differences in efficacy between oxybutynin and propantheline. Controlled randomised trials (n=6) reviewed by Thüroff et al[1998], confirmed a positive, but varying, response to the drug.

Although the effect of propantheline on OAB/DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful (Table 2). No new studies on the use of this drug for treatment of OAB/DO seem to have been performed during the last decade.

3. TROSPIUM CHLORIDE

Trospium is a quaternary ammonium compound with a biological availability less than 10% [Fusgen and Hauri, 2000; Doroshyenko et al., 2005]. The drug has a plasma half-life of approximately 20 h, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [Kim et al., 2006]. Whether or not it contributes to the clinical efficacy of the drug remains to be established.

Trospium is not metabolized by the cytochrome P450 enzyme system [Beckmann-Knopp et al., 1999; Doroshyenko et al., 2005]. It is expected to cross the blood-brain to a limited extent and seems to have no negative cognitive effects [Fusgen and Hauri, 2000; Todorova et al., 2001; Widemann et al., 2002].

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions [Uckert et al., 2000]. Several RCTs have documented positive effects of trospium both in neurogenic [Stöhrer, et al., 1991;
Table 3. Some physico-chemical properties of antimuscarinics (Kay et al., AUA presentation, 2009)

<table>
<thead>
<tr>
<th></th>
<th>5-HMT</th>
<th>Fesoterodine(^1)</th>
<th>Tolterodine</th>
<th>Trospium(^2)</th>
<th>Solifenacin(^2)</th>
<th>Darifenacin(^2)</th>
<th>Oxybutynin(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>logD, Octanol-Water Ratio</td>
<td>0.74</td>
<td>1.42</td>
<td>1.83</td>
<td>-1.22</td>
<td>1.69</td>
<td>2.7</td>
<td>&gt; 3.3</td>
</tr>
<tr>
<td>Permeability (\times 10^6) (cm/s)</td>
<td>6.49</td>
<td>35.5</td>
<td>23.4</td>
<td>0.57</td>
<td>31.5</td>
<td>28.5</td>
<td>30.3</td>
</tr>
<tr>
<td>Brain-Blood Ratio(^3)</td>
<td>0.04-0.07</td>
<td>0.1-0.3(^2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PgP Substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(^1\) Fesoterodine is not detectable in blood after oral administration in humans due to rapid and extensive hydrolysis to 5-HMT by non-specific esterases.

\(^2\) Literature data, except PBEC permeability

\(^3\) Drug-related radioactivity

NA: Not Available
The effect of trospium in urgency incontinence has been documented in several RCTs. Allousi et al. [1998] compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo et al. [2000] investigated 208 patients with DO, who were treated with trospium 20 mg twice daily for two weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 ml; placebo 254 to 255 ml) and in maximum bladder capacity (from 329 to 356 ml; placebo 345 to 335 ml) in the trospium treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann et al. [2000] compared trospium 20 mg twice daily with tolterodine 2 mg twice daily in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary endpoint, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7 and 9%, respectively).

Halaska et al. [2003] studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial comprised a total of 358 patients with urgency syndrome or urgency incontinence. After randomisation in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). Urodynamic measurements were performed at the beginning, and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 ml after 26 weeks and 115 ml after 52 weeks (P=0.001). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin due to better tolerability.

Zinner et al. [2004] treated 523 patients with symptoms associated with OAB and urgency incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo controlled trial. Dual primary end points were change in average number of toilet voids and change in urgency incontinence episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (-2.37; placebo -1.29) and urgency incontinence episodes (-59%; placebo -44%). It significantly increased average volume per void (32 ml; placebo: 7.7 ml), and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43; placebo: 0.17) - and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%).

In a large US multicenter trial with the same design, and including 658 patients with OAB, Rudy et al. [2006] confirmed the data by Zinner et al. [2004], both with respect to efficacy and adverse effects.

An extended release formulation of trospium allowing once daily dosing, has been introduced and and its effects tested in controlled trials [Staskin et al., 2008; Dmochowski et al., 2008]. These RCTs demonstrated similar efficacy as found with previous formulations. The most frequent side effects were dry mouth (12.9%; placebo 6.5%) and constipation (7.5%; placebo 3.8%) [Dmochowski et al., 2008].

Intravesical application of trospium may be an interesting alternative. Frölich et al. [1998] performed a randomised, single-blind, placebo-controlled, monocentre clinical trial in 84 patients with urgency or urgency incontinence. Compared to placebo, intra-
vesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed [Walter et al., 1999], thus offering an opportunity for treatment with minimal systemic antimuscarinic effects.

Trospium has a well-documented effect in OAB/DO, and tolerability and safety seems acceptable (Table 2).

4. TOLTERODINE TARTRATE

Tolterodine is a tertiary amine, rapidly absorbed and extensive metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound [Nilvebrant et al., 1997], and significantly contributes to the therapeutic effect of tolterodine [Brynne et al., 1997; Brynne et al., 1998]. Both tolterodine and 5-HMT have plasma half-lives of 2-3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1-2.4 % of the dose; 5 – 14% of 5-HMT is eliminated in the urine [Brynne et al., 1997]. Whether or not the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim et al. [2005] and Chuang et al., [2008], do not support such an effect.

The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT, implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [Hills et al., 1998; Clemett et al., 2001; Salvatore et al., 2008]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily [Appell et al., 2001] in a 12-week randomized, double blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urgency incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main outcome measures adjusted for baseline (see also below: oxybutynin chloride). Dry mouth, the most common adverse event, was reported by 28% and 33% of participants taking OXY-ER and TOLT-IR, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study [Dionko et al., 2003], OXY-ER at 10 mg/d or TOLT-ER at 4 mg/d were given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence episodes (primary end point), total (urgency and non urgency) incontinence, and micturition were recorded in seven 24-hour urinary diaries at baseline and at weeks 2, 4, 8 and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (n=391) or TOLT-ER (n=399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8% of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable; including adverse events involving the central nervous system.
In the ACET (Antimuscarinic Clinical Effectiveness Trial) [Sussman and Garely, 2002] study, which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study one) and to 5 mg or 10 mg of OXY-ER (study two). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4 mg group (12%) than either the OXY-ER 5 mg (19%) or OXY-ER 10 mg groups (21%). More patients in the OXY-ER 10 mg group than the TOLT-ER 4 mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4 mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2 mg group, 59% in the OXY-ER 5 mg group and 60% in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; p=0.05). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the the open label design of the study.

Zinner et al. [2002] evaluated the efficacy, safety, and tolerability of TOLT-ER in older (> or =65) and younger (<65) OAB patients, in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability endpoints were evaluated, relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (<65: ER 22.7%, placebo 8.1%; > or =65: ER 24.3%, placebo 7.2%). A few patients (< 2%) experienced severe dry mouth. No central nervous system (cognitive functions were not specifically studied), visual, cardiac (per electrocardiogram), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg once daily were comparable in the two age cohorts (<65: 5.5%; > or =65: 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman et al. [2003] presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily (n=398) or placebo (n=374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo), and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine upon experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo (P<.001).

In the IMPROVE in Patients: Assessing symptomatic Control with Tolterodine ER (IMPACT) study [Elinoff et al., 2005], the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open label, primary care setting. Patients with OAB symptoms for ≥3 months received TOLT-ER (4 mg once daily) for 12 weeks. By week 12, there were significant reductions in patients’ most bothersome symptom: incontinence, urgency episodes, nocturnal and daytime frequency. The most common adverse events were dry mouth (10%) and constipation (4%), and it was concluded that in primary care practice, bothersome OAB symptoms can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs [Dmochowski et al., 2007a; 2007; Barucha et al., 2008; Choo et al., 2008; Coyne et al., 2008; Rogers et al., 2008; Rovner et al., 2008a; see further: Novara et al., 2008, Chapple et al., 2008]. Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo was performed. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 ms absolute QTc or 60 ms change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval [Malhotra et al., 2007].

Olsansky et al. [2008] compared in a randomized, placebo-controlled, double blind, crossover study, the effects on heart rate of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day and placebo in 162 healthy volunteers. They found that tolterodine, but not darifenacin and placebo, significantly increased mean heart rate per 24 hours. The proportion of subjects with an increase > 5 beats/min was significantly greater in those receiving TOLT-ER (1 out of 4) than with darifenacin (1 out of 10).

In a prospective, open study, Song et al. [2006] compared the effects of bladder training and or tolterodine as first line treatment in female patients with OAB. One hundred and thirty-nine female patients with OAB were randomized to treatment with bladder training (BT), tolterodine (2 mg twice daily) or both for 12 weeks. All treatments were efficacious, however,
combination therapy was the most effective. Mattiasson et al. [2003] compared the efficacy of tolterodine 2 mg twice daily plus simplified bladder training (BT) with tolterodine alone in patients with OAB in a multicenter single-blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine + BT than with tolterodine alone (33% vs. 25%; p<0.001), while the median percentage increase in volume voided per void was 31% with tolterodine + BT and 20% with tolterodine alone (p<0.001). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine + BT (~87%). It was concluded that the effectiveness of tolterodine 2mg twice daily can be augmented by a simplified BT regimen. However, Millard et al. [2004] investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OAB. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence, however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program.

The beneficial effect of TOLT-ER in men with benign prostatic enlargement (BPE) and LUTS, including the beneficial effect of TOLT-ER in men with benign pelvic floor muscle exercise program.

Darifenacin is a relatively selective muscarinic M3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M3 receptors relative to M1, M2, M4 or M5 receptors. Theoretically, drugs with selectivity for the M3 receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [Andersson, 2002]. However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg per day. The clinical effectiveness of the drug has been documented in several RCTs [Haab et al., 2004; Cardozo and Dixon 2005; Steers et al., 2005; Chapple et al., 2005; Foote et al., 2005; Hill et al., 2006; Haab et al., 2006; Zinner et al., 2006; Chapple et al., 2007; Abrams et al., 2008, Chancellor et al., 2008; Dwyer et al., 2008; for reviews, see Guay, 2005; Zinner, 2007; Novara et al., 2008; Chapple et al., 2008]. Haab et al. [2004] reported a multicentre, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients (19–88 years; 85% female) with OAB symptoms for more than 6 months, and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomised (1:4:2:3) to once-daily oral darifenacin controlled-release tablets: 3.75 mg (n=53), 7.5 mg (n=229) or 15 mg (n=115) or matching placebo (n=164) for 12 weeks. Patients recorded daily incontinence episodes, micturition frequency, bladder capacity (mean volume voided), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads and nocturnal awakenings due to OAB using an electronic diary during weeks 2, 6 and 12 (directly preceding clinic visits). Tolerability data were evaluated from adverse event reports. Darifenacin 7.5 mg and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg, respectively, was significantly superior to placebo for (median) improvements in micturition frequency (7.5 mg: -1.6; 15 mg: -1.7; placebo -0.8, frequency of urgency per day (-2.0; -2.0; -0.9), and number of incontinence episodes leading to a change in clothing or pads (-4.0; -4.7; -2.0). There was no significant reduction in nocturnal awakenings due to OAB. The most common adverse events were mild-to-moderate dry mouth and constipation with a CNS and cardiac safety profile comparable to placebo. No patients withdrew from the study as a result of dry mouth and discontinuation related to constipation was rare (0.6% placebo versus 0.9% darifenacin).
In a dose titration study on 395 OAB patients, darifenacin, allowing individualized dosing (7.5 or 15 mg), was found to be effective and well-tolerated [Steers et al., 2005]. A 2-year open-label extension study of these investigations [i.e., Haab et al., 2004; Steers et al., 2005], confirmed a favorable efficacy, tolerability and safety profile [Haab et al., 2006].

A review of the pooled darifenacin data from the three phase III, multicentre, double blind clinical trials in patients with OAB was reported by Chaplle et al. [2005] After a 4-week washout/run-in period, 1,059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency and frequency) for at least six months were randomized to once-daily oral treatment with darifenacin: 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, -8.8 [-68.4%; placebo -54%, P<004]; 15 mg, -10.6 [-76.8%; placebo 58%, P<0.001]. Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6% of patients; darifenacin 15 mg 2.1%; placebo 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase III studies in older patients (≥65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability and safety profile [Foote et al., 2005, Zinner et al., 2005; Hill et al. 2006].

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin, on the ‘warning time’ associated with urinary urgency. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks’ washout, 2 weeks’ medication-free run-in and a 2-week treatment phase [Cardozo and Dixon, 2005]. Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-hour clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant (p<0.004) increase in mean warning time with a median increase of 4.3 minutes compared with placebo (darifenacin group from 4.4 to 1.8 minutes; placebo from 7.0 to -1.0 minutes). Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a ≥30% increase in mean warning time. There were methodological problems associated with this study; it utilized a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinical-centred environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study [Zinner et al., 2006] on 445 OAB patients, darifenacin treatment (15 mg) resulted in numerical increases in warning time, however, these were not significant compared to placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health related quality of life (HRQoL) in patients with OAB [Abrams et al., 2008], and such improvements were sustained as shown in a two-year extension study [Dwyer et al., 2008]. It was shown that neither the positive effects on micturition variables, nor on HRQoL produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioural modification programme including timed voiding, dietary modifications and Kegel exercises [Chancellor et al., 2008].

Several studies have been devoted to study possible effect on cognition by darifenacin. Neither in healthy volunteers (19-44 years) and healthy subjects (≥60 years), nor in volunteers 65 years or older, could any effect of darifenacin (3.75-15mg daily) be demonstrated, compared to placebo [Kay and Wesnes, 2005; Lipton et al., Kay et al., 2006; Kay and Ebinger 2008].

To study whether darifenacin had any effect on QT/QTc intervals [Serra et al., 2005] performed a 7-day, randomized, parallel-group study (n = 188) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses, alongside controls receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic T_max versus placebo were -0.4 and -2.2 milliseconds in the darifenacin 15mg and 75 mg groups, respectively, compared with
Darifenacin 15 mg per day given to healthy volunteers did not change heart rate significantly compared to placebo [Olshansky et al., 2008]. Darifenacin has a well-documented beneficial effect in OAB/DO (Table 2), and tolerability and safety seems acceptable.

6. SOLIFENACIN SUCCINATE

Solifenacin succinate (YM905) is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90%). The mean terminal half-life is 45-68 hours [Kuipers et al., 2002; Smulders et al., 2002; 2004]. It undergoes hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) Cmax and AUC0-inf were increased by only approximately 40% and 56%, respectively [Swart et al., 2006]. Solifenacin has a modest selectivity for M3 over M2 (and M1) receptors [Abrams and Andersson, 2007].

Two large-scale phase 2 trials with parallel designs, comprising men and women, were performed [Chapple et al., 2004a, Smith et al., 2002]. The first dose-ranging study evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [Chapple et al., 2004a]. Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase 3 studies of patients with OAB included at least 8 micturitions per 24 hours and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (-2.21), 10 mg (-2.47), and 20 mg (-2.75), but not in patients receiving placebo (-1.03) or tolterodine (-1.79). This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there was a numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. As the 5 mg and 10 mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies.

The second dose-ranging study of solifenacin 2.5 mg to 20 mg was carried out in the United States (USA) [Smith et al., 2002]. This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 mg and 20 mg solifenacin. The number of micturitions per 24 hours showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested. Efficacy was demonstrated at this time. The 5 mg, 10 mg, and 20 mg dosing groups experienced significant increases in volume voided; the 10 mg solifenacin dose was associated with significant reductions in episodes of incontinence.

In one of the early RCTs, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice daily), or placebo [Chapple et al., 2004b]. It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (-8%), mean micturitions/24 h were significantly reduced with solifenacin 10 mg (20%), solifenacin 5 mg (17%), and tolterodine (15%). Solifenacin was well tolerated, with few patients discontinuining treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg twice daily.

Cardozo et al. [2004] randomized 911 patients to 12-week once daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo. The primary efficacy variable was change from baseline to study end point in mean number of micturitions per 24 hours. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia and incontinence episodes per 24 hours, and mean volume voided per micturition. Compared with changes obtained with placebo (-1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (-2.37) and 10 mg (-2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: -1.63, 61%; 10 mg: -1.57, 52%), but not with placebo (-1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of urgency and mean volume voided per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo). A 40-week follow up of these studies [i.e., Chapple et al., 2004b and Cardozo et al., 2004] demonstrated that the favourable profile, both in terms of efficacy and tolerability was maintained over the study period [Haab et al., 2005].
The STAR trial [Chapple et al., 2005; 2007] was a prospective, double blind, double-dummy, two-arm, parallel-group, 12-week study conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and TOLT-ER 4 mg once daily in OAB patients. The primary effect variable was micturition frequency. After 4 weeks of treatment patients had the option to request a dose increase, but were dummed throughout as approved product labelling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was “non-inferior” to tolterodine concerning the primary effect variable, micturition frequency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (-2.85 vs -2.42), incontinence (-1.60 vs -0.83), urgency incontinence (-1.42 vs -0.83), and pad usage (-1.72 vs -1.19). More solifenacin treated patients became continent by study endpoint (59 vs 49%) and reported improvements in perception of bladder condition (1.51 vs -1.33) assessments. However, this was accompanied by an adverse event incidence which was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30% and 6.4%, tolterodine 23% and 2.5%). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9 and 7.3%) in both groups.

A number of studies and reviews have further documented the effects of solifenacin [Cardozo et al., 2006; Chapple et al., 2006; 2007; Maniscalco et al., 2006, see also Chapple et al., 2008; Novara et al., 2008]. In a pooled analysis of four RCTs, Abrams and Swift (2005) demonstrated positive effects on urgency, frequency and nocturia symptoms in OAB dry patients. In an analysis of four phase III clinical trials, Brubaker and FitzGerald [2007] confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OAB (reductions of nocturia episodes with 5 mg: -0.6, p<0.025; with 10 mg: -0.6, p<0.001 vs placebo: -0.4) but without nocturnal polyuria.

Kelleher et al. [2006] and Staskin and Te [2006] presented data showing efficacy in patients with mixed incontinence. A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (≥65 years) patients, and also showed a high level of persistence in a 40 week extension trial [Wagg et al., 2005]. Improvement of QoL by solifenacin treatment has been documented in several studies [Kelleher et al., 2005; Garely et al., 2006].

In female volunteers, aged 19 to 79 years, the effect of 10 mg and 30 mg solifenacin on the QT interval was evaluated at the time of peak solifenacin plasma concentration in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial. The QT interval prolonging effect appeared greater for the 30 mg (8 msec, 4.13; 90%CI) compared to the 10 mg (2 msec, -3, 6) dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Michel et al. [2008] studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, post-marketing surveillance study. They concluded that “in real-life conditions, i.e. with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comediations, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure”.

Solifenacin has a well-documented beneficial effect in OAB/DO (Table 2), and the adverse event profile seems acceptable.

7. FESOTERODINE FUMARATE

Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases [Michel, 2008]. This compound, which is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic receptor antagonist [Ney et al., 2008]. All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, since the parent compound remains undetectable upon oral dosing. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Since the renal clearance of 5-HMT is about 250 mL/min, with >15% of the administered fesoterodine dose excreted as unchanged 5-HM, this raises the possibility that 5-HMT also could work from the luminal side of the bladder [Michel, 2008].

Fesoterodine is indicated for use at doses of 4 and 8 mg once daily. In clinical studies both doses of fesoterodine were consistently superior to placebo in improving the symptoms of OAB [Chapple et al., 2007; Nitti et al., 2007], with 8 mg/day having significantly greater effects than 4 mg/day [Khullar et al., 2008]. Analysis of pooled data on QoL, using King’s Health Questionnaire and ICI Questionnaire-short Form, showed that both doses of the drug caused a significant improvement of QoL. Compared to TOLT-ER (4 mg), fesoterodine (8 mg) had statistically significant advantages for improving incontinence episodes, severe urgency with incontinence, mean voided volumes and number of continent days a week [Chapple et al., 2008; Khullar et al., 2008]. Adverse events were characteristic for an antimuscarinic, dry mouth being the most frequently reported – it was
was rated as mild to moderate in most cases. In one phase III study it was seen in 7%, 16% and 36% of patients receiving placebo, 4 and 8 mg/d fesoterodine, respectively [Nitti et al., 2007], whereas in the other phase III study it was 7.1%, 21.7% and 33.8% in the same groups (16.8% for 4 mg/day TOLT-ER) [Chapple et al., 2007].

Kelleher et al. [2008] evaluated the effect of fesoterodine on HRQoL in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase III studies were analysed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolfenedine extended release (tolfenedine-ER) 4 mg. By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo.

A study on possible effects on QT-intervals has been performed [Michel, 2008]. This included parallel groups of 64-68 subjects each who were treated for 3 days with 4 mg/d fesoterodine, the highly supratherapeutic dose of 28 mg/d fesoterodine, the active control moxifloxacin 400 mg/day or placebo. Both the standard dose of 4 mg/day and the highly supratherapeutic dose of 28 mg/d did not provide any evidence of QT-prolongation (e.g., QTc for 28 mg/day from 404.5 ± 16.7 to 400.1 ± 14.0 ms, delta: -5.0 ± 7.9 ms).

Fesoterodine has a well-documented beneficial effect in OAB (Table 2), and the adverse event profile seems acceptable.

II. DRUGS ACTING ON MEMBRANE CHANNELS

1. CALCIUM ANTAGONISTS

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone. Two major groups of calcium channels include the voltage-gated [Caterall et al., 2003] and the store-operated channels (Leung et al., 2008). While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute only to a limited if any extent to the regulation of bladder smooth muscle tone [Schneider et al., 2004 a; b]. On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle tone including including Q-type [Frew and Lundy, 1995] and L-type channels [Wuest et al., 2007]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in vitro with tissue from multiple mammalian species, including humans [Frazier et al., 2008]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [Wuest et al., 2007]. In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [Wegener et al., 2004].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical instillation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [Fröhlich et al., 1998]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg per day) did not significantly improve the number of incontinence episodes as compared to placebo [Nagle et al., 2002]. Larger studies with clinical endpoints related to effects of calcium channel inhibitors have not been reported in incontinent patients (based upon a Medline search using the MeSH terms “calcium channel blockers” and “urinary incontinence”). Moreover, it should be noted that despite a long-standing and wide-spread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (Table 2).

2. POTASSIUM CHANNEL OPENERS

In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist [Gutman et al., 2003]. With regard to bladder function, ATP-dependent (KATP) and big calcium-activated (BKCa) channels have been studied most intensively. The BKCa channels also appear to be important physiologically as their activation can cause hyperpolarization of bladder smooth muscle cells and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, e.g., β-adrenoceptor agonists [Frazier et al., 2008]. Openers of both KATP [Howe et al., 1995; Hu et al., 1997; Martin et al., 1997] and BKCa channels [Hu et al.,
randomized, placebo-controlled clinical study on the channel openers in OAB patients. Nevertheless, one has led to a considerable hesitancy to study potassium therapeutic window for clinical use. This consideration the degree of selectivity offers a sufficiently large cardiovascular system, it remains unclear whether compounds of this class have a certain degree of et al., 1995; Shieh et al., 2007]. While some doses may considerably lower blood pressure [Howe also affect cardiovascular function, and in effective muscle. Therefore, potassium channel openers may not only in bladder, but also e.g. in vascular smooth channel openers to inhibit non-voiding contractions in vivo in animal models of DO [Howe et al., 1997; Martin et al., 1997; Tanaka et al., 2003] and this also includes activators of the KCNQ type of potassium channels [Streng et al., 2004]. Although potassium channel openers are believed to mainly act directly on smooth muscle cells [Gopalakrishnan and Shieh, 2004], they may also at least in part affect bladder function by modulating the activity of afferent neurones [Tanaka et al., 2003].

While the above data demonstrate the potential of potassium channel openers to inhibit non-voiding detrusor contractions, these channels are expressed not only in bladder, but also e.g. in vascular smooth muscle. Therefore, potassium channel openers may also affect cardiovascular function, and in effective allows considerable lowering blood pressure [Howe et al., 1995; Shieh et al., 2007]. While some compounds of this class have a certain degree of selectivity for the bladder as compared to the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study potassium channel openers in OAB patients. Nevertheless, one randomized, placebo-controlled clinical study on the KATP opener ZD0947 has been reported [Chapple et al., 2006]. While ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, it also failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option and may never become one due to a lack of selectivity for bladder over cardiovascular tissues (Table 2).

III. DRUGS WITH “MIXED” ACTION

Some drugs used to block DO have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined “direct” action on bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage operated Ca\(^{2+}\) channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsade de pointes) in some patients [Connolly et al., 1991; Stewart et al., 1992].

1. OXYBUTYNIN CHLORIDE

Oxybutynin is a tertiary amine that is well absorbed, and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [Waldeck et al., 1997], but occurs in much higher concentrations after oral administration [Hughes et al., 1992]. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [1988]. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [Hughes et al., 1992; Douchamps et al., 1988].

Oxybutynin has several pharmacological effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [Kachur et al., 1988]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [Waldeck et al., 1997; Nilvebrant et al., 1988]. The drug was shown to have slightly higher affinity for muscarinic M1 and M3 receptors than for M2 receptors [Nilvebrant et al., 1986; Norhona-Blob et al., 1991], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other anti-muscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantage of the newer formulations lies in improved dosing schedules and side-effect profile [Appell et al., 2001; Diokno et al., 2003; Dmochowski et al., 2002]. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability.

Available formulations of oxybutynin were overviewed by McCrery and Appell [2006].
**a) Immediate-release oxybutynin (OXY-IR)**

Several controlled studies have have shown that OXY-IR is effective in controlling DO, including neurogenic DO [Yarker et al., 1995; Andersson and Chapelle, 2001]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [1998] summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24 h was 33% (data on placebo not presented). The overall “subjective improvement” rate was reported as 74% (range 61% - 100%). The mean percent of patients reporting an adverse effect was 70% (range 17% - 93%). Oxybutynin, 7.5 to 15 mg/day, significantly improved quality of life of patients suffering from overactive bladder in a large open multicenter trial. In this study, patients’ compliance was 97% and side effects, mainly dry mouth, were reported by only 8% of the patients [Amaranco et al., 1998]. In nursing home residents (n=75), Ouslander et al. [1995] found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double blind, cross-over trial. On the other hand, in another controlled trial in elderly subjects (n=57), oxybutynin with bladder training was found to be superior to bladder training alone [Szorny et al., 1995].

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [Szoller et al., 1996; Kim et al., 1996].

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [Baigrie et al., 1988; Jonville et al., 1992]. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [Hussain et al., 1998]; no changes were found. It cannot be excluded that the commonly recommended dose 5 mg x 3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg x 2 with following dose-titration would reduce the number of adverse effects [Amaranco et al., 1998].

**b) Extended release oxybutynin (OXY-ER)**

This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [Appell et al., 2003]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [Chancellor et al., 2001].

The effects of OXY-ER have been well documented [Siddiqui et al., 2004]. In the OBJECT study [Appell et al., 2001], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6% to 6.1%; TOLT-IR 24.1% to 7.8%), total incontinence (OXY-ER from 28.6% to 7.1%; TOLT-IR 27.0% to 9.3%), and frequency (OXY-ER from 91.8% to 67.1%; TOLT-IR 91.6% to 71.5%) and both medications were equally well tolerated. The basic study was repeated as the OPERA study [Diochno et al., 2003] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence, however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should not be compared with ER entities of the other.

Greater reductions in urgency and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with OXY-IR. In the 1999 study [Anderson et al., 1999], 105 patients with urgency or mixed incontinence were randomized to receive 5-30 mg OXY-ER once daily or 5 mg of OXY-IR 1-4 times/day. Dose titrations began at 5 mg and the dose was increased every 4-7 days until one of three endpoints was achieved. These were 1) the patient reported no urgency incontinence during the final two days of the dosing period; 2) the maximum tolerable dose was reached; the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percentage reduction in weekly urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR but dry mouth was reported statistically more often with OXY-IR. In the 2000 study [Versi et al., 2000], 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study,
OXY-ER again achieved a >80% reduction in urgency and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naive patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naive population [Gleason et al., 1999].

In an RCT comparing different daily doses of oxybutynin (5, 10 and 15 mg), Corcos et al. [2006] found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day.

c) Transdermal oxybutynin (OXY-TDS)

Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [Davila et al., 2001] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study [Dmochowski et al., 2002] the 3.9-mg daily dose patch significantly (vs placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 ml; placebo from 175 to 182 ml). Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%). In a third study [Dmochowski et al., 2003] OXY-TDS was compared not only to placebo but to TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, 2-way crossover study [Appell et al., 2003]. Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared to OXY-ER which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Dmochowski et al. [2005] analyzing the combined results of two RCTs concluded that transdermal oxybutynin was shown to be efficacious and well tolerated. The most common systemic side effect was dry mouth (7.0 % vs placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1 %. Also Cartwright and Cardozo [2008], reviewing published and presented data concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics – however, this benefit was offset by the rate of local skin reaction. Sahai et al. [2008] in a recent review largely confirmed these conclusions.

d) Other administration forms

Rectal administration [Collas and Malone-Lee, 1997] was reported to have fewer adverse effects than the conventional tablets. Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults [Lose and Norgaard, 2001; Fader et al., 2007; George et al., 2007; Guerra et al., 2008], although adverse effects may occur [Kasabian et al., 1994; Palmer et al., 1997].

e) Effects on cognition

Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children [see, e.g., Kay et al., 2006; Klausner al Steers, 2007; Kay and Ebinger, 2008], although adverse effects should be taken into consideration when prescribing the drug.

Oxybutynin has a well-documented efficacy in the treatment of OAB/DO (Table 2). Despite the adverse effect profile, it is still an established therapeutic option.

2. PROPIVERINE HYDROCHLORIDE

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Murz [2001]. The drug is rapidly absorbed (t_{max} 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [Walter et al., 2003]. Several active metabolites are formed which quantitatively and qualitatively differ from the mother compound [Haustein et al., 1988; Muller et al., 1993; Wuest et al., 2006; Zhu et al., 2008; Sugiyama et al., 2008]. Most probable these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified [Michel and Hegde, 2006]. The half-life of propiverine itself is about 11-14 h. An extended release preparation was shown to be effective [Junemann et al., 2006; May et al., 2008].
Propiverine has combined antimuscarinic and calcium antagonistic actions [Haruno, 1992; Tokuno et al., 1993]. The importance of the calcium antagonistic component for the drug’s clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al [1998] collected 9 randomized studies on a total of 230 patients, and found a 17% reduction in micturitions per 24 hours, a 64 ml increase in bladder capacity, and a 77% (range 33-80%) subjective improvement. Side effects were found in 14% (range 8-42%). In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine’s superiority over placebo [Stöhrer et al., 1999]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo [Wehnert et al., 1989], and propiverine, oxybutynin and placebo [Wehnert et al., 1992; Madersbacher et al., 1999], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared [Stöhrer et al., 2007]. The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [Schulte-Baukloh et al., 2006; Grigoleti et al., 2006], with a low incidence rate of adverse events: <1.5% [Grigoleti et al., 2006].

Madersbacher et al. [1999] compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner et al. [2000] investigated in a double-blind, multicentre, placebo-controlled, randomized study, the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years), suffering from urgency, urgency incontinence or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine – 2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes.

In a randomised, double-blind, multicentre clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days [Junemann et al., 2005]. The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary endpoint. Secondary endpoints were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, post void residual urine, and quality of life. It was found that the mean maximum cystometric capacity increased significantly (p < 0.01) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups.

Abrams et al. [2006] compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring (AUM) parameters, safety, and tolerability in OAB patients. Patients (n=77) received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. They found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 yr was performed by Marschall-Kehrel et al. [2008]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23% of side-effects were reported for propiverine and 20% for placebo.

Yamaguchi et al. [2008] performed a multicentre, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at endpoint in number of voids/24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. It was found that at endpoint, there were greater reductions in mean (SD) voids/24 hours with all drug regimens than with placebo. All active treatments
improved the volume voided and QoL vs placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg.

Propiverine has a documented beneficial effect in the treatment of OAB/DO (Table 2), and seems to have an acceptable side effect profile.

3. FLAVOXATE HYDROCHLORIDE

Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% [Guay, 2003]. The drug is extensively metabolized and plasma half-life was found to be 3.5 h [Sheu et al., 2001]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [Cazzulani et al., 1988; Caine et al., 1991]. The main mechanism of flavoxate’s effect on smooth muscle has not been established. The drug has been found to possess a moderate calcium antagonistic activity, to have the ability to inhibit phosphodiesterases, and to have local anesthetic properties; no antimuscarinic effect was found [Guarneri et al., 1994]. Uckert et al. [2000], on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable. It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhythmic bladder contractions in anesthetized rats [Oka et al., 1996].

The clinical effects of flavoxate in patients with DO and frequency, urgency and incontinence have been studied in both open and controlled investigations, but with varying rates of success [Ruffman, 1988]. Stanton [1973] compared emepronium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor overactivity and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered as 200 mg 3 times daily. In another double-blind, cross-over study comparing flavoxate 1200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, and utilising both clinical and urodynamic criteria, Milani et al. [1993] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects of flavoxate with those of placebo, have not been able to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily [Briggs et al., 1980; Chapple et al., 1990; Dahm et al., 1995].

In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared to other therapeutic alternatives, is not well documented (Table 2).

No RCTs seem to have been performed with flavoxate during the last decade.

IV. α-ADRENOCEPTOR (AR) ANTAGONISTS

Even if it is well known that α1-AR antagonists can ameliorate lower urinary tract symptoms in men with BPE [Andersson et al., 2002], there are no controlled clinical trials showing that they are an effective alternative in the treatment of OAB/DO in this patient category. In an open label study, Arnold [2001] evaluated the clinical and pressure-flow effects of tamsulosin 0.4 mg once daily in patients with lower urinary tract symptoms (LUTS) caused by benign prostatic obstruction (BPO). He found that tamsulosin produced a significant decrease in detrusor pressure, increase in flow rate and a symptomatic improvement. In a study where tamsulosin was given alone, or together with tolterodine, to patients with male LUTS, monotherapy with the drug was not effective [Kaplan et al., 2006]. An RCT, comprising 364 women with OAB, revealed no effect of tamsulosin vs placebo [Robinson et al., 2007]. On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were successfully treated with an α1-AR antagonist [Kessler et al., 2006, Low et al., 2008].

α1-AR antagonists have been used to treat patients with neurogenic DO [Abrams et al., 2003]; however, the success has been moderate. Thus, there is no convincing evidence that α1-AR antagonists are effective in patients with storage symptoms. Although α1-AR antagonists may be effective in selected cases, convincing effects documented in RCTs are lacking (Table 2). In women, these drugs may produce stress incontinence [Dwyer and Teele, 1992].

V. β-ADRENOCEPTOR AGONISTS

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in man [Andersson, 1993]. However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β1-, nor β2- ARs, since they could be blocked by propranolol, but not by practolol or metoprolol (β1) or butoxamine (β2) [Nergard et al., 1977; Larsen, 1979]. On the other hand, early receptor binding studies using subtype selective ligands, suggested that the β-ARs of the human detrusor are primarily of β2 subtype [Andersson 1993], and favourable effects on DO were reported in open studies with selective
β2-AR agonists such as terbutaline [Lindholm and Lose, 1988]. In a double-blind investigation clenbuterol 0.01 mg 3 times daily was shown to have a good therapeutic effect in 15 of 20 women with DO [Grunenberger, 1984]. Other investigators, however, have not been able to show that β-ARs agonists represent an effective therapeutic principle in elderly patients with DO [Castleden and Morgan, 1980], or in young patients with myelodysplasia and DO [Naglo et al., 1981].

However, three subtypes (β1, β2, and β3) have been identified in the detrusor of most species, including humans [Andersson and Arner, 2004; Michel and Vrydag, 2006]. Also the human urothelium contains all three receptor subtypes [Otsuka et al., 2008]. Studies, using real-time RT-PCR, have revealed a predominant expression of β3-AR mRNA in human detrusor muscle [Nomiyama and Yamaguchi, 2003; Michel and Vrydag, 2006] and the functional evidence for an important role in both normal and neurogenic bladders is convincing [Fujimura et al., 1999; Igawa et al., 1999; Takeda et al., 1999; Morita et al., 2000; Igawa et al., 2001; Biers et al., 2006; Michel and Vrydag, 2006; Badawi et al., 2007; Leon et al., 2008]. The human detrusor also contains β2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [Andersson and Arner 2004; Michel and Vrydag, 2006].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species, is activation of adenyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K+ channels, particularly BKCa channels, may be more important in β-AR mediated relaxation than cAMP [Hudman et al., 2000; Frazier et al., 2005; Uchida et al., 2005; Frazier et al., 2008].

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [Murakami et al., 2007; Otsuka et al., 2008]. Murakami et al. [2007] found that the relaxation responses of the detrusor were not influenced by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka et al. [2008]. However, to what extent a urothelial signaling pathway contributes in vivo and in vitro to the relaxant effects of β-AR agonists in general, and β3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [Fujimura et al., 1999; Woods et al., 2001; Takeda et al., 2002; Koidoh et al., 2002]. For example, Hicks et al. [2007] studied the effects of the selective β3-AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid evoked bladder hyperactivity, without affecting voiding.

A number of β3-AR selective agonists are currently being evaluated as potential treatment for OAB in humans including GW427353 (solabegron) and YM178 [Colli et al., 2007]. Takaku et al. [2007] found that the selective β3-AR agonist, YM187, mediated muscle relaxation of human bladder strips. Chapple et al. [2008] reported the results of a controlled clinical trial with this drug in patients with OAB. Tolterodine and placebo served as controls. The primary efficacy analysis showed a statistically significant reduction in mean micturition frequency, compared to placebo (-2.19 vs -1.18). With respect to secondary variables YM178 (100 mg) was significantly superior to placebo concerning mean volume voided per micturition (26 vs 11 ml), mean number of incontinence episodes (-2.17 vs -1.01), and urgency episodes per 24 hour (-2.30 vs -1.03). The drug was well tolerated, and the most commonly reported side effects were headache and gastrointestinal adverse effects. The results of this proof of concept study showed that the principle of β3-AR agonism may be useful for treatment of patients with OAB (Table 2). However, to show that this class of drugs offers a viable therapeutic alternative or complement to current treatment of LUTS/OAB requires further well designed RCTs.

VI. PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [Andersson 1999; Andersson and Arner, 2004]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [Andersson et al., 2007]. There are presently 11 families of PDEs, some of which preferentially hydrolyse either cAMP or cGMP [Andersson et al. 2007].

As a basis for PDE inhibitor treatment of LUTS, Uckert et al. [2001] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably hydrolyse either cAMP or cGMP.
detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone. Significant dose-dependent relaxations were also induced by human cAMP analogs [Truss et al., 2001]. With these studies as a background, Truss et al. [2000] presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine showed statistically significant results only for one parameter [Truss et al., 2001]. Studies with other PDE 1 inhibitors than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the in vitro contractile response of guinea pig [Longhurst et al., 1997] and rat [Nishiguchi et al., 2006; Kaiho et al., 2008] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig bladder [Gillespie, 2004]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose-limiting effect [Giembycz, 2005]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

Nitric oxide (NO) has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [Andersson and Wein, 2004]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. [1994] examined the effects of isoproterenol, prostaglandin E1 and E2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al. [2006] characterized the distribution of PDE 5, cGMP and PKG1 in female pig and human urethra, and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil and tadalafl, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations.

The distribution of PDEs in the male urethral structures does not seem to have been studied. The observation that patients treated for erectile dysfunction with PDE 5 inhibitors had an improvement of their LUTS, has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study [Sairam et al., 2002] that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS, this observation has been confirmed in several well-designed and conducted RCTs [McVary et al., 2007a,b; Stief et al., 2008].

McVary et al. [2007a] evaluated the effects of sildenafil (50-100 mg daily for 12 weeks) on erectile dysfunction and LUTS in men 45 years or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function (IIEF) and 12 or greater on the International Prostate Symptom Score (IPSS). In 189 men receiving sildenafil significant improvements were observed in IPPS (-6.32 vs -1.93, p<0.0001), Benign Prostatic Hyperplasia Impact Index (-2.0 vs -0.9, p<0.0001), mean IPSS quality of life score (-0.97 vs -0.29, p<0.0001) and total Self-Esteem and Relationship questionnaire scores (24.6 vs 4.3, p<0.0001). Interestingly, there was no difference in urinary flow between the groups (p=0.08). Significantly more sildenafil vs placebo treated patients were satisfied with treatment (71.2 vs 41.7, p<0.0001). Sildenafil was well tolerated.

In an RCT, treatment with tadalafl once daily, in addition to improving erectile function in men with LUTS, was demonstrated to produce a clinically meaningful and statistically significant symptomatic improvement of LUTS [McVary et al., 2007b]. In another RCT, vardenafil given twice daily for eight weeks to men with ED and LUTS, was shown to significantly improve LUTS, erectile function, and quality of life Stief et al. [2008].

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to such an effect was found. However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstitial cells, and suburothelial afferent nerves).

PDE-5 inhibitors have a documented effect in men with LUTS/OAB (Table 2). The place of PDE-5 inhibitors in the treatment of OAB/DO remains to be established. Specifically, there seems to be no published information the effects of these drugs in women with OAB/DO.
VII. ANTIDEPRESSANTS

1. IMIPRAMINE

Several antidepressants have been reported to have beneficial effects in patients with DO [Martin and Schiff, 1984, Lose et al., 1989]. However, imipramine is the only drug that has been widely used clinically to treat this disorder.

Imipramine has complex pharmacological effects, including marked systemic antimuscarinic actions [Baldessarini, 1985] and blockade of the reuptake of serotonin and noradrenaline [Maggi et al., 1989], but its mode of action in DO has not been established [Hunsballe and Djurhuus, 2001]. Even if it is generally considered that imipramine is a useful drug in the treatment of DO, no good quality RCTs that can document this have been retrieved.

It has been known for a long time that imipramine can have favourable effects in the treatment of nocturnal enuresis in children with a success rate of 10-70% in controlled trials [Hunsballe and Djurhuus, 2001; Glazener et al., 2003]. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [Bigger et al., 1977; Giradina et al., 1979]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [Baldessarini, 1985].

The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have been performed during the last decade [Hunsballe and Djurhuus, 2001]. No good quality RCTs have documented that the drug is effective in the treatment DO (Table 2). However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

2. DULOXETINE

Duloxetine is a combined noradrenaline and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al., 2002]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser et al., 2003]. The effects of duloxetine were studied in a placebo-controlled study comprising 306 women (aged 21-84 years) with OAB, randomly treated with placebo (153) or duloxetine (80-mg/day for 4 weeks, which was increased to 120-mg/day for eight weeks [Steers et al., 2008]. The primary efficacy analysis compared the treatment effects on mean change from baseline to endpoint in the mean number of voiding episodes per 24 hours. Patients randomized to duloxetine had significant improvements over those randomized to placebo for decreases in voiding and incontinence episodes (-1.81 vs -0.62), for increases in the daytime voiding intervals (29 vs 7 minutes), and for improvements in I-QoL scores at both doses of the drug. Urodynamic studies showed no significant increases in maximum cystometric capacity or in the volume threshold for DO. The most common treatment-emergent adverse events with duloxetine (nausea, 31%, placebo, 4.6; dry mouth, 16%, placebo, 1.3; dizziness, 14%, placebo 0.7; constipation, 14%, placebo, 3.3; insomnia, 13%, placebo1.3; and fatigue, 11%, placebo 2.0) were the same as those reported by women with SUI (see below) and were significantly more common with duloxetine than placebo. Also in females with mixed incontinence, improvement of the OAB component has been demonstrated [Bent et al., 2008; Schagen van Leeuwen et al., 2008]. For assessment, see Table 2.

VIII. CYCLOOXYGENASE (COX) INHIBITORS

Human bladder mucosa has the ability to synthesize eicosanoids [Jeremy et al., 1987], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [Downie and Karmazyn, 1984; Leslie et al., 1984]. Even if prostaglandins cause contraction of human detrusor [Andersson, 1993], it is still unclear whether prostaglandins contribute to the pathogenesis of DO. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. [1980] performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg three times daily. The drug was shown to have favourable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer [1983] studied the effects of flurbiprofen 50 mg x 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids and decreased the number of urgent voids compared to baseline. Indomethacin 50 to 100 mg daily was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study.
Botulinum toxin (BONT) is a neurotoxin produced by Clostridium botulinum. Of the seven subtypes of BONT, sub-type A (BONT-A) is the most relevant clinically. Most of the intravesical experience reported on BONT-A deals with Dyspor®, however, BONT-A toxin is also available under the trade names of Dyspor®, and Xeomin. Bladder experience with the latter was, however, never reported. Available information indicates that Botox® is roughly three times more potent than Dyspor® [Cruz and Silva, 2004; Nitti et al., 2006]. However this relation has never been clearly defined. Therefore at a bladder setting these equivalents should be approached with caution for clinical reviews, see Nitti et al., 2006; Patel et al., 2006; Cruz and Dinis, 2007; Karsenty et al, 2008. In addition to sub-type A, recent reports have investigated the detrusor injection of BONT sub-type B (Neurobloc®, Miobloc®). For further details see section 9.1.9.

BONT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 [Dong et al., 2006] through its heavy chain and is internalized by the nerve terminal. Upon cleavage, the light chain is released in the cytosol, where it impedes binding of neurotransmitter-containing synaptic vesicles to the plasma membrane. This is achieved through the N-ethylmaleimide-sensitive factor attachment protein (SNARE) complex made up of synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin. BONT-A cleaves SNAP 25 rendering the SNARE complex inactive [Humeau et al., 2000; Chancellor et al., 2008]. Subtype B, acts preferentially through the inactivation of VAMP [Humeau et al., 2000].

BONT-A application was extensively evaluated in striated muscle. Paralysis occurs by prevention of ACh release from cholinergic motor nerve endings [Humeau et al, 2000]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Muscular paralysis recovers within two to four months time. During this time axons are developing lateral sprouts and eventually regenerate completely [de Paiva et al., 1999]. As parasympathetic cholinergic nerves are also fundamental for detrusor contraction the blockade of ACh release was immediately put forward as the rationale for the neurotoxin effect when injected in the bladder. However axon sprouting concomitant with clinical remission has not been documented in the detrusor [Haferkamp et al., 2004]. Furthermore fragments of cleaved SNAP 25 are detectable in bladder biopsy specimens of patients treated intravesically with BONT-A long after they become undetectable in striated muscle [Schulte-Baukloh et al., 2007]. These facts indicate that additional mechanisms of action are probably operative in the bladder. BONT-A inhibits the spinal cord release of glutamate, Substance P (SP) and CGRP by sensory nerves [Aoki et al., 2005; Purkiss et al., 2000; Meng et al., 2007] as well as the release of neuropeptides at the peripheral extremities [Lucioni et al., 2008; Rapp et al., 2006]. In the bladder, BONT-A has been shown to reduce the suburothelial immunoreactivity for TRPV1 or P2X3 [Apostolidis et al, 2005]. Furthermore BONT-A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury [Khera et al, 2004; Smith et al., 2008]. Morenilla Palao et al. [2004] have shown co-localization of SNARE proteins and TRPV1 in sensory nerves and that BONT-A impedes TRPV1 trafficking from intracellular vesicles to the plasma membrane during inflammation.

BONT-A may decrease the levels of neurotrophic agents in the bladder tissue. Neurogenic DO (NDO) patients produce more Nerve Growth Factor (NGF) in the bladder than control individuals [Giannantoni et al, 2006; Liu et al, 2008] and a significant decrease can be detected after intravesical the application of...
the toxin. As NGF is paramount for sensory nerve growth, maintenance and plasticity, this finding may point toward another mechanism whereby BONT-A acts upon the bladder.

**b) BONT-A injection protocol**

When the treatment was first described in 1999, BONT-A (Botox®) was diluted in normal saline in order to obtain a concentration of 10 Units/ml [Schurch et al., 2000]. Under visual control through a rigid cystoscope and a flexible 6 Fr injection needle, 30 injections of 1 ml (10 Units (U) of BONT-A toxin) were done in 30 different locations above the trigone to prevent vesico-urethral reflux (**Figure 13**). Additional refinements have been added to this technique along the following years, including the use of a local anaesthetic agent (4% lidocaine) and a flexible cystoscope [Harper et al., 2003]. For Dyspor® the technique was similar, including the number of injection sites. Only the dilutions were different taking in consideration that 500-1000 U were used [Cruz and Silva, 2004].

The effect of BONT-A after increasing the dose per injection site and decreasing the number of injected sites was investigated in one study. Patients were randomized to receive 300 U either in 10 or 30 sites [Karsenty et al., 2005]. The authors reported that 10-site injection was quicker and less painful and that no differences in efficacy between the two procedures could be detected up to 24 weeks. Another variation is the neurotoxin injection in the trigone. The suggested risks of injecting bladder trigone has never been demonstrated, whether Botox® or Dyspor® was used [Karsenty et al., 2007; Mascarenhas et al., 2008; Citeri et al., 2008]. However, this does not mean that trigonal injections bring marked benefits to the treatment. One trial concluded that 100 U of Botox® injected only in the trigone were less effective and durable than when administered in the detrusor [Kuo et al., 2007]. Injection in the sub-urothelial space was also assayed on the suggestion that in this position the BONT-A effect could be more pronounced in sensory than in parasympathetic motor fibers (Kuo et al., 2005). However, in one comparative study injection of 100 U of Botox® in the suburothelial space was less effective than in the detrusor [Kuo et al., 2007]. Another variable of the injection technique is the diluent volume. Most studies used 1.0 mL per injection, although a few used 0.5 mL [Grosse et al., 2005; Schulte-Baukloh et al., 2005], 0.2 mL (Kuo et al., 2004), or even 0.1 mL per injection site [Rapp et al., 2004]. In conclusion, at this point it must be concluded that further controlled studies designed to compare different number and locals of injections sites are necessary.

c) **Effect of BONT-A on NDO adult patients**

Following the preliminary report of BONT-A (Botox®, 200 or 300U) detrusor application in 21 patients with traumatic spinal cord injury resistant to antimuscarinic drugs [Schurch et al., 2000a; b], a large multicenter non-controlled clinical trial was conducted in Europe enrolling 231 NDO patients, most with spinal cord injury [Reitz et al., 2004]. Botox®, 300 U was injected in 30 points in the detrusor above the trigone. Data were available for 200 patients. In 180 incontinent patients, this study, which still represents the largest trial conducted with BONT-A, brought urinary continence to 132 and a marked improvement to 48 patients. A marked increment of the volume for first detrusor contraction and decline of maximal detrusor pressure were observed during urodynamic evaluations up to 36 weeks after injection. No injection related complications or toxin side effects were reported. Several other non-controlled studies
published subsequently confirmed these observations [see, Patel et al., 2006; Dmochowski et al., 2007; Karsenty et al., 2008 for review].

Botox® and Dyspor® efficacy in NDO was also demonstrated in small double blind placebo controlled trials [Schurch et al., 2005; Ehren et al., 2007]. Fifty-nine NDO patients due to spinal cord injury were randomized to receive Botox®, 200 U, 300 U or placebo. BONT-A treated patients showed a significant reduction in incontinence episodes and amelioration of urodynamic parameters versus placebo that were maintained in the 6 month observation period. Unfortunately the study was not powered to detect differences between 200 and 300 U of BONT-A [Schurch et al., 2005]. In a further subanalysis, a single dose of BONT-A 300 U significantly improved total and subscale I-QoL scores compared with placebo at all time points [Schurch et al., 2007].

Another small single center study randomized a total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of either 500 U of Dyspor® or placebo [Ehren et al., 2007]. Intake of tolterodine and episodes of urinary leakage were registered. Cystometry was performed after 6, 12 and 26 weeks and quality of life was assessed. Patients in the BONT-A arm had a significantly higher cystometric capacity at 6 and 12 weeks. Maximum detrusor pressure and episodes of urinary leakage and tolterodine consumption were significantly lower in the BONT-A than in the placebo group.

In general, the reported duration of BONT-A effect in NDO patients (Botox®, 300U) ranged between 6 and 9 months at the first injection [see, Cruz and Silva, 2004; Dmochowski et al., 2007; Karsenty et al., 2008 for reviews]. The duration of subsequent injections was investigated by three studies along several consecutive injections. Del Popolo et al. [2008] studied the long term effect of BONT-A (Dyspor®) in 199 spinal cord injured patients over a period of 6 years. Initial doses ranged from 500 to 1000 but subsequently the 1000 U dose was abandoned to avoid side effects (see below). The duration of the effect averaged 12 months and was similar for all the three doses. Urodynamic and clinical improvements detected at the first injection were maintained at each re-injection, associated with a highly significant improvement in patient’s satisfaction. Reitz and co-workers [2007] studied intradetrusor BONT-A (Botox®) injections in 20 patients who received at least five intradetrusor injections for long term treatment of NDO. Continence, volume to first detrusor contraction, maximum cystometric capacity, maximum detrusor pressure and compliance at baseline improved significantly after the first injection and at all re-injections. Injection intervals, in average 7 months, tended to lengthen with repeat injections albeit insignificantly. Another study used Botox® 300 U or Dyspor® 750 U in 44 and 22 spinal NDO patients, respectively. Although most of the patients had 2-4 injections, a few had up to 7 consecutive injections. The interval between subsequent injections averaged 9-11 months at all injections. The antimuscarinic use decreased substantially. Significant improvements were found in clinical parameters and in cystometric capacity, whereas compliance improved only after the second treatment. The incidence of DO was significantly reduced. Four patients had transient adverse events after Dyspor® [Grosse et al., 2005].

The onset of BONT-A effect starts within the first 2 weeks after neurotoxin injection [Cruz and Silva, 2004; Dmochowski et al., 2007; Karsenty et al., 2008]. This time course was further evaluated in a small open-label prospective study that specifically investigated the chronology of the BONT-A effects. Urgency, nocturia and frequency were shown to improve as soon as two days after neurotoxin injection in NDO patients [Kalsi et al., 2008].

The majority of the patients included in the BONT-A trials, whether open label or controlled, were spinal cord injured patients [Cruz Silva., 2004; Dmochowski et al., 2007; Karsenty et al., 2008]. The few patients with multiple sclerosis that were included were never analyzed separately. Such a gap was filled recently with the study of BONT-A in a MS cohort. Forty-three MS patients suffering from severe urgency and incontinence were treated with 300 U BONT-A (Botox®) [Kalsi et al., 2007]. Highly significant improvements in urgency, incontinence episodes, frequency and nocturia were observed. In addition, bladder capacity, volume to detrusor overactivity and maximal detrusor pressure also improved. The mean duration of the effect was 9.7 months. Similar results were seen with repeat treatments. However, all but one of the treated patients had to perform self-catheterization after treatment. In spite of this drawback, authors concluded that the treatment was likely to have a major impact on future management of multiple sclerosis patients with detrusor overactivity [Kalsi et al., 2007].

d) BONT-A and urinary tract infection (UTI) in adult NDO patients

A consequence of BONT-A treatment only recently noticed is a decrease in the incidence of urinary tract infections in NDO patients. In 30 SCI patients, Gamé et al. [2008] observed that the number of pyelonephritis, orchitis and prostatitis in the six months before BONT-A, 1.75±1.87 per patient, decreased to 0.2±0.41 in the first six months after treatment. In 17 SCI patients that received BONT-A (Botox®) injections for a period of six years, the number of urinary tract infection at the sixth year was 1.8±0.5 per year, significantly lower than at baseline, 6.7±2.1 [Giannantoni et al., 2008]. In a multicentre, cross-sectional retrospective cohort study, data from 214...
NDO patients treated in seven German centers were collected. The rate of urinary tract infections in 12 months preceding and in the 12 months following BONT-A (Botox®) treatment was 68% and 28%, respectively [Boy et al., 2008]. The reason for these findings is unclear but may lie in a decreased maximum detrusor pressure resulting in less bladder wall ischemia and vesico-ureteral reflux.

e) BONT-A in NDO children

In children, the dose of BONT-A (Botox®) should be calculated according to body weight. Doses of between 12 U/kg of weight up to a maximum dose of 300 U [Schulte-Baukloh et al., 2002] and four U/Kg [Corcos et al., 2002] have been used for Botox®. The maximum suggested Dysport® dose was 20 U/kg up to a maximum of 400 U [Altaweel et al., 2006, Akbar et al., 2007]. BONT-A has been essentially assayed in children with myelomeningocele [Schulte-Baukloh et al., 2002; Schulte-Baukloh et al., 2003; Corcos et al., 2002; Riccabona et al., 2004; Kajbafzadeh et al., 2006; Altaweel et al., 2006]. Like in adults, the toxin increased bladder capacity and decreased maximal detrusor pressure. In 26 children with a mean age of 6.9 years, 19 of them (73%) became completely dry between clean intermittent catheterizations while 88% reported a global improvement in urine incontinence. Interestingly, of the 15 children who had vesicoureteral reflux before the procedure, 11 (73%) found improvement, which either disappeared or decreased in grade. BONT-A also improved bowel function in 66% of the children with intestinal problems [Kajbafzadeh et al., 2006].

The success rate in terms of continence and cessation of antimuscarinic medication may, however, be substantially inferior to that seen in adults, potentially due to irreversible bladder wall changes associated with longstanding detrusor overactivity [Altaweel et al., 2006]. In a group of 20 children with myelomeningocele continence was achieved in only 13 children. At a second injection, this number also did not change appreciably [Altaweel et al., 2006].

f) BONT-A in idiopathic DO (IDO) patients

When compared to NDO, information existing on the use of BONT-A in IDO patients refractory to antimuscarinic agents is more scarce and based on small clinical trials. However, the results of BONT-A application in the bladder of NDO patients and the success of recent trials are pushing more and more clinicians to offer the neurotoxin to their patients before its approval for bladder administration.

In the first report, by Radziszewski and Borkowski [2002], 300 UI of Dyspor® were injected in 10-20 bladder sites of 12 IDO patients. Bladder capacity increased significantly, all patients became continent and no side effects were reported, including urinary retention. However subsequent studies reported in general a high incidence of voiding dysfunction. Kuo [2004] reported on 18 IDO patients detrusor injections of BONT-A (Botox®, 200 U). Continence was regained in seven patients (39%) and another seven (39%) reported some degree of clinical improvement. Mean duration of effect was 5.3 months. However, six (33%) patients required clean intermittent catheterization (CIC) at one month to empty their bladders [Kuo et al., 2004]. Popat et al. [2005] also injected 200 U of Botox® in the detrusor and reported at 16 weeks a clear improvement in urgency, urgency incontinence frequency and maximal cystometric capacity. Six patients (19.3%) required prolonged CIC. Suburothelial injections were suggested to decrease the incidence of urinary retention, by preferentially targeting suburothelial sensory fibers. However, in 20 patients who received suburothelial BONT-A (Botox®, 200 U) urinary retention occurred in six (30%) [Kuo et al., 2005].

The results of these open label studies were confirmed in two albeit small double-blind, placebo controlled trials in which patients were randomized to intradetrusor injections of 200 U BONT-A (Botox®) or placebo [Sahai et al., 2007; Brubaker et al., 2008]. Sahai et al. [2007] used maximum cystometric capacity as primary outcome measure and changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry, reflex detrusor volume and QoL questionnaires as secondary outcome measures. Follow-up occurred at four and 12 weeks after injection, at which point the study was unblinded. Further followup in the BONT-A group occurred at 24 weeks. Significant increases in maximum cystometric capacity were observed at four and 12 weeks in patients treated with BONT-A compared to placebo. BONT-A also reduced frequency and urgency incontinence episodes at four and 12 weeks. Urgency was significantly reduced only at four weeks in BONT-A group. Post-void residual increased at four weeks in patients receiving BONT-A, but differences to placebo became insignificant by 12 weeks. Despite significant improvements in quality of life observed among patients treated with BONT-A, 37.5% of them required intermittent self-catheterization to empty the bladder. Brubaker et al. [2008] randomized 28 women to Botox® 200 U and 15 for placebo. Approximately 60% of the women who received BONT-A had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days or less for placebo. Post-void residual urine increased in 43% of the women in the BONT-A group (12 out of 26 women) and urinary tract infection developed in 75% of these women (9 of 12). These numbers exceeded by far the expected ranges and forced the suspension of screening and injection. Median duration of urinary retention after the first injection was approximately 664
confirmed these data [Schurch et al., 2007]. Fifty-
randomized, double blind placebo controlled trial
similar for both groups of patients. A multicenter,
obsverved. Percent improvement in QoL score was
weeks for both the NDO and IDO subgroups were
significant decreases in QoL scores at four and 16
Incontinence Impact Questionnaire (IIQ-7). Highly
of the Urinary Distress Inventory (UDI-6) and
32 NDO and 16 IDO patients, using the short forms
studies. Kalsi et al. [2006] examined QOL changes in
intravesical BONT-A has been addressed in several
Quality of life (QoL) in NDO patients treated with
g) Effect of BONT-A on quality of life
improved as soon as four days in IDO patients,
improvement after detrusor, suburothelial and bladder
and urgency sensation in 86% and 82% of patients,
respectively, during an average period of six months.
Temporary urinary retention occurred in four % of the
cases, with additional 15% reporting moderate voiding
difficulties. In a recent update of this experience
[Schmid et al., 2008] an increase in the duration of
BONT-A effect upon repeated injections was observed.
Kuo and co-workers [2007] randomly compared
detrusor, suburothelial and bladder base injections
of 100 U BONT-A (Botox®) in 45 IDO patients
refractory to antimuscarinic therapy. Urgency scores
improved significantly in all groups. However, duration
of clinical improvement was different in the three
groups. Percentage of patients with clinical
improvement after detrusor, suburothelial and bladder
base injections was 67%, 47% and 13% by six months
and to 20%, 20% and 6.7% at nine months,
respectively. At three months significant increases in
cystometric capacity and post-void residual compared
to baseline were found in the detrusor and suburothelial
but not in the bladder base group. Vesicouretal reflux was not identified in any patient after BONT-A
injection into the trigone.
The definition of an ideal dose of BONT-A for IDO
patients as well as the ideal local of injections will
require further well designed clinical trials. In addition
it is unclear at this time what percentage of IDO
patients can stop antimuscarinic medication. For
assessment, see Table 2).
A small open-label prospective study specifically
investigated the chronology of the BONT-A effects in
IDO patients. Urgency, nocturia and frequency
improved as soon as four days in IDO patients,
therefore slightly later than in NDO cases [Kalsi et
al., 2008].
g) Effect of BONT-A on quality of life
Quality of life (QoL) in NDO patients treated with
intravesical BONT-A has been addressed in several
studies. Kalsi et al. [2006] examined QOL changes in
32 NDO and 16 IDO patients, using the short forms
of the Urinary Distress Inventory (UDI-6) and
Incontinence Impact Questionnaire (IIQ-7). Highly
significant decreases in QoL scores at four and 16
weeks for both the NDO and IDO subgroups were
observed. Percent improvement in QoL score was
similar for both groups of patients. A multicenter,
randomized, double blind placebo controlled trial
confirmed these data [Schurch et al., 2007]. Fifty-
ine NDO patients with urinary incontinence received
a single dose of BONT-A (200U or 300 U, Botox®) or
placebo. I-QoL scores improved significantly with
BONT-A, whether 300U or 200 U were used. A single
center, double blind, placebo controlled study was
performed by Ehren et al. [2007] to evaluate the effect
of a single injection of 500 U of BONT-A (Dysport®)
on quality of life in 31 NDO patients with incontinence.
Patients were randomized to intravesical injections
of either 500 U of BONT-A or placebo. Patients in the
BONT-A group showed improved quality-of-life
parameters compared to the placebo group [Ehren et
al., 2007]. Unlike the previous studies, in which patients
had various neurological conditions, a recent study
measured the efficacy and impact on quality of life of
BONT-A (300 U of Botox® ®) in 43 patients with
multiple sclerosis [Kalsi et al., 2007]. There was a
45% decrease in urinary frequency, 77% decrease in
incontinence episodes, 78 % decrease in micturition
episodes associated with urgency and a 47 %
decrease in nocturia. Although 98% of patients had
to perform self-catheterization after treatment, there
were sustained improvements in all quality-of-life
scores with a mean duration of effect of 9.7 months.
Results were maintained with repeat treatments (two
injections in 18 and three in two patients) for 11.7
months.
h) Side effects of intradetrusor BONT-A
One of the most frequent side effects reported after
intradetrusor BONT-A injection is bladder pain
[Karsenty et al., 2008; Del Popolo et al., 2008].
Hematuria may also occur, most of the times mild in
nature. The most feared one, paralysis of the striated
musculature due to circulatory leakage of the toxin has
never been reported. Transient muscle weakness
was however reported with Dysport® application in
several studies [Wyndaele and Van Dromme, 2002;
Akbar et al., 2007; Del Popolo et al., 2008]. Among
199 NDO patients followed during 8 years, five
developed hypostenia when injected with 1000 U of
Dysport®. In another study with 44 patients, three
adults also treated with 1000 units developed muscular
weakness which subsided after 5 to 7 weeks [Akbar
et al., 2007]. No such cases were reported with Botox®
BONT-A [Karsenty et al., 2008]. The reason for the lack
of transient muscle weakness among Botox®-treated
patients is unclear but might be related with the larger
size of its molecule which limits diffusion into the blood
stream. The risk of hyposthenia associated with
Dysport® might be avoided by using lower doses of
the toxin, no more that 750 units for adults and 20 U/kg
for children [Akbar et al., 2007; Del Popolo et al.,
2008]. In addition, caution should be used in selecting
high risk patients for botulism including children,
patients with low pulmonary reserve or patients with
myasthenia gravis. Aminoglycosides should be
avoided during BONT-A treatment since they might
blockade motor plates and therefore enhance BONT-
A effect.
Fear of vesicoureteral reflux, which for long precluded trigone injections [Schuch et al., 2000a; Reitz et al., 2004] seems unfounded whether Botox® or Dysport® is used [Karsenty et al., 2007; Mascarenhas et al., 2008; Citeri et al., 2008; Eichel et al., 2008]. However trigonal injections may not enhance BONT-A effects, as observed in a study with IDO patients [Kuo et al., 2007].

In IDO patients the commonest complication is urinary retention. When injecting 200 U of Botox® a 20-30% rate of prolonged urinary retention might be expected which will require prolonged clean intermittent catheterization to ensure bladder emptying [Kuo et al., 2004; Popat et al., 2005; Kuo et al., 2005; Sahai et al., 2007]. Open-label trials which used lower doses (100 U of Botox®) reported a lower incidence of this complication [Schmid et al., 2006; Kuo et al., 2007].

Although it is a concern frequently raised, at this moment there is no evidence that repeated BONT-A injections cause detrusor atrophy or bladder wall fibrosis. Whether Dysport® or Botox® was used repeated injections in NDO patients in the short to medium term did not decrease bladder compliance, which would presumably be the case if fibrosis were to develop [Del Popolo et al., 2008; Reitz et al., 2007].

Histological inspection of injected bladders did not show inflammatory changes, fibrosis, or dysplasia after repeated treatments and independently of the neurogenic or non-neurogenic origin of the detrusor overactivity [Haferkamp et al., 2004; Compérat et al., 2006; Apostolidis et al., 2008]. Rather the reverse, one study demonstrated that NDO patients treated with BONT-A had less fibrosis than nontreated patients [Compérat et al., 2006]. Curiously, the presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

### i) Cost-effectiveness of BONT-A in NDO patients

Economic aspects of BONT-A are a concern due to the price of the drug and the need for repeated cystoscopies, very often performed under general anaesthesia and under close monitoring to detect and treat eventual episodes of autonomic dysreflexia. Nevertheless, in UK, in a cohort of 101 patients with detrusor overactivity, 63 of whom of neurogenic origin, BONT-A treatment was shown to be cost-effective in both NDO and IDO cases [Kalsi et al., 2006].

Costs were based on the resources used by typical patients in UK and in the cost-effectiveness of 200-300 U BONT-A (Botox®) compared with standard care [Kalsi et al., 2006]. In Germany BONT-A (Botox®) treatment halved costs for incontinence aids and for urinary tract infection treatment in 214 NDO patients [Boy et al., 2008].

### j) BONT-B

Some humans repeatedly injected with BONT-A may develop resistance to the toxin, possibly due to antibody formation. Although this event seems very rare in the case of bladder injections, a minimum interval of three months between two BONT-A injections is generally recommended to decrease its occurrence. If resistance appears, recent reports [Dykstra et al., 2003; Pistolesi et al., 2004; Reitz et al., 2004] investigated the replacement of BONT-A serotype by BONT-B. At this moment, empiric doses of BONT-B are being used, as there are no clear potency equivalents for the two serotypes and between BONT-B brands.

In three patients with spinal NDO, bladder injection of 5000 U [Pistolesi et al., 2004] or 7500 U [Reitz and Schuch, 2004] of BONT-B (Neurobloc®) restored bladder function for six months [Reitz and Schuch, 2004]. Interestingly, one patient experienced dry mouth and dry eyes that resolved within 20 days. As this side effect was not reported after bladder BONT-A application, it is possible that different toxin serotypes have some different degrees of organ affinity. Dykstra et al. [2003] carried on a dose escalation study with BONT-B (Miobloc®) in 15 female patients with OAB. They used doses of 2500, 3750, 5000, 10,000, and 15,000 U injected at 10 sites. Only one patient failed to respond, and a clear dose-dependent effect was observed, with the longest response seen in those injected with 15,000 U. Two patients, both injected with 15,000 U, experienced dry mouth and general malaise. In another study involving IDO and NDO patients, in which BONT-B (Neurobloc®) 5000 U were used, Hirst and coworkers [2007] observed a limited duration of action, with most of the symptomatic beneficial effects wearing off by 10 weeks in most of the patients. The short duration of action for BONT-B at safe doses may, therefore, limit the clinic usefulness of this serotype.

### 2. CAPSAICIN AND RESINIFERATOXIN (RTX)

#### a) Rationale for intravesical vanilloids

The rationale for intravesical vanilloid application in patients with DO was offered by the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent upon a sacral micturition reflex [de Groat et al., 1997]. The C-fiber micturition reflex is usually inactive but it was shown that it is enhanced in patients with chronic spinal-cord lesions above sacral segments [de Groat et al., 1997] in those with chronic bladder outlet obstruction [Chai et al., 1998] and in those with IDO [Silva et al., 2002]. In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of suburothelial C-fibers expressing TRPV1 [Brady et al., 2004]. Curiously, NDO patients who responded better...
to intravesical RTX exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas non-responders experience a non-significant variation [Brady et al., 2004]. A decrease in TRPV1 expression in urothelial cells of NDO patients was also demonstrated after intravesical application of RTX [Apostolidis et al., 2005].

Changes in sub-urothelial C-fiber innervation expressing neuropeptides [Smet et al., 1997] or TRPV1 [Liu et al., 2007] were also reported in patients with sensory urgency. In IDO patients, responders to intravesical RTX are closely associated with the over-expression of the receptor in the bladder mucosa [Liu et al., 2007]. In women with sensory urgency, TRPV1 mRNA expressed in trigonal mucosa was not only decreased but also inversely correlated with the bladder volume at first sensation of filling during cystometry further indicating that TRPV1 plays a role in premature bladder sensation [Liu et al., 2007].

b) Intravesical capsaicin

Intravesical capsaicin for NDO was studied in six non-controlled [Fowler et al., 1992; Fowler et al., 1994; Geirsson et al., 1995; Das et al., 1996; Igawa et al., 1996, Cruz et al., 1997, De Ridder et al., 1997] and 1 controlled clinical trial [de Seze et al., 1998]. Capsaicin was dissolved in 30% alcohol and 100-125 ml (or half of the bladder capacity if lower than that volume) of 1-2 mM solutions were instilled into the bladder and left in contact with the mucosa for 30 minutes. Best clinical results were found among patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70-90% of the patients [Fowler et al., 1994, Cruz et al., 1997; De Ridder et al., 1997]. In patients with complete spinal cord lesions the success rate was much lower [Geirsson et al., 1995].

Only one small randomized controlled study compared capsaicin against 30% ethanol, the vehicle solution. Ten patients received capsaicin and found a significant regression of the incontinence and urge sensation. In contrast, only 1 among the 10 patients that received ethanol had clinical improvement [de Seze et al., 1998].

The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound. In particular, the possibility of triggering autonomic dysreflexia with capsaicin, especially in patients with higher spinal cord lesions has progressively restrained its use. The relevance of capsaicin might however be back with a recent observation by de Sèze et al. [2006] with a new capsaicin formulation. They conducted a double blind placebo controlled study with a glucidic solution of capsaicin in 33 NDO patients. The glucidic-capsaicin treated group showed improvement both in symptoms and urodynamic parameters above the comparator arm [de Sèze et al., 2006]. The global tolerance of this new capsaicin formulation was excellent.

c) RTX in NDO

Resiniferatoxin (RTX) has the advantage over capsaicin in being much less pungent [Cruz et al., 1997]. Intravesical RTX application in NDO patients was evaluated in five small open-label studies [Cruz et al., 1997; Kuo, 2003; Lazzeri et a., 1997; Lazzeri et al., 1998; Silva et al., 2000]. Different RTX concentrations, 10 nM, 50 nM, 100 nM and 10 µM were tested. RTX brought a rapid improvement or disappearance of urinary incontinence in up to 80% of the selected patients and a 30% decrease in their daily urinary frequency.

Furthermore, RTX also increased the volume to first detrusor contraction and maximal cystometric capacity. In general, in patients receiving 50-100 nM RTX the effect was long-lasting, with a duration of more than six month being reported. In patients treated with 10 µM doses, transient urinary retention may occur [Lazzeri et al., 1998].

In a recent placebo-controlled study, the urodynamic effects of RTX in NDO patients were specifically evaluated. Only in the RTX arm was a significant increase in first detrusor contraction and maximal cystometric capacity found [Silva et al., 2005]. RTX also caused a significant improvement in urinary frequency and incontinence [Silva et al., 2005].

RTX, 600 nM was compared against BONT-A (Botox®, 300U) in a study involving 25 patients with NDO due to chronic spinal cord injury. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity, although BONT-A turned out to be more effective [Giannantoni et al., 2004].

d) RTX in IDO

The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 ± 109 mL to 440 ± 153 mL at 30 days, and to 391 ± 165 mL at 90 days. An increase in mean MCC from 291 ± 160 mL to 472 ± 139 mL at 30 days and to 413 ± 153 mL at 90 days was also observed (Figure 14). These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [Silva et al., 2002]. Subsequent small open label studies confirmed these observations using either a single high (50-100 nM) or multiple low (10 nM) dose approaches [Kuo et al., 2003; Dinis et al., 2004; Kuo et al., 2005].

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials. One, involved 54 patients randomized to receive four weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle
solution, 10% ethanol in saline [Kuo et al., 2006]. Three months after completing the four intravesical treatments, the RTX treated group had 42.3% and 19.2% of patients feeling much better or improved, respectively. This was significantly more than in the placebo group, 14.2% and 7.1% respectively. At six months treatment remained effective in 50% patients in the RTX group but only in 11% in the placebo group [Kuo et al., 2006]. Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 ml of either RTX 50 nM or placebo. Patients were followed-up only for four weeks. During this period a single 50 nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence [Rios et al., 2007].

e) RTX and urgency

The involvement of bladder C-fibers in IDO has led some investigators to explore the role of these sensory afferents to the genesis of urgency. In a non-controlled study involving 12 male patients with LUTS associated with benign prostate enlargement (BPE), mean International Prostate Symptom Scores (IPSS) halved following intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely due to improvements in scores related to urgency, in addition to improvement in nocturia and frequency [Dinis et al., 2005]. In another open-label study 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain/discomfort, and without urodynamic evidence of DO received one single 50 nM RTX solution. A trend towards an improvement of urgency was noticed [Apostolidis et al., 2006]. In a more recent study involving first a placebo instillation and one month later a 50 nM RTX administration to 23 patients with refractory urgency, a significant decrease in the number of episodes of urgency were detected after RTX treatment when compared with the placebo treatment [Silva et al., 2007].

At the moment and probably in the near future, a lack of stable preparations of RTX available for easy bladder instillation will make further investigation of the compound difficult. Different origins of the vanilloid and different ways for preparation and storage of the solutions might have caused substantial differences in the amount of active compound effectively administered to the patients. In addition, RTX adheres to plastics, another reason to the enormous discrepancies have been observed among RTX studies, with some claiming good results and others not demonstrating any superiority of RTX over placebo. Development of new, user-friendly formulations is needed.

Capsaicin and RTX will also face the concurrence of small molecule TRPV1 antagonists that act as a blockade of TRPV1 receptors rather than desensitizing them. Some of these compounds are already entering preliminary clinical trials. The interested reader might find an extensive review on small molecule TRPV1 antagonists elsewhere [Szallasi et al., 2006]. Very recently an experimental study was presented showing that one of these compounds (GRC 6211) active by oral route could reduce frequency of bladder reflex contractions as well as spinal c-fos expression in rat models of cystitis (Figure 15). Interestingly in the optimal therapeutic doses, this TRPV1 antagonist had no effect on the bladder activity of intact animals [Cruz et al., 2008; Charrua et al., 2008].

X. OTHER DRUGS

1. BACLOFEN

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex in several points along its central pathway [De Groat, 1997; Pehrson et al., 2002]. As a GABA agonist on GABA(B) receptors, baclofen was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [Taylor and Bates, 1979]. To overcome this inconvenience, intrathecal baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [Bushman et al., 1993]. Baldo et al. [2000] could find a rapid (24 hours) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric whereas maximal detrusor pressure decreased. At ten days the volume to first detrusor contraction had increased from 143 ml to 486 ml. Contrasting with the limited published clinical experience, some recent experimental data may revive the GABAergic system as a target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA(B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [Pehrson et al, 2002]. In spinally intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes whereas intrathecal application of baclofen induces urethral relaxation during isovolumetric bladder contractions. These results indicate not only that GABA receptor activation in the spinal cord exerts inhibitory effects on DSD after SCT but also that decreased activation of GABA(A) receptors due to hypofunction of GABAergic mechanisms in the spinal cord might be responsible at least in part for the development of DSD after spinal cord transaction (SCT) [Miyazato et al., 2008a]. These findings are reinforced by the observation that glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased after
Figure 14: Effect of intravesical resiniferatoxin in patients with idiopathic DO

Figure 15: Effects of the TRPV1 receptor antagonists, GRC-6211, on rat spinal c-fos expression induced by instillation of acetic acid into the bladder. Unpublished information, courtesy F. Cruz
spinal cord transection. Therefore, stimulation of spinal GABAergic mechanisms can be useful for the treatment of detrusor overactivity after spinal cord injury [Miyazato et al., 2008b]. For assessment, see Table 2.

**XI. COMBINATIONS**

Combining the current $\alpha_1$-AR antagonists with other agents might theoretically provide improved symptom relief. One such example is the combination of $\alpha_1$-AR antagonists with 5$\alpha$-reductase inhibitors, which has proven to improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [McConnell et al., 2003, Roehrborn et al., 2008]. Other combinations have also been tested with varying degrees of success. Traditionally muscarinic receptor antagonists have been contraindicated in patients with BPH due to fears of urinary retention. However, this dogma has been questioned and several studies have been performed in which $\alpha_1$-AR antagonists are combined with muscarinic receptor antagonists with promising results [Athanasopoulus et al., Lee et al., 2004; 2005; 2008; Ruggieri et al., 2006; Kaplan et al., 2006; Novara et al., 2006; Mc Vary, 2007; Rovner et al., 2008]. Speculatively, several other combinations can be suggested [Andersson, 2008].

**XII. FUTURE POSSIBILITIES**

**1. PERIPHERALLY ACTING DRUGS**

**a) Vitamin D$_3$ receptor analogues**

Rat and human bladders were shown to express receptors for vitamin D [Crescioli et al., 2005], which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D$_3$ have also been shown to inhibit benign prostatic hyperplasia (BPH) cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [Crescioli et al., 2002; 2003; 2004]. Experiments in rats with bladder outlet obstruction [Schröder et al., 2006] showed that one of the analogues, BXL-628 (elocalcitol), at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle which occurred with increasing bladder weight [Schröder et al., 2006]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [Morelli et al., 2007]. Upregulation of his pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [Peters et al., 2006; Christ and Andersson, 2007]. The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that elocalcitol was able to arrest prostate growth within 12 weeks in men aged $\geq$50 years with prostatic volume $> 40$ ml [Colli et al., 2006]. In an RCT enrolling 120 female patients with OAB, where the primary endpoint was an increase in the mean volume voided, a significant increase vs placebo (22% vs 11%) was demonstrated [Colli et al., 2007]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB, requires further RCTs.

**2. CENTRALLY ACTING DRUGS**

Many parts of the brain seem to be activated during storage and voiding [see, Griffiths 2007; Fowler et al., 2008; Griffiths and Tadic, 2008], and there is increasing interest in drugs modulating the micturition reflex by a central action [Andersson and Pehrson, 2003]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, since selective actions may be difficult to obtain. Holstege [2005], reviewing some of the central mechanisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that “the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level.”

**a) Gonadotropin-releasing hormone antagonists**

The beneficial effects of the 5$\alpha$-reductase inhibitors, finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GNRH; also known as luteinizing hormone-releasing hormone: LH-RH) agonists is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [Schroeder et al. 1986; Peters et al 1987; Bosch et al., 1989; Eri and Tveter, 1993]. With LH-RH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration.

Debruyne et al. [2008] demonstrated in a phase 2 RCT that the LH-RH antagonist cetorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS $\geq$ 13, peak urinary flow rates 5-13 ml/s), rapidly caused a significant improvement in the mean IPSS: the peak decrease was -5.4 to -5.9 vs -2.8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug
offered a safe and effective treatment of male LUTS. Further studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

**b) Gabapentin**

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [Striano and Striano 2008]. It was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimetic capable of crossing the blood-brain barrier [Maneuf et al., 2003]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [Maneuf et al., 2003]. It has been suggested that it acts by binding to a subunit of the αδ unit of voltage dependent calcium channels [Gee et al., 1996; Striano and Striano, 2008]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone et al. [2006] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim et al. [2004] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other αδ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives.

**c) Tramadol**

Tramadol is a well-known analgesic drug [Grond and Sablotzki, 2004]. By itself, it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ-receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and noradrenaline reuptake [Grond and Sablotzki, 2004]. This profile is of particular interest, since both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OAB/DO, as shown in a placebo controlled study with duloxetine [Steers et al., 2008].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [Pehrson et al., 2003]. Tramadol also inhibited DO induced by apomorphine in rats [Pehrson and Andersson, 2003] – a crude model of bladder dysfunction in Parkinson’s disease. Singh et al. [2008] gave tramadol epidurally and found the drug to increase bladder capacity and compliance, and to delay filling sensations without adverse effects on voiding. Safarinejad and Hosseini [2006] evaluated in a double-blind, placebo-controlled, randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol sustained release every 12 h for 12 weeks. Clinical evaluation was performed at baseline and every two weeks during treatment. Tramadol significantly (p<001) reduced the number of incontinence periods per 24 hours from 3.2±3.3 to 1.6±2.8) and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of LUTS/OAB, the study suggests efficacy for modulation of micturition via the μ-receptor.

**d) NK1-receptor antagonists.**

The main endogenous tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [Lecci and Maggi, 2001; Saffroy et al., 2003; Covenas et al., 2003]. NK1 receptor expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated [Ishizuka et al., 1994] in normal, and more clearly, rats with bladder hypertrophy secondary to BOO. Capsaicin-induced detrusor overactivity was reduced by blocking NK1 receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [Seki et al., 2002]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 1995a].

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction [Gu et al., 2000]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 2000]. Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [Massaro and Lenz, 2005], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed
incontinence (with predominantly urgency urinary incontinence), as shown in a well designed pilot RCT [Green et al., 2006]. The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly (p<0.003) decreased the average daily number of micturitions (-1.3±1.9) compared with placebo (-0.4±1.7) at 8 weeks. The average daily number of urgency episodes was also significantly (p<0.047) reduced (-23.2±32%) compared to placebo (-9.3±40%), and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. The results of this initial proof of concept study suggest that NK-1 receptor antagonism holds promise as a potential treatment approach for OAB.

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI): urethral support, vesical neck function, and function of the nerves and musculature of the bladder, urethra, and pelvic floor [DeLancey, 1997; Mostwin et al., 2005]. Anatomical factors cannot be treated pharmacologically. However, women with SUI have lower resting urethral pressures than age-matched continent women [Henriksson et al, 1979; Hilton et al, 1983], and since it seems likely that there is a reduced urethral closure pressure in most women with SUI, it seems logical to increase urethral pressure to improve the condition.

Factors which may contribute to urethral closure include tone of urethral smooth and striated muscle and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacological evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released noradrenaline [Andersson, 1993; Andersson and Wein, 2004]. A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated muscles. Several drugs may contribute to such an increase [Andersson, 1988; Zinner et al., 2004], but relative lack of efficacy or and side effects have limited their clinical use. For assessments, see Table 4.

### C. DRUGS USED FOR TREATMENT OF STRESS URINARY INCONTINENCE

Several drugs with agonistic effects on α-ARs have been used in the treatment of SUI (Table 4). However, ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [Andersson et al., 2002]. The original Agency for Healthcare Policy and Research Guidelines (Agency for Healthcare Policy and Research, 1992) reported 8 randomized controlled trials with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0% to 14%, percent reduction in continence as 19% to 60%, and percent side effects and percent dropouts as 5% to 33% and 0% to 4.3% respectively. The most recent Cochrane review on the subject [Alhasso et al., 2005] assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in two, norepinephrine in three, clenbuterol in three, terbutaline in one, eskornade in one and RO 115-1240 in one). The authors concluded “there was weak evidence to suggest that use of an adrenergic agonist was better than placebo treatment”. The limited evidence suggested that such drugs were better than placebo in reducing the number of pad changes and incontinence episodes, and in improving subjective symptoms. There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination.

### Table 4. Drugs used in the treatment of stress incontinence. Assessments according to the Oxford system (modified)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Clenbuterol</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>2</td>
<td>D</td>
</tr>
<tr>
<td>Midodrine</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Norephedrine (phenylpropanolamine)</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Estrogen</td>
<td>2</td>
<td>D</td>
</tr>
</tbody>
</table>

### I. α-ADRENERGOPETTOR AGONISTS

For assessments, see Table 4.
Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation, they caused discontinuation in only 4% of the total.

The date of the most recent amendment to this review is listed as 15 May 2007; no new trials were identified at that time. The update of 2005 [Alhasso et al., 2005] included seven new randomized controlled trials over the 2003 report, cited in the last consultation. The final statement on "what's new" reads, "The conclusions still provide limited support for the use of adrenergics but side effects may cause dropout, and some side effects may be dangerous. Further trials are needed".

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [Andersson et al., 2002]. Kernan et al. [2000] reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States.

Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some [Bent et al., 2003] had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the Food and Drug Administration of the US decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulate α1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate and the clinical usefulness seems to be limited by adverse effects [Alhasso et al., 2003; Radley et al., 2001; Weil et al., 1998].

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman et al. [2004] reported on a phase two randomized crossover study with Ro 115-1240, a peripheral active selective α1L-AR adrenoceptor partial agonist [Blue et al., 2004] in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug.

### II. β-ADRENOCEPTOR ANTAGONISTS

The theoretical basis for the use of β-AR antagonists in the treatment of stress incontinence is that blockade of urethral β-ARs may enhance the effects of noradrenaline on urethral α-ARs. Propranolol has been reported to have beneficial effects in the treatment of stress incontinence [Gleason et al., 1974; Kaisary, 1984] but there are no RCTs supporting such an action. In the Gleason et al. [1974] study the beneficial effects become manifest only after 4 to 10 weeks of treatment; a phenomenon difficult to explain. Donker and Van der Sluis [1976] reported that β-blockade did not change UPP in normal women. Although suggested as an alternative to β-AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β-AR blockade.

### III. β-ADRENOCEPTOR AGONISTS

β-AR stimulation is generally conceded to decrease urethral pressure [Andersson, 1993], but β2-AR agonists have been reported to increase the contractility of some fast contracting striated muscle fibers and suppress that of slow contracting fibers of others [Fellenius et al., 1980]. Some β-AR agonists also stimulate skeletal muscle hypertrophy – in fast twitch more so than slow twitch fibers [Kim et al., 1992]. Clenbuterol has been reported to potentiate the field stimulation induced contraction in rabbit isolated periurethral muscle preparations, an action which is suppressed by propanolol and greater than that produced by isoproterenol [Kishimoto et al., 1991]. These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yaminishi et al. [1994] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β-AR blockade.

Yasuda et al. [1993] described the results of a double blind placebo controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7±17.9 g to 6.0±12.3 g for drug and from 18.3±29.0 g to 12.6±24.7 g for placebo, raising questions about the comparability of the 2 groups. The "significant" increase in maximum urethral closure pressure (MUCP) was from 46.0±18.2 cm H2O to 49.3±19.1 cm H2O, versus a change of -1.5 cm H2O in the placebo group. 56/77 patients in the clenbuterol group reported some degree of improvement versus 48/88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko et al. [2000] investigated the effects of clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy to pelvic floor exercises. The frequency and volume of stress incontinence and the patient’s own impression were used as the basis for
the assessment of efficacy. The improvement of incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi et al. [1997] reported positive results with clenbuterol (20 mg twice daily for one month) in nine of 14 patients with mild to moderate stress incontinence after radical prostatectomy. No subsequent published reports have appeared. Further well-designed RTCs documenting the effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

1. IMIPRAMINE

Imipramine, among other pharmacological effects, inhibits the re-uptake of noradrenaline and serotonin in adrenergic nerve endings. In the urethra this can be expected to enhance the contractile effects of noradrenaline on urethral smooth muscle. Gilja et al [1984] reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean maximal urethral closure pressure (MUCP) from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement.

Lin et al. [1999] assessed the efficacy of imipramine (25 mg imipramine three times a day for three months) as a treatment in 40 women with genuine stress incontinence. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60% (95% CI 11.8-75.2). There are no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

2. DULOXETINE

As mentioned previously, duloxetine is a combined serotonin and noradrenaline reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al., 2002]. The sphincteric effects were reversed by α1-AR (prazosin) and 5HT2 serotonergic (LY 53857) receptor antagonism, while the bladder effects were mediated by temporal prolongation of the actions of serotonin and noradrenaline in the synaptic cleft (Figure 16) (Fraser et al, 2003). Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 hours [Sharma et al., 2000].

There are many studies, including RCTs, documenting the effects of duloxetine in SUI [Norton et al., 2002; Dmochowski et al., 2003; Millard et al., 2004; Van Kerrebroeck et al., 2004; Cardozo et al., 2004; Kinchen et al., 2005; Ghoneim et al., 2005; Hurley et al., 2006; Castro-Diaz et al., 2007; Bump, 2008]. A Cochrane review of the effects of duloxetine for stress urinary incontinence in women is available, the last substantive amendment listed as 25 May 2005 [Mariappan et al., 2005]. Fifteen reports were deemed eligible for analysis, nine primary studies and six additional reports related to one or two of the primary references. An additional analysis “performed under the auspices of the Cochrane Incontinence Group” was performed on just the nine primary trials comparing duloxetine and placebo, and published separately [Mariappan et al., 2007]. The results can be summarized as follows. Subjective “cure” in the duloxetine 80 mg daily (40 mg twice daily) was higher than in the placebo group (10.8 % vs 7.7%, overall relative risk (RR) = 1.42; 95% confidence interval (CI), 1.02-1.98; p = 0.04). The estimated absolute size of effect was about three more patients cured of every 100 treated. Objective cure data, available from only one trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in I-QoL (weighted mean difference (WMD) for 80 mg: 4.5; 95% CI 2.83-6.18, p < 0.00001). Patient global impression of improvement (PGI-I) data also favored the drug (RR for better health status 1.24, 95% CI 1.14-1.36; p < 0.00001). Adverse effects in six trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. Nausea was the most common adverse event and the incidence ranged from 23 to 25% and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness and insomnia, overall RR 1.30 (95% CI, 1.23-1.37). Across these six trials 17% in the drug group withdrew, 4 % in the placebo arm. In the 2007 article the authors conclude by saying that further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost effective compared to other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that “longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications”. Hashim and Abrams [2006] suggested that in order to reduce the risk of nausea, begin with a dose of 20 mg twice daily for two weeks, then to increase to the recommended 40 mg twice daily dosage.

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union (European Medicines Agency, Scientific Discussion, 2005) for women with moderate to severe incontinence (defined as 14 or more episodes per week). It was withdrawn from the Food and Drug Administration (FDA) consideration process in the United States for the treatment of SUI, but is approved for the treatment of major depressive disorder (20-30 mg twice daily
initially, 60 mg once daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), and generalized anxiety disorder (60 mg once daily). The product information contains a “black box” warning of “increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders”, noting also that “depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide” (Prescribing Information, revised December 2007, Eli Lilly and Company, Indianapolis, Indiana 46285).

Other warnings and precautions in the United States Product Information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding selective serotonin reuptake inhibitors (SSRIs) and SNRIs), abrupt discontinuation (may result in dizziness, paresthesias, irritability and headache), inhibitors of CYP1H2 or thioridazine (do not administer concomitantly), potent inhibitors of CYP2D6 (may increase concentration), and others.

### 3. MALE STRESS URINARY INCONTINENCE

Although a problem of significant magnitude, especially after total prostatectomy for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention. Tsakiris et al. [2008] searched for articles on this subject published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using α1-AR agonists, β2-AR antagonists or SNRIs.

Only one of these included a comparison arm [Filocamo et al., 2007]. 40 mg twice daily duloxetine plus pelvic floor exercises vs pelvic floor exercises (PFE) with placebo. The results suggested a positive effect of drug, but were a bit confusing. Of those patients completing the four-month trial (92/112) 78% of the drug treated patients vs 52% of those in the placebo group were dry. However, one month after the end of the study, the corresponding figures were 46% vs 73%, a shift still observed two months later.

The authors of the review article suggest further larger and well designed studies on duloxetine for this potential usage.
Urinary incontinence most often results from too much pressure generated by the bladder and/or too little resistance generated by the bladder outflow tract during the storage phase of the micturition cycle (urgency incontinence and stress urinary incontinence, respectively). More rarely, incontinence can also occur in the presence of too little pressure and/or too much resistance being developed which can lead to a markedly distended bladder and urinary retention and, secondarily, to overflow incontinence [Abrams et al., 2002].

Based upon theoretical reasoning, animal studies [Kamo et al., 2005; Gu et al., 2004] or reports of drugs which can cause overflow incontinence [Anders et al., 1985], a variety of medical approaches to the treatment of overflow incontinence have been proposed [Chutka and Takahashi, 1998; Hampel et al., 2005].

These include direct or indirect muscarinic receptor agonists and $\alpha_1$-AR antagonists. The use of the former is based upon the idea that stimulation of muscarinic receptors may overcome a hypo-contractile state of the detrusor. However, a recent systematic review of controlled clinical studies on the use of direct and indirect parasympathetic agonists in patients with an underactive detrusor has shown that these drugs do not exhibit consistent benefit and may even be harmful [Barendrecht et al., 2007]. In contrast, the use of $\alpha_1$-AR antagonists has repeatedly been shown to beneficial in patients with acute urinary retention [McNeill et al., 2004; 2005].

However, neither parasympathomimetic drugs nor $\alpha_1$-AR antagonists have ever been tested systematically in the treatment of overflow incontinence. Accordingly, a Medline search using the keyword “overflow incontinence” did not yield a single randomized controlled trial for its treatment, and not even a case series with a meaningful number of patients was retrieved. Therefore, it must be concluded that there is no empirical basis to select medical treatments for overflow incontinence and all previously recommended treatments must be rated as “expert opinion” at best. Moreover, any medical treatment for overflow incontinence will have to be evaluated as compared to catherization or surgery but also for such comparison no clinical data are available.

---

1. ESTROGENS AND THE CONTINENCE MECHANISM

The estrogen sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. For women to remain continent the urethral pressure must exceed the intravesical pressure at all times except during micturition. The urethra has four estrogen sensitive functional layers all of which play a part in the maintenance of a positive urethral pressure 1) epithelium, 2) vasculature, 3) connective tissue, 4) muscle.

Two types of estrogen receptor, ($\alpha$ and $\beta$) have been identified in the trigone of the bladder, urethra and vagina as well as in the levator ani muscles and fascia and ligaments within the pelvic floor [Smith et al., 1990; Copas et al., 2001; Gebhardt et al., 2001]. After the menopause, estrogen receptor $\alpha$ has been shown to vary depending upon exogenous estrogen therapy [Fu et al., 2003]. In addition exogenous estrogens affect the remodeling of collagen in the urogenital tissues resulting in a reduction of the total collagen concentration with a decrease in the cross linking of collagen in both continent and incontinent women [Falconer et al., 1998; Keane et al., 1997]. Studies in both animals and humans have shown that estrogens also increase vascularity in the peri-urethral plexus which can be measured as vascular pulsations on urethral pressure profilometry [Robinson et al., 1996; Endo et al., 2000; Versi and Cardozo, 1986].

2. ESTROGENS FOR STRESS URINARY INCONTINENCE

The role of estrogen in the treatment of stress urinary incontinence has been controversial despite a number of reported clinical trials [Hextall, 2000]. Some have given promising results but this may have been because they were small observational and not randomized, blinded or controlled. The situation is further complicated by the fact that a number of different types of estrogen have been used with varying doses, routes of administration and duration of treatment. For assessment, see Table 4.

Fantl et al. [1996] treated 83 hypo-estrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine estrogens 0.625 mg and medroxyprogesterone 10 mg cyclically for three months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables did not change significantly in either...
group. Jackson et al. [1996] treated 57 post menopausal women with urodynamic stress or mixed incontinence with estradiol 2 mg or placebo daily for six months. There was no significant change in objective outcome measures although both the active and placebo groups reported subjective benefit.

There have been two meta-analyses performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee the use of estrogens to treat all causes of incontinence in post menopausal women was examined [Fantl et al., 1994]. Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost, maximum urethral closure pressure increased significantly but this result was influenced by only one study showing a large effect.

In the second meta-analysis Sultana and Walters [1990] reviewed eight controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment for stress urinary incontinence but may be useful for the often associated symptoms of urgency and frequency. Estrogen when given alone therefore does not appear to be an effective treatment for stress urinary incontinence.

Several studies have shown that estrogen may have a role in combination with other therapies e.g. α-AR agonists. However, PPA (the most widely used α-AR agonist in clinical practice) has now been restricted or banned by the US Food and Drug Administration (FDA). In a randomized trial Ishiko et al. [2001] compared the effects of the combination of pelvic floor exercise and estriol (1 mg per day) in 66 patients with post meno-pausal stress urinary incontinence. Efficacy was evaluated every three months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress incontinent patients in both groups three months after the start of therapy and concluded that combination therapy with estriol plus pelvic floor exercise was effective and could be used as first line treatment for mild stress urinary incontinence. Unfortunately this has not been reproduced in other clinical trials.

Thus even prior to the more recently reported secondary analyses of the heart and estrogens/progestogen replacement study (HERS) [Grady et al., 2001] and Women’s Health Initiative (WHI) [Hendrix et al., 2005] it was already recognized that estrogen therapy had little effect in the management of urodynamic stress incontinence [Al-Badr et al., 2003; Robinson and Cardozo, 2003].

3. ESTROGENS FOR URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

Estrogen has been used to treat post menopausal urgency and urgency incontinence for many years but there have been few controlled trials to confirm that it is of benefit [Hextall, 2000; for assessment, see Table 2]. A double blind multi centre study of 64 post menopausal women with “urgency syndrome” failed to show efficacy [Cardozo et al., 1993]. All women underwent pre-treatment urodynamic investigation to ensure that they had either “sensory urgency” or DO. They were randomized to treatment with oral estriol 3 mg daily or placebo for three months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Estriol produced subjective and objective improvements in urinary symptoms, but was not significantly better than placebo.

Another recent randomized controlled trial from the same group using 25 mg estradiol implants confirmed the previous findings [Rufford et al., 2003], and furthermore found a high complication rate in the estradiol treated patients (vaginal bleeding).

Evidence from large clinical trials

The HERS study included 763 post menopausal women under the age of 80 years with coronary heart disease and intact uteri [Grady et al., 2001]. It was designed to evaluate the use of estrogen in secondary prevention of cardiac events. In a secondary analysis 1525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet (N=768) or placebo (N=757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged or worsened. The results showed that incontinence improved in 26% of the women assigned to placebo compared to 21% assigned to hormones whilst 27% of the placebo worsened compared with 39% of the hormone group (P=0.001).

This difference was evident by four months of treatment, for both urgency and stress urinary incontinence. The number of incontinent episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group (p<0.001). The authors concluded that daily oral estrogen plus progestogen therapy was associated with worsening urinary incontinence in older post menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.
The Women’s Health Initiative (WHI) was a multi-center double blind placebo controlled randomized clinical trial of menopausal hormone therapy in 27347 postmenopausal women age 50–79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23296 participants at baseline and one year. The women were randomized based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg per day of conjugated equine estrogen (CEE) plus 2.5 mg per day of medroxyprogesterone acetate (CEE+MPA), whereas those who had undergone hysterectomy received estrogen alone (CEE). At one year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE+MPA: RR, 1.7 95% confidence interval CI (1.61-2.18); CEE alone RR 2.15 mg, 95% CI, 1.77-2.62, followed by mixed urinary incontinence CEE+MPA: RR 1.49 95% CI 1.10-2.01. On CEE alone RR was 1.79 95% CI, 1.26-2.53. The combination of CEE and MPA had no significant effect on developing urgency urinary incontinence RR, 1.15; 95% CI, 0.99-1.34 but CEE alone increased the risk, RR 1.32; 95% CI, 1.10-1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE+MPA; RR, 1.38 95% CI 1.28-1.48; CEE alone: RR, 1.47 95% CI, 1.35-1.61. Quantity of urinary incontinence worsened at one year in both active groups, CEE+MPA: RR, 1.20 95% CI, 1.06-1.76; CEE alone: RR, 1.59 95% CI, 1.39-1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE+MPA: RR 1.18 95% CI, 1.06-1.32. CEE alone: RR 1.29 95% CI, 1.15-1.45 at one year. Thus based on this secondary analysis of data from a huge study conjugated equine estrogen alone or in combination with medroxyprogesterone acetate was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after one year of therapy.

The Nurses Health Study [Grodstein et al., 2004] was a biennial postal questionnaire starting in 1976. In 1996, 39436 post menopausal women aged 50–75 years who reported no urinary leakage at the start of the study were followed up for four years to identify incident cases of urinary incontinence. 5060 cases of occasional and 2495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased amongst post menopausal women taking hormones compared to women who had never taken hormones (oral estrogen: RR1.54 95% CI 1.44, 1.65; transdermal estrogen: RR1.68, 95% CI 1.41, 2.00; oral estrogen with progestin: RR1.34, 95% CI 1.24, 1.44; transdermal estrogen with progestin: RR1.46, 95% CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

CONCLUSIONS

Estrogen has an important physiological effect on the female lower urinary tract and its deficiency is an etiological factor in the pathogenesis of a number of conditions. However the use of estrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of estrogen for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events, and therefore the secondary analyses have only been based on self reported symptoms of urinary leakage without any objective data. Despite this all of these large randomized controlled trials show a worsening of pre-existing urinary incontinence both stress and urgency, and an increased new incidence of urinary incontinence with both estrogen and estrogen plus progestogen. However, the majority of patients in all of these studies were taking combined equine estrogen and this may not be representative of all estrogens taken by all routes of administration.

In a systematic review of the effects of estrogens for symptoms suggestive of an overactive bladder the conclusion was that estrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [Cardozo et al., 2004].

It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urgency incontinence may be a manifestation of urogenital atrophy in older post menopausal women rather than a direct effect on the lower urinary tract [Robinson and Cardozo, 2003]. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal estrogen therapy there is currently no evidence that estrogens with or without progestogens should be used in the treatment of urinary incontinence.

II. OTHER STEROID HORMONE RECEPTOR LIGANDS

Progesterone and progestogens are thought to increase the risk of urinary incontinence. Lower urinary tract symptoms especially stress urinary incontinence, have been reported to increase in the progestogenic phase of the menstrual cycle [Hextall et al., 2001]. In similar studies progesterone has been shown to increase β-AR activity leading to a decrease in the urethral closure pressure in female dogs [Raz et al., 1973]. However, in the WHI there appeared to be no difference whether or not progestin was given in addition to estrogen [Hendrix et al., 2005].
Selective estrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both estrogenic and anti-estrogenic effects. In the clinical trials of levormeloxifene there was a fourfold increase in the incidence of incontinence leading to cessation of the clinical trial [Hendrix et al., 2001]. However raloxifene has not been shown to have any effect at all on urinary incontinence [Waetjen et al., 2004].

There are no reported clinical trials evaluating the effect of androgens, and in particular testosterone, on urinary incontinence in women.

### III. DESMOPRESSIN

The endogenous hormone vasopressin (also known as anti-diuretic hormone) fulfils two main functions, i.e. it can contract vascular smooth muscle and can stimulate water reabsorption in the renal medulla. These functions are mediated by specific vasopressin receptors of which two major subtypes exist, the V₁ and the V₂ receptors of which the V₂ subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to a central diabetes insipidus, and genetic defects in the gene encoding the V₂ receptors can cause nephrogenic diabetes insipidus [Insel et al., 2007]. Accordingly, a (relative) lack of vasopressin is believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria, which can lead to symptoms such as nocturia [Matthiesen et al., 1996]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist.

Based upon these considerations, vasopressin receptor agonists have been explored for the treatment of the symptom nocturia (both in children and in adults) and, more recently, for the treatment of OAB in general. Most studies related to the treatment of nocturia with vasopressin analogues have been performed using desmopressin, which shows selectivity for anti-diuretic over vasopressor effects and is available in formulations for oral, parenteral and nasal administration: an oral lypohlsate formulation [Vande Walle et al., 2006] has recently been approved in some countries. Vasopressin receptor agonists with pronounced vasopressor effects such as terlipressin have mainly been tested in other indications, e.g., acute oesophageal variceal haemorrhage.

The use of desmopressin in children with nocturnal enuresis has been comprehensively reviewed by the Cochrane Collaboration in 2002 [Glazener and Evans, 2008]. Their analysis included 47 randomized controlled trials involving 3448 children, of whom 2210 received desmopressin. According to this analysis desmopressin was effective relative to placebo in reducing bed-wetting (for example at a dose of 20 µg there was a reduction of 1.34 wet episodes/night (95% CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference to placebo after discontinuation of treatment, indicating that desmopressin suppresses the symptom enuresis but does not cure the underlying cause. Moreover, based upon limited data, there was no clear dose-related effect, and there were too few studies to conclusively compare oral vs. nasal administration.

A Medline search using the terms “desmopressin” and “enuresis” did not yield additional studies which would change these conclusions. However, not all children respond sufficiently to desmopressin treatment, and some studies indicate that non-responders may benefit from other medications including tricyclic antidepressants or loop diuretics whereas muscarinic receptor antagonists may be ineffective in such children [De Guchtenaere et al., 2007; Neveus and Tullus, 2008].

Other studies have explored a possible role of desmopressin in the treatment of nocturia in adults. The Medline search for such studies used the terms “desmopressin” and “nocturia” and was limited to clinical studies on de novo nocturia, i.e. excluded subjects in whom childhood enuresis persisted into adulthood. Early studies have mainly investigated the use of desmopressin in the treatment of nocturia in the context of multiple sclerosis. One study with single dose administration reported reductions of nocturnal polyuria, but by design did not assess nocturia [Eckford et al., 1995]. Three placebo-controlled double-blind studies with small patient numbers (16-33 patients total per study) reported a significant reduction of nocturia [Eckford et al., 1994; Valiquette et al., 1996; Hilton et al., 1983]. For example, in the study of Valiquette et al. [1996] performed in patients with multiple sclerosis, the number of nocturia episodes were reduced from 2.35 to 1.09 and the maximum hours of uninterrupted sleep form increased from 3.74 to 5.77 hours. Other controlled studies of similar size, mostly performed in crossover designs, and with treatment for up to two weeks used daytime micturition frequency and urgency incontinence within the first six hours after desmopressin administration rather than nocturia as their primary endpoint and consistently reported efficacy of desmopressin [Kinn and Larsson, 1990; Fredrikson, 1996; Hovend and Fowler, 1998]. While desmopressin treatment was generally well tolerated, at least in one study, four out of 17 patients discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [Valiquette et al., 1996].
Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [Cvetkovic and Plosker, 2005]. In a small open-label study desmopressin was also reported to reduce nocturnal polyuria in spinal cord injury patients [Zahariou et al., 2007]. Other studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. Most studies had a short double-blind period of only two to three weeks. The recruited patient populations were based upon different criteria including having at least two nocturia episodes per night or having nocturnal polyuria. The early studies mostly used desmopressin given either orally [Asplund et al., 1999] or intranasally [Hilton and Stanton, 1982; Cannon et al., 1999], and tended to be very small (725 patients). The original intranasal formulation has meanwhile been withdrawn from the market in several countries due to side effects and unpredictable absorption.

Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and applied higher oral doses (0.1-0.4 mg) for three weeks of double-blind treatment in adults [Mattiasson et al., 2002; Lose et al., 2004; van Kerrebroeck et al., 2007]. The three short-term placebo-controlled studies were of identical design and were designed to identify the most effective dose regimen as well as establishing criteria for selecting those patients most likely to respond safely to desmopressin. A total of 632 patients entered the dose-titration phase with 422 patients entering the double-blind phase of the three NOCTUPUS trials. The aim of the titration phase was to describe the antidiuretic effect in patients with nocturnal polyuria. It has been argued that while these studies consistently demonstrated efficacy over placebo in reducing nocturia episodes, they were performed in patients who were known to be desmopressin responders based upon initial dose-titration phases. To avoid this bias, all patients in the NOCTUPUS trials were washed out following the dose-titration and in order to be randomized it was a requirement that these patients should be back to baseline on their nocturnal diuresis before inclusion in the double-blind phase. Patients on desmopressin had a reduction in mean number of nocturnal voids (from 2.4-2.7 to 1.6-2.0), an increase in mean duration of the first sleep period (from 181-196 to 247-272 minutes) and a decrease in mean nocturnal diuresis (from 1.35 and 1.5 to 0.82 tand 0.9 ml per minute [Hashim and Abrams; 2008].

The efficacy of desmopressin for the treatment of nocturia was also confirmed in a long-term (10-12 months) open-label study involving 249 patients, which was an extension to the above mentioned randomized studies in known desmopressin responders [Lose et al., 2004]. The number of nocturnal voids was decreased throughout the study in males to 1.3-1.6 from a baseline of 3.1 and in females from 2.9 to 1.2-1.3. After the one-month follow-up at the end of the trial when treatment was stopped, the number of nocturnal voids increased following cessation of desmopressin. The mean duration of the first sleep period gradually increased in males from 157 minutes at baseline to 288 minutes at 12 months and in females from 142 at baseline to 310 minutes at 12 months. After follow-up the mean duration of the first sleep period decreased confirming that increased sleep is a real treatment related benefit of desmopressin. There was an improvement in QoL with more than 50% decrease in patients reporting nocturia as the most bothersome symptom as assessed by the ICSmale and BFLUTS questionnaires.

An open-label pilot study in a nursing home setting also reported beneficial effects of desmopressin [Johnson et al., 2006]. Taken together these data demonstrate that oral desmopressin treatment at doses of 0.1-0.4 mg reduces nocturia more effectively than placebo in known desmopressin responders. Hyponatremia appears to occur in few cases only and rarely becomes symptomatic. As the symptom of nocturia can result from many causes, it has also been studied whether desmopressin may be beneficial in patients characterized not only by nocturia. In a small, non-randomized pilot study of men believed to have BPE, desmopressin was reported to improve not only nocturia but also to reduce overall International Prostate Symptom Score (IPSS) [Chancellor et al., 1999].

An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence has reported that intranasal administration of 40 µg desmopressin increased the number of leakage-free episodes after drug administration [Robinson et al., 2004]. One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg oral desmopressin reported a reduction in daytime voids and urgency episode along with an improvement of quality of life, in the first eight hours of the morning after taking desmopressin [Hashim et al., 2008]. These data indicate that desmopressin may be effective in storage symptoms, not limited to nocturia (Level 2, Grade C), and desmopressin may be used as a ‘designer’ drug in the treatment of OAB and incontinence during the daytime. Further studies are required to address this concept using the new oral lyophilisate ‘Melt’ formulation either on its own or in combination with antimuscarinics and/or alpha blockers in patients with OAB and/or BPE.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side effects of demopressin usage is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache,
anorexia, nausea, and vomiting to loss of consciousness, seizures and death. The risk of hyponatraemia seems to increase with age, cardiac disease, and increasing 24-hour urine volume [Rembratt et al., 2003] and has been reported in a meta-analysis to be about 7.6% [Weatherall et al., 2004].

Currently, there are no predictive factors about who may be at increased risk of developing hyponatraemia. However, to reduce the risk of hyponatraemia, it is recommended that patients older than 79 years or with a 24-hour urine volume more than 28 ml/kg should not be given desmopressin [Rembratt et al., 2006]. In those over 65 years, serum sodium levels should be checked at baseline and at three days and seven days after commencing treatment or changing dose. It is probably good medical practice that these serum sodium measurements are also applied to those under 65 years of age, as well as checking sodium levels at three weeks post treatment or change of dose as there is the potential for levels of sodium to change within a three week period [Callreus et al., 2005]. One study showed that hyponatraemia can develop after six months of administration, although not clinically significant [Bae et al., 2007], and therefore serum sodium levels may be checked at six months following administration and then six monthly thereafter. Long-term use of desmopressin does not seem to affect baseline antidiuretic hormone secretion [Bae et al., 2007]. The fluid intake will need to be limited to a minimum from one hour before the dose until eight hours afterwards and there needs to be periodic blood pressure and weight measurements to monitor for fluid overload. Desmopressin is currently the only medication licensed and available for the treatment of nocturia. It is currently licensed for the treatment of nocturia in the oral ‘Melt’ form and in the oral tablet form. For assessment, see Table 2.

F. CONSIDERATIONS IN THE ELDERLY

Almost all randomized controlled trials of antimuscarinics for urinary incontinence include older adults, however only two efficacy sub-analyses of older adults have been reported. The first, TOLT-IR 2 mg twice daily vs. placebo, revealed a significant decrease of 0.7 episodes of incontinence per day (an approximate 25% reduction) among 131 participants with urgency incontinence (mean age 75, range 62-92) [Malone-Lee et al., 2001]. A second, larger study comparing older adults (mean age 74 ± 6) to younger adults (mean age 51± 10) taking TOLT-ER 4 mg, showed equivalent efficacy for the two age groups in reducing incontinence episodes (a mean decrease of 12 episodes per week, an approximate 55% reduction from baseline), with both groups showing significantly greater improvement compared to placebo (placebo response: younger 6, older 7 episodes per week) [Zinner et al., 2002].

A number of explanations exist for why antimuscarinic agents may show reduced efficacy for urgency incontinence in the elderly in the practice setting compared to the research setting. Exclusion criteria for antimuscarinic research trials generally include consumption of other antimuscarinic agents or cytochrome P450 3A4 inhibitors. In practice, older adults are a heterogeneous group, often consuming many medications that may desensitize or alter the response of the individual to antimuscarinics. As well, there is a higher prevalence of concomitant BPE among older men, with storage symptoms showing a variable response to antimuscarinics. Failure to acknowledge the multifactorial nature of urinary incontinence in the elderly often leads to sub-optimal treatment. Urgency symptoms may be exacerbated by consumption of caffeinated beverages, pelvic floor muscle weakness, diuretics or other functional and systemic dysfunctions. Treatment must address all possible etiologies, and not be limited to a solitary intervention.

The side effect profile of antimuscarinics appears to be the same for older and younger patients. Dry mouth is the most frequent adverse effect prompting discontinuation of the drug [Zinner et al., 2002]. Other more serious side effects, such as prolongation of the Q-T interval with some antimuscarinics, have not been systematically studied in the elderly population. The M2 receptor antimuscarinics in particular have the potential to increase resting heart rate (a predictor of mortality in the elderly), however the clinical significance of this remains uncertain [Andersson and Olshansky, 2007]. In practice, older patients may already be taking other antimuscarinic drugs and thus may be habituated or intolerant to the addition of another medication in the same class and the resultant cumulative antimuscarinic load. A number of commonly used medications in the elderly possess antimuscarinic properties [Chew et al., 2008]. These include, among others, amitriptyline, clozapine, olanzepine, paroxetine, furosemide, hydrocodone, lansoprazole, levofloxacin, and metformin.

Of particular concern in the elderly is the possibility that antimuscarinic agents used to treat urgency incontinence may induce subtle or not so subtle cognitive impairment. In experimental studies, administration of scopolamine has been shown to impair memory and attention in older adults [Flicker et al., 1992; Sperling et al., 2002]. Older adults are also prone to develop hallucinations and confusion with scopolamine, and experience significantly greater impairments in delayed memory and psychomotor speed compared to younger individuals.

Antimuscarinic drugs have also been associated with the presence of mild cognitive impairment, a precursor...
been induced. This is especially pertinent because therapy might reveal whether subtle impairments have who are concerned or at risk, before and after initiating neuropsychological test battery for those patients Montreal Cognitive Assessment) or even a full incontinence in the elderly. If antimuscarinics are to risk-benefit ratio in light of other therapeutic options prescribing these medications and fully weigh the linking antimuscarinics and cognition impairment, of three tests. In the absence of more definitive data reduced accuracy scores for immediate recall in one information processing speed. Oxybutynin also significantly slower reaction times than placebo in the second study, darifenacin was compared to oxybutynin compared with placebo [Lipton et al., 2005]. In the first study of 129 older adults aged 65-84, no significant effects on cognition were observed (memory scanning sensitivity, speed of reaction time, and word recognition) compared with placebo [Todorova et al., 2001]. There have also been several published case reports documenting the acute onset of delirium following initiation of tolterodine, incontinent adults with and without dementia [Womack and Heilman, 2003; Salvatore et al., 2007; Edwards et al., 2002; Williams et al., 2004; Tsao et al., 2003]. These deficits resolved upon discontinuation or dose reduction of tolterodine. Two studies have been conducted using darifenacin, but only in continent volunteers [Lipton et al., 2005; Kay et al., 2006]. In the first study of 129 older adults aged 65-84, no significant effects on cognition were observed (memory scanning sensitivity, speed of reaction time, and word recognition) compared with placebo [Lipton et al., 2005]. In the second study, darifenacin was compared to oxybutynin and placebo in a randomized multicentre double-blind parallel-group 3-week study design using 150 healthy volunteers aged 60-83 [Kay et al., 2006]. Darifenacin produced no impairments compared to placebo at 3-weeks, but oxybutynin caused significant memory deterioration in delayed recall compared to the other two groups. Darifenacin was associated with significantly slower reaction times than placebo in the Divided Attention Test, but not in other tests of information processing speed. Oxybutynin also reduced accuracy scores for immediate recall in one of three tests. In the absence of more definitive data linking antimuscarinics and cognition impairment, clinicians are suggested to proceed with caution in prescribing these medications and fully weigh the risk-benefit ratio in light of other therapeutic options that can be equally effective for urgency and mixed incontinence in the elderly. If antimuscarinics are to be prescribed, a short cognitive screen (such as the Montreal Cognitive Assessment) or even a full neuropsychological-test battery for those patients who are concerned or at risk, before and after initiating therapy might reveal whether subtle impairments have been induced. This is especially pertinent because patients are often unaware of their memory deficits [Kay et al., 2006]. A proxy informant, such as the patient's spouse or a relative, may be able to provide more reliable information on possible cognitive changes resulting from the drugs.

A frequently asked clinical question is whether antimuscarinic agents used to treat incontinence should be contraindicated in patients with dementia already taking cholinesterase inhibitors, as the mechanisms of these two medications are diametrically opposed. No studies have examined the cognitive consequences of antimuscarinics in patients with dementia. However, a number of small studies have shown the reverse mechanism to be true, that cholinesterase inhibitors used to improve cognition in Alzheimer's disease precipitate urinary incontinence [Hashimoto et al., 2000]. A Japanese study followed 94 patients with mild to moderate dementia treated with donepezil [Hashimoto et al., 2000]. Seven patients developed urinary incontinence, although the event was transient in most patients. In Scotland, among 216 patients with Alzheimer's disease initiating treatment with a cholinesterase inhibitor, incontinence was precipitated in 6.6%, and those with existing incontinence worsened [Starr, 2007]. Epidemiologic studies also show associations between cholinesterase inhibitors and incontinence [Gill et al., 2005; Roe et al., 2002]. In a large population-based cohort study of 44,884 adults with dementia carried out in Canada, those who were dispensed cholinesterase inhibitors were more likely to subsequently receive an antimuscarinic drug for incontinence compared to those not receiving cholinesterase inhibitors (hazard ratio 1.55, 95% confidence interval 1.39-1.72) [Gill et al., 2005]. This finding was confirmed by a separate study in the U.S. documenting a two-fold risk of taking oxybutynin in dementia patients treated with donepezil compared to those not treated with donepezil [Roe et al., 2002]. This evidence suggests the competing mechanisms of the antimuscarinics and cholinesterase inhibitors may indeed have clinical consequences in some, but not all patients. Should an adverse effect be suspected, then alternate therapeutic options should be pursued. None of the other drug classes used to treat stress, urgency or overflow incontinence have undergone rigorous evaluation in the elderly, however a number of general guidelines apply. Use of α-AR agonists and tricyclic antidepressants are discouraged in the elderly due to blood pressure considerations. Uncontrolled systolic hypertension could occur with the former agents and orthostatic hypotension leading to falls with the latter. There is no evidence that hormonal agents are of benefit for urgency or stress incontinence in older women, although local estrogens may be indicated to treat dysuria resulting from concomitant vaginal atrophy. Finally, removal of any offending agents that could be contributing to incontinence (benzodiazepines, narcotics, diuretics) should be considered.
REFERENCES


Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. BJU Int. 2007 Nov;100(5):987


Andersson K-E. How many drugs for LUTS due to BPH are too many? J Urol. 2008 Sep;180(3):811


Andersson KE, Appell R, Cardozo LD et al. The pharmacological treatment of urinary incontinence. BJU Int 1999 Dec;84(9):923


Andersson KE, Perhson R. CNS involvement in overactive bladder: pathophysiology and opportunities for pharmacological intervention. Drugs. 2003;63(23):2595

Andersson KE, Olshansky B. Treating patients with overactive bladder syndrome with antimuscarinics: heart rate considerations. BJU International 2007;100:1007

Andersson K-E, Persson K. The L-arginine/nitric oxide pathway and non-adrenergic, non-cholinergic relaxation of the lower urinary tract. 1993;Gen Pharmacol 24:833


Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2004 Dec;25(6):785


Arnold EP. Tamsulosin in men with confirmed bladder outlet obstruction: a clinical and urodynamic analysis from a single centre in New Zealand. BJU Int 2001;87(1):24


Bosch RJLH, Griffiths DJ, Blom JHM et al. Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. J Urol 1989;141:68

Boy S, Seif C, Braun PM et al. Retrospective Analysis of treatment outcomes and medical care of patients with neurogenic detrusor overactivity (NDO) receiving BOTOX therapy. European Urology Supplements, 2008;7(9):212

Brady CM, Apostolidis AN, Harper M et al. Parallel changes in bladder suburothelial vanilloid receptor TRPV1 and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int. 2004 Apr;93(6):770


Bump RC, Voss S, Beardsworth A et al. Long-term efficacy of...
Cardozo L, Castro-Diaz D, Gittelman M et al. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):512
Chapple C, Steers W, Norton P et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int. 2005 May;95(7):993
Chapple CR, Yamaguchi O, Ridder A et al. Clinical proof of concept study (Blossom) shows novel b3 adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms...


Corcos J, Casey R, Patrick A et al. A double-blind randomized dose-response study comparing daily doses of 5, 10 and 15 mg controlled-release oxybutynin: balancing efficacy with severity of dry mouth. BJU Int. 2006 Mar;97(3):520


Cruz F, Charrua A, Cruz C et al. GRC 1: A new oral TRPV1 antagonist, decreases the frequency of bladder reflex contractions and noxious input in rats with acute or chronic cystitis. Eur Urol 2008;Suppl 7(3):181.


de Groat WC, A neurologic basis for the overactive bladder. Urology. 1997 Dec; 50 (6A Suppl):36-52; discussion 53


De Guichenaere A, Vande Walle C, Van Sintjan P et al. Desmopressin resistant nocturnal polyuria may benefit from


Downie JW, Karmazyn M. Mechanical trauma to bladder epithelium liberates prostanooids which modulate neurotransmission in rabbit detrusor muscle. J Pharmacol Exp Ther 1984;230:445


Ensrud R, Deane CN, Glickman S. Systemic effects of intravesical atropline sulphate. BJU Int 2001;87:613


Finney SM, Anderson KE, Gillespie JI, Stewart LH. Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? BJU Int. 2006 Sep;98(3):503

Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. Psychopharmacol (Berl) 1992;107:437


Giardina EG, Bigger JT, Jr, Glassman AH et al. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979;60:1045

Grembycz MA. Life after PDE4: overcoming adverse events with...


Gillespie JL. Phosphodiesterase-linked inhibition of nonmicturition activity in the isolated bladder. BJU Int. 2004 Jun;93(9):1325


Gopalakrishnan M, Shie C-C. Potassium channel subtypes as molecular targets for overactive bladder and other urological disorders. Expert Opin Ther Targets 2004; 8: 437


Haaf B, Stewart L, Dwyer P, Darifenacin. an M3 selective receptor antagonist, is an effective and well-tolerated oncedaily treatment for overactive bladder. Eur Urol, 2004;45(4):420


Hegde SS. Muscarinic receptors in the bladder: from basic research to therapeutics. Br J Pharmacol 2006;147:S80


Hextall A, Bidmead J, Cardozo L et al. The impact of the menstrual cycle on urinary symptoms and the results of urodynamical investigation. BJOG 2001;108(11):1193


Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res, 1986;67:87
Kuo HC. Effectiveness of intravesical resiniferatoxin in treating detrusor hyper-reflexia and external sphincter dystonia in patients with chronic spinal cord lesions. BJU Int. 2003 Oct;92(6):597
Kuo HC. Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int. 2005 May;95(7):1023
Lee JY, Kim HW, Lee SJ et al. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int. 2004 Oct;94(6):817
Lee KS, Lee HW, Han DH. Does anticholinergic medication have a role in treating men with overactive bladder and benign prostatic hyperplasia? Naunyn Schmiedeberg's Arch Pharmacol. 2008 Jun;377(4-6):491
Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. Eur Urol. 2008 Apr;30
Liu HT, Kuo HC. Increased expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response to intravesical instillations of resiniferatoxin in patients with refractory idiopathic detrusor overactivity. BJU Int. 2007 Nov;100(5):1086
Lecci A, Maggi CA. Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. Regul Pept. 2001 Sep 15;101(1-3):1
Lose G, Norgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. BJU Int 2001;87:767
Madersbacher H, Halaska M, Voigt R et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int 1999;84:646
propiverine: influence of dosage forms and circadian-time rhythms. antimuscarinic effects of the urinary bladder spasmolytics


Matsui M, Griffin MT, Shethnaz D et al. Increased relaxant action of forskolin and isoproterenol against muscarinic agonist-induced contractions in smooth muscle from M2 receptor knockout mice. J Pharmacol Exp Ther 2003; 305:106


Michel MC, Barendrecht MM. Physiological and pathological regulation of the autonomic control of urinary bladder contractility. Pharmacol Ther 2008;117:297


Murakami S, Chapple CR, Akino H et al. The role of the urothelium in mediating bladder responses to isoprenaline. BJU Int. 2007 Mar;99(3):669


Nilvebrant L, Sparf B. Dicyclomine, benzhexol and oxybutynin distinguish between subclasses of muscarinic binding sites. Eur J Pharmacol 1986;123:133

Nishiguchi J, Kwon DD, Kaino Y et al. Suppression of detrusor overactivity in rats with bladder outlet obstruction by a type 4 phosphodiesterase inhibitor. BJU Int. 2007 Mar;99(3):680

Nitti VW. Botulinum toxin for the treatment of idiopathic and neurogenic overactive bladder: state of the art Rev Urol. 2006 Fall;8(4):198


Norhona-Blob L, Kachur JF. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 1991;256:562


Pehrson R, Andersson KE. Effects of tiagabine, a gamma-aminobutyric acid re-uptake inhibitor, on normal rat bladder function. J Urol. 2002 May;167(5):2241


Sheldon JH, Norton NW, Argentieri TM. Inhibition of guinea pig detrusor contraction by NS-1619 is associated with activation of BKCa and inhibition of calcium currents. J Pharmacol Exp Ther 1997; 283: 1193.


Staskin DR, Te AE. Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. BJU Int. 2006 Jun;97(6):1256


Steers WD, Herschorn S, Kreder KJ et al. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. BJU Int. 2007 Aug;100(2):337


Striano P, Striano S. Gabapentin: a Ca2+ channel alpha 2-delta ligand far beyond epilepsy therapy. Drugs Today (Barc). 2008 May;44(5):353


Tokuno H, Chowdhury JU, Tomita T. Inhibitory effects of propiverine on rat and guinea-pig urinary bladder muscle. Naunyn-Schmiedeberg’s Arch Pharmacol, 1993;348:659


Truss MC, Stief CG, Uckert S et al. Phosphodiesterase 1 inhibition
Vari E, Cardozo LD. Urethral instability: diagnosis based on the relevance of cyclic nucleotide phosphodiesterase isoenzymes in normal human detrusor muscle to various spasmolytic drugs commonly used in the treatment of the overactive bladder. Arzneimittelforschung, 2000;50(5):456
Wehnert J, Sage S. Comparative investigations to the action of Mictonorm (propiverin hydrochloride) and Spasuret (flavoxat hydrochloride) on detrusor vesicae. Z Urol Nephrol, 1989;82:259
Womack KB, Heilman KM. Tolterodine and memory: dry but forgetful. Arch Neurol 2003;60:771
Yamaguchi O, Marui E, Kakizaki H et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int. 2007 Sep;100(3):579


Committee 9

Diagnosis and Management of Urinary Incontinence in Childhood

Chairman
S. TEKGUL (Turkey)

Members
R. JM NIJMAN (The Netherlands),
P. HOEBEKE (Belgium),
D. CANNING (USA),
W.BOWER (Hong-Kong),
A. VON GONTARD (Germany)
## CONTENTS

<table>
<thead>
<tr>
<th>A. INTRODUCTION</th>
<th>E. NEUROGENIC DETRUSOR SPHINCTER DYSFUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. EVALUATION IN CHILDREN WHO WET</td>
<td>F. SURGICAL MANAGEMENT</td>
</tr>
<tr>
<td>C. NOCTURNAL ENURESIS</td>
<td>G. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE AND ENURESIS IN CHILDREN</td>
</tr>
<tr>
<td>D. DAY AND NIGHTTIME INCONTINENCE</td>
<td></td>
</tr>
</tbody>
</table>

702
In this chapter the diagnostic and treatment modalities of urinary incontinence in childhood will be discussed. In order to understand the pathophysiology of the most frequently encountered problems in children the normal development of bladder and sphincter control will be discussed.

The underlying pathophysiology will be outlined and the specific investigations for children will be discussed. For general information on epidemiology and urodynamic investigations the respective chapters are to be consulted.

Normal bladder storage and voiding involve low-pressure and adequate bladder volume filling followed by a continuous detrusor contraction that results in bladder emptying, associated with adequate relaxation of the sphincter complex. This process requires normal sensation and normal bladder outlet resistance. The neurophysiological mechanisms involved in normal bladder storage and evacuation include a complex integration of sympathetic, parasympathetic and somatic innervations which is ultimately controlled by a complex interaction between spinal cord, brain stem, midbrain and higher cortical structures [1].

Achievement of urinary control is equally complex and as yet not fully understood: various developmental stages have been observed [2].

In newborns the bladder has been traditionally described as "uninhibited", and it has been assumed that micturition occurs automatically by a simple spinal cord reflex, with little or no mediation by the higher neural centres. However, studies have indicated that even in full-term foetuses and newborns, micturition is modulated by higher centres and the previous notion that voiding is spontaneous and mediated by a simple spinal reflex is an oversimplification [3]. Foetal micturition seems to be a behavioural state-dependent event: intrauterine micturition is not randomly distributed between sleep and arousal, but occurs almost exclusively while the foetus is awake [3].

During the last trimester the intra-uterine urine production is much higher than in the postnatal period (30ml/hr) and the voiding frequency is approximately 30 times every 24 hours [4].

Immediately after birth voiding is very infrequent during the first few days of life. The first void may only take place after 12 to 24 hours. After the first week frequency increases rapidly and peaks at the age of 2 to 4 weeks to an average of once per hour. It then decreases and remains stable after 6 months to about 10 to 15 times per day. After the first year it decreases to 8 to 10 times per day, while voided volumes increase by three to fourfold.

During the postnatal period, micturition control mechanisms undergo further changes and extensive modulation. Using ambulatory bladder monitoring techniques in conjunction with polysomnographic recordings it has been shown that even in newborns the bladder is normally quiescent and micturition does not occur during sleep [5].

This inhibition (or lack of facilitation) of detrusor contractions during sleep is also observed in infants with neurogenic bladder dysfunction who have marked
detrusor overactivity while they are awake. In response to bladder distension during sleep, an infant nearly always exhibits clear electro-encephalographic evidence of cortical arousal, facial grimaces or limb movements, or actual awakening. Sleeping infants are always seen to wake up before the bladder contracts and voiding occurs. This arousal period may be transient and the infant may cry and move for a brief period before micturition and then shortly afterward go back to sleep. Because this waking response is already well established in newborns, it follows that the control of micturition probably involves more complicated neural pathways and higher centres than has been appreciated. There is also strong evidence that a pronounced reorganisation of pre-existing synaptic connections and neural pathways involved in bladder control occurs during the early postnatal period.

In newborns micturition occurs at frequent intervals and may have an intermittent pattern although bladder emptying efficiency is usually good. In over 80 percent of voids the bladder empties completely [6].

During infancy voiding pressures are much higher than in adults. It has also been noted that these pressures are higher in boys than in girls (mean pdet max of 118 vs. 75 cm H2O, respectively) [7,8]. These higher detrusor pressures decrease progressively with increasing age. In up to 70 percent of infants (up to the age of 3 years) with normal lower urinary tracts, intermittent patterns of voiding were observed. They tend to disappear with increasing age, and are thought to represent variations between individual infants in the maturation of detrusor and sphincteric co-ordination during the first 1 to 2 years of life. Videourodynamic studies have confirmed these findings [5,7,8,9,10].

Between the age of 1 and 2, conscious sensation of bladder filling develops. The ability to void or inhibit voiding voluntarily at any degree of bladder filling commonly develops in the second and third years of life. Central inhibition is crucial to obtain continence.

During the second and third year of life, there is progressive development towards a socially conscious continence and a more voluntary type of micturition control develops. The child becomes more aware of the sensation of bladder distension and the need to urinate, as well as social norms and embarrassment associated with urinary incontinence. Through an active learning process, the child acquires the ability to voluntarily inhibit and delay voiding until a socially convenient time, then actively initiate urination even when the bladder is not completely full, and allows urination to proceed to completion. During the first years of life, gradual development to an adult type of voluntary micturition control that conforms to the social norms depends on an intact nervous system, in addition to at least three other events occurring concomitantly:

- a progressive increase in functional storage capacity,
- maturation of function and control over the external urinary sphincter,
- and most importantly achievement of volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit a micturition reflex [11].

The final steps are usually achieved at the age of 3 to 4 years when most children have developed the adult pattern of urinary control and are dry both day and night. The child has learned to inhibit a micturition reflex and postpone voiding and voluntarily initiate micturition at socially acceptable and convenient times and places. This development is also dependent on behavioural learning and can be influenced by toilet training, which in turn depends on cognitive perception of the maturing urinary tract.

It is understandable that this series of complex events is highly susceptible to the development of various types of dysfunction. Various functional derangements of the bladder-sphincter-perineal complex may occur during this sophisticated course of early development of normal micturition control mechanisms. These acquired “functional” disorders overlap with other types of bladder functional disturbances that may have a more organic underlying pathophysiological basis.

II. NORMAL VALUES

1. NORMAL BLADDER CAPACITY

The bladder capacity increases during the first 8 years of life roughly with 30 ml per year, so with an average capacity of 30 ml in the neonatal period, a child’s bladder volume can be calculated as Y = 30 + 30 X, where Y = capacity in ml and X = age in years (Figure 1) [12].

Hjälmås described a linear correlation that could be used up to 12 years of age: in boys, Y = 24.8 X + 31.6, in girls Y = 22.6 X + 37.4, where Y is capacity in ml, and X is age in years [13].

It should be noted that these data were obtained during cystometric investigations. Cystometric capacity is generally less than normal bladder volumes. Obviously, the relation between age and bladder capacity is not linear for all ages, nor is the relation between body weight and bladder capacity [14].

Another formula to calculate bladder capacity in infants is: bladder capacity (ml) = 38 + (2.5 x age (mo)) [10].
Kaefer and co-workers demonstrated that a non-linear model was the most accurate for the relation between age and bladder capacity, and they determined two practical linear equations:

\[ Y = 2X + 2 \text{ for children less than 2 years old}, \]
\[ Y = \frac{X}{2} + 6 \text{ for those 2 years old or older}; \]

\( Y \) = capacity in ounces, \( X \) = age in years (Figure 2) [15].

None of these formulas have been acquired from a population-based study and do not reflect normal bladder capacity. Normal bladder capacity should be regarded as the maximum voided volume of urine and shows huge variation.

Girls were found to have a larger capacity than boys, but the rate of increase with age was not significantly different between them. Data on ‘normal’ bladder capacity have been obtained in continent children undergoing cystography, with retrograde filling of the bladder.

Data obtained from the International Reflux Study indicate that there is not a linear relation between age and capacity and that there is a huge variability (Figure 3).

2. NORMAL VOIDING

The micturition frequency of the foetus during the last trimester is approximately 30 per 24 hours. It decreases to 12 during the first year of life, and after that it is gradually reduced to an average of 5±1 voidings per day [10, 15].

The normal range for the micturition frequency at age seven is 3 to 7 [16].

By age 12, the daily pattern of voiding includes 4-6 voids per day [17].

Mattson and Lindström emphasize the enormous variability of voiding frequencies in children: also in individual children, the weight-corrected diuresis could vary up to 10-fold [18].

![Figure 1: Bladder capacity using the formula Y = 30 + 30X (Y = capacity in ml, X = age in years)](image1)

![Figure 2: Bladder capacity using the formula Y = (2X + 2) x 28.35 ml < 2 years Y = (X/2+6) x 28.35 ml > 2 years (Y = capacity in ml, X is age in years)](image2)

![Figure 3: Bladder capacities determined by VCUG in the International Reflux Study](image3)
3. NORMAL VOIDING PRESSURES

Bladder dynamics in children have demonstrated developmental changes with age. Detrusor pressures at voiding in children are similar to adults, with a mean maximum pressure of 66 cm H₂O in boys, and 57 cm H₂O in girls [19].

These pressures are lower than those reported in infancy by Yeung et al, who found boys having pressures of 118 cm H₂O and girls 75 cm H₂O [5].

4. NORMAL URINARY FLOW RATES

Urinary flow rates in normal children have been only minimally described. Szabo et al published nomograms for flow rates vs. age in normal children [20].

As in adults, flow rates are clearly dependent upon voided volume, and normal values can only be applied to flow rates that have been registered when voiding at a bladder volume approximating the normal capacity for age [18,21].

B. EVALUATION IN CHILDREN WHO WET

Even with clear definitions, the approach to history-taking and physical examination has to be structured. The child’s complaints at presentation are not synonymous with the signs and symptoms that have to be checked to arrive at a diagnosis. Also, sociocultural aspects and psychomotor development will distort the presentation. Validated questionnaires are very helpful in structuring the history-taking; they at least provide checklists [1].

With a structured approach the diagnosis of monosymptomatic nocturnal enuresis can be made with confidence.

When ultrasound imaging of kidneys and bladder, recording of urinary flow, and measurement of post-void residual are added to history and physical examination, the clinical entities caused by non-neurogenic detrusor and pelvic floor dysfunction can be diagnosed accurately in the majority of cases, and a high level of suspicion can be maintained towards incomplete bladder emptying in both neurogenic pelvic floor dysfunction and structurally caused incontinence. This is important in view of the potential these conditions have to cause irreversible loss of kidney function.

In a minority of incontinent children the non-invasive assessment yields equivocal results, or results suggesting gross deviations from normal function. Only in these situations is there an indication for invasive investigations, such as:

- Invasive urodynamics (cystometry, pressure/flow/EMG studies, videocystometry).
- Renal scans or intravenous urography.
- Cystourethroscopy.

I. HISTORY TAKING

For the paediatric age group, where the history is jointly obtained from parents and child, and where the failure to develop bladder control generates specific problems, a structured approach is recommended, with a questionnaire [1,2].

Level of evidence: 3. Grade of recommendation: B

Many signs and symptoms related to voiding and wetting are new to the parents, and they should be specifically asked for, using the questionnaire as checklist. If possible the child should be addressed as the patient and questioned directly, as the symptoms prompting the parents to seek consultation may be different from those are problematic for the child.

A voiding diary is mandatory to determine the child’s voiding frequency and voided volumes. Checklists and frequency volume chart can be filled out at home, and checked at the first visit to the clinics. History-taking should also include assessment of bowel function; a similar pro-active process using a questionnaire should be followed for defecation and faecal soiling [3].

The general history-taking should include questions relevant to familial disorders, neurological and congenital abnormalities, as well as information on previous urinary infections, relevant surgery and menstrual and sexual functions (in pubertal and older children). Information should be obtained on medication with known or possible effects on the lower urinary tract.

At times it is helpful to more formally evaluate the child’s psychosocial status and the family situation, e.g. using validated question forms such as CBCL (Achenbach) or the Butler forms [4,5].

Child abuse is very often signalled first by symptoms of vesico-urethral dysfunction [6].

At present there are no validated questionnaires to diagnose the cause of incontinence in children.

Level of evidence: 4. Grade of recommendation: C

II. PHYSICAL EXAMINATION

Apart from a general paediatric examination, the physical examination should include the assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S1-S4 (standing on toes,
bulbocavernosus) and anal sphincter tone and control. Special attention should be paid to inspection of the male or female genital region, and of the urethral meatus. Asymmetry of buttocks, legs or feet, as well as other signs of occult neurospinal dysraphism in the lumbosacral area (subcutaneous lipoma, skin discoloration, hair growth and abnormal gait) should be looked for specifically [7].

In examining the abdomen for the presence of a full bladder, full sigmoid or descending colon which is a significant finding with a history of constipation.

Detailed questioning of the parents’ observation of the child’s voiding habits is essential as is direct observation of the voiding, if possible. Children may have their voiding dysfunction ameliorated or even eliminated by correcting anomalies of body position detected when observing the child’s micturition. Children may void in awkward positions, e.g. with their legs crossed or balancing on the toilet without proper support of the legs, thereby preventing the pelvic floor relaxation and obstructing the free flow of urine [8] (Figure 4).

Level of evidence: 4. Grade of recommendation: D

III. URINALYSIS

In order to be comprehensive, physical examination should include urinalysis to identify patients with urinary tract infection, diabetes mellitus, diabetes insipidus and hypercalciuria if indicated [9].

IV. NON-INVASIVE DIAGNOSTIC TECHNIQUES

1. FREQUENCY / VOLUME CHARTS: BLADDER DIARY

The frequency/volume chart is a detailed diary recording each void by time and urine output over 24-hour periods. The chart gives objective information on the number of voidings, the distribution of day and night voids, along with the voided volumes and episodes of urgency and leakage, or dribbling. In order to obtain a complete picture, defecation frequency and/or soiling are often also recorded. Then, this becomes termed as bladder-bowel diary due to its complexity.

From the frequency/volume chart the child’s “functional” bladder capacity may be assessed as the largest voided volume, with the exception of the morning micturition, which actually represents nighttime bladder capacity. Whenever possible, filling out the chart is the responsibility of the child: the parents provide assistance and support. Ideally the chart should cover 3 complete days, but in reality completion over a weekend restricts the record to 2 days.

The frequency volume chart is a reliable non-invasive measure of maximum bladder storage capacity and can be used as an outcome measure in children with bladder dysfunction if care is taken to minimise confounding factors and sources of error during chart completion [10].

The amount of urine voided by a non-supervised child during the day varies considerably since the child’s voidings are dictated more by social circumstances and/or bladder activity rather than by bladder capacity. Children with bladder symptoms void smaller volumes of urine than may be expected from traditional estimates [10]. This is unrelated to either gender, type of presenting incontinence or a positive family history of bladder dysfunction. The only significant influence upon voided volumes recorded on a frequency volume chart is the age effect, and voided volumes, even in incontinent children, increase incrementally with age. The frequency volume chart is useful when comparing the mean voided volume and standard deviation by a child’s age.

Figure 4: Improper position for voiding: the feet are not supported (unbalanced position) and the body is bent forward. Support of the feet will correct this and will allow the pelvic floor muscles to relax properly.
Validation and test/retest data on frequency/volume charts whilst scarce indicate that voiding interval is the most variable parameter. Data in normal children and in children with different categories of incontinence are available for comparison [10-12].

In order to obtain a complete picture it is better to ask for a bladder diary: fluid intake as well as voiding frequency, voided volumes, incontinence episodes and defecation frequency and/or soiling are recorded.

Test/retest evaluation is not available; trend analyses of frequency/volume charts can be extracted from currently available data.

Level of evidence: 3. Grade of recommendation: B

2. QUANTIFICATION OF URINE LOSS

Subjective grading of incontinence may not indicate reliably the degree of dysfunction. For objective grading, 12-hour pad test and frequency/volume charts are validated instruments [12-14].

In children, the 12-hour pad test should also give information about fluid intake. The pad test is complementary to the bladder diary, which denotes more the frequency of incontinence and the distribution of wetting episodes than the quantities of urine lost.

The amount of urine lost during sleep can be determined by weighing diapers or absorbent pads, before and after sleep. To obtain a measure of the total nocturnal urine output, the volume of the early-morning voiding should be added to the amount lost during sleep.

3. SCORING SYSTEMS

At present two scoring systems, based on validated questionnaires have been described. Specific scores correlated with lower urinary tract dysfunction with a specificity and sensitivity of about 90% [15,16].

The value of these scoring systems to determine the cause of incontinence seems to be of limited value to the individual patient, but can be very useful in studies to determine and compare treatment outcome.

Level of evidence: 3. Grade of recommendation: C

4. QUANTIFICATION OF CONSTIPATION

Scoring a plain X-ray of the abdomen (Barr score) yields inconsistent results in grading constipation. [17-19] Reproducibility seems to be best using the method described by Leech [20-22].

A better way to match clues from the medical history with signs and symptoms is the measurement of colonic transit time. As many children with non-neurogenic detrusor and pelvic floor dysfunction habitually use their pelvic floor as an “emergency brake”, anomalous defecation frequency and constipation have a high prevalence in this group.

A non-invasive way to determine fecal retention is the estimation of rectal diameter on ultrasound. In children without constipation the mean diameter was 2,4 and 2,1 cm in two different studies respectively [23-24]. In children with constipation the rectal diameter was on average 3,4 cm in one and 4,9 in the second study. Both studies do not mention specificity nor sensitivity. Finding a dilated and filled rectum on ultrasound while the child feels no need to defecate probably can replace a digital rectal examination.

Overt constipation should be dealt with before embarking on treatment of incontinence or detrusor and pelvic floor dysfunction [25,26].

Level of evidence 3. Grade of recommendation: B

5. URINARY FLOW

Voiding should be analysed in detail in all incontinent children with the exception of monosymptomatic bedwetting where voiding, as far as we know, is normal.

Graphic registration of the urinary flow rate during voiding is a standard office procedure. Flow patterns and rates should be repeated to allow for evaluation, and several recordings are needed to obtain consistency.

Approximately 1% of school children have a voiding that can be labelled abnormal with flattened or intermittent flow curves. The remaining 99% have a bell-shaped flow curve [27]. It should be noted that a normal flow does not exclude a voiding disturbance, nor does an abnormal flow pattern automatically means a bladder or voiding dysfunction, as in asymptomatic normal school children abnormal patterns were also found [28,29].

Flow recordings with a voided volume of less than 50% of the functional capacity are not consistent: they represent voiding on command, and many children will try to comply by using abdominal pressure. A helpful tool in this respect is the bladder scan: before micturition the bladder volume can be assessed [30,31]. If the bladder is still nearly empty the child should be asked to drink some water until the bladder is full enough for a reliable flow.

Urinary flow may be described in terms of rate and pattern and may be continuous, intermittent (in fractions), or fluctuating. An intermittent flow pattern shows a interrupted flow, whereas in fluctuating voiding the flow does not stop completely, but fluctuates due to incomplete relaxation of the sphincter.

Measurement of urinary flow is performed as a solitary procedure, with bladder filling by diuresis (spontaneous or forced), or as part of a pressure/flow study, with bladder filling by catheter. Patterns and rates should be consistent to allow for evaluation, and several recordings are needed to obtain consistency [32].
The same parameters used to characterise continuous flow may be applicable, if care is exercised, in children with intermittent, or fluctuating flow patterns (Figures 5 -7). In measuring flow time, the time intervals between flow episodes are disregarded. Voiding time is total duration of micturition, including interruptions.

Level of evidence: 3. Grade of recommendation: B

6. ULTRASOUND IMAGING OF UPPER AND LOWER URINARY TRACT

In most clinical settings, ultrasound-imaging techniques are routinely used in children with incontinence. Upper tract abnormalities such as duplex kidney, dilatation of the collecting system, and gross reflux nephropathy can be readily detected, but detection of the more subtle expressions of these abnormalities require urological expertise on the part of the ultrasound operator [33].

Lower urinary tract abnormalities are even more difficult to assess for the inexperienced, aside from bladder wall thickness: a bladder wall cross-section of more than 3-4 millimetres, measured at 50% of expected bladder capacity, is suspicious of detrusor overactivity [34,35]. Because only a few studies have been conducted to compare bladder wall thickness in normal children without complaints and in children with lower urinary tract dysfunction, more studies need to be performed to validate these non-invasive techniques [36, 37].

Another possibility is to assess bladder volume and bladder wall thickness to calculate the Bladder Volume / Bladder Wall Thickness index. In children with nocturnal enuresis this index correlated well with response to treatment [38].

a) Post-void residual volume

Except in small infants, the normal bladder will empty completely at every micturition [39].

The identification or exclusion of post-void residual is therefore an integral part of the study of micturition. However, an uneasy child voiding in unfamiliar
surroundings may yield unrepresentative results, as may voiding on command with a partially filled or overfilled bladder. When estimating residual urine, voided volume and the time interval between voiding and estimation of post-void residual should be recorded. This is of particular importance if the patient is in a diuretic phase. In patients with gross vesicoureteral reflux, urine from the ureters may enter the bladder immediately after micturition and may falsely be interpreted as residual urine. The absence of residual urine is an observation of clinical value, but does not exclude bladder outlet obstruction or detrusor pelvic floor dysfunction with absolute certainty. An isolated finding of residual urine requires confirmation before being considered significant, especially in infants and young children.

b) Ultrasound-flow-ultrasound

This combination of imaging and non-invasive urodynamics is a standardised procedure used to obtain representative data on flow rate and flow pattern, as well as post-void residual volumes. With ultrasound, bladder filling is assessed and when the bladder capacity is equal to the functional or expected bladder capacity for age, the child is asked to void into the flowmeter. After recording the flow, post-void residual is assessed again. This procedure avoids the registration of flow rates at unrealistic bladder volumes.

Alternatively children can be asked to use a flowmeter at home: a special flowmeter has been designed to use at home [40]. Because some children have difficulty voiding in a strange environment, this option can overcome this.

7. INVASIVE DIAGNOSTIC TECHNIQUES

The important question (for the incontinent child) “whether invasive diagnostic procedures are necessary” is decided by the results of the non-invasive procedures.

At present there are no studies indicating that a VCUG is useful in children with incontinence, but without urinary tract infections.

In general urodynamic studies will only be done if the outcome will alter the management, and this will also depend on whether the possible treatments being considered are invasive. The diagnostic information needed is that which is necessary to find the correct treatment. Indicators include, straining or manual expression during voiding, a weak urinary stream, previous febrile urinary tract infection, continuous dribbling incontinence or pronounced apparent stress incontinence, or previously identified dilating vesicoureteral reflux.

The finding of genitourinary abnormalities or signs of occult spinal dysraphism at physical examination also indicate the need for further diagnostics. Urinary flow registration will detect the plateau-shaped flow curve typical for structural bladder outlet obstruction, and an intermittent flow suggesting detrusor–sphincter-pelvic floor dys-coordination [32].

A clinically significant post-void residual on repeated occasions clearly points to incomplete bladder emptying. The pad test will detect the cases with obvious stress and urgency incontinence, or continuous dribbling. Ultrasound imaging will raise suspicion of an ectopic ureter.

In short, invasive diagnostics are indicated when the non-invasive testing raises suspicion of neurogenic detrusor-sphincter dysfunction (occult spinal dysraphism), obstruction (especially posterior urethral valves), genitourinary abnormalities (e.g. epispadias), advanced non-neurogenic detrusor-sphincter-pelvic floor dysfunction (as in children with vesicoureteral reflux and upper tract dilatation and/or febrile urinary tract infections), or significant post void residuals.

To diagnose the complex of non-neurogenic detrusor-sphincter dysfunction, recurrent urinary tract infections and vesicoureteral reflux, urodynamic studies are needed in only a minority of all incontinent children.

a) Voiding cystourethrogram (VCUG)

1. TECHNIQUE OF VCUG IN CHILDREN

Cleanse and rinse the external genitalia with lukewarm water: do not use detergents. Use a feeding tube with side holes and a rounded tip (Ch 06-08) or balloon catheter to catheterise the bladder; check the urine for infection. Empty the bladder completely before filling. Use a radio-opaque dye of maximum 30% concentration, at body temperature, and fill the bladder by slow-drip infusion, with a hydrostatic pressure of not more than 40 cm H₂O. Note the volume of the contrast medium instilled. Use fluoroscopy during filling at regular intervals.

Take spot-films (70mm or 90mm camera) with the child in supine position, with partial filling and at the end of filling, in AP projection, of the complete urinary tract. Upper tracts and lower tract should be visible.

When voiding is imminent, change the position of the child so that spot films of bladder and urethra in 3/4 projection can be taken during voiding. Also take a spot film of the upper urinary tract during voiding, as the degree of vesicoureteral reflux (VUR) may change with the pressure generated by the detrusor muscle during voiding. Post-void residual volumes vary very considerably with VCUG. The voiding phase is critically important to VCUG, both for reflux detection and for assessment of voiding dynamics. Without a voiding phase the VCUG is incomplete.
Prophylactic antibiotics are indicated in all children, to minimise the risk for post-VCUG urinary tract infection especially in children with an anatomic abnormality.

2. INDICATIONS FOR VCUG

A VCUG is an invasive procedure and should only be done if the outcome will influence the management. It is indicated in children with recurrent urinary tract infections in order to detect reflux and in children with an abnormal flow pattern to detect bladder outlet abnormalities (like valves, strictures or a syringocele). Presence of hydronephrosis on ultrasound investigation will certainly obviate the need for this investigation.

In children with incontinence the lateral projection during voiding is the most important part of the study. Especially in children with stress incontinence or a neurogenic bladder the position and configuration of the bladder neck during filling and voiding should be noted.

In children with non-neurogenic detrusor-sphincter-pelvic floor dysfunction as well as in children with neurogenic detrusor-sphincter dyssynergia, the proximal urethra may show the so-called ‘spinning top’ configuration, during filling and during voiding. With detrusor and pelvic floor muscles contracting at the same time, the force of the detrusor contraction will dilate the proximal urethra down to the level of the forcefully closed striated external sphincter.

The resulting ‘spinning top’ configuration used to be seen as a sure sign of distal urethral stenosis, a concept held responsible for recurrent urinary tract infections in girls, with urethral dilatation or blind urethrotomy as the obvious therapy. However, urodynamics made it clear that the ‘spinning top’ will only appear when detrusor and pelvic floor contract synchronously, which makes it a functional anomaly, not an anatomical one [41,42].

Women often recall their experience with VCUG as not an anatomical one [41,42].

In children urodynamic investigations should only be performed if the outcome will have consequences for treatment [43,44]. Furthermore like VCUG it may be considered when invasive or surgical interventions are planned. The main question is whether the urodynamic study will provide new information that cannot be obtained otherwise and will influence the further management. From the few studies that have addressed this issue it can be concluded that urodynamic studies in the majority of cases do not provide significant additional information to justify this type of investigation as a routine procedure in children [45-47].

Both children and parents need careful preparation and adequate information before the study is done. It is an invasive procedure and artefacts may occur. Because of the invasiveness of the investigations all children are anxious and this may be reflected in the outcome of the study. Especially during the first filling cycle, when the child does not know what to expect, detrusor overactivity may be seen and the voiding phase can be incomplete due to contraction or incomplete relaxation of the pelvic floor muscles during voiding.

Once the child knows that filling and voiding are not painful a subsequent filling and voiding cycle may show a completely different pattern. The study should be repeated at least 2 or 3 times. Only if during the first filling cycle, no detrusor contractions are seen and also the voiding phase is in accordance with history and uroflow, it is probably sufficient to do only one complete filling and voiding cycle [48].

Still the results may not always be reproducible and it should be stressed that the primary objective is to treat the child and not a “urodynamic abnormality” per se.

Special attention should be given to a pleasant surrounding for the child: one or both parents should be present and young children may be given a bottle. Older children may be distracted by watching a video movie. The child should be awake, unanaesthetised and neither sedated nor taking any drugs that affect bladder function.

During the study the investigator has the opportunity to observe the child and discuss various findings and correlate them to what the child feels and/or normally would do in such circumstances.

In children, the transition from filling phase to voiding phase is not as marked as in adults. To avoid missing this important transition, cystometry and pressure-flow/EMG measurements are performed as one continuous study in paediatric urodynamics.

Electromyography of the pelvic floor muscles is assumed to evaluate the activity of the striated urethral sphincter, in the filling phase and in the voiding phase. Surface skin electrodes are usually used to record the EMG. In children the pelvic floor EMG is probably of much more importance than in adults as it helps to differentiate the different voiding disorders.

Filling the bladder can be achieved by diuresis (natural
fill cystometry) or retrograde by catheter. For retrograde filling by catheter, saline 0.9% or contrast medium at body temperature is recommended in children. Especially in young children some urodynamic parameters, such as capacity and detrusor activity are influenced by the temperature of the filling fluid. Although the clinical relevance is as yet unknown, it is recommended to fill the bladder with fluid of body temperature [49].

When filling by catheter, slow fill cystometry (5 – 10 percent of expected bladder capacity per minute, or < 10ml/min) is recommended in children, as certain cystometric parameters, notably compliance, may be significantly altered by the speed of bladder filling.

Involuntary detrusor contractions may be provoked by rapid filling, alterations of posture, coughing, walking, jumping, and other triggering procedures.

The presence of these contractions does not necessarily imply a neurologic disorder. In infants, detrusor contractions often occur throughout the filling phase.

Bladder sensation is difficult to evaluate in children. Only in toilet-trained cooperative children is it a relevant parameter. Normal desire to void is not relevant in the infant, but can be used as a guideline in children of 4 years and older. Normal desire to void should be considered the volume at which some unrest is noted, e.g. wriggling the toes; this usually indicates voiding is imminent.

In the older child, the volume may be small with the first cystometry, for fear of discomfort. Also involuntary detrusor contractions occur more often during the first filling cycle (49). This is the reason that in paediatric urodynamics at least two cycles of filling are recommended.

Maximum cystometric capacity (MCC) is the volume in the bladder at which the infant or child starts voiding. The value for maximum cystometric capacity is derived from volume voided plus residual volume. Values for MCC should be interpreted in relation to normal values for age.

Compliance indicates the change in volume for a change in pressure. For children with neurogenic detrusor-sphincter dysfunction, data are available relating poor compliance to the risk of upper urinary tract damage [51].

The urethral closure mechanism during storage may be normal or incompetent. The normal urethral closure mechanism maintains a positive urethral closure pressure during filling, even in the presence of increased abdominal pressure or during detrusor overactivity (guarding reflex) [50].

Immediately prior to micturition the normal closure pressure decreases to allow flow.

Bladder outlet obstruction, recorded with a pressure / flow study, may be anatomical or functional in nature. An anatomical obstruction may be present at the bladder neck or in the urethra as a stricture or a stenosis and there is a small and fixed urethral diameter that does not dilate during voiding. As a result, the flow pattern is plateau shaped, with a low and constant maximum flow rate, despite high detrusor pressure and complete relaxation of the urethral sphincter. In a functional obstruction, it is the active contraction of the urethral sphincter or pelvic floor during passage of urine, that creates the narrow urethral segment as a constant or intermittent obstruction. To differentiate anatomical from functional obstruction, information is needed about the activity of the urethral sphincter during voiding.

This information can be obtained, and recorded together with pressure and flow, by monitoring the urethral pressure at the level of the urethral sphincter, or by recording a continuous electromyogram of the pelvic floor as in clinical practice the urethral sphincter is not readily accessible and the electromyogram of the external anal sphincter is often used to monitor activity of the striated urethral sphincter.

This corresponds to activity of the pelvic floor muscles. Also the use of video urodynamics can be very helpful in this respect, as contractions of the pelvic floor muscles can actually be seen during the voiding phase (Figure 8 and 9).

In infants and small children, pelvic floor muscle overactivity during voiding (with post-void residuals) is not uncommon: in all probability it is a normal developmental feature [52,53].

c) Cystoscopy

In by far the majority of children cystoscopy is not indicated. In boys with therapy resistant incontinence, an abnormal flow pattern, especially in combination with a history of (recurrent) urinary tract infection is suspicious of infra-vesical obstruction such as bladder neck obstruction, urethral valves, syringocele etc. A VCUG may not always show these abnormalities and pressure flow curves may be equivocal [55].

In girls the flow may be directed upward, indicating an abnormal meatal position or stenosis. A dorsal meatotomy generally solves this problem. It has been postulated that in girls the abnormal direction of the stream triggers the bulbocavernosus reflex resulting in dysfunctional voiding [56].
Figure 8: Urodynamic study illustrating involuntary detrusor contractions, counter action of pelvic floor muscles (guarding reflex) and incomplete pelvic floor relaxation during voiding resulting in post void residual urine (detrusor overactivity + dysfunctional voiding) [50].

Figure 9: Classification of urinary incontinence in children.

(Over)activity of the urethral sphincter-pelvic floor may occur during the voiding contraction of the detrusor in neurologically normal children; this set of events is termed dysfunctional voiding.

Grade of recommendation: for all diagnostic procedures level B
C. NOCTURNAL ENURESIS

I. DEFINITION

Nocturnal enuresis (NE) is involuntary voiding of urine during sleep, at least three times a week, in children over 5 years of age in the absence of congenital or acquired defects of the central nervous system [1]. Parental concern and child distress affect the clinical significance of the problem [2].

While most children who wet at night after age five are considered nocturnal enuretics, the child's development level is also important. The age criterion of five is arbitrary but reflects the natural course of achieving bladder control [4]. Verhulst et al argue for flexibility due to different age at which boys develop nighttime continence compared with girls [4]. Extrapolation from Verhulst's figures suggests that the prevalence of nighttime wetting for 8-year-old boys equals that for girls at 5 years [4].

Monosymptomatic NE is bedwetting without daytime symptoms. Non-monosymptomatic or polysymptomatic NE describes children with both day and nighttime wetting [5].

II. SEVERITY

Nocturnal enuretics vary in wetting frequency. Although fifteen percent wet each night, most children wet less frequently [4,6]. In a population survey of nearly 1,800 Irish children aged 4 –14 years, Devlin found the frequency of wetting as follows: less than once per week in 33 percent, once per week in 11 percent and 2 to 4 times per month in 25 percent [7]. Some children and parents are concerned about an occasional wet bed, while others accept regular wetting. Clinically severity can be defined as: infrequent (1-2 wetting episodes per week), moderately severe (3 – 5 wetting episodes per week) or severe (6 – 7 wetting episodes per week) [7].

III. PREVALENCE

Bedwetting is common. In the United Kingdom, estimates approximately 750,000 children and young people over 7 years regularly wet the bed. In the United States 5 to 7 million children regularly experience primary NE [8,9,10].

The prevalence of bedwetting varies regionally. In China, where parents take children out of diapers earlier, bedwetting seems to resolve more quickly. For example, in a large survey from Shandon, the proportion of children attaining nocturnal urinary control before age 2 was 7.7%; by age 3, this had increased to 53.1%, and by age 5 to 93%. The overall prevalence of NE was 4.3%, with a significantly higher prevalence in boys than girls. There was no additional decrease in the prevalence of enuresis between 6 and 16 years [11]. This suggests that structured awakening and toileting is effective treatment for monosymptomatic NE, even in small children.

Bedwetting becomes less common with advancing age. In the West, 15 per cent of children each year develop nocturnal bladder control (12). By adulthood, bedwetting is rare. Hirasing et al sampled over 13,000 adults [18-64 years] and found an overall prevalence rate of NE at 0.5% (13). Of these, 12 percent of men and 29 percent of women had daytime incontinence. Despite persistence of wetting into adulthood, 50 percent of men and 35 percent of the women never seek help for their problem. The enuresis prevalence of 0.5% in otherwise healthy adults in Hirasing's study refers to a largely untreated population. Fifty percent of the men had primary enuresis and had never been consistently dry at night. Assuming a prevalence of enuresis of 8 percent in 7-year-old boys, the risk for an enuretic boy to remain so for the rest of his life is 3 percent [12,14].

Many believe adult enuretics represent a “hard core” group with worse symptoms. These individuals are likely to have associated diurnal enuresis or voiding symptoms. One study included 18 males and 29 females with a mean age of 20 years with persistent NE. Of these patients 37 (79%) had moderate or severe symptoms and 17 (38%) also had daytime urinary symptoms. Thirty patients had urodynamics including 12 males and 16 females (93%) with detrusor overactivity. In addition, 73% of patients had urodynamic evidence of functional bladder outflow obstruction, including dysfunctional voiding and detrusor sphincter or detrusor pelvic floor discoordination. Two male patients (6.7%) had an obstructive pattern on urodynamics and subsequent cystoscopic examination confirmed the presence of congenital urethral stricture/values. Sixteen patients (53%) had significantly reduced bladder capacity of less than 300 ml [15-18]. These and other studies suggest that persistent NE after childhood is a serious adult problem requiring some investigation and considerable effort to treat.

IV. INHERITANCE

Bedwetting runs in the family of many children who suffer from bedwetting. In one study, a positive family history was found in 94 families (23%) of 411 probands with PNE, including 49% of fathers, 9% of mothers, 6% of both parents, 6% of the siblings and 30% of
proportion of children who developed secondary enuresis was 3.3 percent at 5 years, 4.7 percent at 6 years, 6.2 percent at 7 years, 7.0 percent at 8 years, 7.5 percent at 9 years and 7.9 percent at 10 years. Secondary NE is associated with a higher incidence of stressful events particularly parental separation, disharmony between parents, birth of a sibling, early separation of the child from parents and psychiatric disturbance in a parent [22, 30,31].

Von Gontard and colleagues found children with secondary enuresis had significantly more emotional difficulties compared to those with primary NE. Their evidence also suggests children with secondary enuresis, compared to those with primary enuresis, are more likely to have behavioural problems, a finding which corresponds to that of McGee et al [32].

Both Jarvelin and Fergusson et al argue that primary and secondary enuretics are similar [30,31]. They believe the two share a common etiological basis. The rate the child acquires primary control influences his or her risk of secondary enuresis. The primary form is the consequence of a delay in maturation of the physiological mechanisms. The child’s capacity to sustain and maintain nocturnal bladder control is manifest in the rate at which he or she acquires control. On the other hand, this capacity determines the child’s susceptibility to lapsing back to night wetting when exposed to stress.

Other sources of secondary enuresis must be excluded prior to proceeding with treatment for enuresis. These include sleep apnea from obstructive airway disease, obesity, constipation and infrequent or dysfunctional voiding. Treatment of sleep apnea from obstructive airway has been shown to improve or eliminate NE in some children following surgery or medical management [34,35]. Obesity has been associated with nocturnal enuresis both independently [36] and in the context of sleep apnea [37].

**Mono-symptomatic versus non-mono-symptomatic NE**

Mono-symptomatic NE refers to those children who report no bladder or voiding problems associated with wetting. Non-mono-symptomatic NE refers to bedwetting, that is associated with detrusor overactivity or voiding problems such as urgency and bladder holding during the day [5].

This classification becomes important when considering the most appropriate treatment intervention.

Many parents are unaware of daytime symptoms when seeking help for bedwetting and when identified these symptoms should be treated prior to intervention for the NE. Between 10-28% of children with NE have associated daytime wetting. If so, these children should be considered day and night incontinent. In these cases, night time incontinence is not any longer an
isolated phenomenon but part of the symptomatology of day and night time incontinence. These children are more resilient to treatment and more vulnerable to relapse [38]. These boys and girls are more appropriately managed in the context of the primary bladder problem.

VII. PATHOPHYSIOLOGY OF MONOSYMPTOMATIC NE

NE stems from a mismatch of bladder capacity, nocturnal urine output and the ability for the child to arouse during sleep. Night wetting is normal until age 5. Delayed maturation in one or more of the following systems results in NE: a lack of stability in bladder function, a lack of arginine vasopressin (AVP) release or response, or relative increased solute excretion during the night [39,40], or an inability to wake from sleep to full bladder sensations [41,42]. Combinations of all three problems may be present.

A unifying and simplistic concept with important clinical implications, is that NE is caused by a mismatch between nocturnal bladder capacity and the amount of urine produced during the night, combined with delayed or incomplete arousal response to the afferent neurological stimulus of the full bladder (Figure 10).

1. INCREASED NOCTURNAL URINE OUTPUT

In normal children, the circadian rhythm of urine production results in a nocturnal reduction in diuresis to approximately 50% of daytime levels [43,44]. In children this is the result of nocturnal release of hormones that regulate free water excretion (arginine vasopressin, AVP) or solute excretion (angiotensin II and aldosterone) and may result from circadian changes in glomerular filtration [45]. In the normal child, this results in increased urine concentration and reduced urine volume during sleep. This is why children who are not enuretic sleep through the night without being wet and do not need to rise to void.

Two thirds of patients with mono-symptomatic NE have been found to have a lack of circadian rhythm of vasopressin, resulting in high nocturnal urine production, which exceeds bladder capacity [46,47,48]. Rittig et al and Norgaard et al demonstrated abnormalities in the circadian rhythm of AVP secretion resulting in increased nocturnal urine output that exceeded bladder capacity in children with nocturnal enuresis [46,47]. These children make more urine at night, and often overcome their bladder capacity and wet early in the night. Abnormalities can also be intrinsic, related to reduced nocturnal circadian changes in glomerular filtration rate (GFR) [45] or in sodium and calcium excretion [49].

Detection of low plasma vasopressin levels, GFR assessments or specific sodium and calcium excretion are difficult to measure. Instead, we look for clinical signs of low vasopressin during the assessment interview. Weighing the diapers and adding the first morning void provides the total nocturnal urine output. if this total exceeds the child’s functional bladder capacity this may indicate nocturnal polyuria. Nocturnal urine output varies appreciably from night to night [50], but seems larger in children with NE who respond best to desmopressin (dDAVP).

Figure 10: Basic pathophysiology of NE or nocturia. When the bladder is full because of (relative) polyuria and/or a reduced bladder capacity, the child either wakes up to void (nocturia) or voids while sleeping (NE).
By the time the child becomes an adolescent, the circadian rhythm is less prominent. In adolescents and adults with nocturnal enuresis, there is no diurnal rhythm of plasma vasopressin concentration. The changes in urine production at night occur from a decrease in the urinary sodium excretion that is not due to differences in concentration of AVP but due to a lack of sensitivity to AVP [51] with resultant increased urine output [39]. There may be a small sub-group of children with impaired renal sensitivity to vasopressin or desmopressin [40,52]. Recent work by Devitt et al suggests that 18 percent of children have ‘normal’ levels of plasma vasopressin release but remain enuretic [48].

These children all failed to respond to a therapeutic dosage of desmopressin. This finding could indicate renal insensitivity to vasopressin but could also be indicative of detrusor overactivity or a small functional bladder capacity.

Total urine output during the night could be helpful in differentiating between the two conditions. The subgroup of patients with NE and increased nocturnal urine output generally has a normal functional bladder capacity and a favourable response to dDAVP [53].

2. DETRUSOR OVERACTIVITY DURING THE NIGHT

The detrusor, in order to function appropriately, needs to be relaxed during filling and allow an appropriate functional capacity. Detrusor overactivity usually causes small voided volumes resulting in a decreased functional bladder capacity [54].

Watanabe and his colleagues, employing EEG and cystometry recording during sleep, discovered that 32 percent of children with NE had involuntary detrusor contractions that resulted in enuresis [60-62]. These children had smaller functional bladder capacities at the point of wetting, than children with enuresis who did not have detrusor overactivity. Functional bladder capacity – defined as the largest daytime void on a frequency- volume (F/V) chart, after excluding the first morning void, may give a reasonably accurate assessment of daytime functional bladder capacity (FBC). Reduced functional bladder capacity, when below 70% of predicted FBC for age, is likely to result in poor response to dDAVP treatment [55]. Daytime bladder capacity is smaller than night time capacity in children without NE [56].

The pattern may be different at night. Yeung et al reported that 44 percent of treatment failures [with desmopressin or the enuresis alarm] have normal daytime bladder function but marked detrusor overactivity during sleep resulting in enuresis [63,64]. Almost none of these children had nocturnal polyuria. Ultrasound studies of the bladder furthermore revealed an increased bladder wall thickness in these children [57].

When further segregated prior to treatment, increased bladder wall thickness and bladder volume predicted the response to therapy in children with their primary nocturnal enuresis (more than three nights weekly). In one study, Yeung, et al [58] correlated ultrasound measured parameters and urodynamic findings. Of 35 children with frequent NE, bladder wall index was normal in only eight patients. It was less than 70% of predicted in 24, and more than 130% in three. When bladder volume and wall thickness index was correlated with ultrasound, 87% of the patients with a normal index exhibited a normal bladder pattern on imaging and 96% of patients with an index less than 70 exhibited detrusor over activity on ultrasound. All the children with a normal index either had a complete or good response to conventional treatment for nocturnal enuresis, whereas only 62% of those with an index less than 70 did not respond to treatment. With longer follow-up, bladder dysfunction had resolved in 38% of the children with an initial index of less than 30, all of whom had a good response to treatment. The bladder dysfunction persisted in the 63% of children who had partial or no response to treatment. What this means is that ultrasound measured bladder parameters may segregate children prior to management of primary nocturnal enuresis into groups that have a favorable outcome and those that do not, following conventional treatment. These studies will become more and more important in helping to predict response of various treatment regimens in the future.

This approach may be even more important in adults with refractory monosymptomatic nocturnal enuresis. Bower, et al. [15] found that in 56 consecutive adolescents and adults compared with 293 normal adults, there were significantly higher childhood scores of urgency, frequency, urge incontinence, infrequent voiding and small volume voids than their normal non-enuretic counterparts. This suggests that adolescents and adults with persistent nocturnal enuresis may have a more significant bladder component particularly since the majority of patients with adult type nocturnal enuresis do not seem to exhibit the nocturnal polyuria problem seen more commonly in the smaller children.

3. LACK OF AROUSAL FROM SLEEP/CNS FUNCTION

The fundamental mechanism resulting in nocturia or NE is that the bladder fills to its capacity during sleep and needs to empty (figure 10). Bladder fullness is due to nocturnal polyuria and/or a reduction of the bladder capacity due to detrusor over activity during sleep. These factors do not fully explain why the enuretic child does not wake up during the night to the sensation of a full or contracting bladder. Regardless of whether the child has detrusor overactivity or nocturnal polyuria, the enuresis event results from the child’s inability to awaken from sleep to empty prior to the wetting episode.
There is a widely held belief amongst parents and some clinicians that enuretics are deep sleepers. This is logical, since many of the children exposed to alarm therapy sleep through the alarm while family members awaken. Nevéus reviewed by questionnaire 1413 schoolchildren between the ages of six and ten and noted that enuresis was associated with subjectively high threshold arousal and significant confusion upon awakening from sleep [42]. Wolfish in a study of 15 enuretic and 18 control boys and girls found that enuretics wet most frequently during the first two-thirds of the night and that arousal attempts were less successful in enuretics than in normals [59]. This might explain why the most heavily endorsed view of both children and parents, regarding the aetiology of NE is a belief in deep sleep [60].

More recently Frietag, et al studied brainstem evoked potentials in 37 children with nocturnal enuresis and compared these aged 8 to 14 years, with 40 controls, mean age 10 years, and found that interpeak latencies of the brainstem evoked potentials were increased in children with nocturnal enuresis, suggesting that a maturational deficit of the brainstem was present in children with nocturnal enuresis. Differences in visually evoked potential latencies might point to a reason beyond functional cortical differences in children with family history of nocturnal enuresis [61].

Feittag’s study would suggest that a maturational effect is present; however, overnight studies in enuretic children with simultaneous sleep electroencephaloepihalographic and cystometry have revealed marked detrusor overactivity, only after sleep at night and not during wakeful periods during the day [62]. Because this pattern has not been observed in normal non-enuretic subjects even during the newborn period, one may hypothesize that this could be due to a small neurologic lesion affecting a tiny area in the vicinity of the Pontine micturition center, the posterior hypothalamus (responsible for secretion of antidiuretic hormone) or the locus coeruleus which may be the cortical arousal center [63].

Another interesting study by Baeyens et al. [64] showed a convincingly significant difference between children with enuresis and control groups, and the startled eye blink reflex which improved with maturation but did not seem to correlate with resolution of enuresis. Clearly there is considerable work that is required to further unravel the mechanisms behind perceived differences in arousal between enuretic and non-enuretic children.

However a raft of evidence counters such a belief. Sleep patterns of children with NE are no different from children who do not have NE [65].

Enuretic episodes occur during all stages of sleep in proportion to the amount of time spent in that stage and appear to occur independent of sleep stage but occur when the bladder is full [66].

Bedwetting children sleep normally but are unable to suppress nocturnal detrusor contractions or awaken in response to them or to bladder fullness. Waking becomes easier as the night progresses. However, several authors have found that children with NE are also more likely to wet in the first third of the night, often in the first two hours following sleep [59,66,67,70,71]. Thus the point of bladder fullness for most enuretic children coincides with a time of night where they find it most difficult to wake from sleep.

VIII. TREATMENT OF NOCTURNAL ENURESIS

The age at which the child and his or her parent begins to be concerned about bedwetting varies. In an important review article, Hjalmas, et al. noted that, “for successful treatment of nocturnal enuresis, the child must be brought to the physician by the parents who are concerned and the physician must have the necessary knowledge about the condition and be motivated to start treatment” [43]. In order to fulfill the requirements, parents, teachers, and nurses in primary care need to understand nocturnal enuresis and be ready to treat the child, regardless of age.

Nocturnal enuresis is thought of as a social problem and less of a medical problem; therefore, since the majority of children stop wetting as they mature and since no ill health follows bedwetting in most cases, there is a tendency for many practitioners to take a “wait and see” approach despite the fact that the family and the child in many cases are quite disturbed. In one study, 3803 French school children age five to ten years noted the prevalence of primary nocturnal enuresis to be 9.2%. The majority of the children noted that bedwetting bothered them and hoped that a doctor could help them. In this survey, a questionnaire was addressed to mothers of enuretic children, 100 school teachers and 100 school doctors. The mothers had a relatively tolerant attitude but two-thirds had consulted a doctor. Most of the doctors had proposed no solution or a “wait and see” attitude or treatment with a drug rather than an alarm. From this study, we may conclude that considerable work needs to be done to help educate not only parents but teachers and even physicians about the importance of treatment of nocturnal enuresis as well as supportive care [72].

The actual timing of treatment for nocturnal enuresis may vary depending on the needs of the child and the parent. Toilet training age may be different in different societies. For example, toileting in Asia may be earlier than in North America or other parts of the
Toilet training should be started when both the child and parents are ready. Most studies appear to show that children start training between 24 and 36 months of age with a current train toward later completion than in previous generations. This is markedly different than noted in some Asian cultures where training appears to begin much earlier. Toilet training should occur in an environment that is comfortable for the child. Unfortunately, toilets in most household bathrooms are adult sized, making it difficult for the child who needs to climb to the top of the toilet to relax. In these cases, a potty chair to toilet train the child, and once the child is old enough, he or she should be transitioned to an over-the-toilet seat with a footstool to allow optimal posture for voiding. Parents should encourage children to relax and take time to completely empty the bladder [43].

It is essential that both the child and his or her parents understand bedwetting pathophysiology and treatment philosophy. The clinician should give the child general advice such as what to eat and drink and to void regularly during the day, abstain from drinking too much during the late afternoon and evening and have relaxed routines at bedtime. The clinician should stress that NE is common and usually represents a delay in maturation without any psychopathological undertone. Up to 19 percent of children will become dry within the next 8 weeks without any further treatment besides good counselling [43,73,74].

1. EVALUATION

Hjalmas, et al. have recommended a careful history which we will summarize in these next few paragraphs. This approach, which has been recommended by the International Children’s Continence Society, provides an excellent guide toward the taking of a history for a child with nocturnal enuresis [43] (Figure 11).

a) The frequency volume chart (FVC)

Parents are asked to record a two-day three-night record. This includes recording the child’s fluid intake and urine output, frequency of micturition and the frequency and pattern of voiding. The largest single micturition is considered the functional bladder capacity. This chart can be performed beginning on a Friday evening and concluding on Sunday any weekend.

b) Symptoms of nocturnal enuresis

A careful history should include questions about the age of onset of nocturnal enuresis, length and circumstances of dry spells, number and time of episodes of nocturnal enuresis or nocturia, presence of daytime voiding symptoms or urinary tract infection, posture while voiding, daytime and evening fluid intake, sleep habits, frequency and consistency of bowel movements and psychosocial situation. One must establish whether or not symptoms represent primary

Figure 11: Schematic work-up in patients presenting with night-time wetting only.
or secondary nocturnal enuresis. It is critical to search for new psychological problems results in secondary nocturnal enuresis, particularly when the child presents with nocturnal enuresis after a prolonged period of dryness. The personality of the child, family situation, school environment, and presence of alternate caregivers might have an appreciable impact on voiding habits and will influence management options [43]. Children may drink large volumes of fluid in the hours before sleep and this may result in nocturnal enuresis or nocturia.

It is helpful to determine the number of hours of sleep and to compare this to standard charts of average duration of sleep by age. Morning fatigue may be the result of obstructive sleep apnea. Other symptoms of sleep apnea include mouth breathing, snoring, and restless sleep [43].

It is important to rule out symptoms of anatomical or physiologic urologic conditions that may lead to nocturnal enuresis. Many of these conditions are covered in other parts of this section, and include a failure to store urine or failure to empty urine. Storage symptoms include increased frequency, urgency, and urgency incontinence including squatting behavior, daytime incontinence and the sensation to need to void again. The clinician must carefully assess daytime wetting, particularly in older children. In many cases, the child may hide these symptoms from the clinician and the family.

Children void four to seven times a day or about every two to three hours [75]. If the child is voiding significantly more frequently than eight or more times a day, this may suggest incomplete emptying or overactive bladder symptoms. Urgency is present in many children and posturing, including squeezing or crossing the legs, squirming while standing or sitting, or physically compressing the genital area with a hand is all suggestive of overactive bladder due to detrusor overactivity which may or may not be associated with dysfunctional voiding. Other causes include urinary tract infection, polyuria from diabetes mellitus or diabetes insipidus which can also cause more frequent voiding [43]. Treatment for these symptoms is covered in other sections within this chapter.

Additional symptoms during the daytime include continuous dribbling between voids that can come from an ectopic ureter bypassing sphincter mechanisms or from failing to empty the bladder or sphincter incompetence. Also continuous leakage can result from neurologic causes or anatomical causes such as epispadias, or a closed bladder extrophy or urogenital sinus.

Lastly, children may have incomplete emptying from true dysfunctional voiding which results from the detrusor contraction at the same time that the sphincter or pelvis floor is contracting. In addition, a detrusor underactivity may result from neuropathy from diabetes mellitus and in some cases conditions such as the prune belly syndrome will result in detrusor underactivity. Lastly, urethral strictures may result in incontinence due to detrusor overactivity with poor bladder emptying. Boys with posterior urethral valves or Cobb's collar may also have incomplete emptying. Lastly, the clinician should be alert for symptoms of constipation and faecal incontinence. It is a common misconception that if a child is stooling once per day then he or she is not constipated. In fact, the best symptom of constipation includes infrequent or painful passage of hard small pellet-like stools. Faecal incontinence may also be present, the principal sign of this being faecal material in the underwear. Excessive stool retention may result in bladder dysfunction. In these cases [76] this may result in increased urethral sphincter and pelvic floor activity and explain the association of voiding dysfunction with incomplete voiding. Treatment of constipation may result in improvement in enuresis.

c) Physical examination

Anatomic and behavioral causes for enuresis may be identified through a careful physical examination. Evidence of improper gait, spinal deformities, and foot abnormalities including asymmetry, high-arched feet, or hammer toes are signs of sacral neuropathy. Physical signs of occult spinal abnormalities such as dimples, tufts of hair, skin discoloration, lipoma, asymmetrical buttocks and gluteal clefts are also important. A careful abdominal examination with particular emphasis on the left lower quadrant may identify the colon full of firm stool. In most cases, a rectal examination is not performed but in some cases this may also be indicated. Occult fecal impaction, poor perineal sensation and reduced anal sphincter tone can be indicative of neuropathy.

In boys, marked narrowing of the urethral meatus (when the meat lips are separated and no mucosa is seen), must be identified and carefully noted. If these signs are present, the boy should be asked to void so the clinician can witness and record the flow rate and residual urine. Narrowed or displaced urinary stream is suggestive of meatal stenosis.

In girls, the introitus should be identified for the position of the urethra. Evidence of wetting or irritation of the labia or vagina should be identified as this could be suggestive of post-void dribbling or incomplete emptying with and incontinence due to either detrusor overactivity or sphincter weakness [77].

d) Laboratory examination

There is very little laboratory examination that is required in patients with nocturnal enuresis other than a urinalysis to rule out UTI and evidence of glycosuria and a urine culture if the urinalysis is suggestive of infection.
Urodynamics and imaging are rarely important in the child with monosymptomatic nocturnal enuresis. If there is any suggestion, however, that daytime wetting is occurring, and then a full evaluation of the daytime problem should precede the evaluation for nocturnal enuresis.

The management of NE depends on:
- the child’s motivation to participate in treatment
- exclusion of confounding psychosocial factors
- providing information and instruction about daily habits, underlining the importance of having regular fluid intake, regular voidings, and relaxed routines at bedtime
- regular review of the new intervention

The therapist should convey a sense of understanding and compassion to both the child and the family. Education about the problem and a realistic discussion about the prognosis will help instil competence in the treatment offered which may improve both compliance and outcome [78]. What follows is taken in part from the excellent review article by Hjalmas, et al [43].

**EVIDENCE BASED RECOMMENDATIONS FOR TREATMENT OF NE**

First line treatment and preliminary steps: Primary and secondary forms of nocturnal enuresis are treated the same if faecal incontinence, constipation or daytime wetting is present, these should be treated first [76].

Initial management: Although treatment modalities like lifting, fluid restriction, dry-bed training, retention control training, psychotherapy, acupuncture, hypnosis all have been used, there is not sufficient data in the literature to strongly recommend any of these [93-100]. However, non invasive behavioural modifications such as resisting over hydration in the evening are appropriate recommendations at the initiation of therapy. The child must void before bed. Excessive calcium or sodium intake should be avoided as well [79].

During the day the child should be instructed to void regularly, not to hold urine until the last minute, and to relax and take time to completely empty. If deemed important by the parents, a letter should be sent to the school to explain this.

Timing of treatment for the child who wets is dependent on the family’s desire and the child’s desire. As a good rule of thumb, children should be six to eight years of age. Some children, however, may want to wait until later. Others may be ready closer to age six. We try very hard not to treat children that are much younger than six, however. It is important for the parents to know that relapses can occur and that the older the child is, the better chance they have the enuresis resolving. The successful treatment of children with nocturnal enuresis has a foundation of realistic expectations and a motivated family [43].

Before starting treatment, a “baseline” meeting with counselling, provision of information, positive reinforcement, reassurance that 15% of children resolve each year, and increasing motivation should occur first. Children are asked to fill out a calendar or chart depicting the wet and dry nights. Children became significantly drier in two non-randomized trials associated with fewer wet nights simply by focusing them more on record keeping and true reward charts [80].

1. PHARMAOCOLOGICAL TREATMENT

We have noted three main causes of enuresis. (1) Nocturnal polyuria, (2) detrusor overactivity, and (3) Disorder of arousal. Pharmacological treatment is designed to address these three areas.

a) Desmopressin

Arginine vasopressin (AVP) or antiuretic hormone (ADH) is normally produced in the hypothalamus and released in the pituitary in response to hyperosmolality or hypovolemic conditions. Vasopressin acts on the collecting ducts and distal tubules to enhance water absorption. AVP by virtue of an independent vasoconstrictor effect is also a potent vasopressor. Desmopressin (or dDAVP) is an analog of vasopressin created by deaminating the cystine residue at position 1 and substituted D-argenine for L-argenine at position 8. These changes result in significantly increased antidiuretic activity but loss of vasopressor activity. The half-life of Desmopressin is 1.5 to 3.5 hours. In a larger portion of children with monosymptomatic nocturnal enuresis, the normal circadian variation in urine production with nocturnal rise of vasopressin is absent. In these cases, dDAVP would seem to be particularly appropriate. Desmopressin is easy to administer and the clinical effects appear immediately. The usual dose is 0.2 to 0.4 mg orally, or 20-40 micrograms intranasally at bedtime. The intranasal form is no longer recommended for nocturnal enuresis in many places around the world. Some patients have a delayed response and a small group of children who do not respond to desmopressin in ordinary dosage will become dry when the dose is increased [81].

Desmopressin may be particularly beneficial in the child with limited numbers of wet episodes per month who wants added security on special nights such a sleepovers, etc.

Nocturnal polyuria is a characteristic of children that respond the best to desmopressin [82].

But detrusor dependent enuresis does not easily respond as well to desmopressin treatment. The presence of daytime urgency of daytime incontinence is common in this group and constipation or faecal
incontinence is a regular finding and these must be treated before offering dDAVP. In the short term, desmopressin is reported to produce more rapid improvement than alarm therapy. The results of various long-term studies which have followed children for six to 24 months after treatment cessation indicate an annual cure rate in children on long-term treatment of approximately 30% [83,84].

1. Tolerability and Safety

Large amounts of liquid should not be consumed the nights when the drug is taken. There have been several reports that note Desmopressin toxicity [85,86,87].

This data would suggest that a fairly rigid regimen of water restriction must be enforced for two hours prior to bedtime and to allow one eight-ounce glass of water at dinner and nothing for the two hours prior to bedtime.

The results of numerous clinical trials have shown that desmopressin is well tolerated even during long-term treatment and associated with a low risk of adverse events. In the SWEET study, only six of 242 children (2.5%) withdrew during the long-term treatment because of very mild adverse events following the administration of intranasal desmopressin. With the exception of water intoxication, which can be serious, this drug seems to be tolerated quite well.

In a survey on hyponatremia in patients with nocturnal enuresis by Robson and Norgard in 1996 was found in the majority of children water intoxication was due to considerable intake of water during the time the child was actually taking the desmopressin.

2. Predictors of Response

The SWEET study found that those who improved or became dry during desmopressin were older (greater than 8 years), had fewer wet nights during baseline, and had only one wet episode during the week and responded initially to the smallest dose of desmopressin used in the study [88,89].

The practical approach, however, is to offer the treatment to enuretic children since it is difficult to absolutely predict those that will respond.

There is considerable evidence that desmopressin works better than placebo. In one study, patients on desmopressin were 4.6 times more likely to achieve 14 consecutive dry nights compared with placebo [90].

However, relapse after short-term treatment is common. Sixty-one percent of 399 patients six to 12 years of age recruited from a primary care in one study responded to desmopressin initially [83]. Using intention to treat analysis 19% (77 of the 399) remained dry off medication and 18% were dry while still on desmopressin, thus not significantly better than the spontaneous cure rate. This suggests that desmopressin, by reducing the urine output over night, reduces nocturnal enuresis but does not significantly affect the resolution rate over time above the spontaneous rate.

Although several studies have shown that dDAVP is a well tolerated and safe drug, even during long-term usage, one has to be aware that dDAVP is a potent antidiuretic drug and that there have been reports on severe water retention with hyponatremia and convulsions, but these are infrequent [91-97].

Level of evidence: 1. Grade of recommendation: A

b) Antimuscarinic drugs

1. Oxybutynin

Oxybutynin should not theoretically be efficacious in children with monosymptomatic nocturnal enuresis. However, because there is considerable overlap in the diagnosis of monosymptomatic nocturnal enuresis, a number of children with few daytime symptoms of overactive bladder may have symptoms of overactive bladder at night. Moreover, it has been shown that on urodynamics 73% of adults with primary nocturnal enuresis have some form of functional bladder outlet outflow obstruction classified as (1) “primary bladder neck dyssynergia” or “detrusor sphincter dyssynergia” [18]. That would suggest then that Oxybutynin might be a useful alternative in some children who are unresponsive to DDAVP. The drug is also indicated in combined day and nighttime incontinence [52, 98,99].

In general, oxybutynin is well tolerated but there are some side effects, namely dryness of the mouth, constipation and vertigo (rare). Constipation can also result in increased residual volumes which may make it difficult for the child to empty prior to bedtime. Oxybutynin treatment in conjunction with desmopressin may have a role in cases with suspected day and night time detrusor overactivity.

Level of evidence : 2. Grade of recommendation: B.

In those children who have NE due to detrusor overactivity during the night, treatment with an antimuscarinic drug should be considered [100]. Because it is difficult to perform a night time cystometry in these children it may be tried in children who have more than 2 wetting episodes per night and who do not respond to dDAVP or be given in combination with alarm or dDAVP [101,99]. At present no studies have been performed to demonstrate its efficacy.

Level of evidence: 3. Grade of recommendation: C
c) Tricyclic antidepressants

Although tricyclic antidepressant drugs, imipramine in particular, have worked in a number of children, most of the studies that recommend this drug are relatively old. The major drawbacks to imipramine therapy are cardiotoxic side effects, in some cases even with therapeutic doses, and the possibility of death with overdose.

Because imipramine and other drugs of the same family have potential cardiotoxic side effects they cannot be generally recommended for treatment of this non-lethal disorder [102].

Although treatment with tricyclic drugs is associated with a decrease of one wet night per week, the lasting cure rate of only 17 percent restricts the use of these drugs [103].

Only in selected cases (like adolescent boys with Attention Deficit Hyperactivity Disorder and persistent NE) it should be considered [104].

Level of evidence: 1. Grade of recommendation: C (due to potential cardiotoxicity).

In addition to dDAVP and imipramine, other drugs, such as carbamazine and indomethacin have been investigated as well: based on study design as well as study outcomes, these drugs are not recommended at this stage [105-107].

d) Inhibitors of prostaglandin synthesis

Because nocturnal polyuria in children with NE may not be entirely attributed to a defect in free water excretion, but rather to an increase in nocturnal excretion of sodium, cyclo-oxygenase inhibitors (like diclofenac), which reduce urinary sodium excretion, have been tried and in a randomised double blind placebo controlled study proved to be effective [128]. Further studies need to be done to elucidate the role of these drugs.

2. ENURESIS ALARM

The enuresis alarm is the most effective means of facilitating arousal from sleep and remains the most effective way to treat mono-symptomatic NE(107,108). Intervention with an alarm is associated with nine times less likelihood of relapse than antidiuretic therapy. Relapse rates in the 6 months following treatment are in the order of 15 - 30 %. Alarm therapy has been shown in a meta-analysis to have a 43 percent lasting cure rate [109,110]. Alarm therapy should be considered in every patient. There is an average success rate of nearly 68% with efficacy increasing with the duration of therapy.

Better results occur with optimal motivation of the child and family and higher frequency of wet nights. Reduced efficacy associated with the lack of concern shown by the child, lack of supervision, inconsistent use, family stress, abnormal scores on behaviour system checklists, psychiatric disorder of the child, failure to awaken in response to the alarm, unsatisfactory housing conditions and more than one wetting episode per night. Enuresis alarms require several months of continuous use and are, therefore, unsuitable for some families [111-112].

For optimal results, alarm therapy requires a motivated family and child with significant commitment to time and effort. We sometimes recommend that this be done during the summer holiday if possible. The impact on other family members should be considered. In some families alarm therapy may wake other members of the family and may increase parental annoyance and place a child at increased risk for physical or emotional abuse. Close follow-up is important to sustain motivation, troubleshoot technical problems and otherwise monitor the therapy [43].

The exact mechanisms for alarm treatment are not known. The effects are not due to classical conditioning as stimulus awakening occurs after and not before wetting. Instead it is clearly an operant type of behavioural approach, i.e. a learning program with positive reinforcement that includes aversive elements. Dryness is reached either by waking up leading to “nocturia” in 35% of children or by sleeping through the night with a full bladder in 65%. Body worn alarms are as effective as bedside alarms (general assessment for alarm treatment [113].

The family should continue alarm therapy for at least 6 to 8 weeks before discarding it as ineffective. Compliance remains a problem: dropout rates are rarely disclosed in reported studies. Proper guidance and instructions are mandatory.

The key to success is not the stimulus intensity of the alarm triggering, but the child’s preparedness to awake and respond to the signal. Comparison of the different types of alarm did not show significant outcomes.

In general it can be stated that alarm treatment is more effective than other forms of treatment and the lasting cure rate about twice as high [114, 115].

Level of evidence 1. Grade of recommendation A

In some cases, alarm therapy can be enhanced using the alarm in addition to other behavioral components. Overlearning (giving extra fluids at bedtime after successfully becoming dry using an alarm) and avoiding penalties may further reduce the relapse rate (108).

3. DRY BED TRAINING

This is a package of behavioral procedures used in conjunction with the enuresis alarm first described by Azrin et al [116]. It incorporates:

• the enuresis alarm
• cleanliness training (encouraging the child to take
responsibility for removing of wet night clothes and sheets, re-making the bed and resetting the alarm),

- waking schedules – to ease arousability from sleep as described above and involving:
  1. for the first night, waking the child each hour, praising a dry bed, encouraging the child to decide at the toilet door whether he or she needs to void, and on returning to bed the child is encouraged to have a further drink.
  2. On the second night the child is awakened and taken to the toilet 3 hours after going to sleep. For each dry night, the clinician moves the waking time later by 30 minutes. If the child is wet on any night, the waking time stays at the time of the previous evening. The clinician discontinues the sense when the waking time reaches 30 minutes following sleep. The clinician restarts the waking schedule if the child begins wetting twice or more in any week, stating again 3 hours after sleep.

High success rates and low drop out have been reported although relapse rates are no different than enuresis alarm treatment alone. Modifications are advocated to remove some of the more punitive elements of the programme but at best, it is a complex, time consuming and demanding technique [113, 117,118].

Hirasing et al found 80 percent success with group administered dry bed training. Girls responded better than boys [119]. The majority of parents were satisfied with the programme but opinions of the children were divided. Factors not related to success were the child’s age, bedwetting frequency, secondary enuresis or family history.

In another study they found a positive effect on behavioural problems [120].

An important component analysis by Bollard & Nettelbeck found that the enuresis alarm accounted for most of the success achieved through dry bed training. They believe that a large proportion of the components of the procedure can be eliminated without sacrificing much of its overall effectiveness and that the waking schedule coupled with the enuresis alarm is as effective as the complete dry bed-training programme [121].

Level of evidence: 2. Grade of recommendation D (no more effective than alarm treatment alone)

4. AROUSAL TRAINING

Arousal training entails reinforcing appropriate behaviour [waking and toileting] in response to alarm triggering. The aim is to reinforce the child’s rapid response to the alarm triggering, not on ‘learning to keep the bed dry’.

The instructions involve:

- setting up the alarm before sleep
- when the alarm is triggered the child must respond by turning it off within 3 minutes
- the child completes voiding in the toilet, returns to bed and re-sets the alarm
- when the child reacts in this fashion he is rewarded with 2 stickers
- when the child fails to respond in this way the child pays back one sticker
- Van Londen et al first described this procedure with a group of 41 children, aged 6-12 years, with predominantly primary enuresis [122].

They reported 98 percent success [14 consecutive dry nights] compared to 73 percent success with alarm monotherapy.

The difference was significant [p<0.001]. Ninety two per cent remained dry after 2 years suggesting very low relapse rate. An extraordinary aspect of this study was the lack of contact between therapist and parents. All those included were parents who had ordered an alarm from a rental agency and were given the instructions with the alarm.

The authors conclude that arousal training is ‘definitely the treatment of choice for enuretic children between 6 and 12 years’. Compared with other studies and considering experience of daily practice one may question the very high success rate in this particular group of patients.

Level of evidence: 3. Recommendation: grade C

The enuresis alarm remains the most effective means of facilitating arousal from sleep. The key to success is not the stimulus intensity of the alarm triggering, but the child’s preparedness to awake and respond to the signal.

5. ACUPUNCTURE

In one randomised controlled trial that examined acupuncture, 40 children were allocated either to dDAVP or acupuncture, 75% of children were dry after 6 month of therapy (while still on medication), while 65% of patients were completely dry after a mean of 12 sessions.

From this study it is concluded that as an alternative, cost-effective and short-term therapy acupuncture should probably be counted among available treatment options. Another meta analysis provides some evidence for the efficacy of acupuncture for the treatment of childhood nocturnal enuresis [123].

Comparison of treatment outcome and cure rates is difficult because of the inconsistent use of definitions, the inclusion of children with daytime symptoms, and the variable follow-up periods in most studies. For a pragmatic approach, see Figure 11.

Level of evidence: 4. Recommendation: grade D
6. COMBINED TREATMENT WITH ALARM AND DESMOPRESSIN

Combined treatment may be superior to alarm alone especially for non-responders of each individual treatment. In this approach, treatments are started at the same time: the rapid action of dDAVP is believed to facilitate the child’s adaptation to the alarm [124, 125]. After 6 weeks the dDAVP is discontinued while the alarm treatment is continued until the child becomes completely dry. Compared with either therapy alone, the combination is particularly effective in children with high wetting frequencies and behavioural problems.

Combination with full-spectrum therapy may even yield higher success rates [126-127]. Van Kampen et al reported their results of ‘full-spectrum’ therapy in 60 patients: they were treated for 6 months with a combination of alarm, bladder training, motivational therapy and pelvic floor muscle training: 52 patients became dry [126].

Hjälmås et al have proposed the following (not validated) protocol [43].

1. careful screening to identify any functional or mechanical outlet obstruction and appropriate management,
2. monotherapy with either alarm or desmopressin for a minimum of 12 weeks,
3. combination of alarm and half-therapeutic or titrated dose of desmopressin that allows wetting up to 4 nights per week,
4. maintain both interventions for 8-10 weeks,
5. increase desmopressin to dose that allows only one wet episode per week,
6. withdraw alarm when dry for one month,
7. reduce desmopressin to half dose after a further 8 weeks,
8. withdraw desmopressin after a further 8 weeks.

7. NON RESPONDERS

About one third of children do not respond to treatment with alarm and/or dDAVP. The majority of these children are likely to have a small nocturnal bladder capacity and suffer from “detrusor dependent NE”. These children may void more frequently than their peers or have urgency and day-time incontinence. They are also often constipated. Prescription of dDAVP plus antimuscarinics should be considered, although evidence from the literature is lacking. Most likely the reduced urinary output during the night leads to a lower filling rate which may reduce the nocturnal involuntary detrusor contractions and enhance the action of antimuscarinic drugs. Treatment success is usually noted between 1-2 months. Treatment should be continued for 6 -12 months, but clinical evidence is lacking.

On the other hand some of these children may have day time incontinence, which was not discovered during the initial workup. They should be given a strict voiding regimen and a combination of dDAVP with the alarm [54].

Some children who remain non-responders to desmopressin in combination with alarm and / or anticholinergic drugs may have absorptive nocturnal hypercalciuria which may be responsible for the NE in some of these patients. With an appropriate (low calcium) diet these patients can become desmopressin responders [129].

NE is a symptom, not a homogeneous disorder. A really efficient treatment will never become possible until we have clarified all the different pathophysiological subgroups that go under the heading of NE.

8. SUMMARY (Figure 12)

Table 1. Response and cure rates of different treatment modalities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Full response</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alarm treatment</td>
<td>65 %</td>
<td>43 %</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>31 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Dry-bed training</td>
<td>40%</td>
<td>18 %</td>
</tr>
<tr>
<td>Imipramine</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

- Gaining the confidence of the child and the family is paramount. The development of structure in the child’s life, early bedtime, careful calendaring, avoidance of fluids late in the day, are critical.
- Secondly, identifying compounding psychological or physiologic factors of the child such as constipation and diurnal enuresis are critical.
- Third, alarm treatment should probably be recommended as the first choice of treatment with the modifications listed above. Single parents have a difficult time with the effort that is required to awaken with the child for the alarm management and, in some cases when children are not frequently wet, dDAVP may provide effective therapy for the last few years that they are at risk. In general, those that do the best with the alarm therapy are those with frequent bedwetting, normal estimated bladder volume, parents who are willing to participate, and true monosymptomatic nocturnal enuresis.

- Desmopressin seems to work best in children
Urinary incontinence in children may be caused by a congenital anatomical or neurologic abnormality, such as ectopic ureter, bladder extrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence and they are referred to as having “functional incontinence.”

- If the initial treatment does not provide satisfactory results in two months, the child can switch to another. In some cases, using both the alarm and Desmopressin can be effective [124,130].
- Lastly, combinations of therapy including Desmopressin plus an antimuscarinic can be used in some cases as well if detrusor overactivity at night is suspected.

D. CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE

Urinary incontinence in children may be caused by a congenital anatomical or neurologic abnormality, such as ectopic ureter, bladder extrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence and they are referred to as having “functional incontinence.”

Previously the bladder in infancy was considered overactive during filling with emptying being initiated by a detrusor overactivity contraction, however natural fill studies in infants demonstrated a stable detrusor during filling and dyscoordinated emptying[1,2,3].

Male infants void with significantly higher pressure than female infants and demonstrate a smaller bladder capacity than girls. However these dysfunctions are transitory as on follow-up detrusor overactivity has resolved, post void residual volumes have improved and voiding detrusor pressures are normalized. A continuous voiding pattern was seen consistently after 2 years of age.

Bladder control is believed to be under influence of the central nervous system. The pontine region is considered to be responsible for detrusor sphincter coordination while the cortical area is responsible for detrusor overactivity control. Formerly it was believed that bladder maturation followed maturation of cortical inhibition processes, However, recent work of CK Yeung suggests bi-directional maturation of both the coordinating influence on the bladder and the pons may be implicated. This implies that a condition such as detrusor overactivity would be the result of loss of cortical control or of deficiency in cortical control, while dysfunctional voiding would be the result of non maturation of the coordination.

With the emergence of functional MRI future studies will be able to illuminate this enigma.[4] This opens an era of corticocentric thinking on lower urinary tract dysfunction away from the current trend of vesicocentric thinking. Detrusor overactivity may be a symptom of a centrally located dysfunction affecting bladder, bowel, sexual function and even mood and behaviour.[2] Indeed many studies indicate that there exists a link between lower urinary tract dysfunction and ADHD (attention deficit and hyperkinesia) [5, 6].
The desire to void is a sensation which, in the developing child, is incorporated into daily life so that voiding takes place at an appropriate time and place. Problems with training or psychological difficulties can have a great impact on the results of training: some parents send their child to the toilet many times, though his/her bladder may be empty [7]. Voiding in these circumstances can only be achieved by abdominal straining. The positive reinforcement that the child receives by voiding even a small amount may lead to the development of an abnormal voiding pattern.

The same is true when children receive negative feedback related to voiding [8]. Urinary incontinence in children may be due to disturbances of the filling phase, the voiding phase or a combination of both. In the new ICCS terminology document these conditions are termed functional bladder disorders or Lower Urinary tract (LUT) conditions. They are divided into either detrusor overactivity (DO) or dysfunctional voiding as the studies tended to look primarily at daytime versus nighttime incontinence and made no effort to evaluate the type of daytime incontinence.

Daytime or combined daytime and nighttime incontinence at least once a week seems to occur in about 2-4 percent of 7-year-old children and is more common in girls than in boys [11]. Overall the rates of prevalence vary from 1 to 10 percent, but in general for 6 to 7 year old children the prevalence is somewhere between 2 and 4 percent, and rapidly decreases during the following years [12-17]. Sureshkumar et al in a population based survey of over 2000 new entrant primary school children [age 4-6 years] in Sydney Australia noted an overall prevalence of daytime wetting of 19.2% defined as at least one daytime wetting episode in the prior 6 months with 16.5% having experiencing more than one wetting episode and only 0.7% experienced wetting on a daily basis [18]. Multivariate analysis showed that recent stress, a history of daytime wetting along the paternal line, and a history of wetting among male sibs were independent risk factors for moderate to severe daytime wetting. Because this was a cross sectional study recall bias may have resulted in an overestimate of risk of daytime wetting being caused by such factors as emotional stress and family history. In addition, urine cultures were not obtained so occult UTIs could not be identified.

In a questionnaire based study supplemented by telephone calls Hellstrom assessed the prevalence of urinary incontinence in 7 year old Swedish school entrants [19]. Diurnal incontinence was more frequent in girls than boys, 6.7% vs 3.8%, respectively. Wetting every week was reported in 3.1% girls and 2.1% of boys. The majority of children with diurnal incontinence had concomitant symptoms: urgency was reported in 4.7% girls and 1.3% boys. Nocturnal incontinence combined with daytime wetting was equally common in males versus females, 2.2% versus 2%, respectively. At the age of 17 years daytime wetting, at least once a week, was found in 0.2 % of boys and 0.7% of girls. A limitation of this study is its dependency on recall. Children with daytime or mixed wetting were found to suffer from urgency in 50.7 percent of the cases, with 79.1 percent wetting themselves at least once in 10 days [20]. Urgency symptoms seem to peak at age 6–9 years and diminish towards puberty, with an assumed spontaneous cure rate for daytime wetting of about 14% per year [20, 21].

Most children are toilet-trained by the age of 3 years, although the mean age may range from 0.75 to 5.25 years, with girls being trained earlier [2.25 years] than boys (2.56 years) [22]. Although a recent study reported day dryness at a mean age of 17.4 months in the majority of countries the age of commencing toilet training has increased [23]. This is thought to be associated with higher education levels in parents and the popularity of the child-oriented approach.
rather than parent-initiated methods [24]. Children who exhibited elimination signals for voiding became dry sooner than those who did not show such signs. There is huge social and cultural variation in toilet training practices with some of the implicated issues being availability of inside toilet, washable versus disposable diapers, working or home-based mothers, rural or urban location and use or not of punishment methods [24].

Swithinbank et al have found a prevalence of day wetting [including also “occasional” wetting] in 12.5% in children age 10-11 years which decreases to 3.0% at age 15-16 years [25]. Based on these findings, it seems that the prevalence of all kinds of daytime incontinence diminishes by 1-2% per year from age 10-11 to age 15-16 years, while daytime incontinence, at least once a month, seems to diminish by 0.2% per year from age 7 to age 17 years. Because of treatment interventions the studies may not recount the true natural history.

A more recent cohort study of all school children in the first and fourth grades in the city of Eskilstuna (Sweden), daytime urinary incontinence (at least once a month) was reported in 6.3% of the first graders and 4.3% of the fourth graders, while bedwetting (at least once a month) was reported in 7.1% and 2.7% and faecal incontinence in 9.8% and 5.6%, respectively. This study demonstrates that soiling and daytime urinary incontinence often coexist.[26]

The natural history of detrusor overactivity in children is not well understood. It is no longer held that an detrusor overactivity in children is idiopathic or due to a maturational delay but more likely to be associated with feed forward loops from the generation of a high pressure system during voiding or filling. Both the interplay of neural drive with motor control and the dynamic nature of the growing bladder could be causative. This is in contrast to the adult population where detrusor overactivity is considered a chronic condition whose origin is unrelated to functional use. There is no long-term data to determine if childhood detrusor overactivity predicts detrusor overactivity as an adult.

By the age of 5 years, unless organic causes are present, the child is normally able to void at will and to postpone voiding in a socially acceptable manner. By this age, night-time and daytime involuntary wetting become a social problem and a cause for therapeutic intervention. In children who present with a change in voiding habits, such as a new onset of voiding dysfunction, one should consider the possibility of child sexual abuse [27].

This is difficult to prove but should be kept in mind, especially when invasive diagnostic and therapeutic procedures are contemplated. One may want to simply ask the parent or caregiver if there were any precipitating events or concerns that they feel may have led to the changes in the child’s voiding habits. The appropriate individuals should be contacted if there is a high index of suspicion. Of adult women with complex urinary symptoms, a significant proportion report sexual abuse as a child.

II. INTRODUCTION TO CLINICAL ASSESSMENT

The evaluation of daytime wetting is based on the medical and voiding history, a physical examination, a urinalysis, bladder diaries and uroflowmetry with postvoid residual. The upper urinary tract should be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [28-31].

Treatment is usually a combination of ‘standard therapy’ (see below), behaviour therapy, bladder training, physiotherapy and medical treatment. Surgery is rarely needed for the management of daytime wetting in the absence of a structural abnormality. The roles of neuromodulation, botulinum toxin and intravesical therapies in the management of pediatric urinary incontinence are less well-defined. Clean intermittent self-catheterization is sometimes necessary in children with poor bladder emptying, due to underactivity of the detrusor and subsequent large residuals, who do not respond to a more conservative approach.

The importance of treatment during childhood was pointed out in a general population study of 1333 adult women. Fifty percent reported symptoms of stress incontinence and 22 percent reported symptoms of urgency incontinence. Eight percent noted severe symptoms. Women who at age six years had wet episodes during the day or were wet several nights per week, were more likely to suffer from severe incontinence and report urgency symptoms: occasional bedwetting was not associated with an increased risk in adult life [31].

III. CONFOUNDING FACTORS: LOWER URINARY TRACT DYSFUNCTION, RECURRENT URINARY TRACT INFECTION AND VESICOURETERIC REFLUX (VUR)

The relationship between detrusor dysfunction and VUR associated with a urodynamic anomaly was first described by Allen and Koff and has been confirmed by several authors [32-35]. Koff demonstrated that
treatment of detrusor overactivity reduced the incidence of infection and resulted in a 3 fold increase in the rate of reflux resolution. In a study by Sillen of children with gross bilateral reflux, extreme detrusor overactivity without signs of bladder outlet obstruction was found in boys. Infant girls with gross bilateral reflux did not show the same degree of detrusor overactivity [36]. Other investigators assessing high grade VUR in newborns noted similar findings. Van Gool et al noted that 40% of 93 girls and boys evaluated for urgency incontinence and recurrent UTIs had reflux [37].

These studies in infants and the association of 'dysfunctional elimination syndromes' with reflux and infection in older children support the controversial suggestion that in some individuals vesicoureteral reflux is a secondary disorder related more to abnormal detrusor function than to a primary anatomic defect at the ureterovesical junction. It has recently been shown that increased intravesical pressure, without reflux may be detrimental for the upper tracts: renal scarring without reflux was described by Vega et al recently [38].

In support of this concept is the common finding of vesicoureteral reflux in children with neuropathic bladders and detrusor-sphincter dysynergia. In such children, the institution of clean intermittent catheterization and anticholinergic therapy leads to the resolution of VUR in a large number of cases. It is believed that the decrease of detrusor overactivity and restoration of functional capacity in combination with regular and complete emptying of the bladder are the responsible co-factors [39].

Koff et al evaluated the effects of antimuscarinic therapy in 62 children with a history of recurrent UTIs, VUR and detrusor overactivity, and compared these children with an age-matched control group with a normal urodynamic study [40]. The overall small sample size and the small number of compliant patients limit the study; however, it did demonstrate a statistically significant difference in the resolution rate of VUR between the treated group and the control group. The overall infection rate was lower in the treated group [16%] compared to the non-medically treated group [63%] and the age-matched control group [71%]. Several authors have documented the relationship between detrusor overactivity and dysfunctional voiding with recurrent UTIs.

Proposed etiologies for the increased incidence of UTIs in these patient populations include a milk back phenomenon whereby bacteria in the proximal urethra are “milked back” into the bladder during contraction of the pelvic floor muscles. Alternatively, decreased blood flow and relative hypoxia during periods of increased detrusor pressure such as during involuntary detrusor contractions and voiding against functional obstruction, may induce transient bladder mucosal injury. Constipation is prevalent among children with bladder symptoms, but often poorly identified by parents [41]. It is a risk factor for recurrent UTIs. Contrary to expectations, findings from the European Bladder Dysfunction Study suggested that symptoms of disordered defecation did not influence the cure rate of treatment for bladder symptoms [42]. In a prospective non-randomized clinical series of day wetting children a strong correlation was found between recurrent urinary tract infections, detrusor overactivity and detrusor-sphincter dysfunction [43, 44]. In a study by Hansson et al, symptoms of an detrusor overactivity, such as urgency and daytime incontinence were found in a high percentage of girls with asymptomatic bacteriuria [45].

In the majority of children with detrusor-sphincter-pelvic floor dysfunction the recurrent infections disappeared following successful treatment of the detrusor dysfunction. This finding confirms the hypothesis that detrusor-sphincter-pelvic floor dysfunction is the main factor responsible for the infections (and to a lesser extent vice versa) [46, 47]. Additionally, since such children typically have coexistent constipation, attempts at restoring normal bowel habits will also contribute to decreasing the risk of UTIs. At present, current opinion is that vesicoureteral reflux as such does not predispose to UTI: however it may facilitate renal involvement [causing pyelonephritis] once bacteriuria has been established in the bladder. This concept has not been scientifically validated and the incidence of renal scars as a consequence of pyelonephritis is reportedly the same, regardless of whether reflux has been documented or not [48]. Those children with VUR in association with detrusor overactivity and/or voiding dysfunction may be at increased risk for upper tract damage given their increased risk of developing UTIs. With this in mind, aggressive treatment of the underlying filling/voiding disorder, the addition of prophylactic antibiotics, and attention to their bowel habits should be given in an effort to decrease the risk of UTIs in this higher risk group [49-52].

In a recent study evaluating retrospectively a large group of children with LUT conditions it was shown that in patients who had urinary tract infection the presence of reflux increased the rate of renal cortical abnormalities.[53]

**IV. CLASSIFICATION**

Numerous classifications have been used for children who present with varying degrees of 'functional' urinary symptoms, unrelated to apparent disease, injury or congenital malformation. In 2006 the International Children's Continence Society (ICCS) released a standardized terminology to provide guidelines for the classification and communication about LUTS in
children [9]. Symptoms are classified according to their relation to the voiding and or storage phase of bladder function.

In addition to gaining a comprehensive history, observing micturition and examining a child form the basis of assessment, the information derived from a 48-72 hour bladder diary, stool record, voiding uroflowmetry and lower urinary tract ultrasonography is essential in making the initial diagnostic classification. Urodynamic investigations elucidate the basis of clinical findings but are first line evaluation techniques only in tertiary referral centers where children have not responded to previous treatment or have symptoms suggestive of neural involvement or anatomical anomalies.

The ICCS has classified daytime LUT conditions into groups that currently align with understanding of underlying pathophysiology. The groups commonly overlap and allocation is based on the 4 symptoms of urinary incontinence, frequency of volitional voiding, micturition volumes and fluid intake.

Over active bladder (OAB) including urgency
• Incontinence
• Dysfunctional voiding
• Underactive bladder

The symptom-specific conditions of
• Voiding postponement
• Vaginal reflux
• Giggle incontinence
• Extraordinary daytime urinary frequency
• Elimination syndrome

The term ‘non-neurogenic dysfunction’ is commonly encountered in the literature and describes the whole spectrum, from simple detrusor overactivity to severe cases with deterioration of the upper tracts. The fact that a neurologic deficit is not demonstrated at the time of evaluation, does not, however exclude the possibility that a neurologic abnormality was present at the onset of the problem.

It has been postulated that detrusor overactivity may eventually lead to poor bladder emptying due to underactivity of the detrusor or severe dys-coordination between detrusor, sphincter and pelvic floor. However, the natural history of many of these children does not confirm this hypothesis, nor the early onset of severe pathology in some of them. Hoebeke et al found no evidence for this dysfunctional voiding sequence: children with functional incontinence have different primary diseases, but all have a common risk of incontinence, UTI, VUR [15%] and constipation [17%] [54].

1. OVER ACTIVE BLADDER IN CHILDREN

The term detrusor overactivity is used to describe the symptom complex of urgency, which may or may not be associated with urgency incontinence and is not a direct result of known neurological damage. Recent suggestions describe DO as a symptom of cortico-central dysfunction that affects multiple systems rather than a dysfunction isolated to the urinary bladder [55]. Urge syndrome is characterized clinically by frequent episodes of an urgent need to void, countered by contraction of the pelvic floor muscles (guarding reflex) and holding manoeuvres, such as squatting and the Vincent curtsey sign. The term urgency refers to a sudden compelling desire to void that is often difficult to defer, unlike the need to void which is experienced by all individuals and may be intense if one holds one’s urine for a prolonged period of time. The symptoms arise from detrusor overactivity during the filling phase, causing urgency. These detrusor contractions are countered by voluntary contraction of the pelvic floor muscles to postpone voiding and minimize wetting. The detrusor contractions can be demonstrated urodynamically, as can the increased activity of the pelvic floor muscles during each contraction.

The voiding phase is essentially normal, but detrusor contraction during voiding may be extremely powerful. The flow rate reaches its maximum quickly and may level off (‘tower shape’). Such strong bladder and pelvic floor muscle contractions have been postulated to result in damage to the bladder mucosa increasing the risk of UTIs. In addition these children may note suprapubic or perineal pain. A cohort of patients presenting with nighttime pain syndromes based on pelvic floor spasms was described by Hoebeke et al. Good response to pelvic floor relaxation biofeedback is described in this study [56].

Over active bladder (OAB) should also be considered in “continent” children with recurrent UTI and vesicoureteral reflux. Depending on fluid intake and urine production, the complaints of incontinence become worse towards the end of the day, due to loss of concentration and fatigue and may also occur during the night. Children usually diminish their fluid intake to minimize wetting, and therefore incontinence may not be the main complaint or symptom.

Frequent voluntary contractions of the pelvic floor muscles may also lead to postponement of defaecation. Constipation and fecal soiling are often found in children with detrusor overactivity [57]. The constipation is aggravated by the decreased fluid intake. Constipation contributes to an increased risk of UTIs and may exacerbate the detrusor overactivity. An investigation of the natural history of combined emptying dysfunction of bladder and bowel using an elimination score in women and without urogy-
naecological problems demonstrated that childhood lower urinary tract dysfunction may have a negative impact on bladder and bowel function in later life [58].

A careful history, physical examination and scrutiny of the child’s bladder diary will identify symptoms of detrusor overactivity. Urine flow rate registration and post-void residual urine measurement help to identify co-existing dysfunctional voiding. Thus in the majority of children, invasive studies such as urodynamic studies are not indicated as part of the initial evaluation. Such studies are reserved for those children with a question of an underlying neurologic defect and those who fail to improve with medical and behavioral therapy, if invasive therapies are being considered. Those children with a history of recurrent UTIs should undergo assessment with a renal/bladder ultrasound and depending on the age of the child and the severity of the UTI(s) a voiding cystourethrogram (VCUG) to assess reflux is occasionally performed [59, 60]. By adopting a structured approach to history and physical examination, the diagnosis of urge syndrome can be made in the majority of children without the need for invasive diagnostic procedures.

**Treatment**

The treatment of urge syndrome involves a multimodal approach, involving strategies such as behavioral modification, antimuscarinic medication, adjunctive biofeedback and neuromodulation. Underlying and potentially complicating conditions such as constipation and UTIs are managed prior to intervention.

Level of evidence: 3. Grade of recommendation: C

### 2. DYSFUNCTIONAL VOIDING

Dysfunctional voiding refers to an inability to fully relax the urinary sphincter or pelvic floor muscles during voiding. There is no identified underlying neurologic abnormality. Children with dysfunctional voiding usually present with incontinence, urinary tract infections and constipation and demonstrate fluctuating or intermittent patterns during repeated uroflowmetry. A recent study report mild and severe obesity occurring in 51% and 31% respectively of children with daytime incontinence. These figures compare to population prevalence rates of 30% and 15% respectively and highlight a potential association between lower urinary tract dysfunction and obesity.

No clear data are available on the possible causes of dysfunctional voiding. It may be that an detrusor overactivity eventually leads to overactivity of the pelvic floor muscles, with subsequent insufficient relaxation during voiding [61]. Alternatively, poor relaxation of the pelvic floor muscles during voiding may be a learned condition during the toilet training years, adopted following episodes of dysuria or constipation or occur secondary to sexual abuse [62]. The child’s environment, in particular toilet conditions and privacy issues, can trigger or exacerbate voiding anomalies [63]. In some girls, anatomical anomalies of the external urethral meatus seem to be associated with a higher incidence of dysfunctional voiding. The urine stream may be deflected anteriorly and cause stimulation of the clitoris with subsequent reflex activity of the bulbocavernous muscle causing intermittent voiding [64]. Since no true structural obstruction can be identified the intermittent incomplete pelvic floor relaxation that occurs during abnormal voiding is termed a functional disorder.

Abnormal flow patterns seen in children with dysfunctional voiding:

- **Fluctuating (Staccato) voiding:** continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity. Voids are commonly prolonged and incomplete.

- **Interrupted voiding:** characterized by unsustainable detrusor contractions resulting in infrequent and incomplete voiding, with micturition in separate fractions. Bladder volume is usually larger than age-expected capacity. Residual urine is often present. Detrusor overactivity may be seen but it may also be absent [43, 47, 59, 65].

Sustained alteration of voiding is associated with subsequent filling phase anomalies such as phasic detrusor overactivity and inappropriate urethral relaxation [66]. Urinary tract infections and kidney damage are common sequelae [67]. Over time, routine incomplete bladder emptying can progress to detrusor over-distension associated with chronic urinary retention. The child with this presentation is often classified as having poor bladder emptying due to detrusor underactivity.

Urinary symptoms associated with dysfunctional voiding range from urgency to complex incontinence patterns during the day and night [68]. Children with dysfunctional voiding have a higher rate of recurrent urinary tract infections than children with no voiding abnormality and also demonstrate increased incidence of higher grades of VUR [54, 69]. Symptoms are significantly more common in children with Attention Deficit Disorder than in ‘normal’ children [70].

Signs of dysfunctional voiding reflect initial “compensatory” overactivity of the detrusor along with poor emptying ability. They may include small bladder capacity, increased detrusor thickness, decreased detrusor contractility, impaired relaxation of the external urinary sphincter/pelvic floor during voiding, weak or interrupted urinary stream and large post-void residual volumes of urine. There may also be ultrasound abnormalities, secondary vesicoureteric reflux, fecal soiling or constipation [54, 71, 72].

**Treatment**

Symptoms are often refractory to standard therapy of
hydration, bowel management, timed voiding and basic relaxed voiding education. Effective intervention requires combination therapy, generally with a sizeable investment of time over a long period. Treatment is aimed at optimizing bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Specific goals are:
- consistent relaxation of the pelvic floor throughout voiding,
- normal flow pattern,
- no residual urine and
- resolution of both storage and voiding symptoms.

Strategies to achieve these goals include pelvic floor muscle awareness and timing training, repeated sessions of biofeedback visualization of pelvic floor activity and relaxation, clean intermittent self-catheterization for large post-void residual volumes of urine, and antimuscarinic drug therapy if detrusor overactivity is present. If the bladder neck is implicated in increased resistance to voiding, alpha-blocker drugs may be introduced. Recurrent urinary infections and constipation should be treated and prevented during the treatment period.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms [73]. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described.

Level of evidence: 4. Grade of recommendation: C

3. UNDERACTIVE DETRUSOR

Children with underactive detrusor function may demonstrate low voiding frequency and an inability to void to completion using detrusor pressure alone. Voiding is of long duration, low pressure, intermittent and often augmented with abdominal straining.

Children with this condition usually present with urinary tract infections and incontinence. Urodynamically, the bladder has a larger than normal capacity, a normal compliance and reduced or no detrusor contraction during voiding. Abdominal pressure is the driving force for voiding. The previously used term ‘lazy bladder’ is incorrect and should no longer be used.

A correct diagnosis can only be made by urodynamic evaluation. Renal function studies, renal ultrasound and VCUG should be performed to assess the extent of renal damage and reflux. Long-standing overactivity of the pelvic floor may in some children be responsible for decompensation of the detrusor, leading to a non-contractile detrusor. However, no data are available to support this theory.

Treatment

Treatment is aimed at optimizing bladder emptying after each void. Clean intermittent (self) catheterization is the procedure of choice to promote complete bladder emptying, in combination with treatment of infections and constipation [which may be extreme in these patients]. Intravesical electrostimulation has been described, but at this time it is still not recommended as a routine procedure for children.

Level of evidence 4. Grade of recommendation C

4. VOIDING POSTPONEMENT

A new classification of voiding dysfunction in which children postpone imminent micturition until overwhelmed by urgency, resulting in urgency incontinence [74]. A recent study comparing children with typical OAB to those with voiding postponement revealed a significantly higher frequency of clinically relevant behavioral symptoms in postponers than in children with OAB, suggesting that voiding postponement is an acquired or behavioral disorder [74]. In the children with voiding postponement only 20% exhibiting a fluctuating voiding pattern. It remains to be determined whether or not voiding postponement can develop in the setting of a perfectly normal urinary tract or whether OAB is a necessary precursor.

Level of evidence 4. Grade of recommendation C

5. GIGGLE INCONTINENCE

In some children giggling can trigger partial to complete bladder emptying well into their teenage years, and intermittently into adulthood [75]. The condition occurs in girls and occasionally in boys and is generally self-limiting. The etiology of giggle incontinence is not defined. Urodynamic studies fail to demonstrate any abnormalities, there is no anatomic dysfunction, the upper tracts appear normal on ultrasound, the urinalysis is normal and there are no neurologic abnormalities [76, 77].

It is postulated that laughter induces a generalized hypotonic state with urethral relaxation, thus predisposing an individual to incontinence, however the effect has not been demonstrated on either smooth or skeletal muscle. It has also been suggested that giggle incontinence is due to laughter triggering the micturition reflex and overriding central inhibitory mechanisms. One small study hinted at an association with cataplexy (a state of excessive daytime sleepiness), suggesting involvement of central nervous structures, however with only 7 subjects further evidence is needed [78].

Since the etiology of giggle incontinence is not known it is difficult to determine the appropriate form of treatment. Positive results have been reported with conditioning training, methylphenidate and imipramine [76, 78-80]. Others have tried antimuscarinic agents and alpha-sympathomimetics. There is no acceptable
evidence that any form of treatment is superior to no intervention.
Level of evidence 3. Grade of recommendation D

6. VESICOVAGINAL ENTRAPMENT

Urinary leakage that occurs in girls a short time after voiding to completion, that is not associated with any strong desire to void, may be the result of vesicovaginal reflux

[81]. Urine may become entrapped in the vagina during voiding due to labial adhesions, a funnel shaped hymen, or an inappropriate position on the toilet. The classic presentation is that of a girl who does not spread her legs apart during voiding and who is not sitting all the way back on the toilet seat, but who is rather sitting near the end of the toilet seat tilting forward. Obesity may be an associated risk factor. Changes in voiding position and treatment of labial adhesions will lead usually to resolution of the urine leakage.

Level of evidence 4. Grade of recommendation C

7. ELIMINATION SYNDROME

This is a term used to describe dysfunctional emptying of bowel and/or bladder presenting with symptoms of detrusor overactivity, constipation and infrequent voiding.

The genitourinary tract and the gastrointestinal system are interdependent, sharing the same embryologic origin, pelvic region and sacral innervation. Although children with voiding disturbances often present with bowel dysfunction, until recently this co-existence was considered coincidental. However, it is now accepted that dysfunction of emptying of both systems, in the absence of anatomical abnormality or neurological disease, is inter-related. The common neural pathways, or the mutual passage through the pelvic floor musculature, may provide a theoretical basis for this relationship, as may the acquisition of environmental and developmental learning. The latter can be influenced by episodes of urinary tract infection, constipation, anal pain or trauma, childhood stressors, reluctance to toilet and poor toilet facilities [57, 63, 82].

There is also evidence to suggest that in severe cases symptoms may have a neurological basis.

The Elimination Syndrome [ES] is seen more frequently in girls than boys and is significantly associated with the presence of both VUR and UTI [83]. VUR is slower to resolve and breakthrough urinary tract infections are significantly more common in children with ES when compared to those without the diagnosis. Infections do not ameliorate with antibacterial prophylaxis. Age of first febrile UTI does not appear to be an etiological factor [84], however, recurrence of UTI in children older than 5 years is associated with the presence of ES [84, 85].

Abnormal recruitment of the external anal sphincter during defecation or at call to stool is considered causative, in that it elicits concomitant urethral sphincter and pelvic floor co-contractions. Thus in both systems a functional obstruction to emptying is generated. In the case of the urinary system, high pressures generated by the detrusor muscle to overcome a decrease in urethral diameter can stimulate detrusor hypertrophy, detrusor overactivity, and lead to incompetence of the vesicoureteric junctions. In the early stages of defecation disorders, bowel emptying is incomplete, infrequent and poorly executed. As the dysfunction progresses stool quality becomes abnormal, the child develops distension of the rectum and descending colon, seems to lose normal sensation and develops fecal retentive soiling. If constipation was not present as a predisposing factor, it rapidly develops [82].

Children with elimination syndrome commonly complain of urinary incontinence, non-monosymptomatic nocturnal enuresis, recurrent urinary tract infections, imperative urgency to void (OAB) exceptional urinary frequency and on investigation are often noted to have poor voiding efficiency, vesicoureteric reflux, constipation, soiling, no regular bowel routine and infrequent toileting. The incidence of children with elimination syndrome and sub-clinical signs and symptoms is unknown.

Assessment follows the same process as for other aspects of pediatric bladder dysfunction, with the addition of a 2 week bowel diary and relevant symptom score. The inclusion of an ultrasound rectal diameter measure, either via the perineum or when assessing the bladder, has been shown to be discriminative for children with elimination syndrome. Urinary flow curve, perineal EMG and post void residual urine estimate, when considered in isolation, are not conclusive for the diagnosis of elimination syndrome. There is no evidence to suggest that anorectal manometry is warranted as a first line investigation in these children. Recently a symptom scale for DES has been developed providing objective assessment for diagnosis and quantification of severity [86].

Treatment

Treatment aims at assisting a child to become clean and dry in the short term, by retraining appropriate bladder and bowel awareness and teaching dynamic elimination skills. As bowel dysfunction is more socially isolating than urinary incontinence, and in the light of evidence that amelioration of underlying constipation can relieve bladder symptoms, most clinicians begin with treatment of the bowel. Strategies include disimpaction [if needed], prevention of stool reaccumulation, and post-prandial efforts to empty the bowel while maintaining optimal defecation dynamics. Once stools are being passed regularly, treatment focuses on teaching awareness of age
appropriate fullness in the bladder and training unopposed emptying (without straining or pelvic floor muscle recruitment), at pre-scheduled times. Pelvic floor awareness training and biofeedback therapy are integral.

There are currently no known studies of the efficacy of treatment in children with elimination syndrome. Several authors have evaluated the outcome of constipation management on bladder symptoms, however until last year the baseline characteristics of subjects were not described adequately enough to allow clear diagnosis of elimination syndromes [57, 87].

Level of evidence 4. Grade of recommendation C

V. PRINCIPLES OF NON PHARMACOLOGICAL TREATMENT FOR ALL DIFFERENT STATES

Treatment of the overactive bladder focuses on both the involuntary detrusor contractions and the child’s response to these. The initial treatment of daytime urinary incontinence involves a behavioral and cognitive approach. The child and parent(s)/caregiver(s) are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are managed. Additional treatment involves pharmacotherapy, pelvic floor muscle relaxation techniques and biofeedback, either alone or in combination.

Although there are many studies reported in the literature assessing the effects of various forms of therapy on daytime incontinence and urinary symptoms, many of these are case series rather than being randomized or controlled trials. The paucity of studies evaluating basic standard therapy initiatives has precluded double-blinded trials of novel and multimodal interventions. Whilst clinically important benefits are commonly described, patient numbers, objective outcome measures and length of follow-up are sub-optimal.

The main objectives of treatment are to normalise the micturition pattern, normalise bladder and pelvic floor overactivity and cure the incontinence, infections and constipation. Traditional therapy for day-wetting children is cognitive and behavioural. Children learn to recognize the desire to void and to suppress this by normal central inhibition instead of resorting to holding manoeuvres [i.e. immediate voiding without postponement] to generate urethral compression. Children with dysfunctional voiding learn to initiate voiding with a completely relaxed pelvic floor and to pass urine in association with a detrusor contraction rather than via generation of abdominal pressure. Dietary changes and bowel regimens are used to treat the constipation [87]. Antibiotic prophylaxis may prevent recurrent UTIs, however, data to support this is limited.

“Bladder training” is used widely, but the evidence that it works is variable [50, 88]. Some authors contend that in less severely affected children a thorough explanation of the underlying causes and the expected progress of resolution is sufficient treatment in itself [37]. More active conventional management involves a combination of cognitive, behavioral, physical and pharmacological therapy methods. Common modes of treatment include parent and child reassurance, bladder retraining (including timed toileting), pharmacotherapy, pelvic floor muscle relaxation and the use of biofeedback to inhibit rises in detrusor pressure associated with urinary incontinence [25, 89-91]. Further treatment options include suggestive or hypnotic therapy and acupuncture. A combination of bladder training programs and pharmacological treatment, aimed specifically at reducing detrusor contractions, is often useful and sometimes necessary.

1. BLADDER REHABILITATION AND UROTHERAPY

Initial intervention for OAB and dysfunctional voiding uses a non-pharmacologic approach. This is often termed Urotherapy. Despite its use for many years there is no set format for urotherapy and many clinical studies utilize differing combinations of therapies, which makes it difficult to evaluate the results [25, 51, 90]. The aim of urotherapy is to normalize the micturition pattern and to prevent further functional disturbances. This is achieved through a combination of patient education, cognitive, behavioral and physical therapy methods.

A Danish report of the outcome of standard urotherapy in 240 children with daytime incontinence noted achievement of dryness in 126 children (55%). Alarm therapy has traditionally been used for the treatment of nocturnal enuresis and was recently used in management of daytime wetting. When a time watch was utilized as a reminder to void at regular intervals 70% of children became dry. An earlier study of a contingent alarm [which sounded when the child wets] versus a noncontingent alarm system (which sounded at intermittent intervals to remind the child to void) over 3 months in 45 children [92] was equally successful for the achievement of continence. Predictors for dryness included a low voiding frequency, larger volumes voided in relation to age-expected storage and fewer incontinent episodes per week [93].

Following a 3 month training programme, 42.8% of daywetting children were cured at 1 month, 61.9% by 6 months, and 71.4% by 1 year [94]. Allen et al [95] reported that urotherapy patients with good compliance with timed voiding were significantly more likely to improve their continence than those with poor
compliance. It has recently been highlighted however, that there is frequently conflict between school rules, routines and toilet facilities and the urotherapy programme components. Adaptive coping techniques added to urotherapy training may enhanced gains in dryness.

In children with OAB and dysfunctional voiding the pelvic floor muscles relaxation is impaired during voiding. Physiotherapy is concerned with re-training of specific muscle groups. Adjunctive physiotherapeutic input offers children different strategies to achieve pelvic floor relaxation during micturition.

Level of evidence 3. Grade of recommendation C

2. ADJUNCTIVE BIOFEEDBACK

Biofeedback is a technique in which physiological activity is monitored, amplified and conveyed to the patient as visual or acoustic signals, thereby providing the patient with information about unconscious physiological processes. Biofeedback may be utilized for the management of both filling phase (detrusor overactivity) and voiding phase (dysfunctional voiding due to pelvic floor muscle overactivity) abnormalities.

Biofeedback can help children to identify how to relax their pelvic floor muscles or recognize involuntary detrusor contractions.

Training with biofeedback can be used as a single treatment [96, 97], or in conjunction with a comprehensive rehabilitation program [98, 99]. It may be performed by a cystometrogram during which the child is taught to recognize and inhibit involuntary detrusor contractions by watching the pressure curve during cystometry. This is invasive and a time consuming process with limited use as a routine treatment.

More commonly pelvic floor muscle relaxation is taught through the use of EMG biofeedback and real-time uroflow. The child sits on a toilet with a flow transducer, watching both the flow curve and EMG on a computer display, and attempts to empty completely in one relaxed void. Ultrasound may be used to determine the post void residual and demonstrate complete emptying. Interactive computer games are commonly used to make biofeedback training more attractive to children [100, 101], however care should be taken that posture and muscle recruitment approximates that of the voiding position.

The results of biofeedback are commonly reported as case series rather than RCTs. Results are generally positive but overall may not be superior to high quality standard urotherapy. The group receiving adjunctive biofeedback in the Vasconcelos study [94] did not achieve greater continence rates at the study end point, although a greater proportion of subjects achieved earlier dryness. Furthermore, the post void residual volumes were significantly reduced in the biofeedback group compared to the standard therapy only group.

Long duration follow-up, whilst desirable, confounds results of intervention in children who are continually growing and maturing. Hellstrom et al report results of a 6 week bladder rehabilitation program inclusive of biofeedback and [90] and note that at 3 years 71% of the children with detrusor overactivity, 70% of those with dysfunctional voiding and 73% of those with a combined disturbance had a normal micturition pattern. The potential for bias from intercurrent events and interventions precludes statements about the efficacy of biofeedback alone.

Level of evidence: 3. Grade of recommendation C

3. CLEAN INTERMITTENT (SELF) CATHETERISATION

In children with an underactive detrusor, bladder emptying can be achieved with timed and double voiding. If this does not adequately empty the bladder clean intermittent self-catheterization (CISC) may be tried [102-104]. This requires careful guidance for both the child and the parents. Sometimes it is necessary to give the child a suprapubic catheter for a while and gradually prepare him/her to accept CISC. Once the infections have cleared and the child is continent it will become easier for both the parents and the child to accept. The frequency of CISC depends on the severity of the problem and may vary between four times a day and once a day before going to bed.

Level of evidence 4 Grade of recommendation C

4. NEUROMODULATION

Neuromodulation has been used in adults for a variety of lower urinary tract symptoms and has recently been applied in children. The use of transcutaneous stimulation with surface electrodes stimulating the sacral root (S3) has shown promising results, especially when tested as part of a randomized controlled trial [105]. Transcutaneous and percutaneous neuromodulation delivered over either the sacral outflow or peroneal region of the ankle at a frequency between 10-25 Hz, has proven a useful adjunctive treatment in children with an detrusor overactivity [22, 24, 25]. Intravesically stimulation can impact function of an underactive detrusor and potentially improve detrusor contractility and enhance bladder emptying [106, 107]).

Electrical current directly affects the central nervous system by artificially activating neural structures; facilitating both neural plasticity and normative afferent and efferent activity of the lower urinary tract. For children with structural abnormalities, for example imperforate anus, electrostimulation is one method of facilitating strength gains in the skeletal muscle and its fascial attachments. Treatment is particularly useful in patients with very little pelvic floor awareness
to stimulate muscle recruitment. Once neural efficiency has improved, training is augmented by active pelvic floor contractions.

A literature search revealed 10 reports of the use of neuromodulation in children with non-neurogenic bladder dysfunction. Only one of these studies was randomized and controlled, whilst the rest were case series. Use of neuromodulation in children with neurogenic LUT dysfunction has been reported in 6 studies, 2 of which were randomized controlled trials. From Table 2 it is clear that different modes of application have been trialed in mostly small series of children. There is minimal standardization of populations, application parameters or outcome measures. Thus evidence is largely drawn from low quality studies. Clearly neuromodulation in children warrants larger, controlled and randomized studies.

Reported changes with neuromodulation include: significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased frequency of urinary tract infection. Significant improvement in urodynamic parameters of bladder compliance, number of involuntary contractions, and bladder volume at first detrusor contraction have also been noted.

More recently the first reports on sacral nerve stimulation with implantable electrodes have been published. In a group of 20 patients between 8 and 17 years old followed prospectively, urinary incontinence, urgency and frequency, nocturnal enuresis and constipation were improved or resolved in 88% (14 of 16), 69% (9 of 13), 89% (8 of 9), 69% (11 of 16) and 71% (12 of 17) of subjects, respectively. Complications were seen in 20% of patients. [108] Due to the uncontrolled design the level of evidence is low. Experience from adults offered this treatment modality suggests future positive development in children to be likely.

Level of evidence: 4. Grade of recommendation D

5. ALARM TREATMENT

Alarm therapy has traditionally been used for the treatment of nocturnal enuresis and has rarely been used for daytime wetting. Only one randomised clinical trial has been published to establish the efficacy of this form of treatment. Halliday et al compared a contingent alarm which sounded when the child wets] with a noncontingent alarm system (which sounded at intermittent intervals to remind the child to void) [92]. Forty-four children participated in the study, 50% were assigned to each form of therapy for a 3 month period. Success was measured as 6 consecutive weeks without daytime wetting. Nine children in the non-contingent group and 6 children in the contingent group had persistent wetting. Although the risk of persistent wetting with the contingent alarm was 67%

6. CONCLUSION

Most clinical studies describe combinations of therapies rather than single interventions, which makes it difficult to evaluate the results. Physiotherapy and biofeedback both focus on the pelvic floor. Relaxation of the pelvic floor during voiding is essential for normal voiding and most of which patients are unable to relax their pelvic floor muscles. Biofeedback is important for showing the children the effect of their efforts. Most studies only state the clinical responses, and do not provide information on urodynamic parameters before and after treatment.

A ‘normal’ flow curve may not mean normal voiding if no information is provided on post-void residual urine. In most papers the inclusion and exclusion criteria are not clearly documented, and it may very well be that the more difficult patients with both storage and voiding dysfunction were included in the study population. Furthermore, different series may describe different groups of patients due to poor definitions and an inadequate classification system. In children with a suspected bladder outlet obstruction, endos-copic investigations should be performed. Most often the anatomic abnormality causing obstruction can be treated at the same time. In girls, a meatal web may cause a deflection of the stream upwards [causing stimulation of the clitoris and bulbocavernous reflex]. A meatotomy may cure this problem, though no information on the long-term effects is available [64].

VI. PHARMACOLOGICAL TREATMENT

Antimuscarinic therapy remains one of the common forms of therapy for the detrusor overactivity. Its use is predicated on the concept that parasympathetic mediated stimulation of muscarinic receptors in the bladder causes detrusor overactivity, which is responsible for the symptoms of detrusor overactivity. Antimuscarinic agents have been demonstrated to increase bladder capacity, increase bladder compliance and decrease detrusor contractions in neurogenic detrusor overactivity. Detrusor overactivity is believed to play a role in many children with functional incontinence, vesicoureteral reflux and
### Table 2. Study parameters in paediatric neuromodulation trials

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Population</th>
<th>Design</th>
<th>N</th>
<th>Mode of application</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gus 2004</td>
<td>Neurogenic (Spina bifida)</td>
<td>RCT</td>
<td>42</td>
<td>Sacral implant</td>
<td>n/s difference from controls for continence</td>
</tr>
<tr>
<td>Marshall 1997</td>
<td>Neurogenic (MMC)</td>
<td>RCT</td>
<td>50</td>
<td>Transcutaneous</td>
<td>n/s difference from controls for continence</td>
</tr>
<tr>
<td>Johnston 2005</td>
<td>Neurogenic (spinal cord injury)</td>
<td>Series</td>
<td>2</td>
<td>FES implant</td>
<td>Suppression of detrusor overactivity in 1 pt</td>
</tr>
<tr>
<td>Han 2004</td>
<td>Neurogenic (MMC)</td>
<td>Series</td>
<td>24</td>
<td>Intravesical</td>
<td>Significant ↓ in faecal incontinence</td>
</tr>
<tr>
<td>De Gennaro 2004</td>
<td>Neurogenic and Non neurogenic</td>
<td>Series</td>
<td>6 / 17</td>
<td>Percutaneous tibial nerve</td>
<td>n/s difference in neuropathic pts 5/9 with incontinence cured</td>
</tr>
<tr>
<td>Gladh 2003</td>
<td>Neurogenic and Non neurogenic</td>
<td>Series</td>
<td>20 / 24</td>
<td>Intravesical</td>
<td>40% cure neurogenic 83% cure non neurogenic</td>
</tr>
<tr>
<td>Hagstrom 2008</td>
<td>Non neurogenic</td>
<td>RCT</td>
<td>25</td>
<td>Transcutaneous sacral</td>
<td>8/13 partial response</td>
</tr>
<tr>
<td>Humphreys 2006</td>
<td>Non neurogenic (severe DES)</td>
<td>Series</td>
<td>23</td>
<td>Sacral implant</td>
<td>3/19 cured of incontinence 2/16 able to stop CIC</td>
</tr>
<tr>
<td>Barroso 2006</td>
<td>Non neurogenic (urge syndrome)</td>
<td>Series</td>
<td>36</td>
<td>Transcutaneous sacral</td>
<td>12/19 “complete” improvement</td>
</tr>
<tr>
<td>Lee 2005</td>
<td>Non neurogenic (infrequent voiding)</td>
<td>Series</td>
<td>12</td>
<td>Intravesical</td>
<td>Signif ↑ max flow rate, signif ↓ PVR</td>
</tr>
<tr>
<td>Bower 2001</td>
<td>Non neurogenic</td>
<td>Series</td>
<td></td>
<td>Transcutaneous sacral</td>
<td>73% improved continence</td>
</tr>
<tr>
<td>Gladh 2001</td>
<td>Non neurogenic (DI diagnosis)</td>
<td>Series</td>
<td>48</td>
<td>Anal plug</td>
<td>18/48 cured</td>
</tr>
<tr>
<td>Hoebeke 2001</td>
<td>Non neurogenic</td>
<td>Series</td>
<td>41</td>
<td>Transcutaneous sacral</td>
<td>56% cured after 1 year</td>
</tr>
<tr>
<td>Trsinar 1996</td>
<td>Non neurogenic</td>
<td>Controlled trial</td>
<td>73</td>
<td>Anal plug</td>
<td>+ve gains in active group</td>
</tr>
</tbody>
</table>
Tolterodine, a nonselective antimuscarinic, is currently being used for the treatment of detrusor overactivity in children with moderate to severe daytime incontinence [51].

Despite the frequent use of anticholinergic therapy, often in conjunction with a behavioral therapy regimen, the outcome of pharmacologic therapy for daytime urinary incontinence is “unpredictable and inconsistent” and there are few randomized studies available to assess drug safety and efficacy. Currently the pharmacologic therapy most widely used in children with detrusor overactivity is oxybutynin [111]. More recently, a long-acting formulation, Oxbutynin- XL, has been approved by the FDA for use in children [112]. Historically, oxybutynin use has been limited by its adverse effect profile with such side effects as dry mouth, constipation, facial flushing and CNS effects. The incidence of side effects seems to be dose-related, both for oral and intravesical administration [113].

The CNS effects are related to the ability for oxybutynin to cross the blood brain barrier. Oxybutynin- XL utilizes a novel delivery system, which results in absorption in the large intestine, thereby bypassing the first pass metabolism in the liver. This leads to a decrease in the amount of active metabolite [produced in the liver]: resulting in a more favorable tolerability profile. The delivery system requires an intact tablet and thus it cannot be cut or crushed to facilitate swallowing. Another method of delivery of oxybutynin is intravesical therapy. This method of delivery also avoids the first pass effect and leads to increased amounts of oxybutynin available compared to immediate release oxybutynin. Its use in the neurologically intact patient is limited by the need for catheterization [114].

There are only a few studies, none randomized and double blinded, assessing the efficacy of oxybutynin in detrusor overactivity in children. Curran et al, in a retrospective review assessed the efficacy of several agents, primarily oxybutynin in children with non-neurogenic detrusor overactivity, confirmed by urodynamic who were refractory to behavioral therapy. Some children were treated with combination therapy. Eighty percent had complete resolution or a significant improvement in their urinary symptoms. The authors noted an average time to resolution of symptoms of 2.7 years [range 0.2 to 6.6], however patients were not followed frequently [115]. In a recent study by Van Hoeck et al, holding exercises with and without oxybutynin showed no beneficial effect of adding oxybutynin [116].

Level of evidence: 3. Grade of recommendation C

Tolterodine, a nonselective antimuscarinic is currently being used for the treatment of detrusor overactivity in adults. It is the first antimuscarinic agent designed specifically for use in detrusor overactivity and is felt to be “bladder selective”. It’s affinity for the bladder compared to other organ systems leads to an improved tolerability profile. The chemical nature of tolterodine makes it less likely to penetrate the blood brain barrier, which is supported by EEG studies [117]. The delivery system of the long acting preparation is such that the capsule may be cracked and “sprinkled” on food. Tolterodine has not been approved for use in children but there are several studies, which evaluate its safety and efficacy in children with detrusor overactivity. Hjälmas reported the results of an open label, dose escalation study using immediate release tolterodine in 33 children [118]. Doses ranged from 0.5 mg po BID to 2 mg po BID for 14 days. The results demonstrated a 21% (23% with 2 mg po BID) mean decrease from baseline in micturition frequency and a 44% mean decrease from baseline for the number of incontinence episodes in children treated with 1 mg and 2 mg po BID. Bolduc et al reported on a prospective crossover study of 34 children followed for > 1 year who were crossed over from oxybutynin to tolterodine because of adverse effects with oxybutynin [119]. Detrusor overactivity was confirmed in 19/20 who had urodynamic studies performed prior to therapy. Children received either 1 mg or 2 mg po BID and the median treatment period was 11.5 months. Efficacy was assessed by a questionnaire and was comparable for oxybutynin and tolterodine. Sixty-eight percent noted a > 90% reduction in wetting episodes at 1 year and an additional 15% noted a > 50% reduction in wetting episodes. Fifty nine percent reported no side effects with tolterodine and 18% reported the same side effect as with oxybutynin, but felt it was less severe. Eight patients [24%] discontinued tolterodine.

Munding et al reported on the use of tolterodine in children with “dysfunctional voiding” manifested as daytime wetting, frequency or urgency [120]. There was no documentation of uroflow studies to make the diagnosis of “dysfunctional voiding” and from the symptoms these children appeared to have detrusor overactivity. Children were started on behavioral modification for 4-6 weeks and pharmacologic therapy was instituted if they failed or had only slight improvement with behavioral therapy. A minimum of 1 month’s follow-up was needed for inclusion, but the mean follow-up was only 5.2 months. Doses ranged from 1 mg po BID to 4 mg po BID. Assessment of results was made by telephone survey. Thirty three percent had > 90% reduction in daytime and nighttime wetting episodes and 60% had > 50% reduction. Four patients [13.3%] had side effects, constipation in 2, dry mouth in 1 and diarrhea in 1.

Reinberg et al performed an open label parallel group retrospective study of the efficacy and safety of immediate release and long acting tolterodine and extended release oxybutynin [121]. Children started
out with the lowest possible dose, 2 mg tolerodine and 5 mg oxybutynin and titrated up according to response and side effects. Children were arbitrarily assigned to therapy based on the formulary restrictions of the health plan and there was an uneven distribution of patients in the treatment groups. Final dose and duration of treatment were not noted. Study nurses asked about side effects and a voiding diary was used to assess efficacy. The authors concluded that extended release tolerodine \( [p < 0.05] \) and oxybutynin \( [p < 0.01] \) were more effective than immediate release tolerodine in improving urinary incontinence symptoms and that extended release oxybutynin was more effective than extended release tolerodine in resolving diurnal incontinence \( (p < 0.05) \). Long term tolerability of tolerodine extended release in a large pediatric population has been shown. [122]

Level of evidence: 3. Grade of recommendation C

One of the drugs which has been investigated in a randomized placebo controlled trial was tolerodine [123, 124]. Because of serious cardiac side effects tolerodine has been withdrawn from the market. Trospium chloride is another agent, which has been used in small series in children. It is currently available in a twice a day dosing formulation. In the adult population, there is a 16% intra-individual variability in bioavailability and 36% inter-individual variability. Absorption is affected by food intake. Trospium's chemical structure make it unlikely to penetrate the blood brain barrier as supported by EEG studies [117]. Lopez Periera et al evaluated the use of trospium in 62 children with documented detrusor overactivity and absence of 'detrusor sphincter dyssynergia' [125]. Children were randomly assigned to 10, 15, 20 or 25 mg of trospium administered in 2 divided doses or placebo. Fifty-eight children were evaluated. Response rates were assessed by incontinence episodes and urodynamic parameters. Overall, 32% had an excellent response, 42% a good response and 8% a fair response. Detrusor overactivity completely resolved in 35%. Four children had medication related adverse effects including headache, dizziness, abdominal cramps and dry mouth.

Level of evidence: 3. Grade of recommendation C

Like trospium, propiverine has been used in children, but results are variable and inclusion and outcome criteria were not in accordance with ICCS definitions making comparison with other studies difficult [19]. Recently a randomized, double-blind, placebo-controlled phase 3 trial with propiverine in children aged 5-10 yr was performed. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. The primary efficacy parameter showed a decrease in voiding frequency (-2.0 episodes for propiverine versus -1.2 for placebo; \( p = 0.0007 \)). Superiority could also be demonstrated for voided volume (31.4 vs. 5.1 ml; \( p < 0.0001 \)) and reduction in incontinence episodes (-0.5 vs. -0.2 episodes per d; \( p = 0.0005 \). This clinical trial showed superior efficacy of propiverine over placebo and good tolerability for the treatment of children suffering from DO and urinary incontinence. [126] This is the first study with level of evidence 1 that shows beneficial effect of anticholinergic therapy.

Level of evidence: 1. Grade of recommendation B/C (only single study)

**Botulinum toxin** is currently being used in children, mainly with neurogenic detrusor overactivity. Initial results seem promising, but more studies need to be done. In children, 300 Units on average, are injected in 30-40 spots [127]. The trigone should not be injected, as there is an increased risk of reflux developing. The results last about 6-9 months. Botulinum toxin is not registered for injection in the detrusor or the sphincter in children. It is off label used and further prospective studies are needed before general recommendation.

One prospective uncontrolled study by Hoebeke et al shows beneficial effects of botulinum toxin in 70% of children with therapy resistant detrusor overactivity. [128]. Injection of botulinum toxin is also possible into the external sphincter, but the results are more variable and last only 3-4 months [129]. Radotic et al describe excellent results in the treatment of dysfunctional voiding. In 20 children good results are described for 17 patients. [130] In a retrospective study by Franco et al, similar results are described in 16 children, however using a higher dosage [130, 131].

Level of evidence: 3. Grade of recommendation C

**Treatment of the overactive pelvic floor and sphincter** is much more difficult. Treatment with *alpha*-adrenergic blockade seems promising, but from the presented studies it is difficult to draw firm conclusions: as most series are small, not randomized and describe a mixed patient population [132-134].

In a more recent uncontrolled study by Donohoe et al a total of 26 patients with Primary Bladder Neck Dysfunction (20 males, 6 females, mean age 12.8 years) were treated with alpha-blockers. Mean average and maximum uroflow rates improved from 5.5 to 12.6 cc per second and from 10.3 to 19.7 cc per second, respectively, while mean EMG lag time decreased from 24.4 to 5.7 seconds and post-void residual urine volume from 98.9 to 8.9 cc [all \( p < 0.001 \)]. Mean follow-up was 31 months and no major adverse side effects were observed. [135] Further randomized controlled studies are needed to define the place of alpha-blockers.

Level of evidence: 3. Grade of recommendation C

Because there is much variability in presenting symptoms as well as the underlying pathology an individual approach is advisable: a step by step algorithm has been developed by Marschall-Kehrel,
E. NEUROGENIC DETRUSOR-SPHINCTER DYSFUNCTION

I. INTRODUCTION

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of lower urinary tract dysfunction which may lead to incontinence, urinary tract infections (UTIs), vesicoureteral reflux (VUR), and renal scarring. Surgery may be required to establish adequate bladder drainage, and potentially, if not managed properly, NDSD can cause renal failure, requiring dialysis or transplantation. Management of neurogenic detrusor sphincter dysfunction in children has undergone major changes over the years. While the use of diapers, permanent catheters, external appliances and various forms of urinary diversion were acceptable treatment modalities; these are now reserved for only a small number of resistant patients [1]. Initially long term renal preservation was the only aim of therapy and early diversion had the best long term results for preserving renal function. Despite some of the complications of ileal conduits and cutaneous urostomies requiring secondary surgery, this form of treatment offered the best outcome for renal preservation with socially acceptable continence [2].

Introduction of clean (self) intermittent catheterization revolutionized the management of children with NDSD. It, not only made conservative management a very successful treatment option, but also made surgical creation of continent reservoirs a very effective alternative with a good quality of life [3].

The most common cause of NDSD in children is neurospinal dysraphism and this condition presents with various patterns of detrusor-sphincter dysfunction within a wide range of severity. About 15 % of neonates with myelodysplasia have no signs of lower urinary tract dysfunction (LUTD) when initially studied [4]. However there is a high chance of progressive changes in the dynamics of the neurological lesion in time and even babies with normal LUT function at birth have a 1 in 3 risk of developing either detrusor sphincter dyssynergia or areflexia by the time they reach puberty [5]. Nearly 60 % of the neonates with neurospinal dysraphism may develop upper tract deterioration due to increased detrusor filling pressures and infections, with or without reflux [6,7].

As our understanding of urodynamic studies has evolved it allowed us to understand the nature and severity of the problems and administer management in a more rational manner differing according to the functional characteristics of each detrusor sphincter unit. Although the last quarter century has witnessed a remarkable progress in understanding pathophysiology, pathogenesis and the management of these children, the main goals of treatment remained the same i.e. the prevention of urinary tract deterioration and the achievement of continence at an appropriate age.

II. PRESENTATION OF NEUROGENIC DETRUSOR SPHINCTER DYSFUNCTION IN CHILDREN

Neurogenic detrusor sphincter dysfunction can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord or the peripheral nervous system. The type and degree of detrusor sphincter dysfunction is poorly correlated with the type and spinal level of the neurologic lesion.
The closure of spinal canal in utero takes place in the caudal direction from the cephalic end and is completed at around 35 days of gestation. The failure of mesodermal in-growth over the developing spinal canal results in an open lesion most commonly seen in the lumbosacral area. The degree of this closure deficiency contributes to a variable presentation of neural injury with varying degrees of LUTD and lower extremity problems. Developmental anomalies that result from defects in neural tube closure are termed as myelodysplasia. This term includes a group of lesions like spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele.

Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children [8].

The neurologic lesions produced by myelodysplasia are variable contingent on the neural elements that protrude within the meningocele sac. The bony vertebral level correlates poorly with the neurologic lesions produced. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion and scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth [9-10].

In occult myelodysplasia the lesions are not overt and often with no obvious signs of neurologic lesion. The diagnosis of this condition has increased since the advent of spinal ultrasonography and magnetic resonance imaging. Yet, in nearly 90% of patients, a cutaneous abnormality overlies the lower spine and this condition can easily be suspected by simple inspection of the lower back. These cutaneous lesions can vary from a dimple or a skin tag to a tuft of hair, a dermal vascular malformation, or an obvious subdermal lipoma [8]. Alterations may be found in the arrangement or configuration of the toes, along with discrepancies in lower extremity muscle size and strength with weakness or abnormal gait. Back pain and an absence of perineal sensation are common symptoms in older children.

Incidence of abnormal lower urinary tract function in patients with spina bifida occulta is as high as 40%. Occult lesions may also become manifest with tethering of the cord later in life. This can lead to changes in bowel, bladder, sexual and lower extremity function.

Sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. Perineal sensation is usually intact and lower extremity function is usually normal and the diagnosis is made when a flattened buttock and a short gluteal cleft is seen on physical examination. This lesion may produce variable degrees and patterns of LUTD.

Cerebral palsy patients may also present with varying degrees of LUTD usually in the form of overactive detrusor and wetting.

Imperforate anus is a rare anomaly and presents with a closed rectum that does not open onto anal skin verge. These children may present with accompanying spinal cord pathology. This is more common when the rectum ends above the pelvic floor muscles and they should undergo a MR imaging for detection. Early detection of this problem in imperforate anus patients is important to improve the child’s chance of maintaining healthy kidneys and becoming continent.

III. CLASSIFICATION: PATTERN RECOGNITION

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of the neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurologic disease or injury. Such systems are based on the localization of the neurologic lesion and findings of the neuro-urologic examination. These classifications have been of more value in adults as neurogenic lesions are usually due to trauma and more readily identified.

In children the spinal level and extent of congenital lesion is poorly correlated with the clinical outcome. Indeed, severe detrusor sphincter dysfunction has been associated with minimal bony defects. Various possible neuropathologic lesions of the spinal cord including syringomyelia, hydromyelia, tethering of the cord and dysplasia of the spinal cord are the causes of these disparities and they may actually extend several segments above and below the actual site of the myelomeningocele. Therefore urodynamic and functional classifications have been more practical for defining the extent of the pathology and planning treatment in children.

The detrusor and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction. Determined by the nature of the neurologic deficit, they may be either in an overactive or in an inactive state. The detrusor may be overactive with increased contractions, with a diminished bladder capacity and compliance or be inactive with no effective contractions; the bladder outlet (urethra and sphincter) may be independently overactive causing functional obstruction or paralyzed with no resistance to urinary flow leading stress incontinence.

These conditions may exist in any combination [9-14].
Urodynamic evaluation (preferably in combination with fluoroscopy) makes pattern recognition possible. Four major types are usually used to describe the detrusor-sphincter dysfunction:

1. Detrusor overactivity with overactivity of the sphincter (mostly dyssynergia),
2. Detrusor overactivity with normal or underactivity of the sphincter,
3. Detrusor underactivity with sphincter overactivity
4. Detrusor underactivity with sphincter underactivity.

Besides these 4 patterns, one can use the ICS classification: overactive detrusor, underactive detrusor, overactive sphincter and underactive sphincter. Sometimes this is more helpful, as the detrusor may be overactive during filling, but underactive during ‘voiding’.

The urodynamic investigation is considered normal when there is suitable age matched capacity, good compliant bladder with no overactivity and normal innervation of the sphincter with normal sacral reflexes and an increase in pelvic floor activity during filling and no activity during voiding. Presence of overactivity during filling with or without decreased capacity and compliance is usually seen when there is upper motor neuron lesion and this is usually accompanied by overactivity of the sphincter and failure to relax during voiding. A lower motor neuron lesion is considered when the detrusor contractions are weak or lost and the sphincter is underactive. Urodynamic investigations make it possible to establish a management plan for each individual patient.

Evidence level 3. Grade of recommendation B

For the very young child the combination of an overactive detrusor and sphincter is potentially dangerous because of the high intravesical pressures, which will put the upper tract at risk (vesicoureteral reflux and hydronephrosis), whereas an underactive detrusor and paralysed sphincter is relatively safe, providing a low-pressure reservoir [15-17].

Level of evidence: 2

IV. MANAGEMENT

The main aim in management of NDSD in children is to ensure and maintain a reservoir with normal age-matched capacity and good compliance that can be emptied completely at low pressures and at regular intervals.

In the first years of life the kidneys are highly susceptible to backpressure and infection. In this period emphasis will be on documenting the pattern of neurogenic detrusor- sphincter dysfunction and assessing the potential for functional obstruction and whether or not there is vesicoureteral reflux [17,18]. Ultrasound studies and a VCUG or video-urodynamics to exclude reflux have to be performed soon after birth. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydrourephrosis or vesicoureteral reflux, and can help identify children at risk for upper urinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks and needs to be repeated at regular intervals, in combination with evaluation of the upper tracts [19].

Level of evidence 3. Grade of recommendation: B

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has lead to a consensus that children do not develop upper tract deterioration when managed early with CIC and antimuscarinic medication [19-22]. Therefore initial treatment should consist of oral or intravesical antimuscarinic drugs in combination with clean intermittent catheterisation, to start soon after birth in all babies and especially in those with signs of possible outlet obstruction [23-27].

Level of evidence 2. Grade of recommendation: B

The early initiation of intermittent catheterization in the newborn period, makes it easier for parents to master it and for children to accept it as they grow older [28,29].

With early management not only are upper tract changes less, but also bladders are better protected and incontinence rates are much lower.

It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance: resulting in a small non-compliant bladder with progressively elevated pressures. It is believed that early institution of intermittent catheterization and anticholinergic drugs may prevent this in some patients [30-32].

Level of evidence 3

Retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with early start of CIC [23,24].

Level of evidence 4

The main disadvantage of CIC is bacteriuria which is found in 60% of the patients, but symptomatic UTIs are less common (20%) with CIC when compared to the group without CIC (40%). Since the risk of reflux is similarly lower with CIC the renal scar rates are
lower. CIC alone when begun in infancy can achieve continence at a rate of 60%. When combined with newer and more potent antimuscarinic drugs continence rates approach 75-80% [33-36].

At present oxybutynin, tolterodine, trospium and propiverine are the most frequently used anti-cholinergic drugs to treat detrusor overactivity in children. Some clinical studies are available, but no randomised placebo controlled studies have been performed [31,37-41].

A prospective controlled trial evaluating trospium in children reports that trospium is effective and safe in correcting detrusor overactivity in children but this study does not include patients with a neurogenic bladder [42].

Two different forms of tolterodine have been investigated in children with neurogenic bladder and extended release formulation of tolterodine is found to be as efficient as the instant release form with the advantages of being single dosage and less expensive [43].

Level of evidence 3. Grade of recommendation: B

Use of medication in children with neurogenic bladder to facilitate emptying has not been studied well in the literature. Few studies investigating the use of alpha-adrenergic blockade in children with neurogenic bladder report good response rates but they are non-controlled studies and long-term follow-up is lacking [44-46].

Level of evidence 4

Use of intravesical oxybutynin in children with poorly compliant neurogenic bladder has been investigated in some studies and incontinence has been shown to be improved significantly in most studies, with "dry and improved" rates ranging from 61% to 83% [47]. Use of lidocain intravesically also has been shown to be effective to improve bladder capacity and compliance and decrease overactivity in children with neurogenic bladder [48]. None of these studies are randomized controlled trials and evidence available is insufficient to strongly recommend this therapy. There are no data available on long term use.

Level of evidence 3. Grade of recommendation: C

In neurogenic bladders that are refractory to antimuscarinics and still remain to be in a small capacity and high-pressure state, injection of botulinum toxin into the detrusor has been introduced to be a new treatment alternative [49-50]. Initial promising results in adults have also initiated its use in children. So far pediatric studies have been open-label studies and prospective controlled trials are lacking [51-53]. Injection of botulinum toxin in therapy resistant bladders seems to be an effective and safe treatment alternative. This treatment seems to be more effective in bladders with evidence of detrusor overactivity, while non-compliant bladders without obvious detrusor contractions are unlikely to respond to this treatment. Dosage in children should be determined by body weight, with caution regarding total dose if also being used for treatment of spasticity, and minimum age [54-57].

Level of evidence 3. Grade of recommendation C

In a single study urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [58].

Intravesical electrical stimulation of the bladder has been introduced more than four decades ago and it has been tested in some open clinical trials in children since 1984. Its practice is limited to a few centres who have reported varying results. The nature of this type of treatment (time consuming and very dedicated personal) does not make it attractive for the majority of treatment centres [59].

Intravesical electrical stimulation of the bladder

Level of evidence 3. Grade of recommendation C

Children with neurogenic bladder also have disturbances of bowel function. Fecal incontinence in these children is frequently unpredictable; it is related to the loss of lower bowel sensation and function, altered reflex activity of the external sphincter and the consequent failure to fully empty the rectum [60].

The majority of children with a neurogenic bladder also have constipation and this is managed most commonly with laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain fecal continence and this may have to be started even at a very young age. With antegrade or retrograde enemas, the majority of these children's constipation can be managed and they may attain some degree of fecal continence [61-65].

Level of evidence 3. Grade of recommendation C

Biofeedback training programs to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management program in achieving fecal continence [66]. Electro-stimulation of the bowel may also offer a variable improvement in some patients [67].

Level of evidence 3. Grade of recommendation D

Biofeedback training programs

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, patients with urinary tract infections should be treated if symptomatic. There is strong evidence not to prescribe antibiotics to patients with bacteriuria without clinical symptoms [68-71]. Bacteriuria is seen in more than
half of the children on clean intermittent catheterization (CIC), but patients who are asymptomatic do not need treatment.

Level of evidence 3. Grade of recommendation B

Patients with vesicoureteral reflux and urinary tract infection often should be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [72].

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. Patients with myelodysplasia have sexual encounters, and studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. Therefore counseling patients regarding sexual development is important in early adolescence.

Children with a good response to antimuscarinic treatment and an overactive sphincter may be continent in between catheterizations. Bladder pressure and (normal) development of the upper tracts will determine whether additional treatment is necessary.

Children with therapy resistant overactivity of the detrusor, or small capacity and poor compliance will usually need additional surgical treatment such as bladder augmentation.

Children with detrusor overactivity but with underactive sphincters will be in a better shape in terms of protecting their upper tracts, but they may be severely handicapped because of their incontinence. Initial treatment will be intermittent catheterization (as it may reduce the degree of incontinence and offers a much better control over urinary infections) in combination with antimuscarinic drugs. At a later age the outlet resistance has to be increased in order to render them continent [73]. There is no medical treatment of proven efficacy that increases bladder outlet resistance. Alpha-receptor stimulation of the bladder neck has not been very effective. Surgical procedures need to be considered for maintaining continence [75-77].

It is important to establish adequate bowel emptying before attempting to correct bladder dysfunction surgically or medically.

Patients with a neurogenic bladder require lifelong supervision and monitoring of renal function is extremely important. Periodic investigation for upper tract changes, renal function and bladder status is mandatory. Therefore repeat urodynamic studies are needed more frequently at younger ages and less frequently at later ages. A repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure.

In case of any apparent changes both in the upper and lower urinary tract or any changes of neurological symptoms, a more detailed examination including urodynamics and MRI of the spine is indicated. Renal failure usually progresses slowly but may occur with startling rapidity in these children.

F. SURGICAL MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN

Intermittent catheterization and drug therapy are usually sufficient in the majority of cases for maintaining continence and preserving upper tracts. Surgical procedures should be considered if conservative measures fail to achieve continence between catheterizations or preserve upper tracts.

Surgical intervention is required for congenital and acquired diseases interfering with the function of the storage function of the bladder, the sphincter mechanisms or which bypass normal sphincter mechanisms. A plethora of different surgical procedures has been proposed to maintain continence by using different mechanisms. Various procedures using different mechanisms for maintaining continence may be used in the same patient.

In many cases measures such as intermittent catheterization and drug therapy are needed in addition to surgery since most of the surgical procedures can achieve ‘dry-ness’, but rarely restore normal voiding.

Patients with bladder neck incompetence pose a real challenge and require a different approach. All surgical procedures to “reconstruct” the bladder neck have one thing in common; an obstruction is created to enhance bladder outlet resistance. Even if successful, normal spontaneous voiding with low pressures without external help is not possible in most patients. Considering the long-term outcome, it may be better not to void spontaneously when bladder outlet resistance is increased because longstanding outlet resistance may cause secondary changes of the bladder wall.

The rarity and complexity of the conditions associated with congenital incontinence in children precludes the establishment of higher levels of evidence because of the rarity and spectrum of the pathology. Results are highly dependent on the skills of the individual surgeon. Therefore graded recommendations for specific procedures cannot be provided. There are no randomized controlled trials (level 1 and 2 evidence). Based on the available literature most studies have a level of evidence 3-4 and grade of recommendation C or D.
I. ABNORMALITIES OF STORAGE

1. BLADDER EXSTROPHY

The incidence of bladder exstrophy is 1 per 30,000 live births. (male to female ratio 2:3.1-6.1). Closure of the bladder is generally performed within the first days of life; pelvic osteotomies facilitate reconstruction of the abdominal wall and may improve ultimate continence [1,2,3]. Some children will develop more or less normal capacities. Even after successful closure there will be some children who end up with a poorly compliant small bladder requiring later bladder enlargement or urinary diversion (ureterosigmoidostomy) [4,5,6,7]. Patients with a good bladder template who develop sufficient bladder capacity after successful primary closure and epispadias repair can achieve acceptable continence without bladder augmentation and intermittent catheterization [8,9,10].

Reconstruction of the bladder neck can either be done at the time of bladder closure or at a later stage. Early reconstruction may facilitate normal bladder function, but should be attempted only at centers experienced with such surgery [11,12]. Continence rates vary from center to center and may range between 43 to 87% [13,14].

2. CLOACAL EXSTROPHY

The incidence of cloacal exstrophy is 1 per 200,000 live births. This is a much more complex deformity that requires an individual approach. Most of these children have anomalies of the nervous system, upper urinary tract and gastrointestinal tract that can adversely affect urinary tract reconstruction. Before reconstructive procedures are considered, an extensive evaluation has to be carried out.

3. AGENESIS AND DUPlication of THE BLADDER are both extremely rare. Agenesis is rarely compatible with life. In bladder duplication other associated congenital anomalies are often observed such as duplication of external genitalia or lower gastrointestinal tract.

4. ABNORMAL STORAGE FUNCTION in combination with other anomalies is usually caused by a neurologic deficit or is secondary to bladder outlet obstruction. Sacral anomalies are frequently seen with cloacal malformations and imperforate anus [15, 16, 17,18].

Posterior urethral valves may cause severe hypertrophy of the detrusor with a small poorly compliant bladder [19,20].

Unfortunately, following valve ablation, these bladders may not return to normal function [21,22].

II. ABNORMALITIES OF SPHINCTERIC FUNCTION

1. EPISPADIAS (without exstrophy): incidence 1 in 60,000 live births, male to female ratio: 3-5:1. All patients with bladder exstrophy also have complete epispadias.

In male patients with complete epispadias and all females the sphincteric mechanism is deficient and the child has complete incontinence. Reconstruction of the bladder neck is either performed at the time of epispadias repair or at a later stage. The bladder function may or may not be normal in these patients [23,24].

2. MALFORMATION OF THE UROGENITAL SINUS occurs exclusively in phenotypic females. The incidence is 1 in 50,000 live births. In patients with classical urogenital sinus or cloaca, the sphincteric mechanism is insufficient and due to associated neurological abnormalities the bladder function may be abnormal.

3. ECTOPIC URETEROCELES protruding into the urethra may be responsible for a partial defect of the bladder neck. In these rare cases, sphincteric incontinence may be the result.

4. SPHINCTER ABNORMALITIES secondary to spina bifida and other neurologic disorders are of particular importance. The sphincter may be overactive (like in detrusor sphincter dyssynergia) or underactive. Overactivity of the sphincter causes secondary changes of the bladder wall (increased collagen type III with decreased elasticity and compliance). Continence is usually achieved with antimuscarinic drug treatment or bladder augmentation (using the overactivity of the sphincter for continence). In cases of incompetence of the sphincter, different types of surgical intervention are possible to enhance the sphincteric mechanism. In general all patients with a neurogenic bladder need Clean Intermittent Catherization (CIC). In patients bound to a wheelchair a suprapubic channel can be created (Mitrofanoff) to facilitate CIC.

5. BYPASS OF SPHINCTERIC MECHANISM

a) Ectopic Ureter is an abnormally located terminal portion of the ureter. Instead of the ureter opening in the bladder, it opens in the urethra, vagina, or uterus. Ectopic ureters occur more frequently in girls and are commonly part of a duplex system: in girls the ectopic orifice of the upper pole moiety drains into the urethra below sphincteric level or vaginal vestibule, thus causing incontinence [25].

When the ectopic ureter represents a single system, the trigone is usually asymmetrical and not well developed. These children may suffer from continuous
incontinence as well as a deficient sphincteric mechanism: this is particularly true in bilateral ectopia of single systems. In these patients the trigone and bladder neck are functionally abnormal and treatment includes surgical reconstruction of the bladder neck. When the upper pole ureter opens in the mid or distal female urethra or outside the urinary tract (i.e. vulva or vagina) incontinence results. Upper pole nephrectomy or ipsilateral uretero-ureterostomy solves the problem.

A rare and a challenging condition is when there are bilateral ectopic ureters. Since bladder is hypoplastic in these children achieving normal bladder capacity and function may require additional procedures to ureteric reimplantation [26,27,28].

b) Urethral duplications

Most patients with urethral duplication will leak urine from the abnormal meatus during voiding. In rare cases, when the urethra bypasses the sphincteric mechanisms, continuous leakage may be present [29].

c) Vesicovaginal fistulas

Acquired fistulas may be traumatic or iatrogenic, following procedures on the bladder neck.

III. EVALUATION AND DIAGNOSIS

A detailed history and physical examination in combination with imaging studies and urodynamic evaluation are the corner stones for successful management. Imaging studies are essential to define the anatomical abnormalities responsible for and associated with incontinence. Ultrasonography of bladder and kidneys as well as a voiding cystourethrogram are the basic studies. In infants and small children sacral ultrasonography can demonstrate normal position and mobility of the spinal cord. The scout film of the contrast voiding cystourethrogram (VCUG) assesses the lower spine and sacrum, intersymphyseal distance, and fecal retention. The contrast films will show bladder configuration, presence of vesicoureteral reflux, incomplete voiding, bladder neck competence, urethral anatomy, and vaginal reflux. Occasionally, an intravenous urogram will provide the clearest assessment of the urinary tract. MRI and CT scanning can be helpful in defining spinal abnormalities as well as congenital abnormalities in the urinary tract.

In addition to imaging studies, urodynamic studies (cystometrography and when needed electromyography of the sphincters and urinary flow studies) are useful for all patients with neurogenic incontinence, and after surgery in some cases of bladder exstrophy and after posterior urethral valves resection to help define the mechanism of any continued incontinence. However in many patients much useful information on the function of the lower urinary tract can be obtained with very basic studies including ultrasound and cystometry.

IV. INDICATIONS FOR SURGICAL PROCEDURES TO CORRECT URINARY INCONTINENCE

1. STORAGE FUNCTION

Reduced bladder capacity is the main indication for simple bladder augmentation. Reduced capacity can be congenital (bilateral single ectopic ureters, bladder exstrophy) or caused by previous surgery e.g. bladder neck reconstruction in exstrophy patients, where a part of the bladder is used to create an outlet resistance. Other indications are low functional bladder capacity as it may be present in neurogenic bladder (meningomyelocele) or bladder scarring from previous surgery or obstruction. Bladder scarring from bilharzia remains common in endemic areas and is increasingly common with immigration to the developed world. In all such cases surgery is indicated when conservative treatment has failed.

Several studies suggest that aggressive early intervention with CIC and anticholinergic therapy improves bladder compliance and may protect children from augmentation surgery [30,31].

Yet in a recent survey has reported that there has been no change in augmentation rates during the last 5 years: they demonstrated significant interinstitutional variability [32].

2. SPHINCTER FUNCTION DURING STORAGE

Most of the diseases in childhood requiring surgical repair for incontinence not only have an influence on bladder capacity but also on sphincter function. Conservative measures to improve sphincter function have limited value and surgery is required in many cases. There are different surgical options; either to increase outlet resistance or to create or implant a new sphincter mechanism. In neurologically normal patients such as classic exstrophy patients, early anatomic reconstruction may allow ‘normal’ bladder and sphincter function. Sling procedures are indicated when the residual sphincter function is not sufficient to avoid incontinence. This may be the case in patients with neurogenic bladder disturbances and urethral incontinence. If there is no residual sphincter function or outlet resistance, an artificial sphincter may be required. Primary urinary diversion (rectal reservoir/continent stoma) offers an alternative solution to this problem.

3. PROCEDURES TO BYPASS THE SPHINCTER

If bladder outlet surgery fails or urethral catheterization is not possible, a continent stoma may be constructed.
Some patients prefer catheterizing through a continent stoma rather than through the sensate urethra. The continent stoma (Mitrofanoff principle) may be combined with bladder augmentation and/or bladder neck reconstruction or closure. An alternative to such procedures would be the use of the anal sphincter for urinary continence with the use of colon as the storage reservoir.

**V. BLADDER RESERVOIR CONSTRUCTION**

1. **URETEROSIGMOIDOSTOMY**

This type of continent urinary reconstruction may be utilized in reconstruction for bladder extrophy, an incontinent urogenital sinus or the traumatic loss of the urethral sphincter. As this reconstruction is totally dependent on the normal function of the anal sphincter, contraindications include incompetence of the anal sphincter, anal prolapse, previous anal surgery, and irradiation. Because of the potential for electrolyte resorption, renal insufficiency is also a contraindication.

Low pressure rectal reservoirs are superior to simple ureterosigmoidostomy because the augmented or reconfigured rectal bladder achieves lower pressure storage and accordingly, enhances continence.

There are two techniques which have been utilized:

- **a) The augmented rectal bladder** in which the rectosigmoid is opened on its antimesenteric border and augmented by an ileal segment. The sigmoid may be invaginated to form a nipple valve to avoid reflux of urine into the descending colon and thus to minimize metabolic complications.

- **b) The sigma-rectum pouch** (Mainz pouch II) in which there is an antimesenteric opening of the rectosigmoid and a side to side detubularization anastomosis. Ureteral reimplantation of normal sized ureters is by a standard submucosal tunnel (Goodwin, Leadbetter). If the ureter is dilated the technique utilizing a serosa lined extramural tunnel may be more appropriate [33,34].

As reported by D’elia et al, the results of these low-pressure rectal reservoirs are excellent with day and night continence better than 95% and complications related to the surgical procedure range from 0 -10% with the sigma-rectum pouch to 34% for the augmented rectal bladder [35]. Late complications for the sigma-rectum pouch range from 6-12.5% and the late complications for the augmented rectal bladder are 17%. Early complications include pouch leakage while late complications are mainly related to the ureteral implantation into the bowel and pyelonephritis. Metabolic acidosis also occurs (69% of the patients had a capillary base excess of −2.5 mmol/L and used oral alkalinizing drugs to prevent hyperchloreaemic acidosis).

Periodic follow-up studies are important to check the upper urinary tract and prevent metabolic acidosis. Due to the risk of malignancy at the ureterointestinal anastomosis, colonoscopy should be performed annually beginning at postoperative year 10 [30, 36,37,38,39].

Level of evidence : 3. Grade of recommendation: B

2. **BLADDER AUGMENTATION, BLADDER REPLACEMENT AND CONTINENT URINARY DIVERSION, USING Intestine**

The indication for bladder augmentation, replacement of the bladder, or the creation of a continent urinary diversion, is either the morphological or functional loss of normal bladder function. The main goal of this surgery is to relieve high pressure and low capacity of the urinary bladder and create a new reservoir with low storage pressures that can be emptied periodically. It is particularly important that the patients understand that spontaneous voiding will not be possible after such surgery and life long intermittent catheterization will be required.

Before deciding on what type of procedure can be performed some significant factors must be addressed. These are:

1. Physical and mental capacity of the patient to do intermittent catheterization.
2. Previous surgery (on urinary tract and bowel)
3. Renal function status (including acid base state)
4. Absence or presence of reflux
5. Outlet resistance
6. The need for a catheterizable channel

The different technical approaches to bladder augmentation or replacement are dependent on the clinical presentation of the patient:

- a simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a catheterizable urethra,
- an augmentation with additional bladder outlet procedures such as bladder neck reconstruction or other forms of urethral reconstruction are required when both the bladder and outlet are deficient. This occurs most commonly in spina bifida or bladder extrophy. It must be appreciated that bladder outlet procedures may complicate transurethral catheterization.
- augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation a continent stoma will be required. Most urologists however prefer to leave the bladder neck and urethra patent as a safety precaution:
when the bladder is very full leakage will occur and it allows transurethral manipulations such as catheterization if the continent reservoir cannot be emptied through the suprapubic catheterizable channel.

• an augmentation with additional continent stoma is utilized primarily following failure of previous bladder outlet surgery. It is advisable also when it can be anticipated that there will be an inability to catheterize transurethrally. An abdominal wall continent stoma may be particularly beneficial to the wheelchair bound spina bifida patient who often can have difficulty with urethral catheterization or who is dependent on others to catheterize the bladder. For continence with augmentation and an abdominal wall stoma, it is essential that there be an adequate bladder outlet mechanism to maintain continence.

• total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urologic reconstruction.

The main contraindications are the inability of the patient to be catheterized, or perform CIC him or herself and the anticipation of poor patient compliance. When there is reduced renal function generally with a creatinine above 2 mg/dl or a creatinine clearance below 40 ml/min/1.73 m², there is a relative contraindication to the use of ileum or colon because of metabolic acidosis secondary to reabsorption. The stomach with its excretion of acid may be used with a low creatinine clearance possibly in preparation for transplantation. It is, however, not wise to use stomach in any voiding patient or one with any questions of an incompetent bladder outlet because of the severe skin irritation that the acid urine may produce (hematuria-dysuria syndrome).

**a) Which intestinal segment should be utilized?**

1. **STOMACH**

Stomach has limited indications primarily because of the complications that have been seen. It is the only intestinal segment suitable in patients with significantly reduced renal function [40,41,42].

Additionally, when no other bowel may be available, as after irradiation or there exists the physiology of a short bowel syndrome, as in cloacal extrophy, this may be the only alternative remaining.

2. **ILEUM / COLON**

Clinically these two intestinal segments appear to be equally useful. In children, sigmoid colon is widely used except in those who have been treated for imperforate anus. Use of the ileocecal region can be associated with transient and sometimes prolonged diarrhea. This segment should be avoided in patients with a neurogenic bowel such as in myelomeningocele or who have been subject to previous pelvic irradiation. If the ileocecal valve must be used, it can easily be reconstructed at the time of performing the ileo-colonic anastomosis. The ileum can be satisfactorily used for bladder augmentation: however because of its smaller diameter a longer segment of ileum is required to create a comparable reservoir to that created from colon. Colon has greater flexibility for ureteral implantation and construction of a continent catheterizable channel.

3. **GENERAL PRINCIPLES**

There are several important principles for bladder augmentation and replacement that should be respected:

• use the minimal amount of bowel and if available use hindgut segments or conduits from previous surgical procedures,

• a low-pressure large capacity reservoir is essential. This requires detubularization of any intestinal segment used.

• for colonic reservoirs a sigmoid segment of 20-30 cm is generally satisfactory. A slightly longer segment of ileum is generally used. The length of the segments can be scaled down in smaller children. Care should be taken not to use more than 50 to 60 cm of ileum in adolescents and comparable lengths in younger children because of reduction of the intestinal resorptive surface.

• the jejunum is contraindicated in intestinal reconstruction of the urinary tract because of its metabolic consequences (hyponatremia, hypercalciemia, and acidosis).

• it is wise to strive to achieve an anti-reflux ureteral anastomosis into the reservoir to avoid the potential for reflux and consequently ascending infection: in high pressure bladders with reflux the reflux usually disappears spontaneously following augmentation [43,44].

• a reliable continence mechanism (continent urinary outlet) must be assured.

• because of the risk of stone formation only resorbable sutures and staples should be used in bladder augmentation and reservoir construction.

4. **BLADDER AUGMENTATION TECHNIQUES**

i. In **gastric augmentation** a 10-15 cm wedge-shaped segment of stomach is resected. Most commonly this is based on the right gastroepiploic artery but can be based on the left one as an alternative. The segment is brought down to the bladder easily in the retroperitoneal space along the great vessels.

ii. When using large or small bowel the segment to
be utilized is opened on the antimesenteric border and detubularized prior to anastomosis to the bladder remnant. The anastomosis of the intestinal segment to the bladder remnant and to itself is usually carried out in one running layer of inverting absorbable sutures.

iii. The techniques for urinary diversion with continent stoma (Mainz pouch, Indiana pouch, Kock pouch) are covered in the chapter on urinary diversion in adults [45,46,47].

Currently, augmentation cystoplasty is the standard treatment for low capacity and/or low compliance bladders secondary to neurogenic, congenital and inflammatory disorders. Due to the relatively high morbidity of conventional augmentation there is renewed interest in alternative methods [48, 49, 50,51,52,53]. These alternative techniques try to avoid the contact between urine and intestinal mucosa and include gastrocystoplasty, bladder auto-augmentation, seromuscular augmentation, alloplastic or biodegradable scaffolds graft with autologous urothelium developed in cell culture, and ureterocystoplasty.

5. SEROMUSCULAR PATCH

To overcome one of the major disadvantages of a conventional augmentation that is mucus formation several techniques have been developed to use intestinal segments free of mucosa. The first attempts at using intestinal segments free of mucosa to improve bladder capacity resulted in viable seromuscular segments covered with urothelial mucosa [67,68]. The intense inflammatory response and shrinkage observed in the intestinal segment discouraged its use in humans [69]. Further attempts consisted of using the association between demucosalized intestinal segments and auto-augmentation. In the initial model using sheep, the animals tolerated the demucosalization procedure poorly, reflected by inflamed, hemorrhagic colonic segments in the animals sacrificed within one month. In addition, colonic mucosa regrowth occurred in one third of the animals [70]. Follow-up studies in a dog model with previously reduced bladder capacity suggested that the contraction of the intestinal patch in seromuscular enterocystoplasty can be avoided by the preservation of both the bladder urothelium and lamina propria, together with the submucosa and muscularis mucosa of the intestinal patch [71,72]. This form of bladder augmentation was shown to prevent absorption of toxic substances like ammonium chloride [73]. Other authors using the same technique to line de-epithelialized gastric patches in the mini-pig model found it useless due to the fibrotic changes and decreased surface of the patch [74].

The initial experience in treating humans with colocystoplasty lined with urothelium were reported by Gonzales and Lima who developed a slightly different technique independently [75,76]. Bladder capacity increased significantly while bladder pressures decreased. Biopsies demonstrated urothelium covering the augmented portion of the bladder in the majority of cases.

Longer term follow-up is now available and although the results are very encouraging, the results seem to be highly operator dependent and the way the mucosa is removed seems to be a crucial factor. Lima et al do no longer preserve the bladder urothelium and use a silicone balloon to prevent the augmented segment from contracting (they remove the balloon after 2 weeks: urine is diverted using ureteral stents): in 123 patients no ruptures were found and only 10% were regarded as failures [77].

Gonzalez et al found seromuscular colocystoplasty in combination with an artificial urinary sphincter successful in 89% of their patients and that it effectively achieves continence with no upper tract deterioration, and concludes that this is their preferred method of augmentation when adverse bladder changes occur after implanting the AUS [78].

Although more authors have now reported their results it still remains a more complex form of augmenting the bladder. This procedure has not receive a general acceptance among the paediatric urological community but is being done in some designated centres [79, 80, 81,82]. A recent comparison of the long term outcome of this technique with standard intestino-cystoplasty has indicated that most of the risks and benefits of augmentation cystoplasty performed using intestine and seromuscular patch appear similar.

Level of evidence 3. Grade of recommendation C

6. AUTO-AUGMENTATION

The principle of auto-augmentation of the bladder is the excision of a great portion of the detrusor while leaving the urothelium intact, creating a large diverticulum for the storage of urine at lower pressures. This urine stored at a low pressure can be drained by intermittent catheterization. The theoretical advantages of this procedure are the low complication rates of the surgery, reduced operative morbidity with shorter stay in the hospital, absence of urine salt resorption, less mucous production in the urine and possibly absence of carcinogenic potential. Although some series showed good results with this procedure [54,55,56,57], most authors have been unable to achieve previously reported success [58].

Long-term results have been rather disappointing. MacNeily et al concluded that of 17 patients with neurogenic bladder following auto-augmentation, 71% were clinical failures and 14 out of 15 were urodynamic failures [59]. Similar findings have been reported by others (60,61). The inability of this procedure to achieve long-term good results may be due to the regeneration of nerve fibers divided during the surgery as well as the ischemic atrophy of the mucosa.
Although there are many potential advantages to this approach to a small poorly compliant bladder the inconsistency of success make it a less favorable option at this time. It is generally felt that pressures can be lowered but that capacity remains unchanged.

More recently, some authors have proposed the laparoscopic auto-augmentation as a minimally invasive procedure for the treatment of low capacity/low compliance bladder [62,63]. Despite the indifferent results some still suggest its consideration before a standard augmentation because of the reasons listed above [64,65,66].

Level of evidence 4. Grade of recommendation C

7. URETERAL BLADDER AUGMENTATION

Another alternative to avoid the morbidity of intestinal bladder augmentation is the use of ureteral segments to improve bladder capacity and/or compliance. Megaureters associated with poorly or nonfunctioning kidneys provide an excellent augmentation material with urothelium and muscular backing, free of potential electrolyte and acid base disturbance, and mucus production [83,84].

Another alternative in patients with ureteral dilation and good ipsilateral renal function, is to combine transureteroureterostomy with ureterocystoplasty [85]. Another alternative in bilateral dilated ureters with preserved renal function is bilateral reimplantation and the use of bilateral distal ends for detubularized bladder augmentation [86,87].

Bladder augmentation with ureter may be effective in a small sub group of patients with ureteral dilatation and poor bladder capacity. Overall long-term results are good and remain so over a longer period of time [88,89,90,91,92,93].

In a recent evaluation of the long term functional outcome of this technique it is reported that ureterocystoplasty provides durable functional urodynamic improvement, yet some patients (4 out of 17 in this series) would eventually need a standard intestinal cystoplasty [94].

Level of evidence 3. Grade of recommendation B

It has been shown that this type of augmentation can also be employed in children who require a kidney transplantation [95,96,97].

8. EXPERIMENTAL METHODS

The artificial bladder has been the topic of speculation and experiment that remains still outside the bounds of clinical application. Somewhat nearer to clinical application may be the concept of tissue engineering using autologous urothelium and bladder muscle cells. These cells may be grown on biodegradable scaffolds—both naturally derived and synthetic—for the temporary support of growing tissues and then can be used for augmenting the bladder. A number of synthetic materials and natural matrices have been used in experimental and clinical settings and major improvement have been gained in techniques of cell harvest, culture, and expansion as well as polymer design.

A range of applications of engineered bladder tissues are at different stages of development. There have been a few in preclinical trials, recent progress suggests that engineered bladder tissues may have an expanded clinical applicability in the future.

Clinical trials with these methods are not far away [98-110].

Although this field of research may represent the future of bladder reconstructive surgery, currently only few experimental studies are available and it may be some time before all this knowledge can be used clinically. We strongly encourage further research in this field.

VI. BLADDER OUTLET SURGERY

1. URETHRAL ENHANCEMENT

In those children where sphincteric incompetence is the only cause of incontinence or plays a mayor role in association with decreased bladder capacity or compliance, surgical procedures to enhance outlet resistance should be considered. In many cases bladder outlet surgery needs to be combined with other procedures aimed at creating a large low pressure storage reservoir.

2. BULKING AGENTS

The injection of bulking substances in the tissues around the urethra and bladder neck to increase outlet resistance in children dates back to at least 1985. However, concern about distant migration of the injected substance and risk of granuloma formation prevented this technique from gaining widespread acceptance [111,112].

The search for safer, biocompatible substances to create periurethral compression has first led to the use of cross-linked bovine collagen, with initially reported success in about 20-50% of children [113,114,115].

Collagen injection appeared to effectively improve urethral resistance, but this did not always translate into satisfactory dryness, besides, the effect of the injection is of short duration and repeated injections were often necessary [116,117]. Because of this collagen is no longer recommended for this indication.

At present the following substances are available and have been tested in children with incontinence: dextranomer / hyaluronic acid copolymer (a nontoxic, nonimmunogenic, non-migrant synthetic substance) and polydimethylsiloxane.
Usually the substance is injected endoscopically in the bladder neck area (finding the best spot is often the most difficult part of the procedure): more than one procedure may be necessary. On average 2.8 – 3.9 ml is injected. More than 50% of patients need more than one injection. Initial results of 75% success have been reported, but after 7 years there is a gradual decrease and only 40% remained dry [118,119,120]. Others have reported success rates of 0 - 70% [121-128].

Despite limited success it remains an option for all patients who are poor surgical candidates and those who want to avoid extensive BN reconstruction.

An alternate route may be the injection around the urethra using laparoscopy [129].

Level of evidence : 3. Grade of recommendation C

3. ARTIFICIAL URINARY SPHINCTER

Since its introduction in 1973 the AUS has undergone major transformations over the years. Different devices are currently in use: one of the most frequently used devices is the AS800-T that has been in use for almost 20 years [130]. It consists of an inflatable cuff, a pressure regulating balloon and a unit containing a pump and control mechanisms. The inflatable cuff can only be implanted around the bladder neck in females and pre-pubertal males. In post-pubertal males the bulbous urethral placement is possible but not recommended for wheelchair patients or those who perform intermittent catheterization [131]. In patients who have had extensive urethral surgery (extrophy and epispadias) it may also not be technically feasible.

Implantation of an AUS requires special training and difficulties may be encountered in the dissection of the space around the bladder neck in obese, post-pubertal males or in patients with a history of previous bladder neck procedures. A 61-70 cm H2O pressure balloon is used exclusively when the cuff is around the bladder neck and a lower pressure balloon when it is around the bulbous urethra. Although high in cost, the artificial sphincter remains the most effective means or increasing urethral resistance and preserving the potential for voiding.

The ideal candidate for AUS implantation is a patient with pure sphincteric incompetence who voids spontaneously and has good bladder capacity and compliance. Unfortunately only a small proportion of children with sphincteric incontinence meet the criteria. The AUS may also be used in patients dependent on clean intermittent catheterization. The compatibility of the AUS with intermittent catheterization and enterocystoplasty is well documented [132,133,134].

The ability to empty the bladder spontaneously or by Valsalva maneuver may be preserved after AUS implantation. In series reporting children with AUS, the majority having neurogenic incontinence, 25% void spontaneously [135]. When the AUS is implanted before puberty, the ability to void spontaneously may be lost after puberty.

Overall, 40 to 50% of neurogenic patients require a bladder augmentation concomitantly or subsequently to the AUS implantation [133,136,137,138].

The continence rate ranges from 63 to 97% [139-146].

Herndon et al reported a success rate of 86% (of 134 patients): 22% voided, 11% had to perform CIC after voiding, 48% only performed CIC through the urethra, 16% performed CIC through a continent channel and 3% used diversion [147]. Mechanical problems occurred in 30% of patients who had an 800 model implanted (versus 64% in the old model). Revisions (in 16%) were significantly less in the 800 model. Erosion occurred in both groups (16%). A major complication was perforation of the augmented bladder in this group (it occurred in 10 patients). In 28% a secondary bladder augmentation was necessary.

Another interesting aspect of the AUS is that in some children the device is either deactivated or no longer functions but they remain dry: others have reported that placing a cuff only without activation is all that is required to make them dry [148].

The complications most commonly encountered in patients with AUS are mechanical failures. The longevity of the present devices is expected to exceed 10 years, although Spiess et al reported a mean lifetime of only 4.7 years [149].

The second most common problem is the development of reduced bladder compliance with time. This may result from an error in the preoperative evaluation or the reaction of the detrusor to obstruction (a reaction noted in some patients with spina bifida). These changes can be seen after many years of follow-up. The results of decreased capacity and compliance may be incontinence, upper tract deterioration, or the development of vesicoureteral reflux. Therefore long term follow-up with ultrasound, renal scintigraphy and if indicated urodynamics is mandatory in all patients with an AUS.

Infection of the prosthesis should occur in no more than 15% of all cases. Erosions of the tissues in contact with the prosthesis are rather infrequent. Bladder neck erosions are practically non-existent when the sphincter is implanted around a “virgin” bladder neck. When the AUS is used as a salvage procedure following bladder neck reconstruction, the erosion rate may be as high as 30% [137]. Despite the high complication and revision rate, AUS results show that acceptable continence rates can be achieved in the long-term. For this reason AUS implantation may be better considered as the initial treatment in selected cases [150].
4. FASCIAL SLINGS

Fascial slings constructed with the fascia of the anterior rectus muscle have been used to increase outlet resistance in incontinent children, particularly those with neurogenic dysfunction since 1982 [151]. The sling is used to elevate and compress the bladder neck and proximal urethra. The dissection around the urethra may be facilitated by a combined vaginal and abdominal approach, however, this option is limited to post-pubertal females [152].

Several technical variations of the sling have been reported. The fascial strip may be a graft or a flap based on the rectus sheath on one side. The fascial strip can be crossed anteriorly or wrapped around the bladder neck to enhance urethral compression.

Although the short-term success rate reported by most authors is encouraging, there are no series reporting detailed results at 5 years [153-154]. Most authors report a greater success when fascial slings are used in conjunction with bladder augmentation and success seems more likely in females than in males [155-158]. In patients with neurogenic incontinence postoperative CIC is recommended.

The pubovaginal sling in girls may also be placed through the vagina: in 24 girls with spina bifida this procedure was successful in 19, while another 3 became dry following additional injections with bulking agent around the bladder neck via a suprapubic needle introduction. CIC was possible in all patients. One patient developed a vesicovaginal fistula [159].

Complications of sling procedures include difficulties with intermittent transurethral catheterization, erosion of the urethra and persistent incontinence. Overall, the increase in outlet resistance provided by slings seems less than that provided by the artificial sphincter. Experience with these procedures suggests an overall success between 50 and 80% in females.

Numerous alternatives are being used nowadays: small intestinal submucosa has been used in 20 children and showed equivalent rates of continence. The advantage being that it is available off-the-shelf. Results were better in girls than in boys (85 vs 43% being dry) [160,161,162].

When combining bladder augmentation with a Gore-tex sling in 19 children the results were bad: because of erosion the sling had to be removed in 14 patients, all except one also had a bladder stone. In this respect this type of sling should not be used [163].

From the data published it presently seems that the AUS provides more consistent results in boys and for girls capable of spontaneous voiding who have not had previous bladder neck surgery. Bladder neck slings may be used for the enhancement of bladder outlet resistance in the majority of patients with neurogenic bladder who need augmentation cystoplasty and whom we do not expect will be capable of voiding spontaneously. Sling procedures are probably equally effective for girls dependant on intermittent catheterization and in conjunction with bladder augmentation. At present, given the cost and lack of effectiveness of injection procedures, their use does not appear justified in incontinent children. The cost of the AUS may restrict its use.

Level of evidence 2. Grade of recommendation B

It is important that one should be aware of the fact that these patients who undergo bladder outlet surgery need long-term follow-up not only because of the complications but also because their bladder behavior may undergo unexpected clinically asymptomatic changes that could negatively affect their upper tracts if augmentation procedure are not performed at the same time [164].

5. BLADDER NECK CLOSURE

In ‘desperate’ cases the bladder neck may be closed, the indication being persistent leakage despite several attempts to enhance outlet resistance by bulking agents or other surgical procedures. Although initial results are acceptable, long-term results are usually disappointing: persistent urinary leakage, stomal stenosis and leakage or stone formation (in up to 40%) [165,166]. One of the most important factors seems to be compliance with intermittent catheterization and bladder irrigation.

6. BLADDER OUTLET RECONSTRUCTION

Surgical procedures to achieve urinary continence are dictated by functional and anatomic deficiencies and by the ultimate goal of either continence (with normal voiding) or dryness (dependent on intermittent catheterization).

Construction of a functional urethra for continence usually implies an anatomic defect without a neurogenic component (epispadias / exstrophy) and includes urethral and bladder neck narrowing and urethral lengthening [167-172].

Such procedures may initially require intermittent catheterization or occasional post voiding catheterization, but bladder empying by voiding is anticipated.

Urethral reconstruction for dryness, however, mandates intermittent catheterization. The goal in surgery to achieve dryness is to create a urethra suited to catheterization, which has closure such that intra-luminal pressures always exceed intravesical pressure. The most dependable procedures for dryness utilize a flap valve or tunnel to achieve urethral closure, although urethral slings, wraps and injections have also been used [173].

Level of evidence 3. Grade of recommendation C

Reconstruction to achieve continence is based on the principle that proximal reduction of the caliber of the
urethra supports the inherent proximal sphincteric mechanism of the bladder neck and proximal urethra. The narrowing must be dynamic to permit closure for continence and yet permit opening with funneling during voiding. Several techniques have been described to achieve this goal [3, 166-176]. Young (1922) performed a “double sphincter technique” that involved the excision of a wedge of tissue at the anterior bladder neck, as well as removal of a wedge of tissue just proximal to the epispidias meatus (external sphincter). Dees (1949) added the concept of lengthening the urethral tube to that of narrowing. In his procedure parallel incisions were made through the existing bladder neck area which created a posterior urethral plate from what had previously been the trigone of the bladder. This is tubularized to give added length to the proximal urethra. The added length provides increased potential for urethral closure and moves the bladder neck and proximal urethra into the abdominal cavity. Leadbetter (1964) modified the Young-Dees procedure by creating muscular flaps from the area of the bladder neck and proximal urethra which were used to wrap the newly created proximal tube. This procedure was popularized by Jeffs (1983) who applied it to a staged repair of extrophy. He supported a lengthened urethra by a suspension. They report their long term continence rate with this procedure as greater than 80%, without the need for CIC or augmentation [177].

Presently, this represents the gold standard for reconstruction for continence, however, modifications of the technique have reported similar or improved results. Most urethral lengthening procedures utilizing the posterior urethra and bladder neck require ureteral reimplantation and preservation of the posterior urethral plate. Because part of the bladder is used to create the functional lengthening of the urethra bladder capacity decreases following the procedure. It also remains to be seen whether the created urethra is actually a functioning urethra: in many patients fibrosis around the urethra prevent it from being really “functional”: in these patients it may act as an anatomic obstruction and long-term follow-up is necessary to follow not only the bladder but also the upper tract.

Surgery for dryness is dependent on the effectiveness of intermittent catheterization and is usually reserved for patients with neurogenic dysfunction or multiple previous surgeries. Procedures to achieve dryness usually create a urethral closure pressure that exceeds bladder pressure.

A flap valve can be constructed by using an anterior or posterior bladder flap (full thickness) to construct a tube that is placed in a submucosal tunnel [171,175,176].

The major disadvantage of these procedures (flap valves) is that the valve will not allow leakage with high intravesical pressures, potentiating renal damage. Therefore, these procedures can be dangerous to the patient who is not totally committed to follow catheterization recommendations.

Unfortunately, the ideal procedure for surgical reconstruction of the bladder neck does not exist. The surgical approach to urinary incontinence in the child must be multifaceted because of the inherent complex and varied nature of the problem.

Recent data would support the concept that very early reconstruction in the exstrophy / epispidias group may result in physiologic bladder cycling which facilitates normal bladder and urethral development. This results in higher potential for continence without the need for bladder augmentation and bladder neck reconstruction (Level 3). More work and clinical experience in this area is strongly recommended (Grade A).

7. ALTERNATIVE CONTINENCE CHANNELS

In the surgical treatment of incontinence in children every effort must be made to preserve the natural upper and lower urinary tract. The bladder is the best urinary reservoir, the urethra the best outlet and the urethral sphincters the best control mechanism. If the bladder is partly or wholly unusable it may be augmented or replaced by a variety of techniques. Urthral failure may occur either because the sphincters are incompetent or because it is overactive and does not allow spontaneous voiding. It would be preferable for the former to be treated by one of the techniques described above and the latter by intermittent catheterization (CIC). If all of these fail, continent supra pubic diversion is indicated.

a) The Mitrofanoff principle

Mitrofanoff’s name is given to the principle of burying a narrow tube within the wall of the bladder or urinary reservoir whose distal end is brought to the abdominal wall to form a catheterizable stoma suitable for intermittent catheterization [178]. The technique is simple and familiar to all urologists who are accustomed to re-implanting ureters. Several narrow tubes are available for the Mitrofanoff conduit [179,180]. In the original description, the appendix was used. However, even if the appendix is still present, it may be unusable in 31% of patients [181].

If no suitable tube is found, a good tube can be formed by tailoring ileum transversely so that only 2-3cm of ileum can be made into a 7-8 cm conduit. This modification was originally described by Yang in humans and by Monti in experimental animals [182,183]. It is increasingly used though great care must be taken in its construction to avoid an internal fistula [184].

The ureter may be used but there may be some difficulty in achieving sufficient calibre with a previously normal ureter. Earlier reports that the Fallopian tube could be used have not stood the test of time.
The Mitrofanoff system achieves reliable continence which is maintained in long term follow-up, for a high proportion of patients. Long-term follow-up data shows that in the original series of Paul Mitrofanoff of 23 patients after a mean follow-up of 20 years, 1 patient had died, but in the other 22 patients no metabolic changes were noted. The bladder neck was closed in 21 patients. Secondary bladder augmentation had to be performed in 8, while in 4 children a non-continental diversion was created. With time the need for additional surgery decreased and after 20 years 16 patients had a good and stable continent diversion [185].

The pressure generated within the lumen of the conduit is 2 to 3 times higher than that within the reservoir so that continence is preserved even when the intra abdominal pressure is raised by straining. Conversely, the pressure in the lumen of a Kock nipple is only slightly higher than that in the reservoir so that continence is less reliable [186,187].

The conduit may be buried either between the mucosal and muscle layers of the reservoir, or may be completely imbrocated in the full thickness of the reservoir wall. Any well supported tunnel of about 2-4 cm will suffice. The choice depends both on the nature of the reservoir and on the conduit [188].

Continence rates of 90-100% with the Mitrofanoff Principle are reported, regardless of diagnosis, reservoir or conduit type [188,189]. Follow-up for at least ten years has shown that the system is resilient [190,191,192].

A modified technique of vesicostomy is described using a gastrostomy button, which could be used as a continent urinary stoma in children with incomplete voiding. Button vesicostomy is a useful addition to the options available for a catheterizable continent urinary stoma in children in the short or medium term(193).

Although perfect continence seems attractive, it may not be in the child's best interests. A 'pop-off' valve may be in the interest of the child if catheterization is impossible or forgotten.

b) The Ileo-cecal valve

The ileo-cecal valve is an obvious sphincter to combine with cecum and ascending colon as the reservoir and the terminal ileum as the conduit. The early continence rate of 94% was not sustained because of high pressures in the tubular reservoir and weakness of the valve [194,195,196].

The Indiana system is based on the competence of the ileo-caecal valve but with a detubularized reservoir [197]. The valve itself is reinforced with non-absorbable plicating sutures and the terminal ileum which forms the conduit is tailored. The best reported continence rate is 96% with a 2% rate of catheterization difficulties.

In the complete Mainz I pouch a length of terminal ileum is intussuscepted through the ileo-cecal valve as a Kock nipple [198]. It is impossible to say whether the nipple or the ileocecal valve (or both) produce the continence which is reported in 96% of patients.

Both these systems work well as complete reconstructions and are widely used as bladder replacements in children. The sacrifice of the ileocecal valve may cause gastro-intestinal complications.

c) Kock pouch

The first workable continent diversion was the Kock pouch [42]. The reservoir is made from 40cm ileum reconfigured to reduce the intrinsic pressure. The continence mechanism is formed by intussusception of 12cm of ileum. In a complete form it requires 72cm of ileum which may be more than can be spared from the gastro-intestinal tract.

Although first described as a mechanism for a continent ileostomy in children the Kock pouch is now not commonly used in children because of the problem with large amount of bowel needed, stone formation and mediocre success with dryness of the catheterizable stoma [199,200].

d) Artificial Sphincter

As a last resort, the AUS may be considered to give continence to a reconstructed outlet. Experimental evidence suggests that AUS cuffs can be placed safely around intestine providing the cuff pressure is low [201]. The AUS has been used successfully around large bowel, in three of four children with follow-up to 11 years [202].

e) Where to place the cutaneous stoma

In patients with spina bifida, particularly non-walkers, the site must be chosen with particular care. The natural tendency is for the spine to collapse with time so that the lower half of the abdomen becomes more pendulous and beyond the range of vision. A low site may seem appropriate in the child, but will become unusable in the adult. It is best to use a high, midline site, preferably hidden in the umbilicus. The site should be determined in a sitting position and marked before surgery because in the supine position the position will change dramatically. In some patients the best position may not be in the midline at all: special care must be taken that the patient can manage bladder emptying and irrigation him/herself.

For most other patients, the site of the stoma should be chosen by cosmetic criteria. The umbilicus can be made into a very discrete stoma; the risk of stenosis is low and it is a readily identifiable landmark. Otherwise, the stoma should be as low on the abdominal wall as possible and certainly below the top of the underpants. However, many surgeons find the best results by placing the catheterizable stoma in the umbilicus.

The problem of stomal stenosis remains ever present.
It can occur at any time so that only follow up of many years could determine whether any system of anastomosis to the skin is better than any other. The published rate of stomal stenosis is between 10 and 20%. The multi-flap V.Q.Z. stoma is claimed to have the lowest rate but follow up is short and it may well not pass the test of time [203].

II. COMPLICATIONS OF CONTINENCE SURGERY IN CHILDREN

1. STORAGE AND EMPTYING COMPLICATIONS

In the short term, it has been shown that the continent diversions can store urine and can be emptied by clean intermittent catheterization (CIC). It is apparent that there is a constant need for review and surgical revision. This observation mirrors the late complications of augmentation cystoplasty for neuropathic bladder where the median time to revision surgery is as long as ten years [204,205].

In general, once continent, they remain continent, although there are occasional reports of late development of incontinence. The problem lies more in difficulties with catheterization, particularly stenosis and false passages which may occur in up to 34% of patients [188]. In a recent retrospective evaluation of 500 augmentations over 25 years with a median follow-up of 13.3 years, the cumulative risk of further surgery at the bladder level was 0.04 operations per patient per year of augmentation and 34 % of the patients needed further surgery for complications. Bladder perforation occurred in 43 patients (8.6%) with a total of 53 events and 125 surgeries done for bladder stones in 75 cases [206].

The principal complications arise because the reservoir is usually made from intestine. Ideally, urothelium should be used and preservation of the bladder epithelium gives fewer complications than enterocystoplasty [207].

Combinations of detrusor myectomy and augmentation with de-mucosalised colon have given promising results in the short term. The surgery is difficult as the bladder epithelium must not be damaged and the intestinal mucosa must be removed completely. When achieved there are no metabolic problems and many patients can void [207].

When augmentation can be done with a dilated ureter, the results are good and the complication rate low even in children with compromised renal function or transplantation [208].

All intestinal reservoirs produce mucus. The amount is difficult to measure and most estimates are subjective. No regime has been shown to dependably reduce mucus production [209].

2. RESERVOIR RUPTURE

The incidence of spontaneous rupture varies between different units. There may be delay in diagnosis although the history of sudden abdominal pain and diminished or absent urine drainage should make it obvious. The patient rapidly becomes very ill with symptoms of generalized peritonitis [210,211]. A ‘pouchogram’ may not be sensitive enough to demonstrate a leak. Diagnosis is best made by history, physical examination, ultrasonography and a CT cystogram. If diagnosed early, catheterization and broad spectrum antibiotics may sometimes lead to recovery. If the patient fails to respond within 12 hours on this regime or if the patient is ill, laparotomy should be performed at once. If there is any instability of the patient laparotomy should be considered as an immediate necessity as bladder rupture in this clinical situation can be lethal.

Level of evidence 2. Grade of recommendation A

Figures are not available on the incidence of this complication in reservoirs made only of bowel but come from patients with intestinal segments in the urinary tract. Most papers report small numbers. In a multicentre review from Scandinavia an incidence of 1.5% was noted. There were eight patients with neurogenic bladder which was said to be disproportionately high [210]. In a series of 264 children with any sort of bowel reservoir or enterocystoplasty, 23 perforations occurred in 18 patients with one death [211]. Therefore, as this complication is more common in children it becomes a very important consideration [212]. A review of 500 bladder augmentation procedures performed during the preceding 25 years, spontaneous perforations occurred in 43 patients (8.6%), for a total of 54 events. The calculated risk was 0.0066 perforations per augmentation-year [213].

Patients and their families should be warned of this possible complication and advised to return to hospital at once for any symptoms of acute abdomen, especially if the reservoir stops draining its usual volume of urine. All young patients with urinary reconstructions including intestinocystoplasty should carry suitable information to warn attending physicians of their urinary diversion in case of emergency.

3. METABOLIC COMPLICATIONS

Metabolic changes are common when urine is stored in intestinal reservoirs and must be carefully monitored. It is uncertain whether they are commoner in children or whether they just live longer and are more closely monitored.

Nurse et al found that all patients absorbed sodium and potassium from the reservoirs but the extent was variable [214]. A third of all patients (but 50% of those with an ileocecal reservoir) had hyperchloremia. All patients had abnormal blood gases, the majority
having metabolic acidosis with respiratory compensation. The findings were unrelated to renal function or the time since the reservoir was constructed.

In 183 patients of all ages at St Peter’s Hospitals who had any form of enterocystoplasty, hyperchloroaeamic acidosis was found in 25 (14%) and borderline hyperchloroaeamic acidosis in an additional 40 (22%) patients. The incidence was lower in reservoirs with ileum as the only bowel segment compared to those containing some colon (9% v 16%). When arterial blood gases were measured in 29 of these children a consistent pattern was not found [215].

In a series of 23 patients, Ditonno et al found that 52% of patients with a reservoir of right colon had hyperchloroaeamic acidosis [216]. In ileal reservoirs, Poulsen et al found mild acidosis but no patients with bicarbonate results outside the reference range [217].

Many authors do not distinguish between patients with normal and abnormal renal function. All of 12 patients in one series with a pre-operative serum creatinine above 2.0 mg% developed hyperchloroaeamic acidosis within 6 months of enterocystoplasty [218]. It is prudent to monitor patients for metabolic abnormalities, especially hyperchloroaeamic acidosis, and to treat them when found [219].

With increasing experience, it has become clear that there is a risk of developing vitamin B12 deficiency, sometimes after many years of follow up. It is likely that resection of ileum in children leads to an incomplete absorption defect. Stores of B12 may last for several years before the serum level becomes abnormal. At a mean follow up of six years, low levels of B12 have been found in 14% of children. There was a corresponding rise in the serum methyl malonic acid which is a metabolite that accumulates in B12 deficiency suggesting that the finding was clinically significant. Similarly, in adults, 18.7% have B12 deficiency at five years. In the adults the mean B12 level was significantly lower when the ileocæcal segment as opposed to ileum alone had been used (413 ng/ml compared to 257 ng/ml) [220,221]. In order to avoid the serious neurological complications, regular monitoring of B12 levels is essential.

In a review of 500 augmentations Starting at 7 years postoperatively, 6 of 29 patients (21%) had low B12 values, while 12 of 29 (41%) had low-normal values [222].

Pediatric patients who have undergone ileal enterocystoplasty are at risk for development of vitamin B12 deficiency. These patients are at the highest risk beginning at 7 years postoperatively, and the risk increases with time. An annual serum B12 value in children beginning at 5 years following bladder augmentation is recommended.

Level of evidence 2. Grade of recommendation B

The stomach has had a checkered career as a urinary reservoir. Its non-absorptive role in the gastro intestinal tract has made it particularly useful in reconstruction of children with inadequate intestine, such as those with cloacal exstrophy. There is little effect on gastro intestinal function. Metabolically, the acid production leading to hypochloroaeamic alkalosis may be positively beneficial in children with renal failure. It produces no mucus and the acidic urine is less easily infected and seldom grows stones. However about a third of children have had serious long term complications, often multiple. The quite severe dysuria / haematuria and the skin complications from the acid urine, particularly, have limited its use [223,224].

4. EFFECTS ON THE GASTROINTESTINAL TRACT

Little attention has been paid to the effects on gastro intestinal motility of removing segments of ileum or cæcum for urinary reconstruction in children. In adults, disturbance of intestinal function has been found to be more frequent and more debilitating than might be expected.

Disturbance of bowel habit does not mean diarrhoea alone. It also includes urgency, leakage and nocturnal bowel actions. It is clear that quality of life may be seriously undermined by changes in bowel habit [225].

It is known that the bowel has a considerable ability to adapt, especially in young animals, when parts are removed. Nonetheless, reconstruction should be undertaken with the smallest length of bowel possible. Particular care should be taken in children with neurologic abnormality in whom rectal control is already poor. Poorly controlled fecal incontinence may occur in a third of patients [226,227].

5. RENAL FUNCTION

Obstruction and high pressures in the bladder during storage have devastating effects on the upper urinary tract. Bladder augmentation eliminates these high pressures. Urinary diversion with recurrent urinary tract infections and stone formation also may have deleterious effects on renal function. It is therefore of utmost importance to evaluate renal function in young children who have undergone undiversion or continent diversion. In the follow-up so far available these procedures do not seem to affect renal function. When function has improved after such surgery it is likely to be the result of eliminating obstruction or high bladder storage pressure.

In rats with near complete nephrectomy the rate of progression of renal failure is no worse in those with ileocystoplasty compared to those with normal bladder [228]. This suggests, experimentally, that storage of urine in small intestine is not, on its own, harmful to renal function.

Clinically, in the longer term, renal deterioration has
been related to obstruction, reflux and stone formation. In one long-term study of Kock pouch patients, these complications occurred at the same rate as that found in patients with ileal conduits: 29% at five to 11 years [229]. Similarly, in a prospective follow-up to a minimum of 10 years, it was found that the deterioration in glomerular filtration rate (GFR), that was found in 10 of 53 patients, was due to a ‘surgical’ cause in all but one [230].

Although a more complicated procedure, a renal transplant can be anastomosed in an intestinal reservoir with similar long-term results as those using an ileal conduit [231,232].

**6. INFECTIONS AND STONES**

The incidence of bladder reservoir stones varies between 12 and 25%. This is higher in children compared to adults. Palmer et al reported an incidence of 52.5% during a follow-up of four years [233]. Renal stones are uncommon, occurring in about 1.6% of patients, an incidence which would be expected in a group with congenital urinary tract anomalies.

In a series comparing the Kock pouch with the Indiana pouch (which does not have staples), 43.1% of 72 Kock reservoirs formed stones compared to 12.9% of 54 Indiana reservoirs [234]. Furthermore, no patient with an Indiana pouch formed a stone after 4 years, but patients with Kock pouches continued to do so at a steady rate up to eight years.

Apart from the presence of a foreign body, several factors have been blamed for the high stone risk. Almost all reservoir stones are triple phosphate on analysis, though Terai et al found carbonate apatite, urate and calcium oxalate in up to 50% of stones from patients with an Indiana pouch [235]. This suggests that infection rendering the urine alkaline is a key factor. Micro-organisms that produce urease and split urea to form ammonia are the main culprits. The incidence of infection in reservoirs is high, 95% in one series, and yet the majority of patients do not form stones, suggesting that there are predisposing factors other than infection and the anatomical abnormality of the urine reservoirs [236].

It has been suggested that the immobility associated with spina bifida may be responsible, but this seems to have been in series with a predominance of such patients and was not confirmed in other studies [237].

The production of excess mucus has also been blamed. The problem is that the measurement of mucus is difficult.

The finding of a spectrum of stone formation from mucus, through calcification to frank stone lends some support to this aetiology. However, it could be a secondary event, with mucus becoming adherent to a stone that has already formed. Many surgeons encourage patients to wash out their reservoirs vigorously with water two or three times a week. There seem to be fewer stones in those that claim to practice regular washing. In a prospective study a regime of weekly washouts did not improve the incidence of stones in 30 children compared to historical controls [238].

Mathoera et al found an incidence of 16% during a follow-up of 4.9 years in 90 patients: girls were more frequently affected than boys and concomitant bladder neck reconstruction, recurrent infections and difficulties with CIC were other risk factors identified, while the frequency of irrigation did not appear to be a risk factor [239].

Mucins are an important component of the epithelial barrier and protect the epithelium from mechanical and chemical erosion. Mucins are known to act as important adhesion molecules for bacteria. Mucins may also enhance the formation of crystals [240]. Mucin expression changes after incorporating the intestinal segment in the bladder. Upregulation of MUC1 and MUC4 expression occurs in transposed ileal segments resembling normal epithelium, whereas ileal segments in enterocystoplasty showed an upregulation of MUC2,3,4 and 5AC expression towards the site of anastomosis with the ileal segment. These changes which may be due to exposure to urine coincide with a change from ileal sialomucins to colonic sulfomucins by a change in glycosylation. The mucins bind calcium and may form a template resembling the crystal structure on which crystals are formed and grow. From these studies it is concluded that inhibition of bacterial adhesion (by using different irrigation fluids based on sugars) could be of eminent importance in the prevention of certain types of infection stones.

An interesting comparison has been made between children with a native bladder alone and those with an augmentation, all of whom were emptying by self catheterization. There was no significant difference in the incidence of stones with or without an augmentation [241].

Stones are associated with inadequate drainage in the sense that CIC through the urethra, the most dependent possible drainage, has the lowest stone rate. Patients with the most ‘up hill’ drainage, that is with a Mitrofanoff channel entering the upper part of an orthotopic reservoir have a higher incidence of stones [239].

Kronner et al made the observation, that the incidence of stones was statistically associated with abdominal wall stomas and a bladder outlet tightening procedure (21.1% compared to 6% in patients with augmentation alone) [236].

Once a bladder stone has been diagnosed it has to be removed: several methods are available, but ESWL should be avoided as it is difficult to remove all
fragments (and small particles may get trapped in mucus and the pouch wall), which may form the focus of a new calculus. Because of the recurrent nature of these stones the least invasive method should be recommended [242,243].

Because of the high incidence of stones following enterocystoplasty several measures should be recommended to the patients and their parents. Regular CIC under hygienic circumstances with adequate fluid intake and irrigation seem to be the most important [244]. It is unclear whether prophylactic antibiotics are useful, but a clinical infection should be treated adequately. Maybe in the future different types of irrigation fluid may prove helpful.

7. GROWTH

The suggestion that enterocystoplasty delayed growth in height seems to have been ill founded. In a group of 60 children reported in 1992 it was stated that 20% had delayed growth [245]. Current follow up of the same group has shown that all have caught up and achieved their final predicted height. Furthermore, measurements in a group of 123 children from the same unit have shown no significant delay in linear growth [246].

Enterocystoplasty may have an effect on bone metabolism even if growth is not impaired. At least in rats with enterocystoplasty there is significant loss of bone mineral density especially in the cortical compartment where there is endosteal resorption. These changes are not associated with HCA and are lessened by continuous antibiotic administration [247,248].

More recent follow-up data shows either no effect on growth or a decreased linear growth [249-252].

8. PREGNANCY

When reconstructing girls it is essential to have a future pregnancy in mind. The reservoir and pedicles should be fixed on one side to allow enlargement of the uterus on the other.

Pregnancy may be complicated and requires the joint care of obstetrician and urologist [253]. Particular problems include upper tract obstruction and changes in continence as the uterus enlarges.

Pregnancy with an orthotopic reconstruction appears to have a good outcome but chronic urinary infection is almost inevitable and occasionally an indwelling catheter is needed in the third trimester [254]. With a suprapubic diversion, catheter drainage for incontinence or retention may be needed in the third trimester [255].

Except in patients with an artificial urethral sphincter and extensive bladder outlet reconstruction, vaginal delivery is usual and caesarean section should generally be reserved for purely obstetric indications (distorted pelvis in spina bifida patients). During the delivery the bladder reservoir should be empty and an artificial sphincter deactivated. The urologist should be present during Caesarean section to ensure protection for the reservoir, the continent channel and its pedicles.

9. MALIGNANCY

The possibility of cancer occurring as a complication of enterocystoplasty is a constant source of worry. Currently cancer following augmentation cystoplasty is a recognized risk factor. It is known to be a frequent complication of ureterosigmoidostomy after 20 to 30 years of follow up. Animal evidence suggests that faecal and urinary streams must be mixed in bowel for neoplasia to occur. However, if it is chronic mixed bacterial infection, rather than the faeces per se, then all bowel urinary reservoirs are at risk.

In patients with colonic and ileal cystoplasties high levels of nitrosamines have been found in the urine of most patients examined [256]. Clinically significant levels probably only occur in chronically infected reservoirs [257]. Biopsies of the ileal and colonic segments showed changes similar to those that have been found in ileal and colonic conduits and in ureterosigmoidostomies. More severe histological changes and higher levels of nitrosamines correlated with heavy mixed bacterial growth on urine culture [258].

In a review by Filmer et al, 14 cases of pouch neoplasm were identified (259). Special features could be found in nearly all the cases. Ten patients had been reconstructed for tuberculosis; four tumors were not adenocarcinomas; one patient had a pre-existing carcinoma; six patients were over 50 years old. Cancer was found in bowel reservoirs at a mean of 18 years from formation. This is a few years earlier than the mean time at which malignant neoplasms are seen in ureterosigmoidostomies.

In a review of 260 patients with a follow-up of more than 10 years, Soergel et al found 3 malignancies (all transitional cell carcinoma): 2 following ileocecal and 1 after cecal augmentation. The age at augmentation was 8, 20 and 24 years respectively: the tumors were found when they were 29, 37 and 44 years old. All had metastatic disease and died. The incidence of malignancy in this group was 1.2%; considering that the development of tumors usually takes 20-25 years the probable incidence of malignancy following enterocystoplasty may be as high as 3.8% [260].

Patients who undergo bladder augmentation with a gastric remnant are at increased risk for malignancy, probably similar to that in patients with enterocystoplasty. In a review of 119 patients underwent augmentation cystoplasty with stomach in 2 institutions, three patients had gastric adenocarcinoma, while the
other had poorly differentiated transitional cell carcinoma. Each case progressed to malignancy more than 10 years after augmentation [261,262,263].

If cancer is going to be a common problem, there will be some difficulty in monitoring the patients at risk [264]. Endoscopy with a small instrument through a stoma may not be sufficient. Ultrasound may not be able to distinguish between tumors and folds of mucosa. Three dimensional reconstruction of computerised tomography may be helpful, though the equipment is expensive and not widely available at present [265]. At present it is advised to perform an annual endoscopic evaluation in all patients following enterocystoplasty starting 10 years after surgery.

10. PSYCHOLOGICAL CONSEQUENCES AND QUALITY OF LIFE

The main justification for performing a bladder reconstruction or continent diversion is to improve the individual’s Quality of Life (QoL).

It would seem logical that continent urinary diversion would be better than a bag. This is not always the case. In adults the only sure advantage is cosmetic. Validated QoL surveys in children have not been reported, primarily because of the lack of suitable instruments [266]. Our prejudice is that reconstruction does, indeed, improve the lives of children. Supporting evidence is very thin and based on experience in adults.

The ileal conduit has been a standard part of urological surgery for over 50 years. It has well known complications but few would seriously suggest that they were more troublesome than those of the complex operations for bladder replacement. In an early investigation into quality of life issues, Boyd et al investigated 200 patients, half with an ileal conduit and half with a Kock pouch: there was little difference between the groups except that those with a Kock pouch engaged in more physical and sexual contact. The only patients that were consistently ‘happier’ were those who had been converted to a Kock pouch [267].

In a recent QoL survey in adults, a wide range of complications were considered to be acceptable, although an ordinary urological clinic would be full of patients trying to get rid of such symptoms: mild incontinence (50%), nocturia (37%), bladder stones (12%), urinary infections (9%), hydronephrosis (5%). Nonetheless, their QoL was judged to be good, primarily because 70% had experienced no adverse effect on their normal daily lives [268].

Quality of life does not mean absence of disease or a level of complications acceptable to the reviewing clinician. It is a difficult concept to measure because lack of validated instruments, difficulties in translating from one culture or language to another, of the difficulties in selecting control groups and variations in clinical situations. Gerharz et al have constructed their own 102 item instrument and compared 61 patients with a continent diversion and 131 with an ileal conduit. Patients with a continent diversion did better in all stoma related items indicating that containment of urine within the body and voluntary emptying is of major importance.

In addition they had better physical strength, mental capacity, social competence and used their leisure time more actively. There was little difference in satisfaction with professional life, financial circumstances and in all interactions within the family including sexual activity [269].
G. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE, ENURESESIS AND FAECAL INCONTINENCE

Since the publication of the ICI report in 2005 [1] an increasing body of studies have been published on psychological factors of incontinence in children including some comprehensive reviews [2-7]. This part makes an update based on the recent literature.

**I. INTRODUCTION**

Children with urinary incontinence, enuresis and faecal incontinence carry a higher risk for manifest behavioral disorders, as well as for subclinical emotional and behavioral symptoms. It is important to assess and integrate psychological factors in treatment for two reasons:

1. As can be seen in the next table 3, the rate of comorbid behavioural and emotional disorders is much higher than possible organic causes [7]. The same care used to exclude organic causes should be applied to the assessment of behavioral aspects. Therefore, even paediatricians and urologists should have a basic understanding of psychological principles in order to treat their young patients adequately.

2. In functional elimination disorders, provision of information, cognitive therapy and behavioural modification are the most effective, first-line approaches to treatment. Medication can be helpful in many cases, but are usually not the mainstay of treatment. Surgery is rarely indicated. As most of the techniques used in “urotherapy” are based on cognitive-behavioural psychotherapy, it is, again, essential be acquainted with the basic psychological principles.

The aim of this chapter is to provide information on comorbid manifest clinical disorders, as well as symptoms which might be emotionally distressing for children and parents, but do fulfil the criteria for a disorder. Often, these will resolve upon attaining continence, while manifest disorders usually do not. In addition, children with psychological disorders are less compliant, so that the failure rate of the incontinence treatment is much higher. Therefore it is recommended that both incontinence and any comorbid psychological disorder need to be treated separately to ensure effective therapy.

Also, the relevance of psychological factors for the different subtypes of incontinence will be considered. The terminology of the ICCS for enuresis and urinary incontinence (8) as well as of the Rome-III classification (9) for faecal incontinence will be used.

**II. CLINICAL BEHAVIOURAL DISORDERS**

The rate of clinically relevant behavioural disorders in children and adolescents lies between 12.0% (ICD-10 criteria) [10] and 14.3% (DSM-IV) [11,12]. The rate of comorbid behavioural disorders is definitely increased in children with all types of incontinence. Comorbidity denotes the co-occurrence of two or more disorders at the same time (concurrent comorbidity) or in sequence (sequential comorbidity). The focus on comorbidity allows a descriptive approach without making reference to possible causal associations. Basically, four combinations are possible:

- A behavioural disorder can be a consequence of the wetting problem
- A behavioural disorder can precede and induce a relapse when a genetic disposition for enuresis is present, for example in secondary nocturnal enuresis
- Wetting and a behavioural disorder can both be due to a common neurobiological dysfunction (such as in nocturnal enuresis and ADHD)
- and finally, with such common disorders, no causal relationship can be present and the two may co-exist by chance.

Psychological disorders (synonyms: psychiatric, psychic, mental disturbances) indicate that there is “a clinically significant behavioural or psychological syndrome or pattern (not a variant of normal behaviour) that occurs in an individual, that it is associated with present distress, disability or impairment and carries a risk for the future development of the individual” (DSM-IV) [11].

<table>
<thead>
<tr>
<th>Nocturnal enuresis</th>
<th>Organic causes</th>
<th>&lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural comorbidity*</td>
<td>20-30%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary incontinence</th>
<th>Organic causes</th>
<th>&lt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural comorbidity*</td>
<td>20-40%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faecal incontinence with constipation</th>
<th>Organic causes</th>
<th>&lt; 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural comorbidity*</td>
<td>30-50%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faecal incontinence without constipation</th>
<th>Organic causes</th>
<th>&lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural comorbidity*</td>
<td>30-50%</td>
<td></td>
</tr>
</tbody>
</table>

* Comparable norms: 10%
Clinically relevant disorders can be assessed by two basic methods: the categorical and the dimensional approach. The categorical method is based on a detailed diagnostic process (including: history, observation, exploration, mental state examination, questionnaires, testing, physical examination and other procedures) and are professional diagnosis according to standardised classification schemes: ICD-10 [10] or DSM-IV [11]. Dimensional assessment is based on symptom scores by questionnaires, but do not represent diagnoses. Cut-offs are defined to delineate a clinical (and sub-clinical) range.

One can differentiate externalising or behavioural disorders with outwardly-directed, visible behaviour (examples: conduct disorders, ADHD, etc.); internalising, i.e. inwardly-directed, intrapsychic disorders such as emotional disorders (examples: separation anxiety, social anxiety, phobias, sibling rivalry, depressive disorders, etc.); and other disorders that do not fit into the two categories, such as anorexia nervosa, tic disorders, autistic syndromes, etc.

### III. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH ENURESIS/ URINARY INCONTINENCE

Children with urinary incontinence show a higher rate of comorbid behavioural and emotional problems than non-wetting children – in both epidemiological and in clinical studies. The overall relative risk is 1.4 – 4.5 times higher (table 4) [7].

#### 1. EPIDEMIOLOGICAL STUDIES

Epidemiological studies have the advantage of revealing representative associations. They often cannot differentiate well between subgroups

Not all epidemiological studies on enuresis actually assess behavioural problems in a standardised form [13]. Therefore, only those studies that clearly define the group of clinically deviant children shall be reported in table 2. If a control group is reported, the relative risk for a behavioural problem can be calculated; otherwise the normative data is used.

**a) Nocturnal enuresis**

In the Isle-of-Wight study, 25%-28% of enuretics were seen by their parents to show problematic behaviour according to the Rutter Child Scale – 3-4 times more often than the controls [14]. Using the same instrument, the longitudinal Study from Christchurch (New Zealand) came to similar rates for the primary children with nocturnal enuresis, while the secondary children with nocturnal enuresis showed a much higher rate of 52% [15]. The same study assessed rates of DSM-III diagnoses at a later age – with marked differences between the primary and the secondary children with nocturnal enuresis [16].

In the Dutch study by Hirasing et al [18] 23% of children with enuresis scored in the clinical range of the CBCL total problem scale. In the cross-sectional Chinese study by Liu et al [17] a third of all wetting children were in the clinical range – 3.6-4.5 more often than the controls. The US-Study by Byrd et al [12] used the 32-item BPI (Behavior Problem Index), which is modelled after CBCL. The rates are lower than in the other studies, but included infrequent wetters of as few as one wetting episode per year.

In summary, the epidemiological studies show clearly that, depending on definitions and instruments used, 20-30% of all nocturnal enuretic children show clinically relevant behavioural problems – 2 to 4 times higher than non-wetting children.

Children with primary nocturnal enuresis were not more deviant than controls in epidemiological studies [16]. Secondary nocturnal enuresis was preceded by a higher rate of weighted life-events [20] and was significantly associated with a higher rate of DSM-III psychiatric disorders, which can persist into adolescence [16]. By adolescence, the attainment of dryness after the age of 10 years increased the risk for behavioural problems - independently of the primary or secondary status [13].

The only epidemiological study addressing monosymptomatic nocturnal enuresis included 8242 children aged 7.5 years [21]. Though not adhering to the ICCS criteria, children with monosymptomatic nocturnal enuresis showed fewer behavioural symptoms than those with daytime problems (i.e. the non-mono-symptomatic forms) – although the differences did not reach significance.

**b) Urinary incontinence (daytime wetting)**

Daytime wetting has been neglected in epidemiological research. Only recently, the first study was published based on a cohort of 8213 children aged 7.5 to 9 years [19]. Children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety (11.4%), attention deficit (24.8%), oppositional behaviour (10.9%) and conduct problems (11.8%). In other words, externalising disorders predominate in daytime wetting children which, in turn, will interfere with treatment. In the same cohort, 10000 children aged 4 to 9 years were analysed. Delayed development, difficult temperament and maternal depression/anxiety were associated with daytime wetting and soiling [22].

#### 2. CLINICAL STUDIES

Clinical studies are limited by selection biases, but allow a much more detailed assessment of patients. Overall, children with nocturnal enuresis have lower rates of comorbid disorders (33.6%) than children with daytime wetting (52.6%) [23]. In another study, the rates were 29% and 46%, respectively [24]. Van
Hoecke et al. [25] could also show that children with daytime wetting (or combined DW/NW) had significantly higher CBCL total problem scores than pure nocturnal enuretics or controls (Table 5).

In an early study of Berg et al [26] nearly 30% of children presented in a paediatric department clinic were deemed “clinically disturbed”. In another study in a paediatric setting, similar rates of 26% were found 20 years later using the CBCL [27]. These rates are almost identical to our own studies in a child psychiatric setting using the same instruments [23]. The rates of a selected group of treatment-resistant children with nocturnal enuresis undergoing Dry Bed Training were 2.2 times higher [28]. In the study of Van Hoecke et al [29], internalizing symptoms predominated in a mixed group of day and night wetting children with significantly higher scores for withdrawal, physical complaints, anxious/depressed, social problems and internalising behaviour scales compared to controls.

According to the ICCS terminology, four subgroups of nocturnal enuresis can be differentiated:

- primary monosymptomatic nocturnal enuresis
- primary non-monosymptomatic nocturnal enuresis
- secondary monosymptomatic nocturnal enuresis
- secondary non-monosymptomatic nocturnal enuresis

Regarding the subtypes of nocturnal enuresis, children with primary nocturnal enuresis showed behavioural problems less frequently (19.5%) than those with the secondary type (75.0%) [23]. The group with the lowest comorbidity – no higher than in the normative population – were those with monosymptomatic nocturnal enuresis (10.0%) without any daytime symptoms such as urge, postponement or dysfunctional voiding. In a replication study, 29% of children with nocturnal enuresis had at least one ICD-10 diagnosis – 24% of those with monosymptomatic and 33% of those with non-monosymptomatic nocturnal enuresis [24].

Regarding the types of behavioural and emotional disorders, externalising disorders predominates [23]. The most specific comorbid disorders with enuresis are ADHD (according to DSM-IV) or the Hyperkinetic Syndrome (according to ICD-10). In our own studies, the rates ranged from 9.3% (HKS) to 13.5% (HKS and ADHD) [23, 31]. ADHD is not associated with any specific type of nocturnal enuresis [30].

In a retrospective study, of patients with ADHD, 20.9% wetted at night and 6.5% during the day. The odds-ratios were 2.7 and 4.5 times higher, respectively, which means that there is unspecific association of ADHD and both night/ daytime wetting [32]. 25% of

---

**Table 4. Epidemiological studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>N</th>
<th>Type of wetting</th>
<th>Incontinent children</th>
<th>Controls</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutter 1973</td>
<td>5-14</td>
<td>4481</td>
<td>NW/DW</td>
<td>Boys: 25.6% Girls: 28.6%</td>
<td>7.9%</td>
<td>3.2</td>
</tr>
<tr>
<td>McGee 1984</td>
<td>7-9</td>
<td>1037</td>
<td>NW</td>
<td>Primary: 30.8% Secondary: 51.9% DSM-III diagnoses</td>
<td>21.6%</td>
<td>1.4</td>
</tr>
<tr>
<td>Feehan 1990</td>
<td>11-15</td>
<td>1037</td>
<td>NW</td>
<td>Total: 23.4% Primary: 0% Secondary: 42.3% CBCL Total &gt; 90th p.</td>
<td>9.5%</td>
<td>2.5</td>
</tr>
<tr>
<td>Liu 2000</td>
<td>6-18</td>
<td>3344</td>
<td>NW</td>
<td>30.3%</td>
<td>9.1%</td>
<td>4.3</td>
</tr>
<tr>
<td>Hirasing 1997</td>
<td>9</td>
<td>1652</td>
<td>NW</td>
<td>23.0% BPI &gt; 90th p.</td>
<td>10.0%</td>
<td>2.3</td>
</tr>
<tr>
<td>Byrd 1996</td>
<td>5-17</td>
<td>10960</td>
<td>NW</td>
<td>16.5% DAWBA</td>
<td>10.2%</td>
<td>1.6 Odd’s ratio</td>
</tr>
<tr>
<td>Joinson 2006</td>
<td>7-9</td>
<td>8213</td>
<td>DW</td>
<td>Separation anxiety: 11.4% Attention/activity: 24.8% Oppositional behaviour: 10.9% Conduct problems: 11.8%</td>
<td>6.8%</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*NW = night wetting (nocturnal enuresis) *DW = daytime wetting (urinary incontinence)
140 children with ADHD were affected by nocturnal enuresis compared to 10.8% of 120 controls [33]. The highest comorbidity rates of 40% for ADHD and nocturnal enuresis were reported by Baeyens et al. [30], possibly due to selection effects. 15% had a combined, 22.5% an inattentive and only 2.5% a hyperactive type of ADHD. In a community based sample, the prevalence rate was much lower [34]. ADHD continued to be present in 72.5% of children in a two-year follow-up indicating a high stability [34]. Children with ADHD continued to wet at follow-up much more often (65%) than controls (37%) (Odds-ratio 3.17) [34]. At a 4-year follow-up, 64% still had ADHD. Of these, 42% continued to wet at night (compared to 37% of the controls) [35].

In clinical practice, children with ADHD are more difficult to treat. In a retrospective study, 113 children with ADHD and nocturnal enuresis had a far worse outcome on alarm treatment than controls (with nocturnal enuresis only): 43% (vs. 69%) were dry at 6 months and 19% (vs. 66%) at 12 months. There was no difference if they were treated with medication, which does not require active cooperation. Non-compliance was reported in 38% of child with ADHD, but only in 22% of the controls [36]. Therefore, the comorbid diagnoses of both enuresis and ADHD require special attention – and both need to be treated separately.

b) Urinary incontinence (daytime wetting)

Far fewer studies have addressed the specific problems of daytime wetting children. In a study in a paediatric setting of 418 children aged 5 – 17 years, day wetting children were described as being more stubborn, oppositional and secretive than nocturnal enuretic children [37]. In a subgroup of 58 children, those with and without urinary tract infections were compared. 11 % of day wetting children with urinary tract infections had a CBCL total score in the clinical range, 35 % of day wetting children without urinary tract infections and 16 % of nocturnal wetters. In other words, the subgroup with a higher risk for behavioural problems were day wetting children without urinary tract infections [37]. In another study, 90 girls with recurrent UTI’s had significantly more behavioural abnormalities than controls [38], so that the issue of behavioural problems in children with and without UTI’s remains to be settled.

ADHD is a common problem among day wetting children, as well. Compared to controls, children with ADHD had more symptoms of incontinence, constipation, infrequent voiding and dysuria [39]. With ADHD, treatment outcome is worse. In a retrospective analysis, 68% of day wetting children with ADHD became dry compared to 91% of controls. Non-compliance was much higher for timed voiding [36].

Table 5. Clinical studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk*

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>N</th>
<th>Type of wetting</th>
<th>Incontinent children</th>
<th>Controls</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Gontard 1999 [23]</td>
<td>5-11</td>
<td>110</td>
<td>NW</td>
<td>33.6%</td>
<td>12.0%</td>
<td>2.8</td>
</tr>
<tr>
<td>von Gontard 1999 [23]</td>
<td>5-11</td>
<td>57</td>
<td>DW</td>
<td>52.6%</td>
<td>12.0%</td>
<td>4.4</td>
</tr>
<tr>
<td>Zink 2008 [24]</td>
<td>5-16</td>
<td>97</td>
<td>NW</td>
<td>29%</td>
<td>12.0%</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>5-16</td>
<td>69</td>
<td>DW</td>
<td>46%</td>
<td>12.0%</td>
<td>3.8</td>
</tr>
<tr>
<td>Berg 1981 [26]</td>
<td>6-13</td>
<td>41</td>
<td>NW</td>
<td>29.3% (26.8%)</td>
<td>10.0%</td>
<td>2.6</td>
</tr>
<tr>
<td>Baeyens 2001 [27]</td>
<td>6-12</td>
<td>100</td>
<td>NW/DW</td>
<td>26%</td>
<td>10.0%</td>
<td>2.6</td>
</tr>
<tr>
<td>von Gontard 1999 [23]</td>
<td>5-11</td>
<td>167</td>
<td>NW/DW</td>
<td>28.2%</td>
<td>10%</td>
<td>2.8</td>
</tr>
<tr>
<td>Hirasing 2002 [28]</td>
<td>6-15</td>
<td>91</td>
<td>NW</td>
<td>21%</td>
<td>10%</td>
<td>2.1</td>
</tr>
<tr>
<td>Van Hoecke 2004 [29]</td>
<td>9-12</td>
<td>84</td>
<td>NW/DW</td>
<td>20.4%</td>
<td>6.1%</td>
<td>3.3</td>
</tr>
<tr>
<td>Zink 2008 [24]</td>
<td>5-16</td>
<td>166</td>
<td>NW/DW</td>
<td>40%</td>
<td>10%</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*NW = night wetting (nocturnal enuresis)  
*DW = daytime wetting (urinary incontinence)
Daytime wetting (urinary incontinence) is a heterogeneous group of disorders. According to the ICCS terminology, following subgroups can be differentiated [8]:

- Over-active bladder including urgency incontinence
- Voiding postponement
- Underactive detrusor
- Dysfunctional voiding
- Obstruction
- Stress incontinence
- Vaginal reflux
- Giggle incontinence
- Extraordinary daytime urinary frequency

Only some of these subgroups have been studied regarding comorbid psychological disorders.

Children with urgency incontinence have previously been considered to have few behavioural problems [40]. 29% of children with urgency incontinence had an ICD-10 diagnosis and 14% had an internalizing disorder. 13.5% had a clinical total problem score in the CBCL – again mainly internalizing problems [41, 42]. The children are distressed by their wetting and family functioning is intact [42]. In a new study, 35% of children with urgency incontinence fulfilled the criteria for an ICD-10 diagnosis [24]. In summary, children with urgency incontinence have only a slightly increased rate of comorbid psychiatric disorders. If they are affected, emotional, introversive symptoms predominate.

Children with voiding postponement, on the other hand, fall into two groups: in some it represents an acquired habit, in others, it is associated with externalising psychological disorders, especially oppositional defiant disorder (ODD). In a systematic study of children with voiding postponement in a paediatric and child psychiatric setting, 53.8% fulfilled the criteria for at least one ICD-10 diagnosis [41]. These were mainly externalizing disorders in a third of all children such as Oppositional Defiant Disorder (ODD). Also, 37.3% of children had a CBCL total score in the clinical range, again, with externalizing symptoms predominating. In addition, family functioning was impaired [41, 42]. In a new sample, 53% of children with voiding postponement had at least one ICD-10 diagnosis [24]. In summary, children with voiding postponement have highly increased psychiatric risks.

Systematic studies on comorbid behavioural problems in children with underactive bladder have not been performed, although by clinical impression the rate of associated problems is high. In the original article, the “lazy bladder syndrome” was described as an acquired behaviour: it has “developed from the habitual neglect of the patient to empty the bladder on getting the urge to micturate” [43].

Systematic investigations of psychological aspects of dysfunctional voiding are rare. Again, in some children it represents an acquired habit, in others severe psychological disturbances are present [44]. Also, dysfunctional voiding following severe sexual abuse and deprivation as well as other familial stressors such as migration has been described in case reports [45].

There have been no systematic investigations of children with giggle incontinence. From clinical experience, they are highly distressed by the symptom and try to avoid situations in which they might be forced to laugh. Social withdrawal, not going to parties and meeting with friends have been observed. It is not known if the rate of behavioural disorders is increased, however.

Regarding the other subtypes of urinary incontinence, not even anecdotal data is available.

### IV. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH FECAL INCONTINENCE (FAECAL INCONTINENCE)

According to the Rome-III classification, two subtypes of faecal incontinence can be differentiated [9]:

- Functional constipation (with or without incontinence)
- Nonretentive fecal incontinence.

#### 1. EPIDEMIOLOGICAL STUDIES

In the large Alspac study of 8242 children aged 7-8 years, children with faecal incontinence had significantly increased rates of separation anxiety, specific phobias, generalised anxiety, ADHD and ODD (Table 6) [46].

In other words, soiling children show a completely heterogeneous pattern of both internalising and externalising disorders. Again, these will require assessment in the individual child, as they will interfere with treatment of the incontinence.

#### 2. CLINICAL STUDIES

As many studies have used the Child Behaviour Check List (CBCL) [47], the results can be compared easily. As shown in table 4, 35% to 50% of all children with faecal incontinence had a total behavioural score in the clinical range in this parental questionnaire. Compared to the normative population (10%), 3.5 to 5 times more children with faecal incontinence have total behaviour scores in the clinical range. As all studies were conducted in a paediatric setting, this rate...
cannot be due to selection effects of mental health clinics. Children with behavioural maladjustment are less compliant than children without psychological disorders (71% vs. 38% non-compliant) – so if these problems are not addressed treatment will be less successful [48].

Encopretic children with constipation have the same rate of behavioural scores in the clinical range as children without constipation (39% vs. 44%, Benninga et al. 1994; and 37% vs. 39%, Benninga et al., 2004). In other words, the two major types of faecal incontinence cannot be differentiated according to the behavioural comorbidity. More importantly, regarding the aetiology, there’s no evidence that one type (i.e. with constipation) has more somatic, while the other type (i.e. without constipation) a more psychogenic aetiology. Also, there is no specific psychopathology typical for faecal incontinence – all types of behavioural and emotional disorders can co-exist.

Internalising clinical behavioural scores (32%) were twice as common as externalizing ones (17%) in one study (54). In others, single behavioural items, denoting oppositional behaviour and attentional problems predominate [49, 55]. Compared to controls, children with faecal incontinence rated significantly higher regarding anxious/depressed behaviour, attentional difficulties and disruptive behaviour on the CBCL subscales. For example, the rate of children with attentional problems in the clinical and borderline range was 6-7 times higher than in controls (20% vs. 3%; norms 5%) [56]. Again, the heterogeneity of behavioural symptoms is apparent.

Only few studies have assessed behavioural and emotional disorders according to standardized child psychiatric criteria. They also show a high general

---

**Table 6. Epidemiological and clinical studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>N</th>
<th>Type of faecal incontinence</th>
<th>Incontinent children</th>
<th>Controls</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joinson 2006 [46]</td>
<td>7-8</td>
<td>8242</td>
<td>Not specified</td>
<td>Separation anxiety: 4.3% Specific phobia: 4.3% Generalised anxiety: 3.4% ADHD: 9.2% ODD: 11.9%</td>
<td>0.8%</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0%</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4%</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9%</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9%</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Clinical studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabel 1986 [49]</td>
<td>6-11</td>
<td>55</td>
<td>Not specified</td>
<td>CBCL Total &gt;90th p.</td>
<td>49%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Young 1995 [50]</td>
<td>5-17</td>
<td>76</td>
<td>Not specified</td>
<td></td>
<td>51%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Nolan 1991 [48]</td>
<td>4-16</td>
<td>169</td>
<td>Not specified</td>
<td></td>
<td>43%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Loening-Baucke 1987 [51]</td>
<td>6-11</td>
<td>38</td>
<td>Functional constipation</td>
<td></td>
<td>42%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Benninga 1994 [52]</td>
<td>5-17</td>
<td>111</td>
<td>Functional constipation</td>
<td></td>
<td>39%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Benninga 2004 [53]</td>
<td>5-17</td>
<td>135</td>
<td>Functional constipation</td>
<td></td>
<td>37%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Benninga 1994 [52]</td>
<td>5-17</td>
<td>50</td>
<td>Nonretentive faecal incontinence</td>
<td></td>
<td>44%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Van der Plas 1997</td>
<td>5-17</td>
<td>71</td>
<td>Nonretentive faecal incontinence</td>
<td></td>
<td>35%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Benninga 2004 [53]</td>
<td>5-17</td>
<td>56</td>
<td>Nonretentive faecal incontinence</td>
<td></td>
<td>39%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
rate and heterogeneity of comorbid disorders. Thus, 34% of 41 children with faecal incontinence had an emotional disorder, 12% a conduct disorder and 10% a hyperkinetic syndrome according to ICD-criteria [57]. In another study of highly selected 85 child psychiatric inpatients with faecal incontinence, 83% fulfilled the criteria for at least one ICD-10-diagnosis. 32% had a hyperkinetic syndrome, 21% an emotional disorder and 9% a conduct disorder [58]. Children with faecal incontinence and urinary incontinence have an even higher rate of behavioural and emotional disorders than children with wetting problems alone [59].

The co-occurrence of faecal incontinence and sexual abuse has been described by several authors [60]. In one study, 36% of abused boys had faecal incontinence [61], but other symptoms can co-exist [62,63]. However, in a retrospective analysis of 466 children having experienced sexual abuse, 429 children with externalising disorders and 641 controls, the occurrence of faecal incontinence did not differ between groups (faecal incontinence in 10.3%, 10.5% and 2%, respectively) [64].

V. SUBCLINICAL SIGNS AND SYMPTOMS

Subclinical behavioural signs and symptoms are common, understandable, adequate reactions towards the wetting problem and not disorders. Many studies have addressed the impact of wetting on children.

1. IMPACT ON CHILDREN

Most children are distressed by enuresis. For example, 35% said that they felt unhappy, 25% even very unhappy about wetting at night in one study (40 children aged 5-15 years) [65]. In a Finnish population-based study, 156 day and night wetting children (from 3375 7-year olds) showed significant differences compared to 170 controls regarding following personality traits [66]: they were more fitful (vs. peaceful), more fearful (vs. courageous), more impatient (vs. calm), more anxious (vs. does not worry) and had more inferiority feelings (vs. feels equal). In a large population-based British study of 8209 children aged 9 years, 36.7% of children consider bed-wetting to be “really difficult” – ranking 8th behind other stressful life-events [67].

In a clinical study, 70.3% of day and night wetting children aged 5 to 11 years could clearly indicate that the wetting was of disadvantage [68]. The types of disadvantages or negative consequences were: social (I can’t sleep at friends’ house, friends can’t stay over night – in 32.1%), affective (I feel sad, ashamed, annoyed – in 16.4%), of isolation (I feel like a baby, nobody is allowed to know about it, I feel different from other children – in 6.7%), of sensation (it feels unpleasant, cold, wet, itchy, nasty – in 32.1%) or referred to direct consequences (I have to take a shower, sleep in pampers, won’t get a bicycle – in 17.6%). Only 4.9% reported any advantages of the wetting at all (I like the wet feeling, get more attention from mother).

One construct of special importance is that of self-esteem. In one study, lower self-esteem in children with enuresis disappeared upon attaining dryness [69]. In another, global self-esteem was significantly lower in children with nocturnal enuresis than in controls [70] and in yet another, the self-esteem total score was higher among enuretics than norms [71]. Therefore, it was concluded that there is no clear evidence that bedwetting leads to lower self-esteem [72] – but there can be no doubt that self-esteem can improve upon attaining dryness [71]. Self-esteem even increases even if treatment of enuresis is not successful [73], showing that care and “good doctoring” for children and parents is of great help – regardless of outcome. Recently, a focus has been on quality of life, which is reduced in children with urinary incontinence [74].

In a population-based study of 75 boys with faecal incontinence were compared to 73 matched controls as shown in table 16.9 [75]. Specifically, encopretic boys showed higher rates of food refusal, general negativism, strong anxiety reactions, lack of self-insurance, poor tolerance to stress, both inhibited and aggressive behaviour, a strong fixation to their mother and difficulties in relationships. Also, children with faecal incontinence tended to feel less in control of positive life events and had a lower sense of self-esteem than children with other chronic conditions [76]. However, in a more recent study, self-esteem did not differ between children with faecal incontinence and controls on the Piers-Harris questionnaire [77]. Although some of these subclinical symptoms will diminish under successful treatment [53,54], it is not known which ones will persist and chronify.

2. IMPACT ON PARENTS

Enuresis and urinary incontinence may be just as distressing for parents as for children. Generally, parents are very concerned about the welfare of their child. In a population based study, 17% worried a great deal and 46% some or a little [78]. In one study, the greatest maternal concerns were: emotional impact, social relationships, smell, extra washing and financial aspects [79]. Mothers of children with nocturnal enuresis had a reduced quality of life scores (bodily pain and emotional role) and more depressive symptoms [80].

Parents also believe that their child should be dry at a very early age, which can induce anxiety and stress: the mean anticipated age of dryness was 3.18 years in one study [81] and 2.75 years in another [82]. Also,
many parents think that emotional factors are the cause of nocturnal enuresis and forget that they might be the effect of the wetting problem instead [81,82].

A minority of parents show an attitude that was described as “maternal intolerance” by Butler et al [79]. Convinced that their child is wetting on purpose, the risk for punishment is increased. The reported rates of punishment varied from 37% [85], 35.8% [81], 23% [82] to 5.6% [84]. In other cultures, punishment is even more common: 42% of Turkish children were spanked and 13% beaten [85]. Chinese parents show a high level of parenting stress associated with externalising behavioural problems or their child [86]. These parental attributions and experiences have to be taken into account in all treatment plans for enuresis, as they can decisively influence the outcome.

Parents of children with faecal incontinence are also stressed and worried the problem (87). In one study, children with faecal incontinence had family environments with less expressiveness and poorer organisation than controls (77). In another study of 104 families, nearly half (51%) had no unusual family problems; 23 had severe and widespread difficulties including sexual abuse; 11 families described moderate difficulties and 18 a single traumatic event [88]. In other words, the atmosphere was warm and supportive without major difficulties in at least half of the families.

VI. GENERAL PRINCIPLES: ASSESSMENT

1. SCREENING QUESTIONNAIRES

Due to this high comorbidity of psychological symptoms as well as disturbances, every child should be screened as part of the routine assessment. The best screening instrument is still a good history and careful clinical observation, which requires some training and experience. The second best approach is screening questionnaires, such as the Child Behavior Check List (CBCL) [47], which contains 113 empirically derived behavioural items. These are checked on a three-point scale and are formulated in simple wording. From these items, eight specific syndrome scales and three general scales can be calculated.

Recently, even shorter screening instruments have been derived from the CBCL. Thus, Van Hoecke et al. (89) validated a short questionnaire consisting of 7 items for emotional problems, 3 for attention problems and 3 for hyperactivity/impulsivity. This is an extremely useful short questionnaire both for clinical and research uses.

Also, other useful questionnaires addressing specific aspects of enuresis have been developed [90]. These assess the subjective views and attributions of parents and children, such as parental intolerance. Another potentially useful questionnaire addresses aspects of everyday burden of enuresis on children and their families [91]. Other non-validated questionnaires for the assessment of children with all types of incontinence can be found in von Gontard and Neveus [8].

For children with faecal incontinence, the Virginia-Faecal incontinence-Constipation-Apperception Test (VECAT), a validated, picture-based questionnaire for children and parents was shown to differentiate well regarding bowel-specific problems [92].

One construct of special interest in children with elimination disorders is that of self esteem.

Well-known self-esteem questionnaires include the Piers-Harris Children’s self – concept scale [93] as well as others [94]. Another important construct is that of health related quality of life (HQOL). This is a complex construct that tries to assess health related wellbeing in different domains of daily life. Generic HQOL questionnaires allow comparison between children with different medical disorders [95,96]. These range from short screening to longer, more detailed questionnaires (such as the KINDL-questionnaire) [97]. Recently, the first specific quality of life questionnaire for children with wetting problems was developed by Bower et al. [98]. These have the advantage that the specific, elimination-related effects on daily life can be assessed. For children with faecal incontinence, health-related quality of life questionnaire with good psychometric properties was described. The Defecation Disorder List (DDL) consists of 37 items and can be used in children with all types of faecal incontinence and/or constipation [99].

2. CHILD PSYCHIATRIC ASSESSMENT

A child psychiatric assessment is a professional procedure with the goal to come to a categorical decision: to see if a diagnosis according to the standardised classification schemes (ICD-10 or DSM-IV) is present in the child or not.

The first step is a detailed developmental, behavioural and family history in much greater detail than provided in the outline in the appendix. The next step is to observe the child as well as the parent-child-interaction, followed by an active exploration of the child. The information gained from history, observation and exploration forms the basis of the mental state examination. This is a descriptive, phenomenological assessment of mental and behavioural signs and symptoms (for example: CASCAP-D) [100].

Questionnaires are always an essential part of child psychiatric assessment. They are a time-economical way to gather information from different informants. They can contribute towards but do not provide a diagnosis. Behavioural questionnaires can again be divided into general and specific questionnaires. The best known, most widely used general parental questionnaire is the Child Behavior Check List, which
has been translated into many languages (CBCL/4-18) [47]. In the meantime, Achenbach and co-workers have produced a whole “family” of questionnaires for different age groups (infants, children – adolescents, young adults) and different informants (parents, teachers and for children themselves starting from age 11). In addition, other specific questionnaires address circumscribed areas such as depressive symptoms or ADHD problems.

An intelligence test is not routinely indicated in the assessment of children with elimination disorders, as the IQ is in the normal range for most children with wetting, as well as soiling problems. However, the rate of elimination disorders is clearly increased in children with general developmental disorders, with mental and physical handicap [101-103]. If a lower intelligence is suspected, one-dimensional tests (such as the CFT or CPM/SPM tests) or multidimensional tests such as the Kaufman or the Wechsler tests can be performed. If specific developmental disorders such as dyslexia or dyscalculia are suspected, specific tests for these circumscribed disorders are indicated. Disorders of speech or language (such as articulation, expressive and receptive speech disorders) require a detailed assessment by an audiologist and speech therapist.

Motor disorders can be assessed clinically by including soft neurological signs in the physical examination of children or by standardized tests such as the Zurich Motor Tests [104,105].

After the diagnostic process has been completed, the child’s disorder is diagnosed according to standardized classification schemes. The two standard classification systems are the ICD-10 [10], which is widely used in Europe and in other parts of the world and the DSM-IV [11] employed in the United States. In child psychiatry, a multiaxial classification is used. Six different axes denoting different domains are used, including:

1. Axis: clinical psychiatric diagnosis (such as anorexia nervosa, depressive episodes, etc.)
2. Axis: specific developmental disorders (such as dyslexia)
3. Axis: intelligence (such as dyslexia, speech and motor disorders)
4. Axis: somatic diagnosis (such as epilepsy and other paediatric diagnoses)
5. Axis: psychosocial risks occurring within the last six months (such as distorted intrafamilial interaction, isolated family and other stressful life events)
6. Axis: the global severity of a disorder (ranging from mild incapacitation to disorders requiring constant supervision and guidance)

Only after the diagnostic process has been completed and discussed with parents and children, should therapeutic interventions be planned.

**VII. GENERAL PRINCIPLES: TREATMENT OF PSYCHOLOGICAL DISORDER**

For most children with elimination disorders, a symptom-oriented approach is sufficient. If, however, another, co-occurring child psychiatric disorder is present, additional types of treatment will be necessary. In these cases, a differential indication for therapy is mandatory. The question is: which treatment is most effective for this child in this family at this moment?

For some disorders (such as ADHD), medication plays a major role. For most others, psychotherapeutical interventions are the first-line treatment. There can be no doubt that psychotherapy in children is effective. In one of the best and largest meta-analysis of 150 studies, Weisz et al. [106] conclude that “psychotherapy with young people produces positive effects of respectable magnitude” (i.e. effect sizes in the medium to large range - 0.5 to 0.8). It has been estimated that over 500 different types of psychotherapies exist in the USA for children and adolescents alone [107]. Of those which have been evaluated, four basic schools of psychotherapy can be differentiated: 1. depth psychology (or psychoanalysis), which addresses and works with unconscious aspects of the psyche; 2. Client-(or child) centred-psychotherapy, which focuses on the current conscious experience of the child and the healing aspects of their therapeutic relationship; 3. Family therapy, which focuses on the interaction between family members but not the individual person; 4. Cognitive-behavioural therapy, focussing on cognitions and observable behaviour.

Before initiating any psychotherapy, a differential indication for therapy as to be made. The first basic question should be: is treatment needed at all? In many cases counselling of parents and child is all that is required. In other cases, changes in the child’s environment (such as changing school) or help from social services can be more useful than psychological treatment in the narrower sense.

The modality has to be considered. Although parents are nearly always included, the focus can be on an individual, group or family therapy. The intensity and duration have to be addressed: is a short focal therapy focussed on one specific problem needed or a longer, more general treatment? The age of the patient plays an important role: while older children and adolescents can be reached verbally, younger children require play or other non-verbal media in their therapy.

Psychotherapies can be combined with other methods, such as pharmacotherapy, but also with speech, occupational, physio-, music- and other types of therapies – if indicated. The decision should no longer be based on personal inclinations. Instead, empirically based “practice parameters” or “guidelines” have been
developed in many countries. These interventions are usually performed on an out-patient basis. Day clinic treatment can be indicated in more severe disorders, which require a more intense approach and management. Finally, in-patient child psychiatric treatment is indicated in severe disorders, in which a more intense type of treatment is possible.

A major part of therapy of incontinence in children is non-pharmacological and non-surgical. The term urotherapy is used in some countries. It is an umbrella term which has been defined as a “type of training which makes use of cortical control of the bladder, teaching children to recognize and employ conscious command over their lower urinary tract. Its main ingredients are information about normal lower urinary tract function and the specific dysfunction in the child, instruction about what to do about it and support and encouragement to go through with the training program” [108].

Although not a psychotherapy in a narrow sense, it employs many psychotherapeutical techniques borrowed especially from counselling and cognitive-behavioural therapies. As these approaches have been shown to be most effective, basic principles and findings shall be outlined.

1. UNSPECIFIC APPROACHES

The first step in any diagnostic and therapeutic process is to create a good relationship to both the child and the parent. One should enquire and talk about all relevant facts, signs and symptoms openly. It is also important to ask about the subjective meanings and connotations. Next, the provision of information is essential, because many facts are not known. It is often forgotten that not only parents but each child needs information, as well. This should be provided in words and concepts that a child understands and in a format that is attractive. Increasing motivation and alleviation of stress and guilt feelings are also part of all patient contacts.

2. COUNSELLING

Counselling is already part of the treatment process, which has been defined as the provision of assistance and guidance in resolving personal, social, or psychological difficulties. For many children, even with psychological disorders, counselling is, in fact, sufficient. Sometimes, it can be helpful to enhance the verbal counselling by other techniques. One simple technique is that of “demonstration”, e.g. actively showing how an alarm works. In “coaching”, parents and children take an even more active role, e.g. they set and activate an alarm themselves. They can be observed and corrected. Other techniques might include “modelling” and “role-playing”. The learning effect is much greater in these active forms of teaching than in solely verbal counselling.

3. COGNITIVE-BEHAVIOURAL THERAPY

Cognitive-behavioural therapy (CBT) is a subtype of psychotherapy that has shown to be effective for many disorders. Cognitive therapy focuses on irrational, dysfunctional conditions, thoughts and beliefs. Cognitive therapy encompasses a whole variety of techniques such as “self-monitoring” (observation and registration), “activity scheduling” (organisation of activities) and “labelling” (using positive suggestive statements). Behavioural therapy concentrates on observable behaviour, which it aims to modify with a variety of techniques. These include “classical conditioning” and “operant conditioning”, which basically means learning by success, which can be achieved by different strategies using positive or negative reinforcement.

4. BASELINE AND OBSERVATION

Baseline and observation are effective techniques used in cognitive-behavioural therapy. Children (and parents) are advised to observe a defined symptom. Different parameters such as frequency (how often it occurs), severity (how marked it is), symptomatology (in what form it occurs) and in which situation (associated factors) can be registered, e.g. in an observation chart. The mere observation and registration actually has a therapeutic effect and many symptoms actually diminish simply if they are observed.

In nocturnal enuresis, children are asked to fill out a calendar or chart depicting the wet and the dry nights symbolically for two to four weeks [109,110]. These non-specific measures have been shown to be successful and are associated with fewer wet nights [3,111]. In one clinical trial, for example, 18% became dry after an 8-week baseline [112]. The authors of the recent Cochrane Review conclude that “simple methods could be tried as first line therapy before considering alarms or drugs, because these alternative treatments may be more demanding and may have adverse effects” [3, 5].

In urgency incontinence, the cognitive aspects are stressed in treatment: children are asked to register feelings of urgency, refrain from using holding manoeuvres, to void and register the voiding (or any wetting) in a chart [113,114]. For children with voiding postponement, timed voiding 7 times a day and registration in a chart is recommended [114].

For all children with faecal incontinence, stool regulation is an essential part of treatment. Children are asked to sit on the toilet three times a day after meal-times in a relaxed mode for five to ten minutes.
5. BIOFEEDBACK

Biofeedback has been shown to be effective in some elimination disorders such as dysfunctional voiding [118]. It is defined as a variety of techniques, by which physiological activity is registered, enhanced and presented to the patient in real time by visual and acoustical signals [118]. In faecal incontinence, biofeedback is no more effective than standard behavioural techniques in faecal incontinence both with [119] and without constipation [120] and is not recommended in a systematic Cochrane Review [6].

6. ALARM TREATMENT

Alarm treatment for nocturnal enuresis is also a type of cognitive behavioural therapy. It works by positive reinforcement, as well as aversive, negative experiences and has been shown to be highly effective and was introduced by Mowrer and Mowrer [121].

It is the most effective form of treatment of nocturnal enuresis with the best long-term results (grade I level of evidence according to reviews and meta-analyses). Houts et al. [122] compiled a systematic review and meta-analysis on 78 randomised studies on nocturnal enuresis. 62% were dry at the end of treatment and 47% at follow-up. The authors conclude that “urine alarm treatments should not only be considered the treatment of choice, but the evidence from this review suggests that cure rather than management is a realistic goal for the majority of children suffering from nocturnal enuresis”.

Lister-Sharp et al [111] provided a systematic review, including only RCT’s on nocturnal enuresis. The likelihood for 14 consecutive dry nights was 13.3 times higher than without treatment. The authors conclude that “in the long term, alarm treatment would appear to be the most clinically effective and because the cost of drug therapy, also the most cost effective intervention”. Mellon and McGrath’s [123] compiled a systematic review on 70 well-controlled outcome studies. With a dryness rate of 77.9%, alarm treatment is deemed clearly efficacious. A comprehensive narrative review was written by Moffat [124] concluding that “all the current evidence suggests that conditioning gives the best long-term outcomes for bed wetters”.

Finally, a Cochrane review of 50 RCT’s involving 3257 children concluded: “Alarm interventions are an effective treatment for nocturnal enuresis. Alarms appear more effective than Desmopressin or tricyclics because around half of the children remain dry after alarm treatment stops” [2].

Therefore, when indicated, alarm has been endorsed as a first line treatment by multidisciplinary European [125], world-wide [126], German [110] and American child psychiatric guidelines [109], as well as various individual authors [127].

The effect of alarm treatment can be enhanced by adding additional behavioural components to the treatment. Programmes that include alarm in addition to other behavioural components showed following general effects: 72% of children became dry at the end of treatment, and 56% remained so at follow-up (meta-analysis) [122], so that combinations were considered as “probably effective” [123].

These specific programmes including alarm are all essentially cognitive-behavioural techniques. Arousal training is a simply and easily performed [128,129]. Children are instructed to turn off the alarm within three minutes, go to the toilet and reset the alarm. This goal is reinforced positively with two tokens. If the goal is not reached, one token has to be returned. The initial success rate (89 %) and the rate of dryness after 2 ? years (92 %) were higher than with alarm treatment alone (73 % and 72 % respectively) [128].

Dry Bed Training is a complicated program starting with an intensive night and maintenance treatment and using positive, as well as negative reinforcers [130]. Despite high success rates reported in early studies [130], recent meta analysis have shown that DBT is no more effective than alarm treatment alone [111]. The likelihood to attain 14 consecutive dry nights was 10 times higher than in controls without treatment – but not different from alarm treatment alone. Also, alarm is the most important component of DBT. DBT without alarm showed only a 2.5 times higher likelihood of attaining dryness than controls. The relapse rates were not improved by DBT compared to alarm treatment alone [111]. As it is a cumbersome treatment, it nowadays it is reserved for children and especially adolescents with therapy-resistant nocturnal enuresis, as it “may augment the effect of an alarm” and “might reduce the relapse rate” (3). Thus, Hirasing et al. [28] could show that behavioural problems were reduced in children with persistent nocturnal enuresis treated with DBT.

Other programmes include the Full spectrum home treatment. This is a combination package including a written contract, full arousal, overlearning and bladder retention exercises [122]. 78.5% of children became
CONCLUSION AND SUMMARY

This review summarised the most important psychological aspects in children with enuresis, urinary incontinence and faecal incontinence. The rate of comorbid clinical behavioural disorders is increased. Children with urinary incontinence are more affected than those with nocturnal enuresis. Children with secondary and non-monosymptomatic nocturnal enuresis have especially high rates of comorbid psychological disorders. The most common single diagnosis is ADHD.

Children with daytime wetting have mainly externalising behavioural disorders. Children with urgency incontinence have a low comorbidity, those with voiding postponement are characterised by oppositional behaviour. Children with faecal incontinence have the highest rate of associated disorders – both internalising and externalising. These disorders will not disappear upon attaining dryness. They have to be addressed, as they will interfere with the incontinence therapy due to low compliance.

Even if comorbid disorders are not present, children and parents are highly stressed by the incontinence. These subclinical symptoms will often recede upon successful treatment.

Questionnaires are useful as screening instruments in the assessment process. If a psychological disorder is suspected, a full child psychiatric assessment and treatment or needed. The basic principles, including those of psychotherapy, are outlined. Psychothe-rapeutic techniques are used in urotherapy, especially cognitive-behavioural elements. Non-pharmacological and non-surgical techniques are most effective for most forms of incontinence based on systematic reviews. Therefore, it is important that psychological aspects are integrated into the treatment of children with incontinence problems.

REFERENCES

B. EVALUATION IN CHILDREN WHO WET


37. Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound


C. NOCTURNAL ENURESIS


773


D. CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE


E. NEUROGENIC DYSFUNCTION


40. Ferrara P, D’Aleo CM, Tarquini E, Salvatore S, Salvaggio E. Side effects of oral or intravesical oxybutynin chloride in children with spina bifida. BJU Int 2001; 87:674-8


xymethylenicillin and erythromycin given for intercurrent infections. BMJ 1989;298:856-9

F. SURGICAL MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN


dogs from acidosis during ammonium chloride loading. J Urol 1997;158:1075-80
85. Talic RF. Augmentation ureterocystoplasty with ipsilateral renal preservation in the management of patients with compromised renal secondary to dysfunctional voiding. Int Urol Nephrol 1999;31:469-70


178. Mitrofanoff P. Cystostomie continente trans-appendiculaire dans le traitement de vessies neurologique. Chirugae Paediatrica 1980;621:297-305


182. Yang WH. Yang needle tunneling technique in creating antireflux and continence mechanisms. J Urol 1993;150:830-4


220. Singh G, Thomas DG. Bowel problems after enterocystoplasty. BJU 1997;79:328-32


229. Singh G, Thomas DG. Bowel problems after enterocystoplasty. BJU 1997;79:328-32


787
G. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE AND ENURESIS IN CHILDREN


110. von Gontard, A. Enuresis und funktionelle Haminkontinenz.


133. Ng, C.F., Wong, S., Hong Kong Childhood Enuresis Study Group: comparing alarms, Desmopressin, and combined treatment in Chinese enuretic children. Pediatric Nephrology 20, 163-169, 2005


Committee 10

Neurologic Urinary and Faecal Incontinence

Chairman

J.J. Wyndaele (Belgium)

Members

A. Kovindha (Thailand),
H. Madersbacher (Austria),
P. Radziszewski (Poland),
A. Ruffion (France),
B. Schurch (Switzerland)

Consultants

D. Castro (Spain),
Y. Igawa (Japan),
R. Sakakibara (Japan)

Advisor

I. Perkash (USA)
Most abbreviations used in the text are given here, some in the beginning of the chapter where they are used

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ach</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AchE</td>
<td>acetylcholine esterase</td>
</tr>
<tr>
<td>AD</td>
<td>autonomic dysreflexia</td>
</tr>
<tr>
<td>ADL</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>AD: Alzheimer’s disease</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>anal sphincter</td>
</tr>
<tr>
<td>AUS</td>
<td>artificial urethral sphincter</td>
</tr>
<tr>
<td>BCR</td>
<td>bulbocavernosus reflex</td>
</tr>
<tr>
<td>BST</td>
<td>betahanechol supersensitivity test</td>
</tr>
<tr>
<td>CC</td>
<td>cystometric capacity</td>
</tr>
<tr>
<td>CIC</td>
<td>clean intermittent catheterization</td>
</tr>
<tr>
<td>CMG</td>
<td>cystometrogram</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
</tr>
<tr>
<td>CPT</td>
<td>current perception threshold</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>CTT</td>
<td>colonic transit time</td>
</tr>
<tr>
<td>CUM</td>
<td>continuous urodynamic monitoring</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebro vascular accident</td>
</tr>
<tr>
<td>CVC</td>
<td>conventional cystometry</td>
</tr>
<tr>
<td>DI</td>
<td>double incontinence</td>
</tr>
<tr>
<td>DLB</td>
<td>dementia with Lewy bodies</td>
</tr>
<tr>
<td>DOA</td>
<td>detrusor over activity</td>
</tr>
<tr>
<td>DRS</td>
<td>digital rectal stimulation</td>
</tr>
<tr>
<td>DSD</td>
<td>detrusor sphincter dyssynergia</td>
</tr>
<tr>
<td>ES</td>
<td>electrical stimulation</td>
</tr>
<tr>
<td>EAS</td>
<td>external anal sphincter</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>EPT</td>
<td>electric perception threshold</td>
</tr>
<tr>
<td>FI</td>
<td>faecal incontinence</td>
</tr>
<tr>
<td>FTD</td>
<td>fronto temporal dementia</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain Barre Syndrome</td>
</tr>
<tr>
<td>ID</td>
<td>indwelling catheter</td>
</tr>
<tr>
<td>IC</td>
<td>intermittent catheterization</td>
</tr>
<tr>
<td>IES</td>
<td>intravesical electrical stimulation</td>
</tr>
<tr>
<td>IWT</td>
<td>ice water test</td>
</tr>
<tr>
<td>LBT</td>
<td>lower bowel tract</td>
</tr>
<tr>
<td>LMNL</td>
<td>lower motor neuron lesion</td>
</tr>
<tr>
<td>LOE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>LS</td>
<td>lumbosacral</td>
</tr>
<tr>
<td>LUT</td>
<td>lower urinary tract</td>
</tr>
<tr>
<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MPdet</td>
<td>maximum detrusor pressure</td>
</tr>
<tr>
<td>MMC</td>
<td>meningomyelocele</td>
</tr>
<tr>
<td>MUP</td>
<td>motor unit potential</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>MSA</td>
<td>multiple system atrophy</td>
</tr>
<tr>
<td>NBo</td>
<td>neurogenic bowel</td>
</tr>
<tr>
<td>NBoD</td>
<td>neurogenic bowel dysfunction</td>
</tr>
<tr>
<td>NDO</td>
<td>neurogenic detrusor overactivity</td>
</tr>
<tr>
<td>NLUTD</td>
<td>neurological lower urinary tract dysfunction</td>
</tr>
<tr>
<td>NUI</td>
<td>neurogenic urinary incontinence</td>
</tr>
<tr>
<td>NVC</td>
<td>natural fill cystometry</td>
</tr>
<tr>
<td>OR</td>
<td>odd ratio</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PF</td>
<td>pelvic floor</td>
</tr>
<tr>
<td>PFD</td>
<td>pelvic floor dysfunction</td>
</tr>
<tr>
<td>PSP</td>
<td>progressive supranuclear palsy</td>
</tr>
<tr>
<td>Psym</td>
<td>parasympathetic</td>
</tr>
<tr>
<td>PVR</td>
<td>post void residual</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SARS</td>
<td>sacral anterior root stimulation</td>
</tr>
<tr>
<td>SCI</td>
<td>spinal cord injury</td>
</tr>
<tr>
<td>SCL</td>
<td>spinal cord lesion</td>
</tr>
<tr>
<td>SDAF</td>
<td>sacral deafferentation</td>
</tr>
<tr>
<td>SIC</td>
<td>sterile intermittent catheterization</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosis</td>
</tr>
<tr>
<td>SNS</td>
<td>sacral nerve stimulation</td>
</tr>
<tr>
<td>SOM</td>
<td>somatic</td>
</tr>
<tr>
<td>SPC</td>
<td>suprapubic catheter</td>
</tr>
<tr>
<td>SSEP</td>
<td>somatosensory evoked potentials</td>
</tr>
<tr>
<td>SSR</td>
<td>sympathetic skin response</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>Sym</td>
<td>sympathetic</td>
</tr>
<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
</tr>
<tr>
<td>TRI</td>
<td>transrectal irrigation</td>
</tr>
<tr>
<td>TURS</td>
<td>transurethral sphincterotomy</td>
</tr>
<tr>
<td>UFM</td>
<td>uroflowmetry</td>
</tr>
<tr>
<td>UI</td>
<td>urinary incontinence</td>
</tr>
<tr>
<td>UMN</td>
<td>upper motor neuron</td>
</tr>
<tr>
<td>US</td>
<td>urethral sphincter</td>
</tr>
<tr>
<td>USo</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UUT</td>
<td>upper urinary tract</td>
</tr>
<tr>
<td>VCU</td>
<td>voiding cystourethrogram</td>
</tr>
<tr>
<td>VSD</td>
<td>vesicosphincteric disorders</td>
</tr>
<tr>
<td>VSU</td>
<td>vesicoureteral reflex</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cells</td>
</tr>
</tbody>
</table>
Neurologic Urinary and Faecal Incontinence

J.J. Wyndaele,

A. Kovindha, H. Madersbacher, P. Radziszewski, A. Ruffion, B. Schurch, Y. Igawa, R. Sakakibara

A. INTRODUCTION

This chapter deals with all aspects of neurologic urinary and faecal incontinence. To combine this information related to two different structures makes this chapter rather unique though there are sufficient arguments to do so, as presented below.

Its content is written from data found in literature with the keywords “neurologic”, “neurogenic”, “bladder”, “bowel”, “lower urinary tract”, “anorectal”, “incontinence”, “continence”, “urinary”, “faecal”, “paralysis”, “dysfunction”, “retention”, “constipation” and the list of the specific neurologic diseases as described in chapter E. Important information from the previous ICI report was used as starting point and some is used as such in this chapter, which is intended to be able to stand alone. For some topics more elaborate information will be found in other chapters as on neurophysiology, diagnostics, urodynamic testing, female, male, frail elderly, faecal incontinence and more. To look up the related information in these chapters will be worthwhile. Also in chapter E not all neurologic diseases will be found as we decided in consensus to look into the most prevalent or consisting of the more challenging in diagnosis and or treatment of incontinence. Other colleagues might have made a different choice.

It is known that the lower urinary tract (LUT) and the lower bowel tract (LBT) are interrelated structures. Embryologically bladder and rectum originate from the same basic structure, the cloaca [1]. Anatomically both viscera lay in close communication and share muscular structures of the pelvic floor.

The innervation of both systems depends on autonomic and somatic nerves (Figure 1) that carry fibres of both. In table 1 a simplified overview is given of the action linked to different peripheral nerves.

Table 1. Overview of function of the abdominal sympathetic (Sym), the pelvic parasympathetic (PSym) and somatic (Som) nerves in the LUT and LBT. US = urethral sphincter, AS = anal sphincter. Exp = only suggested in animal experiments, no clinical evidence.

<table>
<thead>
<tr>
<th></th>
<th>Sym</th>
<th>PSym</th>
<th>Som</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Th 10-L</td>
<td>S2-S4</td>
<td>S3-S5</td>
</tr>
<tr>
<td>Bladder</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bladder neck</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Extern US</td>
<td>exp</td>
<td>exp</td>
<td>+</td>
</tr>
<tr>
<td>Bowel</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intern AS</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Extern AS</td>
<td>exp</td>
<td>exp</td>
<td>+</td>
</tr>
<tr>
<td>Pelvic floor</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Central control of both continence and evacuation is similar and is discussed in the chapter on physiology [2].

Very generally LUT and LBT act quite similar, both are autonomic organs regulated to necessary social requirements by a somatic innervation. The voluntary control depends on accurate sensation [3]. Continence relates to contraction of smooth closing structures (bladder neck and internal bowel sphincter) and striated urethral and anal sphincters. An inhibitory effect on detrusor and lower rectum resulting from contraction of the pelvic floor and anal or urethral sphincter has been named a “procontinence” reaction. Micturition and defaecation need a proper relaxation of these latter structures to permit a physiological reflex evacuation of urine or faeces.

Interactions between both functions have been demonstrated. The filling status of the bladder influences sensation in the rectum and vice versa [4]. A vesico-ano-rectal reflex permits voiding without
Figure 1: Schematic overview of innervation of LUT and LBT

Figure 2: Frequent sites of neurologic pathology causing neurologic urinary and faecal incontinence.
defaecation [5]. When the bladder is full, sensation of rectal filling is decreased. When healthy people visit the toilet to defaecate, the initiation of micturition often precedes that of defaecation, even if both organs are considered equally full [6]. The prevalence of both urinary and bowel dysfunction is high in many neurological diseases.

There is no study so far on correlation between both functions in patients with neurological pathology.

In this chapter levels of evidence (LOE) and grades of recommendation (A) are used as described in the general introduction of this book.

B. PATHOPHYSIOLOGY

With a neurologic lesion the type of dysfunction that follows in LUT and LBT will depend on the site, the extent and the evolution of the lesion.

Traditionally neurological pathology has been divided in suprapontine, suprasacral spinal cord and subsacral (cauda equina and peripheral nerve) lesions (Figure 2).

I. SUPRAPONTINE LESIONS

Patients with lesions above the pons usually continue to have reflex contractions of the detrusor. But the cerebral regulation of voiding and defaecation is often lost. This is the case in lesions as from stroke, head injury, etc, which mostly continue to have a normal coordinated sphincter function. However these patients may purposely increase sphincter activity during an overactive detrusor contraction [7] to prevent urinary incontinence which would otherwise occur. This has been termed "pseudo-dyssynergia" because it is indistinguishable from true dysynergia on a urodynamic record. Urinary incontinence in suprapontine lesions is due to bladder overactivity [8].

II. SPINAL CORD LESIONS

1. SUPRASACRAL SPINAL CORD LESION

When a lesion is located in the spinal cord below the pons detrusor- urethral sphincter dysynergia is a common finding. Incontinence may still be caused by detrusor overactivity but the outflow obstruction can also cause retention.

Patients with lesions above the cone usually suffer from an overactive bowel with increased colonic wall activity and anal tone. The central control of the external anal sphincter is disconnected and the sphincter remains tight thereby retaining stool (Dyssynergia). The connections between the spinal cord and the colon remain intact, permitting reflex coordination and stool propulsion. This type of lesion provokes faecal retention at least in part due to the activity of the anal sphincter. Incontinence can be a consequence of faecal impaction and constipation.

2. CONUS LESION

If the nuclei of the pelvic nerves are destroyed, the detrusor becomes areflexic. Retention of urine can provoke stress incontinence (formerly termed overflow incontinence).

III. SUBSACRAL LESIONS (CAUDA EQUINA OR PERIPHERAL NERVES)

The same effect as from lesions of the conus medullaris can result from lesions of the subsacral nerves (cauda equina or peripheral nerves). If the nuclei of the pudendal nerves are harmed, a paralysis of the urethral sphincter and pelvic floor muscles will occur often with loss of outflow resistance and stress incontinence.

A neurological lesion affecting the parasympathetic cell bodies in the conus medullaris will eliminate the pelvic nerve function of the bowel. No spinal-cord mediated peristalsis will occur. It will be the myenteric plexus that coordinates segmental colonic peristalsis. If the pudendal nerve is also destroyed, there is an increased risk for incontinence. Apart from the non contractile external anal sphincter, also the puborectal muscles lack tone, which leads to reduction of the rectal angle. Constipation and incontinence are frequent.

While most traumatic spinal cord lesions give LUT and LBT dysfunctions which can be predicted fairly well from the level and completeness of injury [9], the LUT and LBT function in many other neurologic diseases such as meningomyelocele are more difficult to categorise [10]. Therefore in this chapter a number of neurologic diseases will be described more in detail.

C. NEUROLOGIC URINARY INCONTINENCE

I. EPIDEMIOLOGY

NLUTD may be caused by various diseases and events affecting the nervous systems controlling the LUT. The resulting lower urinary tract dysfunction (LUTD) depends grossly on the location and the extent of the neurological lesion.

Overall figures on the prevalence of NLUTD in the
general population are lacking, but data are available on the prevalence of the underlying conditions and the relative risk of those for the development of NLUTD. It is important to realise that most of these data show a very wide range of prevalence figures due to low level of evidence in most published data and smaller sample sizes.

**Methodology**: Pubmed search from 2003 till 2008 with search words- epidemiology, neurologic bladder, neurologic incontinence, neurologic patients, prevalence- gave several references which were added to the list of the previous report 2005. Unfortunately only a very limited number gave data on prevalence and only in specific diseases for which a separate search was done. Data on incontinence are not always present in data on “neurologic voiding dysfunction” or “neurologic cystopathy”. No global meta analysis has been found.

In separate searches for specific diseases the prevalence data were also rather limited. Most studies were case series, some retrospective case control studies.

- Several factors can be the cause for this lack of overall data:
  - Neurologic problems of the LUT are not always specifically studied
  - Some disease are rare or have not been studied in detail
  - Series on urologic items deal mostly with urodynamic data, urologic complications or outcome of treatment and include only patients with a known neurologic bladder
  - In some neurologic diseases as spinal cord injury no data are to be found on those who did not develop a neurologic bladder.

**Results**: Following are the data found. While making an interpretation of these data one must realise that incontinence can be a direct consequence of the neurologic dysfunction of bladder, bladder neck or sphincter, but also because of lack of adequate treatment, infection or other anatomical or functional pathology. Literature review does not permit to differentiate between these causes.

1. **BRAIN-BRAIN STEM**

   **a) Brain tumours**

   Brain tumours can cause LUTD in up to 24% of the patients [1]. Mostly case reports-small series have been published more recently [2-3]. In a series of patients with brain tumours voiding difficulty was reported in 46/152 (30 %) of patients with tumours in the fossa posterior, while urinary incontinence occurred only in 3 (1,9 %) [4]. Urinary retention was found in 12/17 children with pontine glioma [5].

   **b) Dementia**

   One can not easily distinguish LUT problems caused by age-related changes of the bladder from those due to other concomitant diseases [6]. Therefore the true incidence of incontinence caused by dementia is not known. It has been shown that in geriatric patients with dementia, incontinence is much more frequent than in non dementia patients [7-8].

   Alzheimer, Lewy body dementia, Binswanger, Nasu-Hakola and Pick diseases frequently cause non-specific NLUTD [9-13]

   The occurrence of incontinence is reported to be between 23% and 48% [14-15] in patients with Alzheimer’s disease. The onset of incontinence usually correlates with the disease progression [16].

   A male to female ratio of dementia related incontinence was found to be 1:15.

   **c) Mental retardation**

   In mental retardation, depending on the grade of the disorder a 12 % -65 % prevalence of LUTD was described [17-18].

   **d) Cerebral palsy**

   LUTD in around 30 – 40 % has been reported [19-20]

   **e) Normal pressure hydrocephalus**

   Only case reports of LUTD [21-23]

   **f) Basal ganglia pathology** (Parkinson (PD), Huntington, Shy-Drager, etc.)

   Parkinson’s disease is accompanied by NLUTD in 37.9-70% [24-26]

   In the Shy-Drager syndrome almost all patients have NLUTD [27] while incontinence was found in 73 % [28]. Gray et al [29] reported that LUT functional disturbances in PD are not disease specific and only correlated with age. Recent, control-based studies gave a prevalence of LUT symptoms (LUTS) of 27-63.9% using validated questionnaires [30-31], or 53% in men and 63% in women using a non validated questionnaire that included a urinary incontinence category [32]. All these values were significantly higher than in healthy controls. The majority of patients had onset of the bladder dysfunction after appearance of motor disorder.

   **g) Cerebrovascular (CVA) pathology**

   CVA causes hemiplegia with remnant incontinence NLUTD in 20-50% of patients [33-34] with decreasing prevalence in the post-insult period [35]. In 1996 Sakakibara et al [36] reported 53 % significant urinary complaints at 3 months. Without proper treatment six
months after the CVA, 20 % - 30 % still suffer from urinary incontinence [37]. The commonest cystometric finding was detrusor overactivity [38-43].

Sakakibara et al [44] reported the urinary symptoms of 39 patients who had brainstem strokes. Almost half the patients had urinary symptoms, nocturia and voiding difficulty in 28 %, urinary retention in 21 % and urinary incontinence in 8 %. A number of case reports describe difficulties with micturition in the presence of various brain stem pathologies [45-46].

2. BRAIN-SPINAL CORD

a) Demyelination

Multiple sclerosis causes NLUTD in 50-90% of the patients [47-49]. One finds 33 % to 52 % NLUTD in patients sampled consecutively regardless of urinary symptoms, with the incidence being related to the disability status [50]. There is almost a 100 % chance of having LUT dysfunction once these patients experience difficulties with walking. NLUTD is the presenting symptom in 2-12 % of the patients, going to 34 % in some studies [51]. LUT dysfunction appears mostly during the 10 years following the diagnosis [52].

b) Spinal cord lesions

Spinal cord lesions can be traumatic, vascular, medical, or congenital. An incidence of 10.4 to 83 per million inhabitants per year and a prevalence of 223-755 per million inhabitants worldwide. One-third of patients with SCI are reported to be tetraplegic and 50 % of patients with SCI have a complete lesion. The patients sustain their injury at mean 33 years old, with a the sex distribution (men/women) of 3.8/1 [53]. Most patients will develop NLUTD [54]. For spina bifida and other congenital nerve tube defects, the prevalence in the UK is 8-9 per 10,000 aged 10-69 years with the greatest prevalence in the age group 25-29 years [55]. In the USA the incidence is 1 per 1000 births [56]. The incidence of urethrovaginal dysfunction in myelomeningocele is not absolutely known, but most studies suggest it is very high 90%-97% [57]. About 50 % of these children will have detrusor sphincter dyssynergia (DSD) [58-59].

c) Disc disease

Disc disease will cause NLUTD in 28-87% of the patients [60-61]. Cauda equina syndrome due to central lumbar disc prolapse has been reported to be relatively rare, the incidence being from 1 to 5 % of all prolapsed lumbar disc [62-70]. Neurogenic dysfunction of LUT without cauda equina syndrome has been described as case reports [71].

d) Spinal stenosis and spine surgery

Spinal stenosis: About 50 % of the patients seeking help for intractable leg pain due to spinal stenosis report symptoms of LUTD such as sense of incomplete bladder emptying, urinary hesitancy, incontinence, nocturia or urinary tract infections [72]. These symptoms may be overlooked or attributed to primary urological disorders. Sixty one-62 % would suffer from NLUTD [73-74]. The prevalence of neurologic disorders more significantly associated with dural sac anteroposterior diameter than with the cross-sectional area of dural sac.

Spine surgery is related to LUTD in 38%-60% [75-76].

3. PERIPHERAL

a) Peripheral neuropathy

1. DIABETES: This common metabolic disorder has a prevalence of about 2.5% in the American population, but the disease may be sub clinical for many years. No specific criteria exist for secondary neuropathy in this condition, but it is generally accepted that 50% of the patients will develop somatic neuropathy and 75-100% of those will develop NLUTD [77-78]. Amongst different types of polyneuropathies in diabetic patients “diabetic cystopathy” occurs in 43% to 87% of insulin-dependent diabetics, with no sex or age differences [79]. It is also described in about 25% of diabetic patients on oral hypoglycemic treatment [80].

b) ALCOHOL ABUSE: Can cause peripheral neuropathy, but its reported prevalence varies widely: 5-15 % to 64% [81]. The NLUTD is probably more present in patients with liver cirrhosis. The parasympathetic system is attacked more than the sympathetic system [82].

Less prevalent neuropathies:
- Porphyria — bladder dilatation in up to 12% of patients [83].
- Sarcoidosis — NLUTD rare [84].
- Lumbosacral zona and genital herpes — Incidence of LUT dysfunction is as high as 28 % if only lumbosacral dermatome-involved patients are considered. The overall incidence is 4% [85-86]. NLUTD is transient in most patients
- Guillain Barré — The prevalence of micturition disorders varies from 25% to over 80% [87-88] regressive in most [89]. The true incidence is uncertain due to the fact that during the acute phase patients are usually managed by indwelling catheter.

4. OTHER

a) Systemic lupus erythematosus (SLE).

Nervous system involvement occurs in about half of patients. Symptoms of LUT dysfunction can occur; however, data on prevalence are rare and give an incidence of 1% [90-91].

b) HIV

Voiding problems have been described in 12% of HIV-infected patients, mostly in an advanced stage of the disease [92-93].
c) Regional spinal anaesthesia
This may cause NLUTD but no prevalence figures were found [94-95].

d) Iatrogenic
Abdominoperineal resection of rectum has been described to cause NLUTD in up to 50 % [96-97]. It would remain a long-term problem in only 10 per cent [98] though it remains open if this means that the neurological lesion heals or that bladder rehabilitation was successful. Surgical prevention with nerve preservation was shown to be important [99-100]. After simple hysterectomy [101] and after radical hysterectomy or pelvic irradiation for cervical cancer, from 8 to 57% NLUTD was described [102-105]. Surgical prevention is also possible here [106]. After radical prostatectomy neurologic dysfunction of the pelvic floor has been demonstrated [107].

CONCLUSIONS

• Neurologic dysfunction of the LUT occurs in many patients with neurologic disease but exact figures are seldom available
• Meta analysis of prevalence data could give a better idea of how important neurologic bladder is in the patients with neurologic diseases and in the prevalence of incontinence in this population.

RECOMMENDATIONS

• Because many diseases or lesions of the innervation can cause pathology of the LUT, patients with known neurologic disease should be evaluated for such dysfunction . (A)
• Such evaluation should be made not only when urinary symptoms occur but also as a standard diagnostic approach if prevalence of neurologic bladder is known to be high in a specific disease .(A)
• If “idiopathic” LUT dysfunctions occur, the possibility of an unknown neurologic cause should be acknowledged and the diagnostic steps taken to make a proper diagnosis. (A)

II. SPECIFIC DIAGNOSTICS

- Methods for diagnosis in neurologic LUT dysfunction and in neurologic urinary incontinence are not very different from what is done in non neurologic patients. It consists of clinical assessment including history and voiding diary, urodynamic studies including cystometry (+ EMG), video-urodynamics, uroflowmetry, pressure-flow study, diagnostic imaging with voiding cystourethrography and ultrasonography of the kidneys and LUT. These methods will be dealt with in the relevant chapters of this book (basic assessment, dynamic testing, imaging and other investigations) but we will highlight briefly some data specially related to neurologic patients.
  - Some tests developed for the diagnosis of neurologic dysfunction have been evaluated more specifically in this chapter: bethanechol supersensitivity test, ice water test.
  - Neurophysiologic studies can be found in the chapter “Clinical Neurophysiological testing”, and only some clinical relevant data on neurologic patients are given here.

Without any doubt before any functional investigation is planned, all “basic” data should be gathered and used for further interpretation of the NLUTD [1-2].

1. HISTORY

The general history aims at gathering information on the neurological and congenital abnormalities, previous urinary complications or treatments. Important are also use of medication with known or possible effects on the LUT, menstrual, sexual and bowel function, and obstetric history. Hereditary or familial risk factors, metabolic diseases and other must be known. Lifestyle factors such as smoking, alcohol, or addictive drug use as well as an evaluation of Quality of life are important.

The signs and symptoms that brings patient to consultation must be documented. Symptoms related to storage and voiding, continence and/or retention, as well as onset and nature of the NLUTD (acute or insidious) should be determined. If appropriate this information should be compared with the patients’ condition before the NLUTD developed.

Very important data are LUTS, urinary incontinence, bladder sensation, mode and type of voiding (catheterization). Warning signs and symptoms that warrant early further investigation are fever, pain, hematuria, catheterization problems, and clinical infections. However, as in non neurologic patients, the “basic tests” also have limitations: individuals with SCI were frequently not accurate at predicting whether they had a UTI based on their symptoms [3]

A urinary diary offers information on the number of voids (frequency and nocturia), the sensation at each void, volumes voided, incontinence, volume and time fluid intake. Voiding diary of 24 hours was shown to be reliable in women with urinary incontinence, but no information is available in patients with neurologic incontinence [4].
2. PHYSICAL EXAMINATION

a) General physical examination

A general impression of patient’s physical and mental possibilities from the beginning is important to guide the choice of investigations or to decide from the start to go for least invasive diagnosis and treatment. Severely impaired mobility, extreme spasticity, severe mental disorder, general weakness, presence of severe complications are all important in this respect. Patients with very high neurological lesions may suffer from a significant drop in blood pressure when moved in a sitting or standing position. Patients with spinal cord lesion above D 6 may develop autonomic dysreflexia.

The physical examination will evaluate external genital organs, perineal skin, lower abdomen, lower back. Palpation per vagina or per rectum is done in search of pelvic organ descensus or cervix-uterus/prostate disease.

b) Neuro-urological examination

As part of a general neurologic examination specific tests are done related to the lumbo-sacral innervation: sensation of touch in the different perineal dermatomes (Figure 3), evaluation of bulbocavernosus, anal and cremaster reflexes, tone of anal sphincter (Figure 4) and possibility to voluntarily contract the anal sphincter/pelvic muscles. A high correlation exists between the clinical neurological findings and the NLUTD in some types of neuropathy such as single level traumatic spinal cord lesions [5-6] but less in other types as in meningomyelocele or combined traumatic spinal cord lesions [7]. Urinary symptoms and pathological urodynamic findings increase along with the degree of motor function impairment in infantile cerebral palsy [8].
CONCLUSION

- A combination of data from a clinical neurological examination gives useful information which acceptably corresponds with the LUT function in patients with one level spinal cord injury but not in meningomyelocele patients
- To decide on a detailed individual diagnosis of LUT function in neurologic patients, history and clinical examination prove insufficient.
- In elderly male neurologic patients with possible BPH related obstruction, symptoms and clinical examination are not sufficient to differentiate between outflow obstruction and neurologic DOA.

3. URODYNAMIC TESTS

Classic urodynamic techniques permit us to get multiple functional parameters in patients with neurologic bladder [9].

The recently published International Urodynamic Basic Spinal Cord Injury (SCI) Data Set proposed data to be included in the urodynamic evaluation of patients with spinal cord injury: Variables included bladder sensation during filling cystometry, detrusor function, compliance during filling cystometry, function during voiding, detrusor leak point pressure, maximum detrusor pressure, cystometric bladder capacity and post-void residual [10].

- CMG + EMG has been studied by several authors:

  Sundin and Petersen [11] used cystometry-electromyography (EMG) investigation in patients with known or suspected neurologic disorders in whom a defect in bladder emptying, in spite of an active detrusor contraction, was found at cystometry. A voluntary control of the external urethral sphincter relaxation— independent of the degree of bladder filling—was found in most of the healthy volunteers. The cystometry-EMG investigation gave reliable information as to whether a DSD exists. Perkash [12] found rhythmic detrusor contractions on cystomanometry with associated marked increase in EMG activity on attempted voiding to be relevant characteristics of patients with DSD. Rodriguez et al [13] used EMG-gas cystometrogram to select SCI patients for removal of the Foley catheter. Important factors governing success were the amplitude of the detrusor contraction, the presence of detrusor-sphincter synergy and the presence of a flaccid sphincter. Mayo and Kiviat [14] used multichannel urodynamic studies in patients with incomplete bladder emptying secondary to suprasacral SCL. They found that bladder pressure and sphincter EMG measurement during voiding, combined with fluoroscopy, are ideal methods to identify the factors responsible for incomplete emptying in problem cases. Also Perlow and Diokno [15] and Koyanagi et al [16] found CMG-EMG very useful in SCI patients.

Blaivas et al [17] described on the basis of CMG-EMG 3 types of dyssynergia: type 1 had a crescendo increase in electromyographic activity that reached a maximum at the peak of the detrusor contraction, type 2 had clonic sphincter contractions interspersed throughout the detrusor contraction and type 3 was characterized by a sustained sphincter contraction that coincided with the detrusor contraction. There was no correlation between the clinical neurologic level and the type of dyssynergia.

Simultaneous recording of intravesical pressure, sphincter electromyography and uroflowmetry (CMG.UFM.EMG study) was compared by Aoki et al [18] with cystometry + EMG. They found some influence of the catheter in the urethra. Micturition pressure and opening pressure were larger with CMG+ EMG, incidence of detrusor-sphincter dyssynergia was greater. The authors also found that the Credé manoeuvre exaggerated the DSD. Urodynamics with EMG permitted Kirby [19] to differentiate between patients with pelvic nerve injury, distal autonomic neuropathy, progressive autonomic failure - multiple system atrophy, and idiopathic Parkinson’s disease. This influenced the selection of patients for transurethral surgery. Pavlakis et al [20] studied CMG concomitant with perineal floor and rectus abdominis EMG and concluded that the addition of EMG can improve the recognition of intravesical pressure elevation owing to voluntary contraction of the abdominal musculature. EAS motor unit potential (MUP) analysis and EMG cystometry were used to differentiate multiple system atrophy (MSA) from Parkinson’s disease in the first five years after disease onset. It showed that involvement of Onuf’s nucleus in MSA is time dependent. Before the fifth year of illness, the prevalence of neurogenic change does not seem to be high, so a negative result cannot exclude the diagnosis of MSA,[21]. Rapidì et al used combined urodynamic and electrophysiological study of diabetic cystopathy [22].

The importance of detrusor pressure has been acknowledged for many years. Also recently Bruschini et al [23] evaluated the upper and lower urinary tract in myelomeningocele patients without adequate urological management with clinical, urodynamic and imaging evaluation. The urodynamic data were correlated with the status of the upper urinary tract (UUT). The cystometry showed detrusor overactivity (DO), poor compliance, increased bladder capacity and normal cystometry in 48, 49, 2 and 1% of the patients, respectively. Detrusor leak point pressure (DLPP) over 40 cm H(2)O was associated with UUT damage. Patients with decrease on functional bladder capacity (FBC) < or= 33% had more renal scars than their counterparts. No difference in cystometric capacity
and intravesical leak point pressure at terminal detrusor overactivity was shown between complete and incomplete spinal cord injury patients in a survey by Moslavac et al [24]. Incomplete SCI patients with neurogenic detrusor overactivity should be tested with cystometry and observed with the same caution as complete SCI patients.

The importance of urodynamic tests for diagnosis and follow-up is demonstrated in the study by Abrahamsson et al [25] on cystometrical changes with untethering in myelomeningocele children. After untethering 35% of the patients experienced improved bladder function and 5% deteriorated. All of the patients who deteriorated before untethering improved afterward, and 90% of those who were stable preoperatively continued to be stable postoperatively. Regular evaluation of bladder function in children with myelomeningocele is recommended. Also Kang et al [26] used urodynamic tests to determine prognostic factors affecting urological outcome after untethering surgery for lumbosacral lipoma.

Perkash and Friedland [27] found simultaneous transrectal ultrasonography helpful. They also recommended not to irritate the bladder when introducing the urodynamic catheter and to examine the entire curve of the CMG and not simply the initial rise. [28]

Pressure-flow study can demonstrate an obstructive pattern (high pressure voiding) also in neurologic patients due to urethral relaxation failure [29-30].

Video urodynamics permit a clear image of bladder neck and urethral sphincter activity during filling and voiding [31-32].

Zerin et al [33] found that the urographic position of the bladder neck in relation to the pubic symphysis was correlated with lower motor neuron (LMN) denervation of the urethral sphincter as detected with electromyography in infants and children with myelodysplasia. They concluded that, although not as precise as urodynamic testing, significant descent of the bladder neck is a reliable urographic finding of complete LMN denervation of the external urethral sphincter in infants and children with myelodysplasia.

CMG filling rate seems to be very important especially in neurologic patients: De Gennaro et al [34] performed continuous urodynamic monitoring over 6 hours (CUM) in children and compared this with standard urodynamics. They found CUM feasible and permitting a better diagnosis than standard cystometry in some. Zermann et al [35] investigated the diagnostic value of natural fill cystometry (NFC) in children with neurologic bladder in comparison to conventional videocystometry (CVC). In 45%, NFC detected new findings compared with CVC diagnoses. CVC findings were confirmed in another 45%.

Hess et al [36] studied how closely the intravesical pressures obtained before filling cystometry resembled those obtained during the filling phase of the CMG. Filling pressures during cystometry were significantly higher than the pressures measured at rest. This study also suggests a strong correlation between both. Ko et al [37] determined in SCI patients with neurologic bladder whether cystometry performed by filling with diuretics (FMCG) reveals different findings compared with conventional CMG. Significant differences were found between both in hyperreflexic neurologic bladders with respect to a decrease in MPdett and increase in compliance with FCMG. However, there were no significant differences in MPdett and compliance in hyporeflexic or areflexic neurologic bladders between the two techniques. Natural filling by the production of urine can change the results of cystometry considerably, and should be considered when performing urodynamic investigations and interpreting the results. Because the effects can increase with the time required to conduct the investigation, effort should be made to decrease the total duration of urodynamic investigations.[38]

In men with SCI, cystometric variables and detrusor overactivity remain consistent over sequential studies as shown in a study by Ockrim et al [39].

The amplitude of the first overactive contraction and the maximal detrusor contraction were found to be statistically greater in female patients with multiple sclerosis and neurogenic detrusor overactivity compared to women with idiopathic overactivity. The threshold volume for detrusor overactivity was greater, likely secondary to the elevated post void residual urine volume in the MS patients. In this study using a cut off value of 30 cm H2O for amplitude of the first overactive contraction achieved a positive predictive value of 88% for identifying multiple sclerosis [40].

The determination of CMG filling sensation is important. In 52 SCI patients, 26 % of those with a supposed complete lesion had sensation of bladder filling during cystometry [41]. Also in 41 patients with myelodysplasia the perception of bladder filling proved, rather unexpectedly, to be present in a majority of patients [42].

In a large cohort study it was clearly shown that impaired perception of bladder filling during CMG is a sign of neuropathy [43]. Ersoz and Akyuz [44] investigated bladder-filling sensation in 73 SCI patients with complete lesions above T11 and below T10 and with incomplete lesions Bladder-filling sensation was present to some degree in all incomplete SCI patients, in 82.4% of the patients with complete lesions below T10, and in 38.9% of the patients with complete lesions above T11. Bladder-filling sensation investigations were reproducible in terms of bladder filling sensation category in 36 SCI patients who had a second CMG. The authors concluded that presence of bladder-filling
sensation in many SCI patients reveal the potential for sensation-dependent bladder emptying, especially in the ones with complete lesions below T10 and the ones with incomplete lesions. The safe use of sensation-dependent bladder emptying was shown to be dependent on the urodynamic situation [45].

Complications of cystometry in patients with neurogenic bladder have been documented. Hematuria, due to the urethral catheter, the development of oedema in the urinary bladder wall and the development of urinary bladder spasm as a result of catheter irritation can occur. One case report of twist and knot formation in the double lumen urethral catheter after cystometry of a patient with a hypo-compliant bladder has been published [46]. Another case report describes bladder rupture during filling cystometry many years after bladder augmentation in a girl with meningomyelocoele [47]. Symptomatic urinary tract infections after cystometry were found not to be infrequent and antibiotic prophylaxis is advocated [48]. Randomised controlled trials (RCTs) comparing effectiveness of prophylactic antibiotics with placebo or nothing in reducing bacteriologically proven UTI after invasive cystometry not only in patients with neurologic bladder were evaluated by Latthe et al [49]. The use of prophylactic antibiotics in urodynamics reduced the risk of significant bacteriuria.

Though urodynamic tests are recommended in all cases of neurologic bladder dysfunction a recent Japanese study showed that cystometry for the evaluation of vesico urethral function was performed routinely by 52.3% of 333 urologists answering a questionnaire survey to examine current practice patterns of physicians in the urological surveillance and management of spinal cord injury patients in Japan.[50].

CONCLUSIONS

- Urodynamic tests are very useful in patients with neurologic urinary incontinence though not as generally applied as often thought (LOE 2)
- A combination with EMG and/or imaging adds to the diagnostic possibilities (LOE 2)
- Filling rate can influence the outcome of several urodynamic parameters (LOE 2)
- Pressure development in the bladder is one of the important parameters to be studied and high leak point pressure is dangerous for the kidneys. (LOE 2)
- Evaluating sensation of filling during CMG is important for the neurological diagnosis and for treatment options. (LOE 2)
- Complications are rare but antibiotic prophylaxis can be advocated (LOE 2)

4. SPECIAL TESTS

a) Ice water test

The ice water test was first described as a way to differentiate upper from lower motor neuron lesions. It is based on the principle that mucosal temperature receptors can elicit a spinal reflex contraction of the detrusor, a reflex that is normally inhibited by supraspinal centers. An upper motor neuron lesion interrupts these inhibitory pathways, resulting in manifestation of the reflex, whereas a lower motor neuron lesion does not. A positive test should therefore theoretically occur in patients with upper motor neuron lesions, whereas those with lower motor neuron lesions and neurologically normal patients should have a negative test. Simultaneous measurement of intravesical pressure permits us to rule out false negative tests.

In the more recent literature Geirsson [51] showed in a large cohort study that 97% of patients with complete and 91% of those with incomplete neurologic DOA had a positive or a false negative IWT. About 75% of the patients with multiple sclerosis, Parkinson’s disease or previous cerebrovascular accident had a positive IWT. All patients with lower motor neuron lesions or pure stress incontinence had a negative IWT. There was a significant correlation between a positive IWT and an abnormal sensation of bladder filling and inability to inhibit micturition voluntarily, as well as between a negative IWT and the occurrence of phasic detrusor contractions during cystometry. The study shows that the IWT is a sensitive test for differentiating upper from lower motor neuron lesions. It is also a useful parameter for functional subdivision of overactive bladders. In patients with voiding dysfunction in the absence of LUT inflammation, a positive test is an indicator of a silent or overt neurological disorder.

Geirsson and Fall [52] used the ice-water test, in patients suspected of DSD (cystometry and needle EMG). A positive test with a high detrusor pressure indicates detrusor-external sphincter dyssynergia whereas the contrary applies to the negative test. All patients who responded to cold stimulation with detrusor contraction but without fluid leakage (called positive non-leakage IWT), presented DSD according to EMG. The authors conclude that in this situation, the cheap, non-invasive and simple IWT can replace a needle EMG study.

Ishigooka et al [53] evaluated urinary bladder sensation to ice water instillation in patients with diabetes mellitus. There was no apparent relationship between prevalence of peripheral neuropathy and that of negative sensation of ice water test. Impairment of ice water perception was less frequent than that of mechanoreceptor sensation in patients with diabetic cystopathy.
Ronzoni et al [54] studied ice-water test in 148 patients with neurologic bladder dysfunction resulting from a traumatic lesion and in 130 patients with neurologic bladder dysfunction and multiple pathogenic disorders. IWT was positive in 95% of patients affected by complete and in 86% of patients with incomplete medullary lesions. The IWT in patients with lower motor neuron medullary lesions was always negative. The test was used diagnostically in patients with lower motor neuron lesions. In those with upper motor lesions it was used as a rehabilitation method during the medullary-shock phase to accelerate the appearance of the micturition reflex. In 9% of patients it was used to induce micturition during cystography. The authors consider IWT as a useful complement to urodynamic examinations in patients with neurological bladder disease.

Chancellor et al [55] determined the clinical utility of IWT during urodynamic evaluation in spinal cord injured (SCI) patients and found that it did not contribute to their management because of the insensitivity and non specificity. Autonomic hyperreflexia can occur during evaluation. The IWT did not influence clinical management in this group of SCI patients.

Repeating the IWT has been shown to increase its positivity [56]. Combining the IWT and EPT will reinforce the results of both tests and can indicate more clearly the possibility of an unsuspected neurologic pathologic finding in patients with idiopathic DOA. In multiple sclerosis it may have pathophysiologic value, indicating a spinal rather than cerebral mechanism of overactive bladder, and diagnostic value, indicating multifocal demyelination. [57]. In vue of these recent data clinical utility should be further assessed.

CONCLUSION

- The literature results from IWT show value in the diagnosis of neurologic bladder and in the differentiation between reflex and areflex neurologic bladders. It was also shown that the outcome can be improved by repeating the test. (LOE 2)

RECOMMENDATION

- The ice water test should be interpreted in the light of all data from the diagnostic evaluation. (B)

b) Bethanechol supersensitivity test

Bethanechol is a muscarinic agonists known to be able to increase bladder sensitivity correlated with improvement in bladder emptying in some non neurologic patients [58] and can be evaluated by studying the sensation of filling and EPT. The Bethanechol test was developed by Lapides et al in 1962 [59] to try to distinguish between a neurologic and a myogenic etiology in the presence of an acontractile bladder. It is based on the observation that after an organ is deprived of its nerve supply, it develops hypersensitivity to the normal excitatory neurotransmitters for that organ. A neurologically intact bladder should have a pressure increase of less than 15 cm H2O above the control value, whereas a denervated bladder shows a response greater than 15 cm H2O. A positive test suggests an interruption in the afferent or efferent peripheral or distal spinal innervation of the bladder. However, the test has been considered not very reliable by some [60].

Penders [61] considered the test reliable when the indications are good (large capacity, hypotonic bladder, clinical suspicion of lower neuron lesion) and when the interpretation is based on a right understanding of its mechanism. Pavlakis et al [62] suggest that the bethanechol chloride supersensitivity test is more sensitive and more specific than perineal floor electromyography in corroborating bladder neuroopathy. Sidi et al [63] studied patients with neurologic or nonneurologic detrusor areflexia with the bethanechol supersensitivity test, EMG of the urethral rhabdospincter and bulbocavernous reflex latency and found the sensitivity of these tests in detecting neurologic areflexia to be 90, 87.5 and 78.1 per cent, respectively, and the specificity 95.6, 76 and 80 per cent, respectively. When all 3 tests were performed together the combined accuracy approached 100 %. They conclude that these combined tests are useful in the diagnosis of patients with equivocal bladder neurologic conditions and in those with subtle neurological lesions. Denervation supersensitivity to bethanechol was demonstrated recently in acute idiopathic autonomic neuropathy [64].

Wheeler et al [65] found the positive BST not diagnostic of neurologic detrusor areflexia because of the many variables that can influence the test. In a later study the same authors [66] suggest that flow rate, surface electromyography, and bethanechol supersensitivity test can not help differentiate neurologic from non-neurologic detrusor failure. Although no one test can accurately differentiate neurogenic from nonneurologic female urinary retention, careful neurourolologic evaluation will help guide to more appropriate management.

The clinical utility has not been studied in detail recently. This seems an interesting subject for clinical research.

CONCLUSION

The literature on the value of the bethanechol test for the diagnosis of neurologic pathology is contradictory. Several authors state that a positive bethanechol supersensitivity test (BST) usually indicates neurologic detrusor areflexia.
5. ELECTRODIAGNOSTIC TESTS

There are several tests that explore the innervation of the LUT and can be of interest in the diagnosis.

\textbf{a) EMG of the urethral sphincter}

EMG of the urethral sphincter has been used for decades in the diagnosis of neurologic LUT dysfunction. Its value in practice remains uncertain as well as the best method to use, needle or surface electrodes. Urethral concentric needle electrodes were found to be superior to surface patch electrodes for evaluating relaxation of the muscle during voiding in non neurologic women [67]. Nordling and Meyhoff [68] used cystometry in combination with urethral and anal sphincter EMG in patients with suspected neurologic bladder dysfunction and found anal sphincter EMG to be highly unreliable. Koyanagi et al [69] also found in male patients with SCI, discordant activities between the anal and the external urethral sphincters in 39%. The degree of bladder dysfunction was related more to the degree of dyssynergia of the urethral than the anal sphincter. But nevertheless Podnar states that although in patients with LUT disorders, external urethral sphincter (EUS) electromyography (EMG) would seem the most appropriate, anal sphincter EMG is the single most useful diagnostic test, particularly for focal sacral lesions, and atypical Parkinsonism [70]. Fowler et al [71] introduced a technique of recording EMG activity of striated muscle in the urethral sphincter by using a concentric needle electrode and an oscilloscope with a delay line and trigger. Individual motor units were isolated and measured. Also Vodusek [72] studied individual motor units. Both conclude that quantitative EMG may be a helpful technique in the investigation of patients with disorders of micturition.

Light et al [73] found in patients with detrusor areflexia and a high spinal cord lesion EMG of the pelvic floor muscles the most predictive neurophysiological test for developing detrusor contractility.

Ziemann and Reimers [74] found the sphincter EMG the most sensitive technique in the diagnosis of chronic pudendal lesions. However, pure afferent lesions cannot be detected by the sphincter EMG. In this case, the BCR, using unilateral stimulation of the dorsal nerves of the penis, provides the opportunity to distinguish between afferent and efferent lesions of the sacral innervation.

Fowler [75] concluded that sphincter electromyography (EMG) has proved to be particularly valuable in identifying patients with parkinsonism who have multiple system atrophy. Tests which examine aspects of nerve conduction velocity have proved to be of lesser value both because such investigations test conduction of nerve fibres rather than levels of innervation, and furthermore examine large myelinated fibre conduction rather than that of the unmyelinated fibres which comprise the autonomic innervation.

De E J et al [76] found a significant disagreement between needle EMG and VCUG for a positive diagnosis of DSD. A combination of EMG and voiding cystourethrogram (VCUG) may identify more cases of DSD than either modality alone and underscores the need for more strict criteria when defining this entity from a urodynamic standpoint.

External urethral sphincter EMG can be used to detect the onset of detrusor contractions in patients with both neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) opening a door for the use of triggered devices to inhibit unwanted contractions through continuous electrical stimulation of sensory nerves [77-78].

EMG of the urethral sphincter has been used recently to investigate retention in multiple-system atrophy [79], LUT function in Machado-Joseph disease [80], the impact of pregnancy and delivery on vesico urethral disorders in patients with multiple sclerosis [81], children with cerebral palsy [82], neurourological findings following sacro-coccygeal teratome resection in the newborn period [83].

\textbf{CONCLUSION}

- EMG can be valuable in the diagnosis of patients with neurologic bladder dysfunction (LOE 2).
- EMG of the anal sphincter is considered unreliable by some (LOE 4).

\textbf{RECOMMENDATION}

EMG of the urethral sphincter can be recommended as diagnostic method in patients with neurologic LUT dysfunction and neurologic urinary incontinence (B B)

\textbf{b) EMG of Detrusor muscle}

Has been very little studied in neurologic patients. La Joie et al [84] recorded simultaneous EMG recordings from the bladder detrusor muscle and the inferior...
rectus abdominis muscle in 6 normal subjects, in 4 patients with LMN bladder disease and in 2 patients with an UMN type of bladder lesion. Results of the study demonstrated that the bladder electrodes did not record remote muscle activity from the abdominal muscles so that any increased detrusor electrical activity with abdominal contraction must have some other explanation such as a possible abdominodetrusor reflex or the production of increased intra-abdominal pressure from abdominal contraction. Also Kaplan and Nanninga [85] analysed of upper motor neuron type neurologic bladders by bladder EMG. Recent data are lacking and therefore we have to consider the technique as not fit for clinical diagnostics today.

c) Dynamic Bulbocavernosus reflex (BCR)

Walter et al [86] studied a dynamic BCR during micturition induced by using periodic dorsal penile nerve stimulation; the evoked reflex response was recorded with an anal sphincter pressure sensing balloon. Results indicate that an enhanced BC reflex is a major factor causing increased urethral resistance during micturition.

Kaiho et al [87] recorded the evoked potential of the BCR (BCR-EP) with a concentric needle electrode at the periurethral striated muscle. They found BCR-EP suppressed during voluntary voiding in normal subjects, but insufficiently suppressed in the patients with neurologic bladder. It was suggested that the measurement of BCR-EP could distinguish involuntary voiding caused by pathological urethral sphincter relaxation from voluntary voiding.

Kaiho et al [88] investigated the change of sacral reflex activity of the striated urethral sphincter in the urine storage phase using evoked potential reaction of the bulbocavernous reflex (BCR) With BCR-EP in normal male subjects and male patients with neurologic bladder due to suprasacral spinal cord injury. Sacral reflex activity was accelerated by bladder filling in both the normal subjects and SCI patients. And the acceleration in the SCI patients was more remarkable than that in the normal subjects. In addition to the conventional evaluation of the integrity of sacral reflex arc by BCR examination, the observation of changes of BCR affected by bladder filling may provide the information for the continuity of sacral segment and supraspinal micturition center.

CONCLUSION

Very little data on detrusor EMG and BCR-EP in literature and thus these techniques have to be considered as experimental.

d) Motor evoked potentials

MEP has been used to assess neurogenic lesions of the somatomotor efferent nervous pathway to the urethral compressive musculature with and simultaneous recording of evoked pressure curves [89]. MEP recording has been shown to be an accurate and easily applicable test for the diagnosis of lumbosacral spinal cord lesions [90].

Examination by transcranial magnetic stimulation (TMS) was shown to be useful in the diagnosis of cervical spondylotic myelopathy but the possibility of negative central motor conduction time (CMCT) findings upon TMS must be borne in mind.

e) Nerve conduction study

Andersen and Bradley [91] showed in patients with diabetes mellitus decreased conduction velocities in patients with the detrusor reflex as well as in detrusor areflexia. The findings indicated that diabetic vesical dysfunction is principally the result of segmental demyelinization in the peripheral nerve supply to the detrusor muscle and urethra.

Vereecken et al [92] found urethral and anal responses produced by electrical stimulation of penis, bladder neck and anus delayed and the duration reduced.

Carbone et al [93] assessed the effect of urinary bladder filling on the excitability of somatic spinal motor neurones in patients affected by overactive bladder secondary to neurologic and non-neurologic causes with the H-reflex evoked by electrical stimuli applied to the tibial nerve at the Poplitea fossa and recorded from the Soleus muscle. In healthy subjects, a progressive reduction in the H-reflex amplitude during bladder filling was observed.

In spinal cord-injured patients affected by a neurologic overactive bladder, bladder filling failed to inhibit the H-reflex amplitude; a decrease in the H-reflex amplitude similar to that displayed by normal subjects was observed in patients with a non-neurologic overactive bladder. By contrast, H-reflex behaviour was unmodified in neurologic under active bladder patients and was similar to normal subjects in psychogenic under active patients. H-reflex modulation may be considered a useful tool in the differential diagnosis of voiding dysfunctions.

CONCLUSION

Not many data are found in literature on nerve conduction studies for LUT neurologic problems.

RECOMMENDATION

There are some arguments that the technique can be useful in the further differentiation of the nerve deficits in cases of neurologic pathology of the bladder (C).
f) Somatosensory evoked potentials (SSEP)

Badr et al [94] described techniques of recording evoked potentials in humans in response to stimulation of the urinary bladder.

Galloway et al [95] described a simple method of sacral evoked response to measure the integrity and function of the lower sacral segments of the cord by stimulation at the urethral and anal sphincters.

Mochida et al [96] studied evoked spinal cord potentials (ESCP) in surgical patients with cervical myelopathy. The presence of neurologic bladder was closely correlated with severe limb symptoms and relatively slow ESCP velocity. However, for 47% of the patients with urinary complaints, findings of urodynamic examinations were negative; these patients probably had pathologic or psychosomatic factors other than neurologic bladder due to cervical myelopathy.

Curt et al [97] studied the significance of SSEP recordings in predicting the recovery of bladder function in acute, traumatic spinal cord injury (SCI). They found a good correlation with the recovery of the external urethral sphincter function but not with the urodynamic impairment.

Somatosensory evoked potentials in response to stimulation of the tibial nerve were recently studied in patients with hyperactive urinary bladder to clarify their role in prognosis of tibial neuromodulation efficacy.[98]

RECOMMENDATION

Somatosensory evoked potentials can be of use in the further diagnosis of nervous deficits related to LUT dysfunction (C).

g) Use epidural recording of evoked spinal cord potentials

These showed clinical value in investigating the pathology of cervical spondylotic myelopathy in patients with normal central motor conduction time in upper and lower limbs [99]

h) Afferent nerve recording on sacral roots

Afferent nerve activity from the sacral dermatome, bladder and rectum can be recorded using cuff electrodes placed on the extradural S3 sacral root in humans but improvements in recording quality and sophisticated signal processing methods are needed for chronic application.[100].

CONCLUSION

Epidural recording and direct measurement on sacral nerves is still experimental.

i) Electro sensation in the LUT

Measurement of the sensory threshold of the LUT towards electrical stimulation was performed by Frankl-Hochwart and Zuckerkandl as early as 1899 [101]. After re-introduction of the technique by Markland et al [102] several authors have studied its value in neurologic bladder dysfunction.

Frimodt- Möller [103] described pathological electro sensation in patients with Parkinson's disease, with multiple sclerosis and meningomyelocoele. He also found abnormal electro sensation in half of patients with diabetes and generalized sensory neuropathy but only in 10% of the diabetic patients with a neurologic bladder.

Kieswetter [104] and Powell and Feneley [105] demonstrated abnormal electro sensation in patients with neurologic LUT dysfunction.

Wyndaele [106] determined the threshold of sensitivity to electrical stimulation in several parts of the LUT in 436 consecutive patients. In the groups with different patterns of disturbed sensation a higher incidence of neuropathy was found than in the group with a normal sensation. Further neurological investigation revealed abnormal innervation in 29% of patients who lacked electro sensitivity in one or more parts of the LUT but who had no previous evidence of neuropathy.

Electro sensation proved present in many meningomyelocoele patients with absent skin sensation and absent reflexes and in many patients with suspected complete spinal cord injury on clinical evaluation [41-42].

Standardization is necessary to come to reproducible results [107].

While it is a dream to be able to determine threshold of different fibre types selectively [108] so far no such fibre selectivity has been demonstrated in the bladder [109].

The clinical utility needs to be further studied.

CONCLUSION

To determine the electro sensation in the LUT is valuable to evaluate the afferent innervation in cases of neurologic bladder. Absent electro sensitivity is valuable to decide on further neurologic tests in patients with LUT dysfunction. (LOE 2)

RECOMMENDATION

The determination of electro sensitivity in the LUT is recommended in patients with a known neurologic disease and in patients with idiopathic LUT dysfunction if neurologic pathology is suspected. (B).
j) Sympathetic skin response (SSR)

Schurch et al [110] assessed the degree of sparing of the descending sympathetic spinal tract and correlated these findings with bladder neck function in SCI patients. Evidence is presented that the integrity of the descending sympathetic spinal tract is necessary for a synergic function of the vesicourethral complex and that sympathetic skin responses are of value in the diagnosis of bladder neck dyssynergia. For lesions below the T12 level other investigative methods to exclude bladder neck dyssynergia are necessary.

Rodic et al [111] investigated whether recording the perineal sympathetic skin response, which reflects the sympathetic function of the thoracolumbar spinal cord, represents a reliable and accurate diagnostic tool for assessing bladder neck competence and incompetence. They found that recording the perineal SSR in addition to that of the hand and foot represents a sensitive diagnostic tool for assessing sympathetic nerve function within the thoracolumbar spinal cord. It is of diagnostic value for evaluating neurologic bladder neck incompetence in spinal cord injured patients.

SSR recordings above a spinal lesion level after urethral electrostimulation might provide a useful and technically simple objective diagnostic tool to assess integrity of autonomic (visceral) afferent nerves from the LUT.

Somatosensory deficits are not always paralleled by viscerosensory loss and vice versa. A recent study showed that SSR were superior to visceral sensory evoked potentials which are more difficult to record. The subjective sensations reported by subjects during stimulation could be confirmed in an objective way in 100% of cases by positive/negative SSR findings.[112] The clinical utility needs to be further studied.

CONCLUSION

These publications indicate that sympathetic skin responses are of value to evaluate the integrity of the LUT related sympathetic function and especially for bladder neck competence, incompetence and dyssynergia. (LOE 2)

RECOMMENDATION

Sympathetic skin responses seem promising and the further study of them are recommended for the evaluation of the LUT sympathetic innervation (B)

III. CONSERVATIVE TREATMENT

Therapeutic principles in different patterns of LUT dysfunction depend on the cause of NUI: dysfunction of the detrusor, dysfunction of the sphincter or a combination of both.

Neurogenic detrusor overactivity leads to reflex-incontinence, detrusor areflexia to incontinence with retention (overflow incontinence). An areflexic (ineptent) sphincter causes neurogenic stress-incontinence, a hyperreflexic (spastic) sphincter overflow-incontinence. Quite often detrusor and sphincter are affected simultaneously by the neurogenic lesions with basically four combinations. In most patients the storage problem, leading to incontinence, is associated with an emptying problem; therefore both aspects have to be considered at the same time.

Therapy of neurogenic incontinence is primarily a conservative one. Timed bladder emptying, by whatever means, controlled fluid-intake and avoidance of urinary tract infections are the prerequisites for successful treatment.

In (a) SUPRASPINAL LESIONS neurogenic detrusor overactivity is mostly combined with normal sphincter function, reflex incontinence is the main symptom and antimuscarinic therapy together with behavioural treatment, especially in patients with cognitive impairment, is the method of choice.

(b) SPINAL LESIONS mostly cause simultaneous dysfunction of the detrusor and the sphincter.

In suprasacral lesions the combination of a overactive detrusor with a hyperreflexic sphincter is characteristic for the spinal reflex bladder.

Basically spontaneous reflex voiding is possible; however, it is uncontrolled, causing reflex-incontinence and is mostly unbalanced and basically unphysiologic. Detrusor contractions are mostly inadequate, and detrusor striated sphincter dyssynergia is present, both leading to unbalanced voiding.

Triggered reflex voiding is recommended only if it is urodynamically safe and reflex incontinence is manageable. The method of choice nowadays to empty an unbalanced reflex bladder and to manage reflex-incontinence is intermittent (self-) catheterisation. However, to achieve the aims of therapy, - a low pressure LUT situation and continence between catheterisations - additional pharmacotherapy may be necessary.
If bladder relaxing agents fail or are not tolerable, electrotherapy is an alternative in incomplete lesions: ano-genital electrostimulation (penile, clitoral, vaginal and anal) can inhibit neurogenic detrusor overactivity by stimulating pudendal nerve afferents.

If none of the above mentioned treatment modalities is effective to control reflex incontinence and if operative procedures are not indicated or possible, appliances, pads or condom-catheters, are the first choice in males and pads in females. To improve outflow, treatment to lower tone and spasticity of the urethral sphincter can be used.

The indwelling catheter – a suprapubic catheter is preferable to transurethral – remains the last resort for conservative therapy.

For complete conus lesions, also named lower motor neuron lesions, areflexia of the detrusor with areflexia of the sphincter is characteristic. Sphincter incompetence causes neurogenic urinary stress incontinence and may be combined with overflow-incontinence if adequate emptying is not achieved.

Basically, regular bladder emptying achieved by bladder expression, according to the individual bladder capacity, in combination with controlled fluid intake may decrease neurogenic urinary stress incontinence. However, continence is hard to achieve. Bladder expression is potentially dangerous. Pharmacotherapy is not helpful in this situation, appliances and condom catheters are therefore often necessary. Continence can often be achieved only by operative therapy.

Areflexia of the detrusor combined with hyperreflexia of the sphincter may occur in epiconal lesions; however, this pattern may be also due to a decompensation of a neurogenic overactive bladder after chronic urinary retention. With this combination overflow incontinence can be controlled by intermittent catheterization mostly without adjunctive additional pharmacotherapy. If intermittent catheterization is not possible, an indwelling catheter, preferable suprapubic, may be needed.

If overactivity of the detrusor is combined with areflexia of the sphincter, a pattern sometimes found in epiconal lesions, especially in myelomeningocele, reflex incontinence is combined with neurogenic stress incontinence. Bladder relaxant agents may abolish or diminish neurogenic detrusor overactivity.

In incomplete lesions electrical stimulation of the pelvic floor musculature may improve sphincter function. Thus the combination of pharmacotherapy to treat reflex incontinence with electrotherapy of the pelvic floor muscle may improve continence. However, with this type of neurogenic LUT dysfunction conservative treatment alone is generally unable to restore continence; therefore either appliances or operative treatment must be considered.

(c) **SUBSACRAL (CAUDA EQUINA AND PERIPHERAL NERVES) LESION** are often incomplete lesions. Hypoactivity or areflexia of the detrusor may be combined with a normally functioning external striated sphincter, a combination which can be seen after intrapelvic surgery, when the pudendal nerves remain intact. On the other hand if the pudendal nerve is lesioned and the pelvic plexus remains more or less intact, a combination of a normally functioning detrusor with a hypo- or areflexic external sphincter may be present. For the neurogenic overactive detrusor, again, pharmacotherapy is the first choice. In the hyporeflexic detrusor cholinergics may increase the tone, and the sensation of filling. If the lesions were incomplete, intravesical electrotherapy was reported to increase detrusor contractility. The chances for pharmacotherapy to improve external sphincter weakness as well as to decrease external sphincter spasticity are poor. Injection of botulinum toxin in the striated sphincter has created a new treatment option.

If conservative treatment fails several surgical options are available. They will be discussed in the corresponding part of this chapter.

Since only some conclusions and recommendations are changed and some new references are added to the 2005 chapter, this chapter presents only the new literature, justifying the changes and actual conclusions and recommendations. For previous references as well as for general outlines please refer to the ICI 2005 chapter. Also some recommendation have been compared/changed according to the recent consortium for spinal cord injury [1].

The following text will not deal specifically with the period of spinal shock or cerebral shock in acute neurological lesions when the urologic treatment consists of proper bladder drainage. For the post shock period or for slowly developing dysfunctions several conservative treatments exist:

1. **BEHAVIORAL THERAPY**
   a) Triggered reflex voiding
   b) Bladder expression (Crédé and Valsalva maneuver)
   c) Toileting assistance

2. **CATHETERS**
   a) Intermittent catheterization
   b) Indwelling urethral catheters
   c) Condom catheter and external appliances

3. **PHARMACOTHERAPY**

4. **ELECTROSTIMULATION**
   a) Electrical Neuromodulation
   b) Repetitive transcranial magnetic stimulation
   c) Deep brain stimulation
   d) Electrical stimulation of the pelvic floor musculature
   e) Intravesical electrical stimulation (IVES)
1. BEHAVIOURAL THERAPY

a) Triggered reflex voiding (references see ICI 2005 report)

BACKGROUND

The true automatic or reflex bladder occurs following recovery from spinal shock in spinal cord lesions not involving the conus or cauda equina. If the efferent branches of the pelvic nerve are involved, the reflex emptying is much less complete, and considerable voluntary straining is required to empty the bladder to a satisfactory degree. The stimulation of the sacral and lumbar dermatomes should be used to elicit reflex contractions of the detrusor in cases with upper motor neuron bladders.

The aims of regular triggered reflex voiding are to achieve balanced voiding, to decrease incontinence and/or to achieve continence. Prerequisites for this type of bladder emptying are: the possibility of collecting the urine in a socially acceptable way and an adequate time needed for bladder emptying. The urodynamic function must be safe (low pressure).

Bladder reflex triggering comprises various manoeuvres performed by patients in order to elicit reflex detrusor contractions by exteroceptive stimuli. The most commonly used manoeuvres are: suprapubic tapping, thigh scratching and anal/rectal manipulation.

Frequency of use, intervals and duration has to be specified for each patient. Integrity of sacral reflex is requested for such voiding technique.

Today, learning triggered voiding should not be done without considering bladder outlet obstruction management, continence, appliances, gender, and level and type (complete or incomplete lesions, paraplegic versus quadriplegic patients) of lesion.

Assessment of management by triggered reflex voiding is difficult because of the mostly retrospective nature of the reports and because the management of concomitant bladder outlet obstruction is not specified or incompletely described.

An additional indication could be a quadriplegic patient who is unable to perform self-catheterization but is able to do tapping or triggered voiding. They may choose this option because it gives more independence.

Before considering triggered reflex emptying, one must check if the bladder situation is urodynamically safe (mainly low pressure bladder) and if regular follow-up is guaranteed. The frequency of check-up is not validated, depends on risk factors, but should be between 6 months and 2 years.

To improve emptying and, control autonomic dysreflexia related to bladder filling and contraction as well as to avoid upper tract damage, alpha-blockers or botulinum toxin sphincteric injections (see related part of this chapter) should be tried before sphincterotomy and/or bladder neck incision is performed.

Triggered voiding should not be recommended as first line management of bladder hyperreflexia and neurogenic LUT dysfunction. Intermittent catheterisation has become the gold standard to achieve continence, upper urinary tract protection and improvement of quality of life (see recommendations in the section of intermittent catheterisation).

CONCLUSIONS

• Reflex voiding is based on an unphysiological sacral reflex. It is potentially dangerous and has a limited role in managing the reflex bladder (LOE3).
• The long-term complication rate is not as high as with indwelling catheter, but enough to suggest a trend to avoid this triggered reflex voiding in detrusor overactivity (LOE2).
• Costs of appliances and of adjuvant therapies (pharmacotherapy, surgery, urethral prosthesis etc) have to be evaluated (LOE 2).
• Treatment of co-existing sphincteric spasticity/ bladder neck obstruction (botulinum toxin, a-adrenolytics) and comorbidity should be taken into consideration (LOE 1 and 2).

RECOMMENDATIONS

• Triggered voiding could be recommended for patients whose situation has proven to be urodynamically safe and stable, and who can manage reflex incontinence. Moreover it is recommended for patients after sphincterotomy and/or bladder neck incision and/or alpha-blockers and or intrasphincteric botulinum toxin injections, in order to improve spontaneous reflex voiding (C).
• Reflex voiding can be recommended only if an adequate follow-up is guaranteed (C).

b) Bladder expression (Crédé and Valsalva) (References see ICI 2005 report)

BACKGROUND

Bladder expression has been recommended for a long time for patients with a combination of an areflexic detrusor with an areflexic sphincter or with an incompetent urethral closure mechanism of other origin (e.g. after sphincterotomy). Difficulties in emptying the bladder by expression may be due to an
inability to open the bladder neck. However, especially in men, these techniques induce a functional obstruction at the level of the striated external sphincter despite complete paralysis of the musculature of the pelvic floor.

Bladder expression comprises various techniques aimed at increasing intravesical pressure in order to facilitate bladder emptying. The most commonly used are the Valsalva (abdominal straining) and the Crédé (manual compression of the lower abdomen).

With increasing time, using Valsalva and Crédé techniques, more than 50% of patients could show demonstrable reflux into the prostate and the seminal vesicles and other complications, e.g. epididymo-orchitis. Moreover, the high pressures could cause reflux into the upper urinary tract with all known complications. The stress to the pelvic floor with these techniques several times a day also has a negative influence on the existing minimal storage function of these structures and therefore makes incontinence worse, causes additional genital-rectal prolapse and hemorrhoids.

Adjunctive therapy to decrease outflow assistance includes alpha-blockers, sphincterotomy or botulinum toxin injections. If effective, they usually cause or increase neurogenic urinary stress incontinence. Expression of the bladder for voiding by Valsalva and Valsalva can be effective. To empty the bladder, the pressures measured may be high and potentially dangerous for the upper urinary tract. Bladder expression is often not safe. Sphincter-hyperreflexia and detrusor-sphincter dyssynergia are contraindications for bladder expression.

CONCLUSIONS

- Bladder expression by Valsalva or Crédé is potentially hazardous for the urinary tract due to functional obstruction at the level of the pelvic floor (LOE 3).
- It is contraindicated if it creates a high intravesical pressure, or/and if vesical reflux or/and a vesico-uretero-renal reflux are present. In addition, hernias, recto-genital prolapse and hemorrhoids as well as urethral pathology (striction formation) and recurrent symptomatic UTIs are further contraindications (LOE 3).
- It may have a negative influence on an existing minimal outflow resistance of a flaccid pelvic floor and therefore incontinence may become worse (LOE 3).
- Alpha-blockers, sphincterotomy or botulinum toxin may reduce the outflow resistance, but may also induce or increase urinary stress incontinence (LOE 3).

RECOMMENDATIONS

- Before recommending bladder expression by Valsalva or Crédé, it must be proven that the situation in the LUT is urodynamically safe. Basically the method is dangerous. (B)
- Exclude contraindications, such as a vesico-uretero-renal reflux, vesical reflux, genito-rectal prolapse, hernias, urethra pathology and symptomatic UTIs before recommending this type of bladder emptying. (B)
- In general, bladder expression should be replaced by CIC in most patients with neurogenic bladder-sphincter dysfunction. (B)
- Adjunctive therapy of outflow obstruction can be considered. (B).
- Valsalva and Crédé guarantee a good quality of life and are cost-effective in the long term only when the indication is proper and when the situation remains stable throughout the years. (B)

c) Toileting assistance: timed voiding, habit retraining, prompted voiding (references see ICI 2005 report)

For a more complete overview consult the chapters “adult conservative treatment” and “frail elderly”.

1. BACKGROUND

Adaptation of the drinking and voiding regimen is determined by education and can be implemented by the patient and/or caregivers.

In patients with neurogenic incontinence related to brain diseases, when independent continence cannot be achieved, social and/or dependent continence is sometimes achievable.

The aim of the behavioural process in adults is to re-establish the control of urinary continence. The goals include correcting faulty habit patterns of frequent urination, improving ability to control bladder urgency, prolonging voiding intervals, increasing bladder capacity, reducing incontinent episodes, and building a patient's confidence in controlling his/her bladder.

Behavioural measures would seem to be beneficial for most neurologic patients in one way or another. Good indications are most common in brain diseases as cerebro vascular disease, Parkinson’s disease, multiple system atrophy, dementia, and cerebral palsy. Other diseases can also be good indications such as multiple sclerosis, incomplete spinal cord injury, transverse myelitis, diabetes mellitus and others. Frail elderly neurologic patients who need assistance can also benefit from these techniques independent of the disease they suffer from.
In dependent patients all these techniques can be proposed and tried, provided that caregivers (physiotherapist, nurse, member of the family…) are aware of them and are motivated to use them.

The following toileting assistance techniques require caregivers’ assistance in many of the patients:
- Timed voiding
- Prompted voiding
- Habit retraining
- Bladder retraining
- Patterned urge response toileting

2. TIMED VOIDING

Timed voiding is characterized by a fixed interval between toileting. It is a passive toileting assistance program. It is initiated and maintained by caregivers. This technique is considered appropriate for patients who cannot participate in independent toileting. It has been used in patients whose incontinence may be associated with cognitive and/or motor deficits. Its aim is more to avoid incontinence than to restore a normal bladder function.

For neurologic patients it has also been considered as an adjunct therapy to tapping and/or Crédé manoeuvre and/or intermittent catheterisation. Timed voiding is one of the first steps of treating too high bladder volumes, as in diabetes patients with loss of bladder filling sensation.

3. HABIT RETRAINING AND PROMPTED VOIDING

Both of these techniques have to be initiated and maintained by caregivers. They are more adapted to patients with brain diseases than to spinal cord diseases and for patients with cognitive and/or motor deficits.

The aim of habit retraining is to help patient to avoid incontinence and/or involuntary bladder contractions by decreasing voiding intervals. Such program has to be adapted to each patient and needs a specific analysis of voiding patterns to select a good individual schedule for voiding. Such a program is very useful for institutionalised patients.

Prompted voiding is used to teach people to initiate their own toileting through requests for help and positive reinforcement from caregiver when they do this. This technique needs an outside individual’s participation in the process. There are no specific evaluations on neurologic patients in literature, though the technique may be useful in patients with incomplete neurologic lesions, and in patients with high dependence and good cognitive function.

CONCLUSIONS

- Behavioural techniques have to be used in conjunction and/or in addition with other therapies (pharmacological treatment, catheterisation) (LOE 2)
- There is no consensus, either on the definition of each technique or on the population that can benefit from it. When available, toileting assistance should be used to improve continence of neurologic impaired patients (LOE 3)
- There is still some evidence that prompted voiding is able to decrease incontinence episodes. Long-term effect of this therapy is not validated. Moreover there is evidence that patients who should have more benefit of this technique are those with less cognitive impairment and higher dependency (LOE 2/3)

RECOMMENDATIONS

- Behavioural techniques could be recommended as a part of each individual rehabilitation program. (C)
- No guidelines or consensus on correct intervals between bladder emptying has been reported. They should be fixed, but have to be adapted to voiding diary and other related factors as was detailed in the previous report: bladder volume, fluid intake, post-void residual urine volume, urodynamics parameters. (C)
- The mental status of a patient must be taken into consideration, and a rehabilitation program realistically tailored to the patient’s possibilities. (B/C).

2. CATHETERS

All technical aspects of incontinence devices can be found in the chapter “Technical aspects of continence devices” of this report. Detailed description of catheter use in neurologic patients can be found in the previous ICI 2005 report under “Conservative management in neurogenic urinary incontinence”, page 697 and following. Only literature data published since are summarized here.

a) Intermittent catheterization [IC]

1. BACKGROUND

Intermittent catheterization (IC) and self-catheterization (ISC) have become properly introduced during the last 40 years. In general, the purpose of catheterization is to empty the bladder and of IC is to resume normal bladder storage and regularly complete urine evacuation. With IC and ISC there is no need to leave the catheter in the LUT all the time, thus avoiding complications of indwelling catheterization (ID).

It is clear that IC can improve incontinence or make patients with neurogenic bladder continent if bladder capacity is sufficient, bladder pressure kept low, urethral resistance high enough, and if care is taken
to balance between fluid intake, residual urine and frequency of catheterization. In young children with SCI, early clean intermittent catheterization and use of anticholinergics appear to prevent upper tract deterioration, improve continence and decrease infections. Serial urodynamics confirm increasing safe capacity with growth in most children. [2,3].

The main aims of IC and ISC are to empty the bladder and to prevent bladder overdistension in order to avoid complications and to improve urological conditions. The optimal post-void residual indicating the need to start bladder catheterization remains to be clarified, though Dromerick et al. [4] (LOE 2) demonstrated in a series of stroke patients that a post-void residual greater than 150ml is an independent risk factor for development of UTI.

2. Technique

There exists neither one best technique nor one best material, as both depend greatly on patients’ individual anatomic, social and economic possibilities [5] (LOE 1).

Two main techniques have been adopted, a sterile IC (SIC) and a clean IC (CIC). The sterile non-touch technique involves the use of sterile materials handled with sterile gloves and forceps. In an intensive care unit, some advocate wearing a mask and a sterile gown as well [6].

De Ridder et al. [7] compared the performance of SpeediCath hydrophilic-coated catheters versus uncoated polyvinyl chloride (PVC) catheters, in traumatic spinal cord injured patients presenting with functional neurogenic bladder-sphincter disorders. This 1-year, prospective, open, parallel, comparative, randomised, multi centre study included 123 male patients, > or =16 y and injured within the last 6 months. Primary endpoints were occurrence of symptomatic urinary tract infection (UTI) and hematuria. Secondary endpoints were development of urethral strictures and convenience of use. The results indicate that there is a beneficial effect regarding UTI when using hydrophilic-coated catheters. Bjerklund Johansen et al. evaluated patient openness to changing and satisfaction with catheters used in intermittent catheterisation (IC) for urinary retention from neurogenic bladder dysfunction. They also compared patient response to conventional catheters and a novel packaged hydrophilic catheter: LoFric Primo [8]. 409 neurogenic patients were recruited and 378 (283 males, 95 females; mean age: 43.5 yr) completed a 12-d trial of the novel catheter. Patients evaluated their current catheter at recruitment and the novel catheter after the 2-wk trial by questionnaire. Patient satisfaction was expressed on a Visual Analogue Scale for seven topics covering use and general satisfaction. The main finding was that more than 50% of the patients wished to continue with the novel catheter and reported increased satisfaction regarding introduction of the catheter, handling, time spent, and perception of IC, general satisfaction, and ability to cope with daily life. Kovindah and Madersbacher investigated whether a silicone catheter reused over years for clean intermittent catheterization (CIC) was safe for spinal cord injured (SCI) men [9]. A cross-sectional study was obtained from SCI men who had used CIC with a reusable silicone catheter for more than a year. The clinical outcome, especially with regard to urethral abnormalities with this reusable silicone catheter was as good as with a disposable one. However, to reuse urinary catheters, one should consider the increased risk of infection. Therefore, these authors suggest that for SCI patients in developing countries, CIC with a reusable silicone catheter may be a suitable and safe choice if one cleans and applies it. In the same way, Getliffe performed a systematic Cochrane review summarizing current evidence on the relationship between sterile single-use catheters or clean reused catheters and the incidence of UTI’s [10]. 13 trials met the inclusion criteria on intermittent catheterization protocols. There was considerable variation in length of follow-up, definitions of UTI, and numbers of subjects. Attrition was a problem for several studies, and all were underpowered. Several studies were more than 10 years old, and outcome measures were imprecise, making it difficult to draw conclusions on the benefit of one catheterization method over another. They concluded that there are no definitive studies illustrating that incidence of UTI’s is affected by sterile single-use or coated catheters compared to clean reused catheters. However the current research base is weak and design issues are significant. Based on the current data, it is not possible to state that one catheter method is better than another and further research on the topic is strongly recommended (LOE1).

Frequency of catheterization: This depends on many factors as bladder volume, fluid intake, postvoid residual, urodynamic parameters (compliance, detrusor pressure). Usually it is recommended to catheterize 4 – 6 times a day during the early stage after spinal cord lesion. Some will need to keep this frequency if IC is the only way of bladder emptying. Others will catheterize 1 – 3 times a day to check and evacuate residual urine after voiding or on a weekly basis during bladder retraining

Adjunctive therapy: To overcome high detrusor pressure antimuscarinic drugs or other bladder relaxants can be indicated. For those who develop a low compliance bladder, upper tract deterioration or severe incontinence, injection of Botulinum toxin in the bladder wall or surgery, such as bladder augmentation, may be necessary.

3. Complications

If catheterization is begun by patients with recurrent
or chronic UTI and urinary retention, the incidence of infection decreases and patients may become totally free of infection. If symptomatic infections occur, improper CIC or misuse often can be found. Chronic infection persists if the cause of the chronicity remains. Treatment of UTI is necessary if the infection becomes symptomatic. Lindehall et al. evaluated the rate of complications associated with catheterization and the risk of urethral lesions in girls with myelomeningocele treated with clean intermittent catheterization for a minimum of 10 years. They found that there were remarkably few problems associated with clean intermittent catheterization despite long treatment periods and use of noncoated polyvinyl chloride catheters. Clean intermittent self-catheterization and large size catheters were associated with few complications [11]. Similarly, they evaluated the risk for urethral lesions and epididymitis in boys with neurogenic bladder dysfunction treated by clean intermittent catheterization (CIC) for a minimum of 10 years and found that the overall rate of complications was low. The incidence of major urethral lesions did not increase during puberty. Self-catheterization and 12C catheter or greater seemed to be protective against major lesions [12] (LOE3). As opposed, Chen et al found that the incidence of urethral strictures increases with a longer follow-up and bladder stone formation was found to be associated with long-term use of CIC in SCI patients [13] (LOE3).

4. Health related quality of life

Oh et al aimed at determining the psychological and social status of patients using clean intermittent catheterization for neurogenic bladder according to health-related quality of life (HRQOL). They conducted a prospective trial involving 132 patients (81 men and 51 women, mean age 41.8 years, range 18 to 80 years) using clean intermittent catheterization because of neurogenic bladder secondary to spinal cord injury [14]. The 150 controls (90 men and 60 women) lived in the same region as the patients and were frequency matched to ensure equal age and sex distributions. HRQOL was measured using the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36). Their findings suggest that patients using clean intermittent catheterization because of neurogenic bladder secondary to spinal cord injury generally exhibit a reduced quality of life in all health domains as assessed by the SF-36 (LOE3) [15].

CONCLUSIONS

- **IC is effective and safe to treat the neurogenic bladder in the short term and in the longterm.** (LOE 1)
- **Complications such as UTI are regularly seen and seem to be related to both the catheterization itself and the existing LUT condition (LOE 2)**

RECOMMENDATIONS

- **Urethral and bladder complications seem to increase in the long term (LOE 3)**
- **In order to reduce and prevent complications, appropriate materials and correct techniques should be taught and performed (LOE 3)**
- **Adequate frequency of CIC, a non-traumatizing technique and suitable materials are the key factors for a successful outcome (LOE 2)**
- **Patients using clean intermittent catheterization because of neurogenic bladder secondary to spinal cord injury generally exhibit a reduced quality of life in all health domains as assessed by the SF-36. (LOE1).**

Implications for research

- There is a clear need for robust research in the area of IC, both evaluating clean vs. sterile PVC catheter use and hydrophilic vs PVC use (both sterile and reused). Researchers need to consider the design of the study if comparisons across trials are meaningful. Although cross-over designs mean lower sample size and control for within subjects variation, unless the data at cross-over point is available, these studies cannot entered into a meta-analysis. There it is recommended that journal editors who are publishing cross-over trials request that the authors include first set of data before cross-over (10).
b) Indwelling Urethral Catheters – transurethrally/ suprapublically

1. Transurethral catheterisation (ID)
   a. Background

In early 19th century, a urinary catheter with a balloon bag (Foley catheter) was developed. After the World War I, the majority of spinal cord injured (SCI) as well as other neurologic patients were treated with indwelling urethral catheterization (ID) or suprapubic catheterization (SC) due to difficulty in voiding or urinary incontinence. Nowadays, intermittent catheterization (IC) is recommended for neurologic patients. Nevertheless many choose ID as a mean of treating urinary incontinence due to difficulty in performing IC or persistent leakage between catheterizations. In developing countries ID is still the method of choice for those with urinary retention or incontinence.

Studies have shown that ID causes various complications such as urethral trauma and bleeding, urethritis, fistula due to pressure effect caused by improper size of the urethral catheters and improper technique of securing the catheters, bladder and renal stones, cystitis, acute and chronic urinary tract infection (UTI), bladder neck incompetence, meatus and urethral sphincter erosion, and bladder carcinoma. Many of these complications were related to long-term use. Therefore many experts advocate removal of the urethral catheter as soon as possible, and usage of other methods such as IC or SC to decrease urethral complications. However, nowadays the complications of ID seem less, due to better materials, the use of smaller size catheters and a proper technique of securing the catheter. For CIC wet patients contemporary balloon catheter indwelling at night seems to decrease risk of febrile episode due to UTI as compared to CIC alone [16]. The contemporary balloon catheter used consisted of a reusable balloon catheter and a reservoir to inflate the balloon. The patients self-inserted the catheter every night before sleeping, and then removed it the next morning. After use, the catheter is washed with tap water, and stored in a special purpose case filled with disinfectant (LOE3). Transurethral ID needs a lot of meticulous skill and care. Materials used should be sterile and handled properly by a well-trained person. In some centers, a well-trained catheter team has proved to lessen complications related to catheterizations. It is suggested that more frequent catheter change should be performed in patients with recurrent urinary tract infections (once a week or every two weeks) (LOE 4).

The study by Pannek (LOE 3) reported 0.11% incidence of bladder cancer amongst SCI individuals (48 out of 43,561 patients) which is similar to that observed in the general population [17]. However, more than 60% of the patients with SCI initially presented with muscle-infiltrating bladder cancer. The expression of inducible nitric oxide synthase was demonstrated in patients with SC or ID by Wall et al [18] (LOE 3), a finding which may potentially lead to the sustained production of nitric oxide and its oxidative products, the nitrosation of urinary amines and the formation of potentially carcinogenic nitrosamines in the bladder. Hamid et al.[19], however, in their retrospective series, did not find bladder cancer on bladder biopsies in patients with SC I and a mean catheter time of 12.1 years.

A case of osteomyelitis of the pubis was reported by Stern et al.[20] LOE 3).

b. Antibiotic prophylaxis

Routine antibiotic prophylaxis for patients with SC or ID is not recommended. Attempts at eliminating bacteriuria associated with indwelling or intermittent catheters are generally unsuccessful [21] (LOE 4).

For prevention of UTI, general cleanliness and local hygiene should be encouraged. If the patient has a symptomatic UTI, it is important to check for catheter blockade and complications as urinary stones. Symptomatic urinary infections have to be treated with the most specific, narrowest spectrum antibiotics available for the shortest possible time.

Guidelines for selecting antimicrobial agents in SCI patients are similar to guidelines for the treatment of complicated urinary infections in the general population. Characteristics of the quinolones make them well suited for treating UTI in SCI patients [22] (LOE 4).

CONCLUSIONS

- Transurethral ID is not a safe method for a long-term use in neurologic patients. (LOE 2)
- To control urinary incontinence, ID is effective if there is no blockade or urethral/bladder neck erosion (LOE 3)
- Catheters size 12-16F with as large a lumen as possible and smaller (5-10 ml) self-retaining balloons are recommended for adults to minimise the pressure effect on the bladder neck and to maximise time to blockage by incrustation. (LOE 4)
- Use of less irritating catheters and closed drainage system should be encouraged to minimise complications. (LOE 2)
- If available, siliconised catheters may be used with more frequent change. (LOE 3)
- Frequency of change largely depends on materials and size of catheter lumen e.g., every 1-2 weeks for siliconised latex catheters, every 2-4 weeks or longer for silicone or hydrogel-coated catheters. (LOE 3)
2. Suprapubic Catheterisation — Special Aspects

An alternative to indwelling urethral catheterization is an indwelling catheter placed through the lower abdomen into the dome of the bladder, called a suprapubic catheter (SC).

Overall the benefit and risks of the SC are very similar to the indwelling urethral catheter including the risk for urinary tract infection, stone formation, bladder cancer, and maintenance cost of catheter and bag. However, there are several benefits and one key disadvantage. Its advantages include: minimized risk of urethral trauma in men and women, minimized risk of urethral destruction in neurologically impaired women with even relatively short-term indwelling urethral catheters, and minimized urethral pain. The key disadvantage is that it requires a minor ‘surgical’ produce to insert the suprapubic catheter with potential to injure structures adjacent to the bladder, especially the large intestine [23]. The preferred insertion technique appears to be quite variable by region and country. There is no evidence that there is one best way to insert the SC.

Long-term management of the neurogenic bladder with the SC is a controversial topic in neurourology. The issue of controversy is that some rehabilitation centers across the world highly favor the suprapubic catheter as a safe and effective long-term management of the neurogenic bladder. On the other hand, a large number of experts have personal experience with suprapubic tube complications during its long-term use.

The literature on suprapubic catheterization is limited, and most of publications are 20 years or older. There are no prospective studies and no RCT’s on suprapubic catheterization. The bias of single center case series is the short follow-up with a worrisome large number of patients who are lost for follow-up. It is unclear if these patients may have developed complications and have died or were treated with alternative bladder management at a different hospital.

CONCLUSIONS

- Suprapubic catheter is a reasonable alternative to indwelling urethral catheter, but both are clearly inferior to intermittent catheterization (LOE 3).
- It is a safe and effective short-term management of urinary retention. (LOE 3)
- It is not recommended for the routine use for the long-term management of the neurogenic bladder. (LOE 2)
- Complications of SC are similar to that of ID, except the unique complication of bowel perforation and no urethral complications. (LOE 3)
c) Condom catheter and external appliances

**BACKGROUND**

Male patients with neurogenic bladder and chronic urinary incontinence can be candidates for a condom catheter (CC) connected to a urine or leg bag to collect the urine. However, some have difficulty in applying CCs, e.g., due to overweight and/or some degree of penile atrophy or retraction.

**CONCLUSIONS**

- Condom catheter still has a role in controlling urinary incontinence in neurologic male patients (LOE 3)
- Long-term use may cause bacteriuria, but it does not increase the risk of UTI when compared to other methods of bladder management. (LOE 3)
- Complications may be less if applied properly with good hygiene care, frequently change of the CC and maintenance of low bladder pressures. (LOE 3)
- Special attention should be paid to people with dementia (LOE 3)

**RECOMMENDATIONS**

(All grades of recommendation = B/C)

- To have better control of leakage, a more secure CC should be used, and patients should be educated and cooperative.
- To prevent latex allergy, a silicone CC should be used and serological examination of latex-specific IGE is recommended in addition to patient history to better identify patients at risk.
- To prevent compressive effects, choose proper size CC with self-adhesive.
- To prevent infection, a daily change of the CC could help.
- To prevent bladder and upper tract damage, regular bladder emptying with low bladder pressures and low post void residual should be pursued.

3. PHARMACOTHERAPY

Detailed data on pharmacotherapy are presented in a specific chapter of the Committee on Pharmacologic treatment. Our chapter deals only with specific issues of pharmacotherapy in neurologic patients. We strongly recommend consulting the Drug Treatment chapter for levels of evidence and recommendations. References can also be found in the ICI 2005 chapter on conservative management of the neurogenic bladder.

The principal causes of urinary incontinence in this subpopulation are neurogenic detrusor overactivity (NDO) and/or incompetence of urethral closing function. To improve urinary incontinence the treatment should aim at decreasing detrusor activity, increasing bladder capacity and/or increasing bladder outlet resistance. This picture is blurred by the occurrence of detrusor/sphincter dyssynergia which can be present concomitantly with NDO.

Pharmacologic therapy has been particularly helpful in patients with relatively mild degrees of neurogenic bladder dysfunction. Patients with more profound neurogenic bladder disturbances may require pharmacologic treatment to improve results of other forms of management such as intermittent catheterization. Although the two most commonly used classes of agents are antimuscarinic and alpha-adrenergic blockers, the drugs used for treating neurogenic bladder/urethral dysfunction should be classified as follows. (Most but not all drugs action was evaluated in neurologic patients).

**Drugs for incontinence due to neurogenic detrusor overactivity and/or low compliant detrusor**

- **a) Bladder relaxant drugs**
  1. **Oxybutynin**
  2. **Propiverine**
  3. **Trospium**
  4. **Tolterodine**
  5. **Propantheline**
  6. **Oxyphenyclimine**
  7. **Flavoxate**
  8. **Tricyclic Antidepressants**
  9. **Solifenacin Succinate**
  10. **Darifenacin**
  11. **Fesoterodine**

- **b) Intravesical application**
  1. **Oxybutynin, Lidocaine, Nociceptin/Orphanin FQ, Atropine**
  2. **Vanilloids**
     a. Capsaicin
     b. Resiniferatoxin
  3. **Botulinum toxin**

**Drugs for incontinence due to neurogenic sphincter deficiency**

- **a) Alpha-adrenergic agonists**
- **b) Estrogens**
- **c) Beta-adrenergic agonists**
- **d) Tricyclic antidepressants**
Drugs for facilitating bladder emptying

a) Alpha adrenergic blockers
b) botulinum toxin
c) Cholinergics

DRUGS FOR INCONTINENCE DUE TO NEUROGENIC OAD AND/OR LOW COMPLIANT DETRUSOR

a) Bladder relaxant drugs

Antimuscarinic agents are by far the most useful drugs in the management of the neurogenic bladder: they are used to suppress NDO.

General indications of pharmacological treatment in NDO are to improve or eliminate reflex incontinence, eliminate/ prevent a high intravesical pressure and enhance the efficacy of intermittent catheterization (IC), triggered voiding and indwelling catheters. Neurogenic detrusor overactivity is mostly associated with a functional outflow obstruction due to detrusor-sphincter-dysynergia (DSD). For the most part, pharmacotherapy is used to suppress reflex NDO completely and facilitate IC. On the other hand bladder relaxant drugs would seem to decrease detrusor- contractility also during voiding. With this situation residual urine may increase and must then be assisted or accomplished by IC. It must be stressed that with the current level of knowledge antimuscarinic therapy is not a causative treatment, but a symptomatic one.

1. OXYBUTYNIN

Oxybutynin hydrochloride is a moderately potent antimuscarinic agent with a pronounced muscle relaxant activity and local anesthetic activity as well. In a prospective, 12-week dose titration trial of controlled release oxybutynin (OXY-XL), Bennett et al. [24] evaluated the efficacy and tolerability of higher dose oxybutynin chloride in patients with neurogenic bladder and multiple sclerosis, spinal cord injury or Parkinson’s disease. A 7-day washout period was used before initiation of the starting dose of 10 mg OXY-XL. Doses of OXY-XL were increased by 5 mg at weekly intervals to a maximum dose of 30 mg per day guided by patient perception of efficacy versus side effect. At the end of the study statistically significant decreases in the number of voids in 24 hours, episodes of nocturia and incontinence episodes were observed. Residual urine remained unchanged. No patient experienced serious adverse events (LOE2). In a prospective, open label trial of 3 formulations of oxybutynin (tablets, syrup and extended release tablets), Franco et al [25] evaluated the efficacy and safety of oxybutynin in children with NDO due to neurological conditions. The effect of treatment on average urine volume per catheterization and on secondary urodynamic outcomes was evaluated. Maximal cystometric capacities increased, and mean detrusor and intravesical pressures were significantly decreased at week 24. Improvements in bladder function were consistent across all oxybutynin formulations (LOE2).

2. PROPIVERINE

In a randomized, double-blind, prospective multicenter clinical study, Stöhrer et al. [26] compared the efficacy and tolerability of propiverine and oxybutynin in patients with neurogenic detrusor overactivity. Propiverine and oxybutynin were equally effective in increasing bladder capacity and lowering bladder pressure. The trend for better tolerability of propiverine compared to oxybutynin achieved significance for dryness of the mouth (LOE1). Propiverine hydrochloride has also been shown to be effective in neurogenic detrusor overactivity in children and adolescents, even in some of those cases unresponsive to other anticholinergics [27,28]. The low incidence rate of adverse events evidenced a favourable risk-benefit profile of propiverine hydrochloride (LOE3).

3. TROSPURIM

Trospium is a quaternary ammonium derivative with mainly antimuscarinic actions, it’s effectiveness and safety has confirmed in meta-analysis (see reference ICI 2002). Trospium has been shown to significantly reduced the number of urinations, increased cystometric capacity and mean effective volume of the bladder, and reduced the number of urgent voiding in neurogenic patients [29,30] (LOE1).

4. TOLTERODINE

Tolterodine is a potent, competitive muscarinic receptor antagonist specifically developed fro the treatment of overactive bladder. Tolterodine has a high selectivity in vitro and exhibits selectivity for the urinary bladder over the salivary glands in vivo. Several phase II study have demonstrated the efficacy and safety of tolterodine in patients with overactive bladder [32]. Ethans conducted a prospective, randomized, double-blind, crossover trial plus open-label comparative stage, aiming at comparing tolterodine with oxybutynin and placebo in people with neurogenic detrusor overactivity. Tolterodine, when used at at self-selected doses (SSDs) was comparable with oxybutynin at SSDs in enhancing bladder volume and improving continence, but with less dry mouth. Tolterodine at the recommended dosage of 2 mg twice daily improves incontinence and bladder volumes compared with placebo, and without significant dry mouth (LOE1). It seems however that larger doses of tolterodine is needed to achieve best effect on neurogenic bladder [33-34] (LOE3).

5,6,7,8. PROPANTHELINE, OXYPHENCYCLIMINE, FLAVOXATE AND TRICYCLIC ANTIDEPRESSANTS

are used by many clinicians around the world for bladder relaxation in patients with neurogenic bladder. Local reports claim good clinical effectiveness. In
literature no new data in neurogenic patients on their effect and safety have been reported since ICI 2. Flavoxate does not seem to be effective for treating detrusor overactivity (references in ICI 2005 report).

9. SOLIFENACIN Succinate

Solifenacin succinate is a newer anticholinergic drug, used once daily, which has a functional selectivity for the bladder over other organs. Solifenacin has been extensively studied in OAB [35-39] (LOE1). There is up to date no data on the effect of solifenacin in neurogenic detrusor overactivity.

10. DARIFERACIN

Dariferacin is a chiral diphenylacatamide tertiary amine, marketed as a water hydrobromide salt, and is a selective M3 receptor antagonist. It has been shown to have a higher degree of selectivity for the M3 receptor compared with other anticholinergics. It is extensively metabolized by the liver after oral dosing. Metabolism is mediated by CYP enzymes to its main metabolite. Dariferacin has been extensively studied in OAB [40-43] (LOE1). There is up to date no data on the effect of Dariferacin in neurogenic detrusor overactivity.

11. FESOTERODINE

Fesoterodine acts functionally as a prodrug. It is rapidly and extensively hydrolysed by nonspecific esterases to 5-hydroxymethyl tolterodine. The conversion is rapid and virtually complete such that, after oral dosing, only the metabolite, not the parent compound, can be detected in patient plasma. This active metabolite, responsible for the antimuscarinic activity of fesoterodine is also the active metabolite of tolterodine, 5-hydroxymethyl tolterodine (5-HMT). In contrast to tolterodine, the conversion of fesoterodine to 5-HMT bypasses the CYP system, although CYP3A4 and CYP2D6 are involved in subsequent inactivation of the active metabolite. Phase 3 trials have suggested that fesoterodine is an effective and well-tolerated therapy for OAB [44-46] (LOE1). There is up to date no data on the effect of fesoterodine in neurogenic detrusor overactivity.

b) Intravesical application

1. OXYBUTYNIN, PROPANTHELINE, NOCICEPTIN/ORPHANIN FQ, ATROPINE

Since the first use of the intravesical application by Brendler et al. [47], there have been over 100 peer review articles reporting successes of intravesical oxybutynin to treat overactive bladder and NDO. The main findings were, at least at short term follow up, an improvement of overactive bladder symptoms, including a decreasing number of incontinence episodes, an increase of maximum bladder capacity and a decrease of the detrusor overactivity in the urodynamic recordings. George et al. compared the therapeutic response of intravesical oxybutynin, propantheline, and capsaicin in the treatment of neurogenic detrusor overactivity [48]. Oxybutynin 5 mg in solution or propantheline 15 mg in solution and capsaicin were instilled intravesically in each patient. Urodynamic studies were done before and after the intravesical instillation of each drug. There was a significant difference in therapeutic response between intravesical oxybutynin, propantheline, and capsaicin in the treatment of detrusor overactivity for leak volume (LV) and leak frequency at 2nd week. When comparing responses of oxybutynin and propantheline, more subjects demonstrated improvement with intravesical propantheline than oxybutynin for reflex volume, detrusor leak point pressure, clean intermittent catheterization volume, and LV (LOE3). Up to now there is however no standard instillation protocol concerning the use of intravesical oxybutynin for overactive bladder. The doses vary between 5-30 mg diluted in 30-40 ml saline [48-49]. Also the instillation frequency is not standardized and varies between 1 to 3 times /d.

Nociceptin/orphanin FQ (N/OFQ), where F and Q represent the first and last amino acid, respectively, phenylalanine (F) and glutamine (Q), is a hepta-decapeptide that exerts several physiologic actions at both the central and the peripheral level by activating a specific G-protein-coupled receptor named nociceptin orphan peptide (NOP) receptor. Among the, animal studies have demonstrated that N/OFQ exerts a robust inhibitory effect on the micturition reflex in the rat [50]. Lazzeri et al. recently studied the feasibility, safety and efficacy of daily intravesical instillation of 1 mg of the endogenous peptide N/OFQ in a selected group of patients who performed clean intermittent catheterization for neurogenic detrusor overactivity (NDO) [51]. A total of 18 patients with NDO and incontinence on clean intermittent catheterization were prospectively randomized to receive 1 mg nociceptin/orphanin FQ in 10 ml saline or placebo (saline) at the first catheterization for 10 days. Mean daily urine leakage episodes significantly decreased from 2.18 at baseline to 0.94 during nociceptin/orphanin FQ treatment, while no significant changes were reported in the placebo group. The total mean voiding diary bladder capacity significantly increased in patient receiving nociceptin/orphanin FQ, while mean voiding diary bladder capacity remained unchanged in patients receiving placebo. The urodynamic parameters recorded during the study showed an increase in cystometric capacity and a decrease in maximum bladder pressure compared to baseline only in patients assigned to the nociceptin/orphanin FQ group. These findings support the use of nociceptin/orphanin FQ peptide receptor agonist as an innovative approach for controlling neurogenic detrusor overactivity incontinence (LOE2).

Fader et al. [52] tested the efficacy and side effect
profiles of intravesical atropine compared to oxybutynin immediate release (IR) when used by individuals with multiple sclerosis. They performed a study to determine the most effective dose of atropine. Eight participants used increasing doses of intravesical atropine (2 to 6 mg in 20 ml NaCl 0.9%) during a 12-day period. Bladder diary data showed that the instillation of 6 mg atropine 4 times daily was most effective for increasing bladder capacity (voided/catheter volumes). Afterwards they performed a randomized, double-blind crossover trial. Participants received 14 days of treatment with oral oxybutynin IR 5 mg twice daily (range 2.5 twice to 5 mg 4 times daily) or with intravesical atropine, followed by 14 days of alternative treatment. Participants recorded a bladder diary and rated side effects and quality of life. The primary outcome variable was bladder capacity. A total of 57 participants with multiple sclerosis completed the study. Average change in bladder capacity was higher in the atropine arm. Changes in incontinence events and voiding frequency were not statistically different between the arms. Changes in total side effect and dry mouth scores were significantly better in the atropine treatment arm. These findings suggest that intravesical atropine is as effective as oxybutynin immediate release for increasing bladder capacity and it is probably better with less antimuscarinic side effects (LOE2).

2. Vanilloids

Have been discussed in the ICI 2005 report, and references before 2002 are to be found there.

a. Capsaicin (CAP) (see background and reference ICI 2002)

The use of capsaicin is still largely experimental and limited by the fact of prolonged and painful excitation of the sensory c-fibers. The alcoholic solvent may be a major factor in the poor tolerability of alcoholic CAP instillation, as suggested by the result of one placebo controlled study showing that side effects appeared to be the same after intravesical instillation of CAP diluted in 30% ethanol as after instillation of ethanol alone (LOE2).

b. Resiniferatoxin (see background 2002)

Resiniferatoxin (RTX) acts without the potent neuronal excitatory effect of capsaicin, and therefore elicits less discomfort. Groups comparing RTX in saline or 10% ethanol with CAP in 30% ethanol found better tolerability of RTX (see ICI 2002). The difference in tolerability of the 2 vanilloids (CAP vs. RTX) was usually attributed to the differential pungency of the 2 agents. Nevertheless, because we know the role of the solvent in the irritative effect on bladder mucosa, it is reasonable to assume that differential effects could be related to the use of different vectors. From a technical point of view the choice of the solvent is limited because of the poor hydrosolubility of CAP, imposing the use of an alcoholic, lipidic or glucidic vector. The safety of the lipidic solution could be imperfect because of difficulty of achieving complete elimination of lipidic solution from the bladder. On the contrary, a glucidic solution may represent a safe and valuable alternative to the alcoholic vector. De Seze et al. [53] compared the efficacy and tolerance of intravesical instillations of CAP and RTX using a glucidic solvent for CAP and the 10% ethanol solvent for RTX in a controlled randomized, double blind study in patients with severe urinary incontinence due to spinal cord injury. On day 30, improvement was found clinical and uroodynamical respectively in 78% and 83% of patients treated with CAP vs. 80% and 60% treated with RTX. No significant difference between the 2 groups was observed. The benefit remained in two-thirds of the 2 groups on day 90. There were no differences in regard to incidence, nature or duration of side effects in CAP vs. RTX treated patients. These results once more strongly argue for the importance of accounting the role of vanilloid solute when interpreting efficacy and tolerance of vesical vanilloid instillation in detrusor hyperreflexia cases. They suggest that a glucidic solution is a valuable solvent for CAP instillation (LOE2).

RTX seems to have a beneficial effect on NDO (LOE 2). However, good randomized controlled studies are needed to determine its place in the treatment of NDO. Also the optimum doses (concentration) as well as the inter treatment intervals need to be determined.

Moreover, the long-term safety of vanilloid agents, particularly concerning mutagenic and carcinogenic effects on the bladder wall is not perfectly known. The use of CAP solved in ethanol seems not to cause morphological changes in the bladder urothelium in patients receiving repeat instillation for as long as 5 years. To our knowledge the long-term safety of RTX remains unproven. Furthermore, RTX belongs to the family of tumor promoting phorbol esters, strengthening the need to ensure the safety of RTX before extending its therapeutic applications.

3. Botulinum toxin A See background ICI 2002

Botulinum neurotoxin (BoNT) decreased neurogenic detrusor overactivity in four full published LOE1 studies [54-56], one LOE2 study [57], and several LOE3 studies. Only 5 complete full publications [54-57] and three abstracts[58-60] were included in this chapter. The majority of the studies involved only participants with neurogenic bladder. Two studies had participants for which as a group, the aetiology of overactive bladder was mixed. In one LOE1 study, 59 patients with spinal cord injury and MS were enrolled in a single treatment, randomized, placebo-controlled, 6-month safety and efficacy study [54]. Patients received either BoNT-A or placebo. Injections were given into the detrusor muscle, leaving out the bladder base and trigone. Injection volume was 30 cc and 30 sites...
were injected. A single administration of 200 or 300 units of Botox® into the detrusor muscle was well tolerated and more effective than placebo in reducing the frequency of incontinence episodes, enhancing bladder function, and improving quality of life.

In another LOE1 study, the use of BoNT was studied for refractory neurogenic and non-neurogenic detrusor overactivity [55]. Twenty patients were injected with either placebo (20 ml normal saline) or BoNT-B (Myobloc®, 5000 IU diluted up to 20 ml). After six weeks, treatments were crossed over. The primary outcome was the paired difference in change in average voided volumes. Secondary outcome measures included frequency, incontinence episodes, and paired differences in quality of life, as measured by the King’s Health Questionnaire. There were significant paired differences in the change in average voided volume, urinary frequency, and episodes of incontinence between active treatment and placebo. There were also differences in the change in quality of life affecting five domains of the King’s Health Questionnaire. This study is limited in that the study population was comprised of a mixed population of patients, with diverse aetiologies of detrusor overactivity (neurogenic and non-neurogenic). This limits the generalizability of the findings. The absence of a sustained washout period before the crossover might have biased the findings, and the low dose of BoNT-B used may have affected the duration of the results.

In another study, BoNT-A injection was compared to resiniferatoxin intravesical instillation into the bladder in 25 patients with spinal cord lesions and concomitant neurogenic detrusor overactivity [57]. There was a significant decrease in catheterization and incontinence episodes for both treatments at 6, 12, and 18-months of follow-up. However, the BoNT injections provided superior clinical and urodynamic benefits as compared to intravesical resiniferatoxin. There were no significant side effects with either treatment (LOE1).

A recently published study compared a single injection of BoNT-A (500 units Dysport®, diluted in 25 ml saline and injected into 25 injection sites) to placebo in 31 patients with neurogenic detrusor overactivity and urinary incontinence. Time of follow-up was 26 weeks. Patients in the BoNT-A group had a significant change regarding intake of anticholinergic drugs, cystometric bladder capacity, maximum detrusor pressure, frequency of urinary leakage and quality of life parameters (LOE1) [61].

There is one study (LOE3) that addressed different injection technique. Karsenty et al. compared to different technique of injections of 300 units of BoNTA (Botox®) [58]. They compared 10 versus 30 injections sites and reported a significant reduction in post-procedure pain only in the group receiving 10 injections. There was no significant difference found in any other measures including incontinence episodes or cystometric capacity. In addition to the study from Schurch et al. two trials (LOE2) assessed the efficacy of different doses of Botox® (100 versus 300 and 200 versus 300) [59,60]. No study reported significant difference between the different dose and the confidence interval were wide.

The safety seems to be quiet acceptable though generalised paraparesis/fatigue has been described especially in patients with high spinal cord lesions. The effect resolves spontaneously after 4-6 weeks.

There are several major reviews coming up in literature that will highlight the actual knowledge of long-term treatment, overall safety and different techniques of application.

### DRUGS FOR INCONTINENCE DUE TO NEUROGENIC SPHINCTER DEFICIENCY

Several drugs, including alpha-adrenergic agonists, estrogens, beta-adrenergic agonists and tricyclic antidepressants, have been used to increase outlet resistance. No adequately designed controlled studies of any of these drugs for treating neurogenic sphincter deficiency have been published. In certain selected cases of mild to moderate stress incontinence a beneficial effect may be obtained.

### DRUGS FOR FACILITATING BLADDER EMPTYING

#### a) Alpha adrenergic blockers

Alpha-adrenoceptors have been reported to be predominantly present in the bladder base, posterior urethra and prostate. Alpha-blockers have been already reported to be useful in neurogenic bladder by decreasing urethral resistance during voiding (references ICI 2005 report). Only new references are mentioned here.

Tamsulosin has been shown to improve bladder storage and emptying in MS and SCI [62].

Abrams et al. [63] evaluated the efficacy and safety of tamsulosin in patients with neurogenic lower urinary tract dysfunction secondary to suprasacral spinal cord lesions in a 4-week randomized controlled trial (RCT) followed by a 1-year, open label, long-term study. A total of 263 patients were randomized to 4-week double-blind therapy with placebo, or 0.4 or 0.8 mg tamsulosin once daily. The primary efficacy parameter was maximum urethral pressure (MUP). In the long-term study but not in the RCT trial there was a statistically significant mean decrease in MUP from baseline to end point. In the long-term study tamsulosin also decreased maximum urethral closure pressure, improved several cystometry parameters related to bladder storage and emptying, and increased to a statistically significantly degree, from baseline to end point, mean voided volume based on the micturition diary. There was statistically significant improvement for the International Prostate Symptom Score Quality of Life. Both doses were effective and well tolerated. (LOE1)
b) Botulinum toxin

In a LOE1 study, the effects of botulinum toxin versus placebo was studied on DSD in 86 multiple sclerosis (MS) patients[64]. The study employed a single transperineal injection of BoNT-A, 100 units in 4 cc normal saline, or placebo, into the striated sphincter with EMG guidance. The primary endpoint was post void residual volume at 30 days. The secondary endpoints included voiding and urodynamic variables. Results showed that a single injection of BTX did not decrease post-voiding residual volume in this group of MS patients. These findings differ from those in patients with spinal cord injury and may be due to lower detrusor pressures in MS patients.

c) Cholinergics

In general, bethanechol chloride seems to be of limited benefit for detrusor areflexia and for elevated residual urine volume. Elevated residual volume is often due to sphincter dyssynergia. It would be inappropriate to potentially increase detrusor pressure when concurrent DSD exists.

CONCLUSIONS

- Bladder relaxant agents, including oxybutynin, propiverine, trospium and tolterodine have a documented suppressive effect on incontinence by controlling overactive bladder, thereby improving storage function (LOE 1).
- However, all of these drugs presently available have considerably high incidence of side effects (dry mouth, constipation, urinary retention, etc.), which limits their usage. Tolterodine, propiverine, trospium and controlled-release oxybutynin have significantly less side effects compared to immediate-release oxybutynin (LOE 1).
- High doses of OXY-XL seem safe and effective in patients with neurogenic bladder (LOE 3)
- Although the oral application is the usual way, intravesical instillation or intrarectal (oxybutynin) may be an alternative (LOE 4).
- Intravesical instillation of capsaicin/resiniferatoxin has been reported to improve spinal reflex incontinence for several months after instillation (presumably blocking sensory input). Resiniferatoxin is preferable (LOE 3).
- Botulinum toxin injections into the detrusor muscle was reported to improve incontinence and increase functional bladder capacity in spinal cord injured patients with neurogenic DOA (LOE 1).
- Long-term α-adrenergic antagonists are effective and well tolerated in patients with MS and suprasacral spinal cord lesion with neurogenic lower urinary tract dysfunction (LOE1)
- Data on the use of botulinum toxin (BonT) for DSD are conflicting. BoNT is probably safe and effective for the treatment of DSD in spinal cord injury patients (LOE2). However, on the basis of one LOE1 study, BonT does not provide significant benefit for the treatment of DSD in MS patients,
- There is no adequately designed controlled study of any drug for neurogenic sphincter deficiency.

RECOMMENDATIONS

- Bladder relaxant agents should be recommended for the treatment of reflex incontinence evoked by neurogenic detrusor overactivity in patients in whom IC alone is unable to control it (A).
- Titration of the dosage of these drugs individually should be done to achieve maximum therapeutic effect and minimal side effect. If one drug is not tolerated, try another drug as it may have less side effects (C/D).
- BoNT should be offered as a treatment option for neurogenic detrusor overactivity (A).
- Vanilloid intravesical therapy still remains experimental and therefore is not recommended except within clinical trials (C/D)
- Further attempts for the treatment of NDO should be undertaken to develop the ideal drug in terms of good efficacy, tolerability and safety (D).
- For decreasing outlet resistance in neurogenic bladder a-adrenergic antagonists may be used (B/C).
- BoNT may be considered for DSD in spinal cord injury patients (B)
- For neurogenic sphincter deficiency no effective drugs are available up to now; further research is needed (D).
- For detrusor areflexia no effective drugs are available up to now (IC remains the gold standard) ; further research is needed
4. ELECTROSTIMULATION

a) Electrical Neuromodulation

1. BACKGROUND

In the last decade sacral nerve neuromodulation has been confirmed as a valuable treatment option for patients with symptoms of overactive bladder. The success with sacral neuromodulation has increased the interest in other neuromodulation techniques.

The current techniques of neuromodulation for treating overactive bladder – which includes detrusor overactivity of neurologic origin - are (a) anogenital hypertension, (b) pudendal nerve stimulation, (c) sacral nerve neuromodulation, (d) percutaneous posterior tibial nerve stimulation (Stoller afferent nerve stimulation, SANS), (e) magnetic stimulation and f) deep brain stimulation.

It is not really known how neuromodulation works, however, there is strong evidence that neuromodulation works at a spinal and at a supraspinal level [65]. For more details about possible mechanism of actions see ICI report 2005.

2. PUDENDAL NERVE STIMULATION

It has been shown that electrical stimulation of pudendal nerve afferents can inhibit bladder contractions in patients with SCI, and bladder capacity can be increased by continuous [66] as well as conditional stimulation [67] (LOE3). Implants such as the InterStim® system have made this treatment modality commercially available (see sacral nerve stimulation). Common to these implantable systems is that they use continuous stimulation. Detrusor inhibition is in principal only necessary during an involuntary contraction and, thus, stimulation could be turned off between contractions. Such a stimulation scheme could have a number of advantages. Power consumption may be decreased and, thus, extend battery lifetime. Furthermore, continuous stimulation of a reflex may lead to habituation, which would be minimized or prevented by conditional stimulation. Hansen et al.[68] examined the effect of the automatic, event driven electrical stimulation of pudendal nerve afferents on bladder capacity in patients with SCI. The study included 2 women and 14 men older than 18 years with NDO, bladder capacity below 500 ml and complete or incomplete suprasacral spinal cord injury. Detrusor pressure (Pdet) was recorded during ordinary, natural bladder filling. In a similar subsequent recording Pdet was used to trigger electrical stimulation when pressure exceeded 10 cm H2O. Of the 16 patients enrolled in this study 13 had increased bladder capacity together with a storage pressure decrease as a result of automatic, event driven electrical stimulation. During stimulated filling Pdet never exceeded 55 cm H2O. Thus, storage pressure was sufficiently low to prevent kidney damage. An average bladder capacity increase of 53% was achieved (LOE 3).

3. CHRONIC PUDENDAL NERVE STIMULATION

Direct pudendal nerve stimulation has beneficial effects on numerous pelvic floor function impairments such as urinary and/or fecal incontinence, retention, and constipation. In preceding literature the implant technique required a fairly complex and invasive surgery, although recent advances with percutaneous placement of the lead through an introducer have made the procedure much less invasive. Spinelli et al.[69] performed staged procedure similar to that of sacral neuromodulation (SNM) to place tined lead near the pudendal nerve, using neurophysiological guidance. They named this approach chronic pudendal nerve stimulation (CPNS).

Fifteen neurogenic patients (eight male, seven female) with symptoms of urge incontinence due to neurogenic overactive bladder underwent CPNS. All patients had complete neurophysiological and urodynamic evaluation at baseline and follow-up and were asked to complete voiding and bowel diary for 7 days. During screening, average number of incontinent episodes per day decreased from 7+/- 3.3 to 2.6+/- 3.3 (<0.02, paired t-test). Eight patients became continent, two improved by more than 88% (from 9 to 1 daily incontinence episodes) and two patients reduced the number of incontinence episodes by 50%. The implantable pulse generator (IPG) was subsequently implanted in those 12 patients. Three patients without improvement did not continue to second stage. In implanted patients with 6 months follow-up, urodynamic evaluation showed an objective improvement in the maximum cystometric capacity which increased from 153.3+/- 49.9 to 331.4+/- 110.7 ml (<0.01, paired t-test). The maximum pressure decreased from 66+/- 24.3 to 36.8+/- 35.9 cmH2O (P=0.059, paired t-test). Eight patients reported significant improvement in bowel function (LOE3).

4. POSTERIOR TIBIAL NERVE STIMULATION

Posterior tibial nerve stimulation was described 20 years ago as a minimally invasive treatment for urge incontinence due to neurogenic detrusor overactivity (NDO) in spinal cord injury (SCI) patients. Interestingly, the site involves the Sanyijioa (Sp6) point use in Chinese acupuncture for urinary incontinence problems.

Pudendal nerve afferent (S2 to S4) are well know to suppress NDO but it is not intuitively obvious that PTN afferents should have similar effect. However, the PTN is derived from L4 and L5 and S1 to S3 nerve roots and therefore shares common roots with those serving bladder functions. In few reports, SCI and Parkinson patients have been treated with PTN because of NDO and neurogenic incontinence. PTN seems to increase cystometric bladder capacity, enhance bladder volume at which hyperreflexic contraction and associated leakage occurs [70,71] (LOE3).
b) Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex induces a long-lasting modulation of spinal cord excitability [72]. Thus, it represents a potentially useful tool for the treatment of neurogenic urinary disturbances. Centonze et al. [73] investigated the effects of high frequency (5 Hz) excitatory rTMS over the motor cortex on LUT dysfunction in a population of 10 MS patients complaining of urinary symptoms. All but one of the patients reported an improvement of voiding phase LUT symptoms and a significant reduction of post void residual volume. In patients with pure detrusor underactivity, this finding seems to be produced by a better contraction of the detrusor muscle, with consequent increase of Pdet@Qmax and Qmax.

Notably, a similar finding was reported in female Fowler’s syndrome patients after sacral neuromodulation, a procedure that probably shares some central actions with rTMS. In patients with DSD, on the other hand, rTMS produced negligible effects, although the observation of a reduction of Pdet@Qmax seems to suggest a better relaxation of the urethral sphincter (LOE3).

c) Deep brain stimulation

1. Subthalamic nucleus deep brain stimulation (STMN-DBS)

A large proportion of patients suffering from Parkinson’s disease presents with urinary dysfunction including urgency, increased frequency or incontinence as predominant symptoms [74]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established as a surgical treatment of motor symptoms in Parkinson’s disease patients [75]. However, data from experimental urodynamic measures in men [76] and animal models [77] have also demonstrated a significant influence of STN-DBS on urinary bladder function. In these studies, the main effect of STN-DBS appeared to be a normalization of urodynamic parameters in the storage phase with a delayed first desire to void and an increased bladder capacity. Herzog et al. aimed at investigating the effect of STN-DBS on the neural mechanisms underlying cerebral bladder control. Using PET to measure changes in regional cerebral blood flow (rCBF), 11 patients with bilateral STN-DBS were studied during urodynamically bladder filling in STN-DBS ON and OFF condition. A filled bladder led to a significant increase of rCBF in the anterior cingulate cortex, which was further enhanced during STN-DBS OFF.

A significant interaction between bladder state and STN-DBS was observed in lateral frontal cortex with increased rCBF when the bladder was filled during STN-DBS OFF [78,79] (LOE3).

2. Thalamic deep brain stimulation

The precise mechanisms underlying cerebral regulation of lower urinary tract function are still poorly understood. Essential tremor (ET) is not known to induce lower urinary tract symptoms (LUTS) or neuropathological changes in the thalamus. Consequently, DBS in patients with ET offers the unique opportunity to investigate the role of the VIM nucleus in lower urinary tract function. Kessler et al. [80] evaluated the effect of thalamic DBS on urodynamic parameters in patients with ET. Seven patients were examined (two females, five males) with ET 15–85 mo after implantation of DBS leads into the ventral intermediate nucleus of the thalamus. They compared urodynamic parameters during thalamic DBS (ON state) and 30 min after turning the stimulator off (OFF state). In the ON compared with the OFF state, there was a significant decrease in bladder volume at first desire to void (median, 218 ml vs. 365 ml, p = 0.031), at strong desire to void (median, 305 ml vs. 435 ml, p = 0.031), and at maximum cystometric capacity (median, 345 ml vs. 460 ml, p = 0.016). No significant differences between the ON and OFF state were detected for changes in detrusor pressure during filling cystometry, bladder compliance, maximum detrusor pressure, detrusor pressure at maximum flow rate, maximum flow rate, voided volume, and postvoid residual (LOE3).

CONCLUSIONS

- Electrical neuromodulation mostly is not the first line treatment for neurogenic detrusor overactivity. There are some limited reports showing that it may be beneficial (LOE 3).
- Automatic, event driven electrical stimulation in the treatment of NDO is feasible (LOE 3).
- Chronic pudendal nerve stimulation is feasible. Neurophysiological guidance seems to be mandatory to place the lead near the pudendal nerve either using perineal or posterior approach (LOE3).
- Enhancing corticospinal tract excitability by rTMS might be useful to ameliorate detrusor contraction and/or urethral sphincter relaxation in MS patients with bladder dysfunction (LOE3).
- Thalamic deep brain stimulation resulted in an earlier desire to void and decreased bladder capacity, suggesting a regulatory role of the thalamus in lower urinary tract function (LOE3).
- STN-DBS appeared to be a normalization of urodynamic parameters in the storage phase with a delayed first desire to void and an increased bladder capacity (LOE3).
CONCLUSIONS

- Although from the theoretical point of view and based on limited personal clinical experiences electrical stimulation via anal or vaginal plugs could be able to improve the strength of pelvic floor musculature, including that of the striated sphincter muscle, there is no study published which deals with this matter (LOE 4)

RECOMMENDATION

If pharmacotherapy fails to relax the hyperreflexic detrusor, electrical neuromodulation may be optional in patients with neurogenic detrusor (C/D)

- Although the setup for automatic, event driven electrical stimulation is not suitable in a clinical setting, the treatment modality is promising and it warrants further investigation (D).

- Further studies on chronic pudendal nerve stimulation must be carried out to identify the best stimulation parameters and to verify the long term results (D).

- The thalamus may be a promising target for the development of new therapies for lower urinary tract dysfunction. Further investigation on this matter is critical before one speculates, that the thalamus will emerge as a target for treatment of lower urinary tract symptoms such as urgency and bladder pain (D).

- STN-DBS might ameliorate bladder dysfunction and that this modulation may result from facilitated processing of afferent bladder information (D).

e) Intravesical electrical stimulation (IVES)

BACKGROUND (read ICI 2002 page 741 and following)

The afferent stimuli induced by IVES travel along afferent pathways from the LUT to the corresponding cerebral structures. This “vegetative afferention” results in sensation of bladder filling/urge to void, with subsequent enhancement of active contractions, and possibly also in voluntary control over the detrusor. Feedback training is mediated by enabling the patient to observe the change of the detrusor pressure on a water manometer, which enables the patient to notice when a detrusor contraction takes place. This also facilitates voluntary control.

The technique involves a catheter with a stimulation electrode, introduced into the bladder and connected to the stimulator. Saline (0.9 %) is used as the current leading medium within the bladder. The neutral electrode is attached to the skin in an area with preserved sensation, usually in the lower upper abdomen.

Intravesical electrical stimulation of the bladder (IVES) is still a controversial therapy for patients with neurogenic detrusor dysfunction.

It is worthwhile to apply intravesical electrostimulation, bearing in mind inclusion and exclusion criteria, especially to verify functional afferent fibers within the bladder and the cortex. Intravesical electrotherapy is able to improve neurogenic bladder dysfunction, primarily by stimulating a-delta mechanoaffersents inducing bladder sensation and the urge to void and consequently increasing the efferent output with improvement of micturition and conscious control. Therefore IVES is the only available option to induce/improve bladder sensation and to enhance the micturition reflex in incomplete central or peripheral nerve damage. However, proper indication is crucial and this type of therapy should only be applied in those with afferent fibers between the bladder and the cortex, proved by the evaluation of viscerosensory cortical evoked potentials. If these conditions are respected, IVES can be effective. In ICI 2002 30 studies about IVES have been reviewed. The conclusions for this consultation are not different from what was given in 2002.

Techniques of electrical stimulation involving surgery are to be found in the surgery section.
CONCLUSIONS

- Basic research during the last decade has proved the underlying working concept of IVES (LOE 3)
- The results reported in the literature are controversial, mainly because of different inclusion and exclusion criteria (LOE 3).
- In the only sham-controlled study the treatment period is too short and the inclusion and exclusion criteria are not really defined (LOE 3).
- The alternative may be either life long intermittent catheterization or bladder augmentation. In this regards IVES is cost-effective (LOE 3)

RECOMMENDATIONS

- Intravesical electrotherapy is able to improve neurogenic bladder dysfunction, inducing bladder sensation and the urge to void and consequently increases the efferent output with improvement of micturition and conscious control in patients with incomplete central or peripheral nerve damage. However, proper indication is crucial and this type of therapy should only be applied in those with afferent fibers between the bladder and the cortex, (B/C)
- IVES is the only available option to induce/improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage. (B)
- Selection of patients is crucial and IVES should be applied only if afferent fibers between the bladder and the cortex are still intact and if the detrusor muscle is still able to contract. If these premises are respected, IVES is effective. (B)
- The ideal indication is the neurogenic hyposensitive and hypocontractile detrusor (C)

IV. SURGICAL TREATMENT

1. SACRAL NEUROMODULATION

Literature survey with the words neurogenic bladder; spinal cord injury; spina bifida; meningomyelocele; multiple sclerosis, sacral neuromodulation

Two indications for neuromodulation are clearly valid in urology: urinary incontinence (for overactive bladder syndrome) and chronic urinary retention (aside from vesicosphincteric dyssynergia) [1]. We will not discuss in detail the principles of these treatments and their modalities, which are covered in detail in a specific committee report of this ICI. We will focus solely on the possible application of sacral neuromodulation in patients with neurological bladder dysfunction symptoms.

a) Hypotheses on the modes of action of neuromodulation

The first effects of electricity on the bladder were reported during electro stimulation treatment of pelvic floor muscles (with the aid of electrodes situated in the anus, the vagina, on the penis...) during urinary incontinence reeducation [2-6]. Inhibition of bladder contractions by electrostimulation was seen. Tanagho and Schmidt, the pioneers of neuromodulation, attributed the benefits of neuromodulation in urinary incontinence to a hypertrophy of the pelvic muscles allowing better efficacy and better control [7]. Now, it has long been known that voluntary contractions of the pelvic floor muscles cause a reflex along the somatic afferent branches of the pudendal nerve that leads to relaxation of the bladder. However, such explanation seems simplistic and poorly explains other reported effects of urinary neuromodulation (in the treatment of vesical hypocontractility or pelvic pain). The most widely held hypothesis today is that neuromodulation allows a restoration of normal vesical reflexes [8] [9] [10](LOE4). This hypothesis explains that the stimulation can inhibit the guarding reflex pathway and restore normal urination or turn off supraspinally mediated hyperactive voiding by blocking ascending sensory pathways and therefore decreasing incontinence. The role of cortico-subcortical structures was recently emphasized in studies of incontinent [11, 12] (LOE4) or retentive patients [13](LOE4).
Regardless of the hypothesis authors agree that the somatic afferents are the vectors for neuromodulation signals. Actually, the visceral nerve fibers cannot be activated by the intensities normally used today with this technique [14](LOE4). Despite data obtained in animals [15](LOE4), it seems that neuromodulation cannot be effective in patients with a non functional peripheral nerve circuit.

b) Sacral neuromodulation in the treatment of reflex urinary incontinence in patients with a neurological bladder dysfunction

There is little in the literature concerning sacral neuromodulation (SNM) in this specific indication. Many studies recorded results for incontinence and for retention at the same time, without always separating the results.

Since the technique’s first stages, Vodusek [5, 6](LOE4) reported that non-muscular electrical stimulation of the sacral somatic afferents can induce bladder inhibition in patients who present with detrusor overactivity secondary to a medullar lesion, be it due to trauma or to multiple sclerosis (MS).

Two points must be kept in mind when treating patients with neurological bladder:

- the disappearance of wettings between catheterizations can be considered a success by itself in patients who have already used intermittent catheterization (however, in able-bodied patients treating retention with intermittent catheterization is most often considered a failure);
- On the other hand (especially, for example, in comparison with botulinum toxin injections), neuromodulation does not systematically require the use of intermittent catheterization. If this is the case, then stopping the neuromodulation current quickly causes cessation of bladder paralysis; the treatment’s reversibility is therefore a strong point that must be considered when devising a therapeutic plan.

The main published series are summarized in Table 2. Author definitions for neurological pathology differed widely: some authors considered a history of pelvic surgery as a possible etiology while others included only patients with medullar neurological lesions. Despite this, several points considering the neurological etiology of the bladder dysfunction can be discussed.

A majority of the authors consider that a diagnosis of multiple sclerosis is not a contra-indication for neuromodulation [10, 16, 17](LOE3-4). However, it seems important to propose this treatment only in patients who present with a stabilized form of multiple sclerosis. In addition, patients must be clearly informed that the results of neuromodulation may be altered by the evolution of their underlying illness.

Patients with incomplete medullar lesions, whether of traumatic or other origins, may benefit from neuromodulation [10, 18-23](LOE3-4). On the other hand, all authors agree on excluding patients with complete medullar lesions from neuromodulation’s scope of application. This attitude rests upon a cluster of arguments. First, the presumed modalities of neuromodulation’s actions, such as this, were given above (LOE4). In addition, the clinical data, especially from the Hohenfellner series [20](LOE3), support among others those reported by Schurch et al in 2003 [24](LOE4). These authors published a study in which they recorded external anal sphincter (EAS) electromyographic activity caused by stimulation of the S3 sacral root during a PNE test in three patients who presented with detrusor hyperactivity and vesicosphincteric dyssynergia at the same time secondary to a complete traumatic medullar lesion. They describe a reflex response with early and late latency in the three patients. They also demonstrated that the EAS contraction observed during the PNE represented an indirect motor response mediated by the afferent nerves towards the spinal cord. Despite the recording of an EAS motor response in the three patients, they did not obtain any urodynamic or clinical effect. This suggests the participation of supraspinal neuronal centers—spino-bulbo spinal pathway—in the SMN mode of action. However, these data are contradicted by an experimental study using bilateral neuromodulation in the cat [15] (LOE4).

The use of chronic neuromodulation of the pudendal nerve, appears promising [23] (NP3). Pudendal nerve stimulation and electrode positioning were carried out under neurophysiological monitoring (using a St. Mark’s electrode) in order to guide the electrode in Alcock’s Canal as close as possible to the pudendal nerve. Electrode implantation was carried out by a rear approach under local anesthesia according to the method described by the same authors in 2003 [25, 26]. Naturally, these short term results must be confirmed in a larger prospective patient sample. On the other hand, a recent anatomical study [27] demonstrated that the technique for implanting electrodes at the pudendal level can be slightly risky (NP4).

Guys et al [28] determined sacral neuromodulation results to be encouraging. The authors demonstrated significant but limited urodynamic differences between implanted and children without implant (LOE3). However, the clinical translation of these modifications has not been reported. It must be emphasized that, in the absence of electrodes adapted to child sizes, the study was carried out using an implant that was put in use immediately without a test period. Moreover, the utilization of percutaneous electrodes is no longer possible. This necessitates a surgical placement attaching the electrode to the sacral periosteum. Frequent displacements in adults have been seen. A
Table 2. Results of sacral neuromodulation (test and implantation) in neurogenic patients. NP: Not precised, NA: Not applicable; LOE: Level of evidence MS: Multiple sclerosis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>LOE</th>
<th>Year</th>
<th>n</th>
<th>Follow-up (months)</th>
<th>Neurological Pathology</th>
<th>Type of trouble</th>
<th>Number of patients tested</th>
<th>Test success Criteria</th>
<th>Number of implantation</th>
<th>Success criteria after the implantation</th>
<th>Number or percentage of success after the implantation at the end of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruud Bosch et al [17]</td>
<td>4</td>
<td>1996</td>
<td>5(5)</td>
<td>6</td>
<td>MS 5</td>
<td>Incontinence</td>
<td>NA</td>
<td>&gt;50%</td>
<td>5</td>
<td>&gt;50%</td>
<td>4/5</td>
</tr>
<tr>
<td>Ruud Bosch et al [18]</td>
<td>4</td>
<td>1998</td>
<td>6(6)</td>
<td>24</td>
<td>MS 5</td>
<td>Incontinence</td>
<td>NA</td>
<td>&gt;50%</td>
<td>6</td>
<td>&gt;50%</td>
<td>5/6</td>
</tr>
<tr>
<td>Chartier-Kastler et al [10]</td>
<td>4</td>
<td>2000</td>
<td>9(9)</td>
<td>43,6</td>
<td>MS 5</td>
<td>Incontinence</td>
<td>23</td>
<td>&gt;50%</td>
<td>9/26</td>
<td>&gt;75%</td>
<td>7/9</td>
</tr>
<tr>
<td>Spinali et al [19]</td>
<td>4</td>
<td>2001</td>
<td>196(10)</td>
<td>12</td>
<td>Discal hernia, SCI, Cerebral lesion</td>
<td>Incontinence Retention</td>
<td>NA</td>
<td>&gt;50%</td>
<td>196(10)</td>
<td>&gt;50%</td>
<td>Retention: 66%; Incontinence: 50%</td>
</tr>
<tr>
<td>Hohenfellner et al [20]</td>
<td>3</td>
<td>2001</td>
<td>27(27)</td>
<td>54</td>
<td>SCI 9</td>
<td>Incontinence Retention</td>
<td>27</td>
<td>&gt;50%</td>
<td>12</td>
<td>&gt;50%</td>
<td>1/12</td>
</tr>
<tr>
<td>Scheepens et al [21]</td>
<td>4</td>
<td>2002</td>
<td>211(24)</td>
<td>NA</td>
<td>Incomplete SCI 9, Caudal syndrome, Stroke 3, MS 6, Spina 1</td>
<td>Incontinence</td>
<td>211</td>
<td>&gt;50%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bross et al [22]</td>
<td>3</td>
<td>2003</td>
<td>24</td>
<td>Retention</td>
<td>24</td>
<td>&gt;50%</td>
<td>8/24</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>Guys et al [28]</td>
<td>2</td>
<td>2004</td>
<td>21</td>
<td>Incontinence</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
<td>&gt;50%</td>
<td>NP</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>Spinelli et al [23]</td>
<td>3</td>
<td>2005</td>
<td>15(15)</td>
<td>6</td>
<td>SCI incomplete 7, Various Medullar lesions</td>
<td>Incontinence</td>
<td>15</td>
<td>&gt;50%</td>
<td>12/15</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Wallace et al [16]</td>
<td>3</td>
<td>2007</td>
<td>33(33)</td>
<td>12,4</td>
<td>MS 16, Parkinson, Spina bifida, Stroke 2, Other 6</td>
<td>Incontinence Retention</td>
<td>33</td>
<td>&gt;50%</td>
<td>28/33</td>
<td>&gt;50%</td>
<td>NP (3 neuromodulators removed)</td>
</tr>
</tbody>
</table>
multicenter study on a larger patient population with more severe neurological lesions was done. Essentially, they estimate that the lack of results, especially in the urodynamic study, was due at least in part to the severity of neurological conditions in the population studied.

Despite these encouraging short term results reported by different authors in reflex incontinence secondary to neurological bladder dysfunction, the series published by Hohenfellner et al [20](LOE2) incites some caution. It demonstrates that despite a positive test in about half of the patients tested, long term (54 months) results were poor in almost all patients (1/12 had neuromodulation efficacy).

d) Criteria predictive of successful neuromodulation tests in patients with reflex incontinence secondary to a neurological bladder dysfunction

In 2002 Scheepens et al [21] reported their results of patients tested in their department (six incomplete medullar injuries, five patients with cauda equina syndrome, six with multiple sclerosis, and one with myelomingocele). They found two prognostic factors for poor response (LOE3): The duration of the symptoms (more than seven months in this study) and the existence of a neurological cause for bladder dysfunction. Neurological patients with a very localized and incomplete nervous condition were the most successful. Patients with herniated disc surgery had a greater chance of good response. Patients with complete medullar lesions were a priori poor neuromodulation candidates, as were patients with large sacral lesions.

In general, it is the conviction that urodynamic tests carried out when the electrode is placed are not of value for predicting neuromodulation results. Moreover clinical results of neuromodulation do not necessarily correlate to urodynamic results. Bosch indicated in his series [18] that almost half of the patients considered to have been cured kept a certain degree of bladder overactivity. Essentially, the only publication to find parallelism between urodynamic test data and clinical data was carried out only on injured patients with a neurogenic bladder [10](LOE4). In this particular subgroup of patients, urodynamic monitoring during the acute test may have a benefit. In 2001 Chartier-Kastler [29] et al published the results of a prospective study (NP2) concerning the evolution of urodynamic parameters during the acute phase of the PNE test in 14 patients who presented with a neurogenic detrusor hyperactivity (DH) with UUI (urge urinary incontinence). The authors concluded that the acute phase of PNE was accompanied by a significant change in urodynamic parameters in more than 2/3 of the patients, and that this should be a possible means for selecting patients who present with neurogenic DH who are likely to benefit from the PNE chronic phase. However these promising results are not as yet confirmed.

e) Neuromodulation results in patients with urinary retention in patients with a neurological bladder dysfunction

There are less publications on the urinary retention (especially Fowler’s syndrome) than on urinary incontinence [22, 30-33].

The only study which reported specific results for neurogenic bladders is from Hohenfellner et al [20](LOE3), in which a subgroup of 11 patients had bladder retention problems. Of these patients, three were implanted and there were temporarily satisfactory results in only two. Several years previously the same author published an interesting study on the benefit of bilateral pudendal neuromodulation, especially in patients with urinary retention [34](LOE4). The preliminary results did not appear to have been confirmed in the long term.

It seems that neuromodulation has a marginal place in retention patients with neurological bladder. Patients need to be clearly informed of the high risk of failure. It is also necessary to be especially prudent in patients with cauda equina sequel, who may have the illusion of recovering urination by simply making a greater abdominal push to evacuate their bladder. In reflex incontinence, patients with complete spinal cord or cauda equina lesions are poor candidates (LOE4).

Before attempting sacral neuromodulation, patients also have to be informed that intermittent self-catheterism remains the best therapeutic option in the case of urinary retention in patients with a neurological bladder dysfunction.

RECOMMENDATIONS

• Sacral neuromodulation can have an inhibitory effect on neurological detrusor hyperactivity. (C)

• While sacral neuromodulation has a place in the care of neurological urinary incontinence or neurological urinary retention, the proportion of patients whose condition is improved is much less than in non-neurological pathologies (B).

• The definition of the best indications for sacral neuromodulation (neurological illness) in the care of vesicosphincteric dyssynergia in neurological bladders is still imprecise (D).

• Utilization of neuromodulation in neurology presupposes a urodynamic evaluation and carrying out a clinical test under sacral electrode (C).

• New neuromodulation techniques may allow further improvement of results from the use of neuromodulation in neurology (medial pudendal nerve or pudendal nerve) (D).
2. SURGERY FOR INCONTINENCE ASSOCIATED WITH POOR BLADDER EMPTYING DUE TO DRETRUSOR UNDERACTIVITY

Search for neurogenic bladder; spinal cord injury; spina bifida; myelomingingocele; multiple sclerosis; sphincterotomy; stent

Introduction

In some cases, incontinence in neurological patients can be aggravated by deficient bladder emptying and retention. Two mechanisms can be involved: detrusor sphincter dyssynergia (DSD) or bladder hypotonicity. This chapter focuses on alternatives that could be proposed to the patient in this situation, when conservative management fails.

a) Surgical treatment of detrusor external sphincter dyssynergia

Detrusor sphincter dyssynergia (DSD) is a characteristic feature of suprasacral and infrapontine lesions.

The aim of sphincterotomy is to produce reflex micturition into a condom catheter, thus protecting the upper urinary tract. For the last thirty years, endoscopic sphincterotomy has been the technique of choice for patients who cannot or do not want to do clean intermittent catheterization. It is invasive, irreversible and the patient has no adaptation period [1, 2](LOE3). This explains the recent development of prosthetic sphincterotomy using a urethral endoprosthesis (or stent).

1. INDICATIONS AND CONTRA-INDICATIONS OF SPHINCTEROTOMY

Indication supposes a diagnosis of a neurological cause of DSD that is complicated by hydronephrosis, vesico-urethral reflux, autonomous hyperreflexia or repeated urinary infections secondary to poor bladder voiding. Patient should have failed or refused intermittent catheterism.

2. MAIN CONTRA-INDICATIONS ARE [3, 4]:

- Impossibility to retain a condom catheter. All sphincterotomy techniques, including stenting, are contra-indicated for men who cannot retain a condom catheter (and a fortiori for women). A semi-rigid penile prosthesis can be placed to help retain the condon catheter [5](LOE3). However, patients must be informed that there is a 20% to 30% risk of erosion and infection of the penile prosthesis for those with spinal cord injury, as opposed to only 2.7% in the general population [6, 7] (LOE3).

- Detrusor acontractility or hypocontractility. Patients with spinal cord injury and no reflex detrusor contraction during urodynamic tests are poor candidates for the various techniques of sphincterotomy.

- Patients who wish to father children and are candidates for vibro/electro-ejaculation and an artificial insemination program.

3. ENDOSCOPIC SPHINCTEROTOMY

Emmett [8] first described endoscopic sphincterotomy in 1948. He performed cervico-prostatic incisions in patients with spinal cord injury, but later realized that the problem lay in the striated sphincter. External sphincterotomy was performed in 1958 by Ross et al. [9]. They carried out heavy cold-blade surgery and placed a catheter (CH 22 to 26) for tamponade since nearly all patients required transfusion (one of the ten patients in the series died after surgery).

A few attempts at surgical sphincterotomy via the perineal and subpubic myotomy routes were tried later. The complexity of these interventions, together with frequent and serious complications, explains why they were abandoned [10] [11]. Spincterotomy with electrocoagulation was finally found to be the best technique.

a. Endoscopic sphincterotomy morbidity

The most frequent morbidity is post-operative hematuria which can be abundant and sometimes difficult to control, requiring transfusion in 2-13% of patients (see Table 3, LOE2-3). Twelve o’clock sphincterotomy seems to offer the lowest risk of hemorrhage, with three and nine o’clock sphincterotomies entailing the highest risk [12] (LOE4).

Post-operative impotence is also a common complication. Rates of up to 56% were reported in early series [13-16](LOE3). More recent series (table1, LOE 2-3), most using a median, or slightly deviated incision, have not seen an affected sexual function. However, it should be noted that the population concerned may have many other reasons (neurological, psychological, etc.) for suffering from erectile dysfunction.

When sphincterotomy is accompanied by complete incontinence there are obvious reasons for psychological difficulties during intercourse. This issue must be discussed with the patient before surgery. In our experience, the fear of this sequel sometimes causes the patient to decide against surgery and is a reason why we propose incontinent prosthesis as first-line therapy, to enable the patient to simulate the effects of surgery.

If striated sphincter section fails, the patient must be checked and the possibility of bladder neck sclerosis investigated. Depending on the particular series, this problem is seen in from 2 to 21% of patients. Section of the bladder neck may then improve voiding, but will result in permanent incontinence. Before surgery, the surgeon must make sure that the patient accepts this situation and can use a condom catheter.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number patients</th>
<th>LOE</th>
<th>Mean Follow-up (months)</th>
<th>Success criteria</th>
</tr>
</thead>
</table>
| Chancellor et al. 1999 [40] | 26              | 2   | 24                      | - PVR decrease 
- Hydronephrosis, VR reflux decrease (100%, 100%) 
- Improved micturition comfort (80%) 
- Improved autonomous hyperreflexia (100%) |
- Decrease in infections (74%) 
- Decrease in hydronephrosis, reflux (66%, 40%) 
- Improved autonomous hyperreflexia (100%) |
| Perkash et al. 1998[42]  | 37              | 2   | 9                       | NK                                                                               |
| Fontaine et al. 1996[50] | 92              | 2   | 20.6                    | - Decrease in hydronephrosis, reflux (100%, 90%) 
- Significant decrease in PVR, micturition pressure 
- Decrease in infections (74%) 
- Improved micturition comfort (73%) 
- Improved autonomous hyperreflexia (93%) |
| Noll et al. (1995) [1]   | 105             | 3   | 59                      | No statistical study, but: 
- Improved autonomous hyperreflexia (42 to 17%) 
- Decrease in mean PVR (180 to 70 ml) 
- Decrease in micturition pressure (from 97 to 37 cm H2O) 
- Decrease in frequency of symptomatic urinary infections (8.1 to 3.6 per year) |
| Rivas et al. 1995 [41]   | 22              | 2   | 12                      | - Improved autonomous hyperreflexia (44%) 
- Significant decrease in PVR, micturition pressure 
- Decrease in hydronephrosis (40%) |
| Riccotone et al. 1995[19]| 11              | 3   | 121                     | - 91% recovery from autonomous hyperreflexia 
- 82% patients needed at least one repeated sphincterotomy |
| Juma et al. 1995 [2]     | 63              | 3   | 132                     | - Renal function (creatinine): normal in 97% of patients 
- on X-ray, 30% of patients showed upper urinary tract impairment. 
- 2/3 patients had more than one sphincterotomy |
| Vapnek et al. 1994[18]   | 16              | 3   | 39                      | - 31% required repeated sphincterotomy 
- 50% failure rate (sub-pubic catheter placed) |
| Namiki et al. 1984[51]   | 9               | 4   | 3                       | - PVR < 50 (100%)               |
| Ruuru et al. 1982[52]    | 11              | 4   | NS                      | - Subjective improvement in micturition comfort (56%) 
- Improved autonomous hyperreflexia (100%) |
| Carrion et al. 1979 [53] | 60              | 3   | 12                      | - Reflux disappeared (86%) 
- Significant decrease in reflux: 75% |
b. Results of endoscopic sphincterotomy

Results are summarized in Table 2 (LOE2-3). Any analysis is made difficult by the absence of univocal criteria of success. Some patients are improved by sphincterotomy, even with a 200 ml residue. Most authors use indirect urodynamic criteria to evaluate success (decrease in bladder pressure during micturition, decrease in PVR). The most obvious result is the improvement in autonomic dysreflexia observed in tetraplegic patients. It also appears that the intervention reduces the rate of symptomatic urinary infections. However, the patient must be informed that surgery will not prevent the chronic bacteriuria so often suffered by these patients [17]. The reported results concerning resolution of hydronephroses and vesicorenal reflux differ, and in each series, there are very few patients. Another essential point, well known in practice but rarely reported, is the recurrence of neurogenic DSD in many patients [2, 18, 19] (LOE3). Riccotone et al (LOE3) [19] reported 82% recurrence of symptoms after ten years of follow-up. Juma et al [2] (LOE3) report similar results after eleven years, with patients undergoing an average of 1.7 sphincterotomies, and about 30% of patient having some impairment of the upper urinary tract. Patients who have undergone this surgery must therefore be regularly monitored to detect any distension of their upper urinary tract.

4. PROSTHETIC SPHINCTEROTOMY

In 1990, Shaw et al. were the first to propose using a wire mesh stent (Urolem™) to treat patients with spinal injury presenting with DSD [20] (LOE3). Since then, various stents have been used.

Table 4 lists the types of stent used for DSD, according to classification criteria [21, 22].

They can be placed in various sections of the urinary tract: prostatic urethra, through the striated sphincter or more distal in the sub-sphincteric urethra. Our review is limited to placement through the striated sphincter for which there are two solutions: temporary or permanent stents.

a. Temporary prosthetic sphincterotomy

Temporary stents make it possible to carry out a therapeutic test to check the feasibility of condom catheterization, check that placing a foreign body in the urethra does not induce autonomic dysreflexia and ensure the patient accepts the mode of micturition. Moreover, during this trial period, it is possible to study how the bladder empties in the seated position, assess the necessity of a combined treatment for smooth muscle sphincter dyssynergia at the level of the bladder neck. Moreover, as this treatment is simple and reversible, it is possible to propose it very early to the patients, rendering the patient autonomous with regard to carer-assisted catheterization, if this were the prior mode of micturition and leaving the possibility to discuss any fertility and sexual issues, and considering the possibilities of preserving sperm.

Finally, for patients with spinal cord injury, the aims of early temporary stent placement (within six months of trauma) are as mentioned above, but with the

Table 4. Urethral stents used in neurogenic DSD

<table>
<thead>
<tr>
<th>Type of stent</th>
<th>Expansion method</th>
<th>Size</th>
<th>Material</th>
<th>Maximal duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary stents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not specific to the striated sphincter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urospiral™ [54]</td>
<td>Non-expandable</td>
<td>21</td>
<td>Stainless steel</td>
<td>&lt;12</td>
</tr>
<tr>
<td>IUC™ [55]</td>
<td>Non-expandable</td>
<td>16-18</td>
<td>Polyurethane</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Second-generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memokath™ [56]</td>
<td>Heat</td>
<td>22/34</td>
<td>Nitinol</td>
<td>&lt;36</td>
</tr>
<tr>
<td>Specific to the striated sphincter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabolo™ [23]</td>
<td>Self-expansion</td>
<td>18</td>
<td>Medical steel</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Permanent stents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urolem™ Wallsten® [57]</td>
<td>Self-expansion</td>
<td>42</td>
<td>Steel alloy</td>
<td></td>
</tr>
<tr>
<td>Titan™ [58]</td>
<td>Balloon</td>
<td>43</td>
<td>Titanium</td>
<td></td>
</tr>
<tr>
<td>Memotherm™ [59]</td>
<td>Heat</td>
<td>42</td>
<td>Nitinol</td>
<td></td>
</tr>
<tr>
<td>Ultraflex™ [60, 61]</td>
<td>Self-expansion</td>
<td>42</td>
<td>Nitinol</td>
<td></td>
</tr>
</tbody>
</table>

835
theoretically added advantages of waiting for recovery of upper limb motility to enable self-catheterization, decrease the risk of nosocomial infection during rehabilitation by reducing carer-assisted catheterization, and relieve nursing load during rehabilitation. The last two points, though logical, are yet to be proved by relevant studies. After using a temporary stent, the patient may choose his mode of micturition; i.e., return to his former state, change to an identical stent, depending on the known life span of the temporary stent, replace by a permanent stent or choose surgical sphincterotomy.

By definition, temporary stents should be self-retaining, easy to remove and must not epithelialize. Apart from the temporary stent Diabolo™, which is under assessment [23], no temporary stent is specific for the external urethral sphincter. The results of two types of temporary stenting (test) for incontinence have been published in the same series[24] (LOE3). In a retrospective study of 147 patients, the authors demonstrated a significant effect on incontinence throughout the mean ten month test period, with very low morbidity (15%). The temporary stents were removed easily from all patients without sequellae. After this period, 62.6% of patients chose permanent sphincterotomy, usually by means of a permanent stent. During the study, the authors abandoned the first used stent (Nissenkorn™), preferring a temporary stent currently being developed, Diabolo™.

Memokath™ stent is another device that has been studied in neurological patients[25-29](LOE3-4). Several authors report complications (38-100%) using this stent, which seems to induce a lot of bladder stones and to be quite difficult to remove especially if it is left longer than 18 months.

b. Permanent prosthetic sphincterotomy

Permanent stents are designed to integrate the urethral wall [30]. They resist the striated sphincter and prevent it closing during reflex contraction. They can be removed if necessary, or at the patient’s request, with recovery of striated sphincter contraction [31, 32].

Permanent stents are made of biocompatible materials such as nitinol (a nickel and titanium alloy) and titanium. They usually consist of a mesh comprising a single (Urolume™) or several threads (Ultraflex™). None of the stents are specifically adapted for the urethral striated sphincter. Three have been reported for treating neurological patients with DSD: Urolume™, Memotherm™ and Ultraflex™. All can be placed under local anesthesia. Table 5 summarizes the principal series published on these devices. Only Urolume™ was studied according to strict prospective criteria [17](LOE1-2). Using stringent clinical and statistical methods, they classified the stent as LOE 1 for effectiveness and morbidity in DSD with a 5-year follow-up. 160 patients with spinal cord injury (mean age: 36.3 years; standard deviation = 12.1 years) in 15 North American centres, were treated prospectively with Urolume™ for DSD. Urodynamic parameters for micturition pressure, PVR and functional bladder capacity were measured before treatment and then 1, 2, 3, 4 and 5 years afterwards. Mean micturition pressure, the primary criterion, was significantly lower

<table>
<thead>
<tr>
<th>Authors</th>
<th>Stent</th>
<th>Year</th>
<th>LOE</th>
<th>n</th>
<th>Efficacy (%)</th>
<th>Mean follow-up (Months)</th>
<th>Complications</th>
<th>Migration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta [27]</td>
<td>Memokath</td>
<td>2006</td>
<td>3</td>
<td>29</td>
<td>89</td>
<td>21</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>Vaidyanathan [29]</td>
<td>Memokath</td>
<td>2002</td>
<td>4</td>
<td>10</td>
<td>90</td>
<td>20</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Low [26]</td>
<td>Memokath</td>
<td>1998</td>
<td>3</td>
<td>24</td>
<td>54</td>
<td>16</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Denys [61]</td>
<td>Ultraflex</td>
<td>2004</td>
<td>3</td>
<td>47</td>
<td>81</td>
<td>19</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Juan Garcia [62]</td>
<td>Memotherm</td>
<td>1999</td>
<td>3</td>
<td>24</td>
<td>100</td>
<td>15</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Rivas [38]</td>
<td>Urolume/</td>
<td>1994</td>
<td>2</td>
<td>46</td>
<td>79</td>
<td>16</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>vs sphincterotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chancellor [17]</td>
<td>Urolume</td>
<td>1999</td>
<td>2</td>
<td>160</td>
<td>84</td>
<td>60</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Chancellor [40]</td>
<td>Urolume/</td>
<td>1999</td>
<td>1</td>
<td>54</td>
<td>81</td>
<td>24</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>vs sphincterotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamid [63]</td>
<td>Urolume</td>
<td>2003</td>
<td>3</td>
<td>12</td>
<td>77</td>
<td>144</td>
<td>NR</td>
<td>16</td>
</tr>
</tbody>
</table>
5 years after stenting. PVR decreased significantly and was maintained after 5 years. Mean bladder capacity remained constant. Hydronephrosis, suffered by 28 patients before surgery, disappeared in 22 (78.6%) and was improved in the others. Autonomic hyperreflexia resolved in 70% of cases. The indwelling catheters of 63 of the 86 (74.4%) patients catheterized before surgery could be removed. The percentage of positive urine cultures remained unchanged after stenting. No case of peri- or post-operative bleeding, soft tissue erosion or bladder lithiasis were observed during the study. One case of prosthetic incrustation occurred during the first year; three during the second year; three during the third year; two during the fourth year and five in the fifth year. Urothelial reaction was reported in 44.4% of cases, but 93.3% of these were mild and none required treatment. No erectile dysfunction was reported. Stents had to be removed from 24 patients (15%), four of whom received new implants. 80% of the patients considered their situation improved by stenting, and 84% of physicians considered the treatment effective. 47 patients required supplementary treatment on the bladder neck (endoscopic section in 20 cases). In the mid-term, prosthetic sphincterotomy using a Urolume™ stent appears to be satisfactory. However, over the long-term, the situation is not so clear. It is not always easy to remove the stent, especially from patients who have not been monitored regularly. Some teams report highly complex surgery for stent removal, especially in the event of associated urethral stenosis [33-36] (LOE3).

5. SHOULD PATIENTS BE OFFERED PROSTHETIC OR ENDOSCOPIC SPHINCTEROTOMY?

Endoscopic sphincterotomy is the preferred standard treatment for DSD, where clean intermittent catheterization cannot be performed. The superiority of a new procedure can only be demonstrated by a randomized clinical study with sufficient follow-up. Two prospective studies were carried out in the US in 1994 by Rivas and Chancellor and indicated that prosthetic sphincterotomy was at least as effective as standard sphincterotomy in patients with spinal cord injury, and offered advantages in terms of morbidity, duration of hospitalization and cost [37, 38]. The two studies were not randomized. Follow-up was too short (mean: 15 months), introducing a bias in the case of Chancellor’s study. He concluded that external sphincter balloon dilatation was as effective as endoscopic and prosthetic sphincterotomy. After sufficient follow-up, external sphincter balloon dilatation was abandoned because it was ineffective in the long-term [39].

A prospective, multicenter, randomized study comparing endoscopic sphincterotomy with prosthetic sphincterotomy was published in 1999 by Chancellor and Rivas, using the Urolume™ stent [40]. Fifty-seven patients in three specialist spinal cord injury centers were included. The study concluded that prosthetic sphincterotomy was as effective as endoscopic sphincterotomy and required shorter hospitalization. As we have already reported, these findings are relevant only for the short and medium-term. The long-term outcome of prosthetic sphincterotomy for incontinence remains unreported. At present, it is vital that stented patients be monitored carefully at least once a year during the years following implant surgery.

6. OTHER SPHINCTEROTOMY TECHNIQUES

As well as prosthesis placement, alternative techniques to surgical sphincterotomy have been reported.

Two authors reported using Nd-YAG lasers for sphincterotomy [41, 42]. Although no randomized study has been conducted, comparison with results from the literature (with very short follow-up), suggests that these techniques are not as good as standard endoscopic sphincterotomy. However, the reported morbidity (particularly hemorrhage) was reduced (LOE2).

External sphincter balloon dilatation was recommended by Chancellor et al. [37], with short-term results similar to those of surgical sphincterotomy. However, the technique has been abandoned by its sponsors and the device has not been distributed, probably indicating poor efficacy in the medium and long-term, compared with other mini-invasive methods such as stenting.

RECOMMENDATIONS

- Where clean intermittent catheterization is not possible, the long-term use of indwelling catheters should be avoided (B).
- Whatever type of sphincterotomy is chosen (surgical or prosthetic):
  - Patients must think carefully about the different modes of micturition possible for them (A).
  - The few studies reporting long-term results of sphincterotomy demonstrate the vital importance of regular patient monitoring for the recurrence of DSD or blockage (B).
  - This mode of micturition is contra-indicated in women and men with acontractile bladder and difficulty in maintaining a condom catheter (B).
  - Men who wish to have children should be warned of the risk of ejaculatory duct obstruction (B).
- For patients who have chosen surgical sphincterotomy:
  - The reference technique involves an elective 11, 12 or 1 o’clock incision of the urethral sphincter (B).
b) Surgery to increase detrusor strength

For some patients, the cause of bladder hypocontractility lies in the bladder wall. In this case, the control circuit functions but the bladder muscle is too weak. At present there is no medical treatment for this situation. The general objective is to reduce peripheral resistances as much as possible and wherever this fails, to propose intermittent catheterization.

However, over recent years, some teams have suggested placing rolled strips of muscle around the bladder. Some authors have also suggested a strip of rectus abdominus muscle. This is easier to perform and may be used essentially for reconstructive surgery, such as bladder extrophy [43-45] (LOE4). The only team to have published results on bladder hypocontractility in man is that of Ninkovic et al. [46] (LOE2). They recently reported interesting results from twenty patients suffering from bladder hypocontractility of neurological origin and requiring self-catheterization. They reported a technique that they had designed in animal experiments [47, 48] (LOE4) and which consisted of transferring a free strip of great dorsal muscle, which was anastomosed to the epigastric vessels and the lowest branch of the intercostal nerve. Out of twenty patients, with a mean follow-up of 44 months, 60% no longer required self-catheterization, with PVR below 100 ml. After complementary surgery on the bladder neck, there was a 90% success rate that was stable over time. The authors reported no heavy morbidity, particularly with regard to the donor site. Other teams need to confirm these results, but it appears to be a very promising approach. Future development could use tissue-engineering techniques to construct vascularized and contractile strips implanted around the bladder with the same procedure.

RECOMMENDATIONS

The use of a free strip of great dorsal muscle on the bladder is a promising technique that needs to be validated further (D).

3. DENERVATION PROCEDURES FOR TREATING REFLEX URINARY INCONTINENCE DUE TO DETRUSOR OVERACTIVITY

a) Introduction

Neurosurgery has a particular role in the management of neurogenic detrusor overactivity [1]. Many different procedures have been described: open surgery for complete or partial rhizotomies (radicotomies) (ventral or dorsal), selective or otherwise. Direct injection of various neurolytic substances has also been suggested. In this part, we consider the main series reported in the literature and will briefly describe the various possible options together with their functional effects and long-term results.

b) Peripheral bladder denervation

The most popular technique today is the injection of botulin toxin which is dealt with also elsewhere in this report. Various techniques of peripheral bladder denervation, such as prolonged hydrodistension or bladder transsection, are no longer used. Some authors have reported transient improvement in certain patients after prolonged hydrodistension, but unfortunately detrusor overactivity recurs rapidly and the procedure is not quite so simple. Moreover, there are no reports for patients presenting specifically with neurogenic detrusor overactivity [2]. Bladder transsection was briefly popular at the end of the 70s [3-5]. It involved complete section of the bladder wall from one urinary meatus to the other. The technique was indicated essentially for urge incontinence and pollakiuria, and rarely in the context of detrusor overactivity. However, a lack of anatomical and physiological information to support the mechanisms of efficacy of the procedure, and a lack of reproducible results from the initial series, explains why it is no longer used.

Another bladder denervation technique was developed by Ingelman-Sundberg [6, 7] (resection of the inferior hypogastric plexus in contact with the bladder). The procedure is technically simple and can be performed under local anesthetic. The surgeon makes an inverted U-shaped vaginal incision in contact with the trigone and dissects the bladder both laterally and posteriorly,

- Although surgical sphincterotomy is the accepted reference treatment for neurogenic DSD, analysis of the literature highlights the lack of reliable efficacy and reproducibility criteria for the technique (B).
- For patients who have chosen prosthetic sphincterotomy:
  - Different types of stent are used, depending on whether sphincterotomy is temporary or permanent. Stents are complementary, and different designs can be used for different situations (B).
  - Surgical complications depend as much on the surgeon’s competence as on the material and may be reduced by experience (C).
  - Clinical studies have demonstrated that neurogenic patients prefer prosthetic sphincterotomy because it is reversible, even when permanent stents are placed (C).
  - Careful follow-up, using yearly cysto/urethroscopy is mandatory when leaving a permanent urethral stent (B).
and as widely as possible. After dissection, the vaginal mucosa is simply closed in one plane by separate sutures. In the most recent paper [6], the authors report up to 54% recovery over a mean follow-up of about three years. However, it should be noted that each published series is from the same group, is always retrospective, the sample size was small (LOE4). Moreover, the technique is said indicated more often for urge incontinence and pollakiuria than for neurogenic detrusor overactivity. However, we mention it here because of its simplicity and the few reported complications.

c) Sacral root surgery

1. Isolated rhizotomy of ventral and/or dorsal sacral roots

Historically, attempts at sacral root surgery first focused on destroying the motor (ventral) sacral roots. Despite various technical artefacts, it was soon clear that this method failed within three to six months.

With a slightly different objective, Brindley [8] developed a technique involving stimulation of ventral sacral roots to obtain controlled and complete bladder voiding in cases of spinal cord injury. He quickly realised that patients only acquired continence if the stimuli causing reflex bladder contraction could be destroyed [9]. Early techniques consisted in selective destruction of the dorsal sacral roots that produce peri-operative detrusor contractions. These selective rhizotomies did not, however, give the best results. Only after complete de-afferentation of the sacral micturition centre by intradural rhizotomy were better results obtained [10-13] (LOE2-3).

Sacral root surgery may be envisaged for patients who cannot undergo electrostimulation of the anterior sacral roots (evolutive diseases such as MS, patients who cannot mount toilets, etc.).

The technique of “selective” dorsal sacral rhizotomy has been studied more extensively. It involves, as described above for Brindley’s technique, making an extra-dural approach to the sacral roots (S2 to S5), isolating and stimulating the dorsal (sensitive) contingent whilst monitoring any changes in urodynamic pressure within the bladder in order to section only those fibres responsible for hyperactivity. To retain reflex erection, S2 must be preserved, at least on one side. This treatment may be proposed for patients with neurogenic detrusor overactivity, and also those with urge incontinence/pollakiuria (this is important since results are more difficult to evaluate in these patients). The literature records only case series without control groups. Preliminary results were promising but were based on a small number of cases with short follow-up times [14-16] (LOE4). The outcome seemed to deteriorate over time. Opsomer et al. [17] reported deterioration after one year for all their eight patients (LOE4). Torrens, one of the first to use the technique, was led to re-evaluate his long-term results [18]. The most recent article by Lucas et al. [19] concerning 22 patients (LOE3), also reported a significant, but less marked, deterioration at four years. At this mean follow-up interval, 39% of patients retained a urodynamically stable bladder with satisfactory clinical response. The authors ascribe these improved results to a more extensive rhizotomy. However, it should be noted that there was a marked heterogeneity of patients in this series, three out of the eight, considered to be “successes”, were patients with leakage due to detrusor overactivity with an indwelling catheter.

A recent original approach to ablative mini-invasive surgery to treat neurogenic reflex urinary incontinence due to detrusor overactivity was reported by Mertens et al. [20]. It consisted in applying a technique used for limb spasticity, microsurgical DREZotomy. The aim is to destroy the dorsal root entry zone (DREZ). This zone, first defined in 1972 by Sindou [21], is a functional anatomical entity that groups together the proximal portion of the dorsal root, the medial portion of the dorso-lateral tract and the superficial layers of the dorsal horn. The technique involves making a micro-surgical lesion (by micro-coagulation) on the ventro-lateral portion of the entry zone, near the apex of the dorsal zone. The effect of DREZotomies is to selectively block nociceptive afferents, and their relays, and myotatic afferents. The procedure blocks the afferents of the mono and polysynaptic reflexes. The benefit of the limited lesion is to avoid complete abolition of tactile and proprioceptive sensitivity and to prevent the development of deafferentation phenomena. To treat neurogenic detrusor overactivity, the lesion must be made on both sides from S2 to S3 or even S4, according to the case. The results from the first series concerned 38 patients treated for incapacitating lower limb spasticity, treated by extended DREZotomy from L2 to S1. It should be noted that 58% of these patients were permanently catheterized. At six months, detrusor overactivity had disappeared in 82% of these patients, with 63% having significantly improved bladder capacity. At 18 months post-surgery, leakage had disappeared in 89% of cases.

Hohenfellner [22], following Brindley’s experience, proposed “neurogenic bladder augmentation” in certain cases. This involved completely destroying the ventral and dorsal sacral roots, possibly followed by continent cystotomy and simplified urinary catheterization. The author reported his experience with eight patients retrospectively (LOE3). After surgery in all patients, bladder capacity increased from about 177 ml to 670 ml, with complete disappearance of detrusor overactivity. Interestingly, continent vesicostomy was proposed to four patients. If these outcomes persist for the long-term, and if no serious (particularly trophic) complication occurs, this therapeutic option could be an alternative to augmentation enterocystoplasty.

2. Percutaneous sacral root block

Sacral root block is an old technique, since Dogliotti [23] proposed it as early as 1931 to relieve vertebral cancer pain by chemically sectioning several dorsal
roots. An injection of alcohol causes denervation due to the fragmentation of myelin in the endoneurium. In the 1950s, Bors [24] applied the technique to the bladder, standardized the procedure and described preliminary results. Later authors reported on a few series (LOE3) [25, 26], but always with the same result; the benefit disappeared after a few months; an example of neurological plasticity. Phenol, considered to be “selective” for C fibers was then tried but the results were no better [27-29].

Chemical destruction of the sacral nerve roots has proved ineffective and is accompanied by a high rate of minor complications (pain), requiring prolonged hospitalization and significant discomfort (LOE3)[25, 26]. Recently, Mulcahy et al. [30] proposed sacral rhizotomy by percutaneous radiofrequency for neurogenic bladder (LOE4). The initial results are interesting but no medium and long-term results have been published.

3. RHIZOTOMY OF POSTERIOR SACRAL ROOTS AND STIMULATION OF THE ANTERIOR SACRAL ROOTS

Electrostimulation to improve micturition in patients with spinal cord injury has been extensively researched since 1954. Direct stimulation of the detrusor, the spinal cone, the splanchnic and sacral nerves have not produced reliable results. Since 1969, G.S. Brindley has developed a set of electrodes for stimulating the spinal roots in the cauda equina. The technique, first tested in baboons, led to the development of an implanted stimulator to induce micturition in paraplegic patients. Sacral rhizotomy performed during implant surgery makes it possible to control bladder hyperactivity and ensure continence.

The equipment comprises two elements. The energy source and the microprocessor for adjusting the stimulation parameters are not implanted. The transmitter transforms the electric current from the energy source into electromagnetic waves, which are picked up by the implanted receptor and re-transformed into an electric current that circulates to the electrodes in contact with the nerve. Depending on the surgeon’s decision, the implant is placed within the membranes of the dura mater or outside them, so as to stimulate the sacral roots from S2 to S4. At the same time, it is essential to perform posterior rhizotomy from S2 to S4 to remove any detrusor overactivity.

Micturition is not continuous: the detrusor cannot be stimulated without also stimulating the sphincter. The parasympathetic fibers and the fibers destined for striated muscles are stimulated together. The response of detrusor smooth muscle fibers causes a gradual increase in pressure, which continues after stimulation has ceased. The “on-off” response to stimulation of striated muscle fibers is different. When stimulation stops, the striated sphincter immediately relaxes, whilst the detrusor continues to contract. A new wave of stimulation increases and maintains sufficient detrusor pressure to cause micturition after stimulation stops. The careful selection of stimulation and stopping times results in a discontinuous, but satisfactory, micturition. Neurotomy of the somatic fibers destined for the striated sphincter is difficult to perform [31](LOE4). Sphincter fatigue due to electrical stimulations, blocking of pudendal nerve motor fibers [32](LOE4) or use of specific detrusor stimulation by performing an anodal block [33] (LOE 4) have been reported, together with poor efficacy.

Stimulation can help defecation and erection, but it should be remembered that the principal object of sacral nerve stimulation combined with posterior rhizotomy is to achieve urine continence and bladder voiding. Erection is a secondary benefit but not an indication for the procedure.

Not all patients may benefit from this surgery. It can only be performed in those with spinal damage who are para- or tetraplegic. The sacral reflex arc must be preserved. Without going into further detail concerning indications for surgery, alternative less aggressive treatments should be preferred. As previously stated, men about to undergo this surgery should be warned that they would lose reflex erection after posterior rhizotomy (although this could be compensated by erection obtained with another set of parameters using sacral anterior root stimulation).

The results of the intervention are summarized in Table 6. Briefly, the outcome with regard to continence and bladder voiding are good (LOE 2-3). Failures result from incomplete rhizotomy, where bladder hyperactivity persists, or from sphincter insufficiency which may be treated by complementary surgical placement of an artificial sphincter [12, 13](LOE3). Incomplete rhizotomy can be surgically repaired [12, 13, 34] (LOE 2-3). In all reported series, mean bladder capacity increased significantly (LOE 2-3). Micturition was obtained by electrostimulation with a post-voiding residue (PVR) of ≤ 50 ml in 69 to 100% of patients. All series reported decreased incidence of urinary infection, but the defining criteria were too varied to allow conclusions to be drawn. Within the limits of a relatively short mean follow-up, it appears that this surgery preserves the upper urinary tract. Posterior sacral rhizotomy probably protects the upper urinary tract from detrusor overactivity. It can solve the problem of pre-operative reflux [34, 35](LOE4). However, posterior sacral rhizotomy should be complete. Indeed, in a series of 500 patients, Brindley [34] (LOE3) reported twelve cases of impaired upper urinary tract, ranging from grade I reflux to upper urinary tract dilation. Amongst these twelve patients, ten had undergone partial or sacral rhizotomy.

The results of the sacral anterior root stimulation on autonomous hyperreflexia (AHR) may be debated. The authors of many studies report a decreased AHR. Schurch [36] focused on the specific problem of AHR and recorded its persistence during stimulation in all patients who had suffered prior to surgery, but with marked improvement in symptoms.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient numbers</th>
<th>Sex ratio (M/F)</th>
<th>LOE</th>
<th>Mean follow-up (extremes)</th>
<th>Pre-op. continence (%)</th>
<th>Post-op. continence (%)</th>
<th>Pre-op. bladder capacity (ml)</th>
<th>Post-op. bladder capacity (ml)</th>
<th>% complete micturition (PVR &lt; 50 ml)</th>
<th>Pre-op. AHR (%)</th>
<th>Post-op. AHR (%)</th>
<th>Pre-op. urinary infections (%)</th>
<th>Post-op. urinary infections (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brindley et al. (1994)[34]</td>
<td>500</td>
<td>271/229</td>
<td>3</td>
<td>4 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barat et al. (1992)[37]</td>
<td>40</td>
<td>26/14</td>
<td>3</td>
<td>2 years</td>
<td>2.5</td>
<td>90</td>
<td>210 (50-500)</td>
<td>463 (200-600)</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Van Kerrebroeck et al. (1996)[38]</td>
<td>52</td>
<td>29/23</td>
<td>3</td>
<td>3.5 years</td>
<td>81</td>
<td>285</td>
<td>592</td>
<td>87</td>
<td>14</td>
<td>4</td>
<td>4.2/year</td>
<td>1.4/year</td>
<td></td>
</tr>
<tr>
<td>Schurch et al. (1997)[36]</td>
<td>10</td>
<td>3/7</td>
<td>3</td>
<td>3.4 years</td>
<td>0</td>
<td>80</td>
<td>160</td>
<td>&gt; 500 ml</td>
<td>100</td>
<td>60</td>
<td>60</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Egon et al. (1998)[12]</td>
<td>96</td>
<td>68/28</td>
<td>3</td>
<td>5.5 years (0.5-14)</td>
<td>1</td>
<td>88</td>
<td>200 (40-600)</td>
<td>565 (300-600)</td>
<td>89</td>
<td>22</td>
<td>0</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>Van der Aa et al. (1999)[35]</td>
<td>37</td>
<td>33/4</td>
<td>3</td>
<td>5.5 years (0.4-12)</td>
<td>-</td>
<td>84</td>
<td>75% &lt; 400 ml</td>
<td>95% &gt; 400 ml</td>
<td>91</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creasey et al. (2001)[39]</td>
<td>23</td>
<td>16/7</td>
<td>3</td>
<td>&gt; 1 year</td>
<td>65</td>
<td>87</td>
<td>243 (30-450)</td>
<td>&gt; 400 ml</td>
<td>69</td>
<td>35</td>
<td>7</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>Bauchet et al. (2001)[11]</td>
<td>20</td>
<td>6/14</td>
<td>3</td>
<td>4.5 years (1-8.5)</td>
<td>0</td>
<td>90</td>
<td>190 (40-600)</td>
<td>460 (350-800)</td>
<td>90</td>
<td>15</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Vignes et al. (2001)[40]</td>
<td>32</td>
<td>-</td>
<td>3</td>
<td>8 years (4-11)</td>
<td>0</td>
<td>90</td>
<td>220 (50-600)</td>
<td>550 (350-600)</td>
<td>80</td>
<td>18</td>
<td>2</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Kluzenberger (2005)[13]</td>
<td>464</td>
<td>244/220</td>
<td>2</td>
<td>6.6 years (6-17)</td>
<td>-</td>
<td>83</td>
<td>173</td>
<td>470</td>
<td>81</td>
<td>-</td>
<td>-</td>
<td>6.3/yr</td>
<td>1.2/yr</td>
</tr>
</tbody>
</table>
CONCLUSION

It is interesting to know the various techniques used for bladder denervation, in order to be able to offer patients the whole range of therapeutic options, should medical treatments fail. Currently, bladder denervation is mainly reserved for those suffering complete spinal cord injuries, but increased selectivity may one day make it possible to perform this type of surgery in patients with less neurological damage.

RECOMMENDATIONS

- No peripheral bladder denervation technique has passed the test of time. The only technique used nowadays (the Ingelman-Sundberg technique) is not sufficiently effective to be used to treat neurogenic bladder hyperactivity (D)
- Injections of neurolytic products to treat detrusor overactivity should be abandoned, since they are ineffective in the medium and long term and expose patients to morbidity (A)
- Sacral dorsal rhizotomies need to be quite extensive to treat successfully neurogenic bladder hyperactivity. So they may be performed only in patients with lower limb neurological impairment (B)
- In certain situations, dorsal rhizotomies can be associated with ventral root stimulators (Brindley’s technique) or even with continent cystostomy (B)
- Electrostimulation of the anterior sacral roots is a validated option for managing neurogenic bladder in patients with spinal lesion, with long-term follow-up (B)
- It must be combined with destruction of all or part of the posterior sacral nerves, and cannot therefore be performed in patients with conserved lower limb motility(B)
- The reflex arc must be intact(B)
- Posterior rhizotomy exposes men to a loss of reflex erection and women to a loss in reflex vaginal lubrication(B)
- It is vital to assess the patient carefully before implantation so as to determine whether he/she will be able to mount a toilet or grasp a urinal handrail (B)

4. SURGERY FOR STRESS UI DUE TO SPHINCTERIC INCOMPETENCE

- Keywords used for the medline research
  neurogenic bladder; spinal cord injury; spina bifida; myéloméningocèle; multiple sclerosis; stress incontinence; artificial urinary sphincter; sling; bulking agent; dextranomer; polydimethylsiloxane; Polytetre-fluoroethylen; collagen
- Introduction
  Patients with bladder dysfunction secondary to a neurological cause may have a certain degree of sphincter dysfunction. In certain cases, this is secondary to a neurological impairment (for example in cauda equina syndrome). In other cases, it could be the consequence of previous surgery (for example sphincterotomy). In women, stress urinary incontinence may be related to simple cervico-urethral hypermobility [1].
  
  It is of course very important to confirm that the bladder reservoir is well-balanced and filling under low pressure; where this is not the case, a treatment addressing the bladder condition would need to be added to that for increasing sphincter resistance.

  The context of the neurological disease, and the presence of any concomitant treatment for detrusor hyperactivity of neurological origin, will require stringent, pre-operative investigation. Indeed, the risk of chronic urinary retention is particularly high in such patients (in certain situations, for example patients already using intermittent catheterization , it could even be the goal of surgery). Patients must be informed therefore of the potential need for intermittent catheterization (IC), and they should be capable to perform intermittent catheterization (IC). A patient who has never used this technique should be trained in order to meet any possible future problem. Two situations can be identified: patients not already using IC, patients already using IC.

  a) Patients not using IC

  1. SUBURETHRAL TAPES

  In this case, a pre-operative assessment to look for prognostic factors must be carried out. This point is already treated in a specific chapter. In patients with a neurological disease, clinical examination should be conducted as in non-neurological patients. The clinical examination may include the Bonney test and testing of continence during a TVT procedure [2]. In the event of peripheral neurological disease with perineal floor denervation, it is especially important to check for any associated urogenital prolapse, a condition often exacerbated by the effort involved in micturition and defecation.
The urodynamic investigation must evaluate the quality of sphincter function, since several studies have suggested that suburethral tape techniques gave poorer results in the event of low urethral closure pressure (LOE 4) [3]. Furthermore, recent research based on prospective comparative studies suggests that in the event of low closure pressure, techniques using tapes placed retropubically give better results than transobturator techniques (LOE 2) [4 , 5-7].

To our knowledge, only one study has specifically assessed the efficacy of suburethral tension-free tape in adult women with neurogenic bladders (the use of suburethral slings will be discussed later). It was a retrospective series with 12 women treated by TVT [8] (LOE3). The study revealed that, for those patients who did not self-catheterize (3/12), the treatment was effective and intermittent catheterization was not required. The authors did not report any particular complication.

For adult male patients, the use of synthetic tapes is increasing since the description of bone anchored tape for post prostatectomy incontinence [9](LOE2). To our knowledge, no specific study on patients with a neurological cause to their incontinence has been reported. We could only suppose that the risk for urinary retention is higher than in the general population and therefore prepare the patient to accept IC before consenting to this type of surgery. The different therapeutic options are presented in the following chapter.

2. Bulking agents

The use of various types of bulking agent has been reported in three main indications: stress urinary incontinence in women, post-prostatectomy incontinence and children incontinence. Various agents have been used. Polytetrafluoroethylene (TEFLON®) was one of the first[10, 11]. It was once very popular for treating vesico-ureteral reflux, but it has been progressively abandoned after several authors reported a possible migration and granulomatous reaction of this product [12, 13](LOE2). Collagen has also been used in this indication [11, 14-21]. More recently, several authors shifted to synthetic products like polymethylsiloxane (MACROPLASTIQUE®) or Dextranomer Hyaluronic Acid copolymer (ZUIDEX®), because they found these type of products easier to use without the risk of allergic reaction or previous contamination which may occur with other biological products [10, 22-28]. Henly et al [29] demonstrated that distant migration of particulate silicone was observed in animals after periurethral injection with polymethylsiloxane (LOE4). This was not demonstrated with dextranomer acid copolymer injections [30] (LOE4).

Bulking agent results in female stress incontinence and post-prostatectomy incontinence will be discussed elsewhere. We will focus our review on patients with a neurological problem (Table 7) [10, 11, 14-28, 31-39].

It is important to underline that although a high proportion of the patients in these studies use intermittent catheterisation, some patients have a good result without using it.

One of the main advantages of this technique is that it is easy to perform, usually as an outpatient procedure. Most of the studies are on children. Usually the authors inject the product in the bladder neck, by a retrograde endoscopic approach, in two to four points. The bulking agent is injected until full lumen closure is noted. Dean et al [28] recently suggested performing an antegrade way for injections, using a percutaneous access to the bladder.

The results of the procedure of injection with all the recent bulking agents used are summarized in Table 7. It is very difficult to compare the results because of the various definitions for the surgical results that are used by the authors. We report what many authors call an improvement, or “social continence”. Many authors do not accept this definition. Therefore, it seems reasonable to consider only the more reliable results, namely the rate of “dry patients” (even if some authors add to this result a notion of “dryness for some hours” between voiding or catheterization). Using this definition, 0 to 36% of the patients are considered as cured using bulking agents (LOE2-3). Moreover, these results are observed after a mean follow up that rarely exceeds 2 years (LOE2-3), although one author has reported long-term lasting effect up to 7 years after the last injection [23].

Two other points have to be underlined in the studies published. The first is that the studies in children mix frequently patients with two types of problems: urological malformations (epispadias, bladder extrophy) or neurogenic bladder (mainly myelomeningocele). This is important to know, because it seems that in children, bulking agents work slightly better in patients with malformations than in patients with a neurological bladder dysfunction [10, 17, 23, 25]. The global results of the series are therefore probably more optimistic than the results that could be specifically observed in neurological patients. The second point is that these children have frequently already had a various amount of surgical procedures, which could modify the results of the injection procedure.

Although the authors have reported no severe complication, there is a controversy regarding a possible greater difficulty to perform a bladder neck surgery after repeated bulking agents injection [10, 23, 25]. Some authors [40] advocate that the number of unsuccessful procedure could be considered as a complication. Most of the authors [23, 25] agree that
Table 7. Results of the bulking agent injection procedures in patients with a neurological bladder dysfunction. DHAC (Dextranomer Hyaluronic Acid Copolymer), PDS (polydimethylsiloxane), PTFE (Polytetrafluoroethylene), NP (Not Precised), LOE (Level of evidence)

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>LOE</th>
<th>Neurogenic bladder/tota l n patients</th>
<th>Bulking agent</th>
<th>Mean or Median age (years)</th>
<th>Male/female</th>
<th>Follow up (years)</th>
<th>Dry (%)</th>
<th>Improved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonard et al [19]</td>
<td>18</td>
<td>3</td>
<td>10/18</td>
<td>Collagen</td>
<td>10.5</td>
<td>12/6</td>
<td>1.3</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Perez et al [18]</td>
<td>32</td>
<td>3</td>
<td>25/32</td>
<td>Collagen</td>
<td>9</td>
<td>23/9</td>
<td>0.9</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Bomalaski et al [17]</td>
<td>40</td>
<td>2</td>
<td>25/40</td>
<td>Collagen</td>
<td>12.1</td>
<td>28/12</td>
<td>2.1</td>
<td>22</td>
<td>54</td>
</tr>
<tr>
<td>Caione et al [26]</td>
<td>16</td>
<td>2</td>
<td>3/16</td>
<td>DHAC</td>
<td>10.1</td>
<td>9/7</td>
<td>1</td>
<td>18.7</td>
<td>56.3</td>
</tr>
<tr>
<td>Sundaram et al [15]</td>
<td>20</td>
<td>3</td>
<td>12/20</td>
<td>Collagen</td>
<td>9.5</td>
<td>12/8</td>
<td>1.3</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Kassouf et al [21]</td>
<td>20</td>
<td>3</td>
<td>20/20</td>
<td>Collagen</td>
<td>13.3</td>
<td>15/5</td>
<td>4.2</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Chernoff et al [20]</td>
<td>11</td>
<td>3</td>
<td>8/11</td>
<td>Collagen</td>
<td>10.6</td>
<td>6/5</td>
<td>1.2</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Block et al [16]</td>
<td>25</td>
<td>3</td>
<td>25/25</td>
<td>Collagen</td>
<td>11.7-21.9</td>
<td>15/10</td>
<td>2.9-4.7</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Hamid et al [24]</td>
<td>14</td>
<td>3</td>
<td>14/14</td>
<td>PDS</td>
<td>41</td>
<td>14/0</td>
<td>2.9</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Godbole et al [Godbole, 2004 #]</td>
<td>15</td>
<td>3</td>
<td>14/15</td>
<td>PTFE, collagen, PDS</td>
<td>10.2</td>
<td>10/5</td>
<td>2.33</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Halachmi et al [22]</td>
<td>28</td>
<td>3</td>
<td>10/28</td>
<td>PDS</td>
<td>12.5</td>
<td>22/6</td>
<td>1</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Misseri et al [27]</td>
<td>16</td>
<td>3</td>
<td>12/16</td>
<td>DHAC</td>
<td>4 to 18</td>
<td>6/10</td>
<td>0.8</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>Lottmann et al [23]</td>
<td>61</td>
<td>2</td>
<td>27/61</td>
<td>DHAC</td>
<td>10.3</td>
<td>41/20</td>
<td>3</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Guys et al [25]</td>
<td>49</td>
<td>3</td>
<td>49/49</td>
<td>PDS</td>
<td>14</td>
<td>21/28</td>
<td>6.1</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Dean et al [28]</td>
<td>34</td>
<td>3</td>
<td>28/34</td>
<td>DHAC</td>
<td>11.7</td>
<td>18/16</td>
<td>0.3</td>
<td>NP</td>
<td>71</td>
</tr>
<tr>
<td>Dyer et al [10]</td>
<td>34</td>
<td>3</td>
<td>12/34</td>
<td>PTFE, DHAC</td>
<td>2.7 (PTFE)/1.4 (DHAC)</td>
<td>NP</td>
<td>NP</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>
there is no need to attempt more than two injections if the patient’s incontinence is not improved or cured on a long-term basis. Gender, previous bladder/sphincter surgery don’t seem to be reliable prognostic factor regarding the success of the injections.

Future studies using autologous myoblasts and fibroblasts are currently under way in patients without neurological impairment [41] and may bring a renewed interest in the field of bladder neck or peri-urethral injections in the next years.

3. ARTIFICIAL URINARY SPHINCTER

The last theoretical option is the use of an artificial urinary sphincter. However, the rate of urinary retention following this procedure is very high in patients with a neurological bladder dysfunction. Therefore, as previously stated for the other treatments, this procedure should be used only after the patient has accepted and is ready to use IC.

b) Patients using IC or prepared to use IC:

A large majority of the series published in this chapter are about children. One of the main questions is whether it is necessary or not it is necessary to perform systematically a bladder augmentation in complement to the treatment of the sphincteric deficiency. A majority of the authors report the necessity to proceed to bladder augmentation in at least a third of their patients. Even with a thorough urodynamic and radiologic preoperative evaluation, some patients will have late bladder compliance deterioration [42-59]. To illustrate that, two retrospective studies were recently published specifically on this topic and gave two opposite conclusions. Snodgrass et al [60] (LOE3) published the retrospective analysis of 30 children (mean age: 8,6 years) who had a bladder neck sling procedure and appendice-vesicostomy without augmentation. At 22 month of mean follow-up, only one patient had to undergo a bladder augmentation procedure. In a subset of the patients (16) who had urodynamics at 24 months, 13/16 had an increase of their maximum bladder capacity at 24 months. However, 67% of the patients have to use anticholinergic therapy. Although this series is interesting, the follow-up is relatively short. On the opposite of this study, Dave et al [61] (LOE3) strongly advocate the case for systematic bladder augmentation. Hence, the authors report a series of 15 children followed at least 5 years after an isolated bladder outlet procedure (5 Pippi-Salle, 5 slings and 5 artificial urinary sphincter). At a mean follow-up of 11.25 years, all the patients underwent a bladder increase procedure, either for recurrence of the incontinence or for upper urinary tract deterioration.

At present, no definitive conclusions can be drawn. The majority of the authors recommend performing a concomitant bladder augmentation when performing a bladder outlet procedures [40] (LOE4). The advent of the botulinum toxin injection in children will perhaps allow having new design for studies that could help to answer to this question.

1. SURGERY OF THE BLADDER NECK

Three main procedures have been described. Historically, the technique of Young[62], later modified by Dees[63] and Leadbetter[64] has been the first used, essentially for reconstruction in cases of extrophy and epispadias. The principle was to dissect extensively the trigone (after ureteral reimplantation) allowing excising most of the tissue from the bladder neck to constrict the trigone around a small catheter. Although some authors[65, 66] described its use in neurogenic patients, it is almost abandoned in this indication. Tanagho [67](LOE3) described a variation of this technique which could be used in difficult situations in incontinent adult patients, when the implantation of an artificial urinary sphincter is not possible [68].

The Kropp’s procedure [69] consists in tubularizing a flap of the anterior bladder wall, pediculized on the bladder neck. This tube is then fixed on the posterior bladder wall between ureteral orifices. In the initial technique, the tube was tunneled submucosally, but this manoeuvre was supposed to augment the risk of tube stenosis [70, 71](LOE3).

The last technique described is the Pippi-Salle technique[72]. It is considered as a variant of the Kropp procedure (also called Kropp-onlay), with an anterior bladder wall flap that is not tubularized. At the beginning, the authors reimplanted systematically the ureters. This was abandoned in the last patients in the absence of reflux [73, 74] (LOE3). In a systematic review, Kryger et al [40] (LOE4) stated that only data on 83 patients for the Kropp technique and 25 with the Pippi sale procedure have been published. Since then, we didn’t found any added study with these techniques. The continence results are good (50-69% for the Pippi Salle procedure, 78-81% for the Kropp procedure) [70, 71] [73, 74] [40]. However, several problems exist with the two techniques. First, the technique doesn’t allow easy endoscopic access to the bladder. This is a major problem, because it prevents or limits future endoscopic procedures (especially uroscopy, botulinum toxin injections). Second, a high percentage of patients (especially male) report catheterisation difficulties in the Kropp technique : 28 to 45% of cases. In Pippi Salle procedure, the continence rate is lower than in the Kropp procedure, but few cases of catheterisation difficulties have been reported [40]. However, a new procedure is necessary in 12 to 17% of cases for uretrovesical fistula [73, 74] (LOE3). Moreover, this procedure has rarely been tried in male patients.

2. COMPLETE BLADDER NECK CLOSURE

This can sometimes be proposed as a complement to continent cystostomy. It is always a difficult
procedure, despite all the technical artefacts presented in the literature (interposition of muscle or omentum), and re-permeation is both frequent and problematic [76]. Moreover, patients with a bladder dysfunction secondary to neurological illness are at high risk of lithiasis of the bladder reservoir or the upper urinary tract, so it does not seem logical to prevent potential endoscopic treatment by closing the ureter (LOE4). Finally, preserving the natural urethra may constitute a safety measure if high pressure persists (dysfunction of the augmentation graft, hyperactive or hypo-compliant residual bladder) or in the event of any complication on the abdominal continent tube [2, 77] (stenosis, transient impossibility to self-catheterize, etc.) (LOE4).

3. APONEUROTIC OR PROSTHETIC BLADDER NECK SLINGS:

For women, suburethral tape can easily be placed during bladder augmentation surgery in order to reinforce stress continence and prevent stress leakage. Results of the main recent series are summarized in Table 8. Complete continence is observed in 83 to 89% of the patients [44, 60, 78, 79] (LOE3). Bladder neck slings appear to provide good results for male children, although the results seem to be less satisfactory than with female patients [60, 79, 80] (LOE3). Studies in adult men need to be awaited.

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>n</th>
<th>LOE</th>
<th>Neurogenic bladder/total n patients</th>
<th>Mean or Median age (years)</th>
<th>Male/female</th>
<th>Bladder augment. surgery (%)</th>
<th>Follow up (years)</th>
<th>Continence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snodgrass et al, 2007 [60]</td>
<td>30</td>
<td>3</td>
<td>30/30</td>
<td>8.6</td>
<td>0</td>
<td>1.9</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Karsenty et al, 2007 [78]</td>
<td>11</td>
<td>3</td>
<td>11/11</td>
<td>42</td>
<td>0/11</td>
<td>100</td>
<td>3.6</td>
<td>72</td>
</tr>
<tr>
<td>Albouy et al, 2007 [80]</td>
<td>14</td>
<td>2</td>
<td>14/14</td>
<td>14</td>
<td>7/7</td>
<td>100</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>Castellan et al, 2005 [79]</td>
<td>58</td>
<td>3</td>
<td>58/58</td>
<td>11.4</td>
<td>15/43</td>
<td>100</td>
<td>4.2</td>
<td>88</td>
</tr>
<tr>
<td>Austin et al, 2001 [42]</td>
<td>18</td>
<td>3</td>
<td>18/18</td>
<td>14</td>
<td>8/10</td>
<td>33</td>
<td>1.8</td>
<td>87</td>
</tr>
<tr>
<td>Barthold et al, 1999 [43]</td>
<td>27</td>
<td>3</td>
<td>26/27</td>
<td>NP</td>
<td>7/20</td>
<td>81</td>
<td>2,1/3,6</td>
<td>28(sling)/50(wrap)</td>
</tr>
<tr>
<td>Kakizaki et al, 1995 [45]</td>
<td>13</td>
<td>3</td>
<td>11/13</td>
<td>13</td>
<td>10/3</td>
<td>69</td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>Gormley et al, 1994 [98]</td>
<td>15</td>
<td>3</td>
<td>15/15</td>
<td>NP</td>
<td>0/15</td>
<td>13</td>
<td>NK(0.5-8.5)</td>
<td>85</td>
</tr>
<tr>
<td>Elder et al, 1990 [99]</td>
<td>14</td>
<td>3</td>
<td>14/14</td>
<td>12.6</td>
<td>4/10</td>
<td>7</td>
<td>1</td>
<td>86</td>
</tr>
</tbody>
</table>

All the authors report a low morbidity rate of this procedure. The risk of urethral erosion is very low with the fascial slings. When the intention of surgery is to induce urinary retention with subsequent postoperative IC, an aponeurotic sling rather than a synthetic sling seems to be more suitable because of the risk of secondary urethral erosion when the sling must be tight [81-84](LOE3). Although these findings have not been confirmed by comparative studies, some authors report up to 80% erosion with bladder neck slings [81] (LOE3). The risk of erosion with synthetic tapes exists also in suburethral tapes, and excessive tension is often evoked [84](LOE4). It is interesting to notice that the only case of male sling erosion to date was described in a patient with a cauda equine syndrome [85](LOE4). New refinements in the technique for male patients involve a higher tension on the tape, and already one case of urethral erosion has been published [82](LOE4). The use of this type of device in patients with underlying neurological illness should therefore be very cautious(LOE4). High bladder pressure when slings are placed is also supposed to be a risk factor for urethral erosion [84] (LOE3).

At present, there are no specific reports concerning the new perineal slings for men (bone-anchored or...
transobturator route) in patients with a neurologic disease. The use of new minimally invasive devices such as ACT and pro-ACT balloons (Uromedica) [86, 87] for patients with a neurological bladder dysfunction has not yet been published.

4. Artificial urinary sphincter (AUS)

Since it was introduced in clinical practice [88], the artificial urinary sphincter is recognized as one of the most effective treatments for urinary incontinence. The benefit lies in the fact that it mimics bladder function as closely as possible to physiologically normal, with low-pressure micturition. Its effectiveness in regard to stress incontinence ranges from 75 to 87%. The satisfaction rate ranges from 85 to 95%. These rates, given for mixed populations of patients mostly suffering stress incontinence after radical prostatectomy, are probably similar to those of neurogenic patients when the bladder reservoir is stable (LOE4) [89].

Before using AUS in neurogenic patients, several factors must be considered. The risk of infection related to bacteriuria is probably higher, even though little information is available to support this statement. For neurological patients, we recommend pre-operative assessment of bacteriuria and urine decontamination before surgery [90] (LOE4). Theoretically, patients must be strong enough to activate the pump of the AUS, either to open the cuff to urinate or during IC [89]. They must also accept the need for IC should the bladder reservoir be hypocontractile. Recent studies seem to indicate that the cycling activation of the pump could be avoided in patients performing IC (LOE3) [47, 91]. Finally, it is necessary to know the ejaculatory status of males in order to discuss where to implant the cuff.

The cuff implantation site in adult patients with a neurological bladder dysfunction is debated. Partisans of bladder neck implantation argue that perineal incisions may cause cicatrisation problems for patients in wheelchairs. Moreover, traumatic catheterization is a well-known risk factor of urethral erosion in the non-neurological population undergoing an AUS [54] (1 to 5.5% in contemporary series). Even if it is recognized that IC is possible in AUS implanted patients [92], the risk of traumatic catheterization could be higher on the bulbar urethral site than on the bladder neck. Finally, the bladder neck implantation retains the possibility for patients to recover antegrade ejaculation [93, 94] (LOE4).

On the other hand, inserting an AUS cuff around the bladder neck is more difficult in adults in comparison with peri-bulbar implantation (LOE4), and the rate of erosion in the published series is higher than in the post-prostatectomy incontinent population [46-59, 95] (which is always implanted around the bulbar urethra). As previously stated, a thorough urodynamic evaluation of the bladder is mandatory to evaluate the possible degradation of bladder reservoir compliance following AUS implantation, which has been reported in several retrospective series (LOE3) [46-59, 95]. The reasons for this change in bladder behaviour are not known, and it has been observed particularly in populations of patients with myelomeningocele [51, 55, 56, 58, 96]. In the event of any doubt on the quality of the bladder reservoir, bladder augmentation should be performed. This may change in the future, with the development of intra-detrusor injection of botulinum toxin, to control incontinence in certain patients [97].

The main results of the recently published series are summarized in Table 9. The continence rate is high, especially when a bladder augmentation has been performed (59 to 100% of the patients) [46-59, 95]. The older series comprise patients with the previous version of the AMS 800 (AMS 792). Therefore, long-term results could be even better as AMS 800 is considered as a better device than AMS 792. The bladder neck or urethral erosion is the main risk with AUS and appears to be higher in these series than it is in the general population (approximately 5 to 15%). These erosions seem to happen more frequently in the first two years after the procedure. However long-term erosions are still possible [50] (LOE3). The average "survival" for AUS exceeds rarely ten years. This particular point has to be explained to the patient, especially when they are very young. However, the majority of the authors consider AUS to be the "gold standard procedure to treat sphincter deficiency, even in patients with a neurological bladder dysfunction [41].

RECOMMENDATIONS

• Suspected neurological bladder requires careful investigation before implanting suburethral tape. Tests must include: a micturition diary, a detailed interview using validated questionnaires, and urodynamic tests to provide the patient with optimum information on post-operative risk of complications and failure (C).

• The clinical assessment must also evaluate the degree of patient handicap to determine whether they may perform self-catheterization. Sub-urethral tape can be used in patients with a neurological bladder. However, it is contraindicated where patients cannot perform self-catheterization (D).

• Autologous slings can be proposed to patients with a neurological bladder dysfunction after careful assessment of their general handicap and if the patient accepts...
Table 9. Results of the artificial urinary sphincter in patients with a neurological bladder dysfunction.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>LOE</th>
<th>Neurogenic bladder/total n patients</th>
<th>Mean or Med age (years)</th>
<th>Male/female</th>
<th>Bladder augment. surgery (%)</th>
<th>Follow up (years)</th>
<th>Continence rate (%)</th>
<th>Cuff Implantation Site</th>
<th>Complication/revision rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bersh et al 2008*[47]</td>
<td>51</td>
<td>3</td>
<td>51/51</td>
<td>38.7</td>
<td>37/14</td>
<td>19.6 (sacral root surgery)</td>
<td>8</td>
<td>70.6% (total) /90.2% (social continence)</td>
<td>Bladder neck</td>
<td>7.8/35.3</td>
</tr>
<tr>
<td>Lai et al [54]</td>
<td>21</td>
<td>8</td>
<td>11/218</td>
<td>46.3</td>
<td>215/3</td>
<td>NP</td>
<td>2.4</td>
<td>69</td>
<td>Peri-bulbar</td>
<td>18.2/36.4</td>
</tr>
<tr>
<td>Lopez Pereira et al [56]</td>
<td>35</td>
<td>3</td>
<td>35/35</td>
<td>14.4</td>
<td>22/13</td>
<td>20/35</td>
<td>5.5</td>
<td>91.4</td>
<td>Bladder neck</td>
<td>11.4/20</td>
</tr>
<tr>
<td>Patki et al [57]</td>
<td>9</td>
<td>4</td>
<td>9/9</td>
<td>38.2</td>
<td>9/0</td>
<td>NP</td>
<td>5.9</td>
<td>77</td>
<td>Peri-bulbar</td>
<td>22/43</td>
</tr>
<tr>
<td>Murphy et al [100]</td>
<td>30</td>
<td>3</td>
<td>13/30</td>
<td>54</td>
<td>29/1</td>
<td>NP</td>
<td>NP</td>
<td>23</td>
<td>Peri-bulbar</td>
<td>33/70</td>
</tr>
<tr>
<td>Herndon et al [52]</td>
<td>13</td>
<td>4</td>
<td>107/134</td>
<td>10</td>
<td>94/41</td>
<td>85/134</td>
<td>7.5</td>
<td>86%</td>
<td>Bladder neck (122), peri-bulbar (12)</td>
<td>16/41</td>
</tr>
<tr>
<td>Castera et al [48]</td>
<td>49</td>
<td>3</td>
<td>38/49</td>
<td>14</td>
<td>39/10</td>
<td>9/49</td>
<td>7.5</td>
<td>67</td>
<td>Bladder neck (37), peri-bulbar (12)</td>
<td>20/12</td>
</tr>
<tr>
<td>Shankar et al [95]</td>
<td>45</td>
<td>4</td>
<td>NP</td>
<td>11</td>
<td>45/0</td>
<td>NP</td>
<td>7</td>
<td>89</td>
<td>Bladder neck</td>
<td>4.4/6.7</td>
</tr>
<tr>
<td>Kryger et al [53]**</td>
<td>32</td>
<td>3</td>
<td>29/32</td>
<td>6.7/14.5</td>
<td>25/7</td>
<td>9/32</td>
<td>15.4</td>
<td>100/</td>
<td>Bladder neck/peri-bulbar</td>
<td>41/95</td>
</tr>
<tr>
<td>Elliott et al [49]</td>
<td>32</td>
<td>3</td>
<td>10/323</td>
<td>Global: 60.4</td>
<td>313/10</td>
<td>NP</td>
<td>5.7</td>
<td>NP</td>
<td>Bladder neck/peri-bulbar</td>
<td>Global: 26.2/28.6</td>
</tr>
<tr>
<td>Fulford et al [50]</td>
<td>61</td>
<td>3</td>
<td>34/61</td>
<td>26</td>
<td>43/18</td>
<td>7/34</td>
<td>10 to 15</td>
<td>88</td>
<td>Bladder neck (female)/peri-bulbar (male)</td>
<td>29.4/91.2</td>
</tr>
<tr>
<td>Levesque et al [55]</td>
<td>54</td>
<td>3</td>
<td>49/54</td>
<td>10/12</td>
<td>34/20</td>
<td>23/54</td>
<td>NP (&gt;10)</td>
<td>59.3</td>
<td>Bladder neck</td>
<td>24/67</td>
</tr>
<tr>
<td>Singh et al [59]</td>
<td>90</td>
<td>3</td>
<td>90/90</td>
<td>26</td>
<td>75/15</td>
<td>NP</td>
<td>4</td>
<td>92</td>
<td>Bladder neck/peri-bulbar</td>
<td>16.7/28</td>
</tr>
<tr>
<td>Simeoni et al [58]</td>
<td>10</td>
<td>7</td>
<td>107/107</td>
<td>13.7</td>
<td>74/33</td>
<td>22/107</td>
<td>5</td>
<td>76.6</td>
<td>Bladder neck (98)/peri-bulbar (9)</td>
<td>22.3/19.6</td>
</tr>
<tr>
<td>Gonzales et al [51]</td>
<td>19</td>
<td>3</td>
<td>19/19</td>
<td>8.4</td>
<td>19/0</td>
<td>7/19</td>
<td>8</td>
<td>84.2</td>
<td>Bladder neck</td>
<td>5/100</td>
</tr>
<tr>
<td>Belloli et al [46]</td>
<td>37</td>
<td>3</td>
<td>37/37</td>
<td>13-19</td>
<td>35/2</td>
<td>2/37</td>
<td>4.5</td>
<td>59</td>
<td>Bladder neck (33)/peri-bulbar (4)</td>
<td>10.8/38</td>
</tr>
</tbody>
</table>

* AUS modified**AUS modified and two groups of patients depending of their age at AUS implantation
5. SURGICAL ALTERNATIVES EXCLUDING DENERVATION PROCEDURES TO TREAT REFLEX INCONTINENCE DUE TO NEUROGENIC DETERUSOR OVERACTIVITY

**Keywords**
- neurogenic bladder; spinal cord injury; spina bifida; myelomeningocèle; multiple sclerosis; bladder augmentation; enterocystoplasty; gastrocystoplasty; sigmoidocystoplasty; colocystoplasty; ureterocystoplasty; autoaugmentation; detrusorectomy

### a) Bladder augmentation using intestinal segments

The aim of bladder augmentation is to provide long-term protection to the upper urinary tract by reducing the risk of impairment due to high bladder pressure, as well as to improve micturition comfort [1].

First performed in man in 1889 by Von Mickulicz [2] who used a segment of small intestine, the technique has regained popularity since the 1970s after the introduction of intermittent catheterization [3].

Unlike complete bladder replacement, enterocystoplasty preserves the integrity of the trigone of the bladder with the urethra and ureters and reimplantation is not necessary. A segment of the gastrointestinal tract is then removed and sutured onto the bladder.

Various augmentation techniques using different segments of the gastrointestinal tract (caecum, colon, and ileum) have been described.

1. **INDICATIONS**

Bladder augmentation is indicated wherever bladder capacity and compliance is reduced, or in the event of detrusor overactivity, when all conservative treatments (medical treatments, detrusor injections of botulinum toxin and/or neuromodulation of the posterior sacral roots) have failed [1, 4].

Before performing bladder augmentation, it is essential to ensure that:

- There is no malignant disease or lithiasis in the bladder.
- Renal function is normal and the upper urinary tract is unimpaired (screen particularly for lithiasis).
- There is no gastrointestinal tract disease (Crohn’s disease, hemorrhagic rectocolitis, short gut syndrome, etc.).
- The patient is capable of, and willing to, perform self-catheterization. This can be combined with continent cystostomy, a topic to be dealt with in a separate chapter.

2. **TECHNICAL PRINCIPLES**

There are two stages to the surgical procedure: first bladder preparation and then augmentation. Usually open surgery is performed, but recently laparoscopy has been reported [5, 6](LOE3). At present, except for technical articles on laparoscopy, there are no publications comparing this technique with open surgery.

The bladder can be prepared either by clam cystoplasty or by supratrigonal cystectomy. The preferred preparation depends on the quality of the detrusor, and more particularly on whether the bladder has retained its visco-elastic properties. Where the detrusor is very fibrous and thick, supratrigonal cystectomy should be envisaged, since exclusion of the ileal patch may occur. Nowadays, supratrigonal cystectomy is often performed because compliance disorders in a bladder that has retained its visco-elastic properties can be treated effectively by detrusor injections of botulinum toxin [7].

a. **Bladder preparation**

• **CLAM CYSTOSTOMY**

Clam cystoplasty involves freeing the anterior/posterior surfaces and dome of the bladder and then sectioning from front to back in the sagittal plane. The bladder can be opened either in the transverse plane or sagittal plane, the incision starting and ending about 2 cm above the bladder neck. The lateral surfaces are not freed. The umbilical arteries are preserved to maintain vascularization of the bladder dome.
Supratrigonal cystectomy involves resection of the bladder tegument and sparing the trigone. The bladder is freed under the peritoneum and the right and left umbilical arteries ligated and sectioned. The bladder tegument is completely freed and the bladder pedicles ligated and sectioned laterally up to the trigone, which is preserved. During the bladder dissection, care must be taken to spare the ureteral vascularization. Supratrigonal cystectomy is performed by making a circular incision with an electric scalpel into the tegument 1 to 2 cm above the trigone.

Ureteral reimplantation must be carefully discussed in the event of vesicoureteral reflux. Several authors have reported that improved bladder compliance precludes the need for vesicoureteral reimplantation (LOE 3) [8-11]. They have reported a resolution rate of about 85% for vesicoureteral reflux, classified below grade IV. For grade V reflux, improvement was observed in 2/3 of patients. It is important to point out that, except for the work of Simforoosh [8], these consistent results were obtained in small heterogeneous series of children (neurogenic bladders and congenital anomalies). The results were published after relatively short mean follow-up times (1 to 5 years).

Recently, Hayashi et al. [12] reported on 22 patients treated by ureteral reimplantation during bladder augmentation (LOE 3). Their work was original in that it gave detailed account of renal function after long-term follow-up (mean: 12 years). In the hands of this experienced team, ureteral reimplantation during bladder augmentation did not result in greater morbidity and 97% of patients recovered. Renal function was preserved and satisfactory.

It is therefore too early to rule out the need for ureteral reimplantation during bladder augmentation, especially for cases of grade V reflux. However, it is clear that improved compliance will reduce some vesicoureteral reflux.

b. Intestinal segments

The choice of intestinal segment depends on patient’s history and the local conditions. All segments of the gastrointestinal tract may be used, except the jejunum because of the risk of water-electrolyte disorders. The most frequently used segment in adults is the ileum because it is easy to remove, is close to the bladder and may be shaped easily into a reservoir. Colon segments are used more often in children.

The removed intestinal segment must always be detubularized to reduce peristalsis to a minimum and to obtain a reservoir with low pressure. The segment is then placed and sutured onto the bladder in the form of a patch. For supratrigonal cystectomy, the intestinal segment needs to be longer and fashioned into a neo-bladder [4].

The main objective is to reduce mucus secretion and prevent the reabsorption of urine by the intestinal mucosa that leads to metabolic acidosis. Two variant techniques have been proposed but not developed extensively, probably because they involve relatively major surgery for the benefits they bring.

The first is seromuscular colocystoplasty lined with urothelium. This involves removing the detrusor, leaving the bladder mucosa intact, and then covering it with a demucosalized sigmoid patch [13].

The second technique is seromuscular enterocystoplasty. After preparing the bladder, a segment of the ileum or the sigmoid is removed and detubularized. The mucosal membrane of the intestinal segment is surgically removed, or destroyed by argon beam [14] and the segment is then placed on the prepared bladder [15].

c. Results of enterocystoplasty

The main published series for patients undergoing surgery for neurogenic bladder are summarized in Table 10.

Early morbidity and mortality

Peri-operative mortality is estimated between 0 and 3.2% (LOE 2-3). The most frequently reported early morbidity (LOE 2-3) is prolonged post-operative ileus. It occurs in up to 11.7% of cases [16-18]. However, it should be noted that systematic and prolonged use of a nasogastric catheter is no more justified in neurological patients than in the general population (LOE3) [19]. Other common complications include episodes of febrile urinary infection (4.8 to 9%), urinary fistula (0.4 to 4%) that usually resolve and thrombo-embolic complications (1 to 3%). When the pelvis has been irradiated, the patient must be warned of the increased risk of enteric- or colovesicular fistula.

Late morbidity

Chronic bacteriuria always occurs with intermittent catheterization and should not be considered a complication [20](LOE4).

The risk of calculus in the enlarged reservoir ranges from 10 to 50% [21-24] (LOE 2-3). It would appear that there is a higher risk of developing upper urinary tract lithiasis than in the general population [25-27] (LOE3).

After bladder augmentation, intestinal transit disorders are frequent and probably underestimated (0 to 30% of cases [17, 28-30]). Several explanations have been proposed (ileocecal valve not preserved, biliary salt malabsorption, etc.). Somani et al. recently conducted
<table>
<thead>
<tr>
<th>Authors</th>
<th>LOE</th>
<th>Total number of patients (neurological patients)</th>
<th>Type of bladder augmentation</th>
<th>Max BC pre-op</th>
<th>Max BC post-op</th>
<th>DP pre-op</th>
<th>DP post-op</th>
<th>Mean Follow-up (months)</th>
<th>Increased compliance (% patients)</th>
<th>Post-op continence status</th>
<th>Results for quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaivas (2005) [45]</td>
<td>3</td>
<td>76 (41)</td>
<td>Ileum, cecum</td>
<td>166</td>
<td>572</td>
<td>53</td>
<td>14</td>
<td>108</td>
<td>NP</td>
<td>Cured 70%/ Improved: 18%</td>
<td>NP</td>
</tr>
<tr>
<td>Mor (2004) [44]</td>
<td>3</td>
<td>11(11)</td>
<td>Ileum</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>115</td>
<td>NP</td>
<td>Cured/improved: 82%</td>
<td>NP</td>
</tr>
<tr>
<td>Quek (2003) [72]</td>
<td>3</td>
<td>26(26)</td>
<td>Ileum</td>
<td>201</td>
<td>615</td>
<td>81</td>
<td>20</td>
<td>96</td>
<td>92</td>
<td>Cured: 69%/Improved: 27%</td>
<td>NP</td>
</tr>
<tr>
<td>De Foor (2003) [38]</td>
<td>3</td>
<td>105 (47)</td>
<td>Stomach, ileum, colon</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>88,8</td>
<td>NP</td>
<td>Cured/improved: 92%</td>
<td>NP</td>
</tr>
<tr>
<td>Medel (2002) [73]</td>
<td>3</td>
<td>26(26)</td>
<td>Stomach, ileum, colon</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>45.6</td>
<td>100</td>
<td>Cured: 84.6% Improved: 5.4%</td>
<td>NP</td>
</tr>
<tr>
<td>Nomura 2002 [74]</td>
<td>3</td>
<td>21(21)</td>
<td>Ileum</td>
<td>149</td>
<td>396</td>
<td>&gt;60</td>
<td>NP</td>
<td>66</td>
<td>100</td>
<td>Cured/improved: 95%</td>
<td>NP</td>
</tr>
<tr>
<td>Shekarriz (2000) [16]</td>
<td>3</td>
<td>133(100)</td>
<td>Ileum, sigmoid, autoaugmentation</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>64</td>
<td>NP</td>
<td>Cured/improved: 95%</td>
<td>NP</td>
</tr>
<tr>
<td>Arikan 2000[75]</td>
<td>3</td>
<td>18(18)</td>
<td>Sigmoid</td>
<td>86</td>
<td>370</td>
<td>NP</td>
<td>NP</td>
<td>40</td>
<td>NP</td>
<td>Cured/improved: 95%</td>
<td>NP</td>
</tr>
<tr>
<td>Chartier-Kastler (2000) [17]</td>
<td>2</td>
<td>17</td>
<td>Ileum</td>
<td>174.1</td>
<td>508</td>
<td>65.5</td>
<td>18.3</td>
<td>75.6</td>
<td>100</td>
<td>Cured/improved: 88.5%</td>
<td>NP</td>
</tr>
<tr>
<td>Venn (1998) [76]</td>
<td>3</td>
<td>267 (152)</td>
<td>Ileum</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>36</td>
<td>NP</td>
<td>Cured/improved: 86.6%</td>
<td>NP</td>
</tr>
<tr>
<td>Herschorn (1998) [43]</td>
<td>2</td>
<td>59(59)</td>
<td>Ileum, cecum, sigmoid</td>
<td>220</td>
<td>531</td>
<td>48.9</td>
<td>15.8</td>
<td>72.6</td>
<td>100</td>
<td>Cured: 67% Improved: 28.8%</td>
<td>Excellent: 69.5% Good: 20.3%</td>
</tr>
<tr>
<td>Flood (1995) [40]</td>
<td>2</td>
<td>122 (59)</td>
<td>Ileum, sigmoid</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>37</td>
<td>95</td>
<td>Cured: 75% Improved: 20%</td>
<td>NP</td>
</tr>
</tbody>
</table>

**Table 10. Main series concerning gastro-intestinal bladder augmentation in neurological patients with bladder dysfunction (Max BC: Maximal Bladder capacity, DP: Detrusor pressure at the maximal bladder capacity)**
Table 10. (Ctd) Main series concerning gastro-intestinal bladder augmentation in neurological patients with bladder dysfunction (Max BC: Maximal Bladder capacity, DP: Detrusor pressure at the maximal bladder capacity)

<table>
<thead>
<tr>
<th>Authors</th>
<th>LOE</th>
<th>Total number of patients (neurological patients)</th>
<th>Type of bladder augmentation</th>
<th>Max BC pre-op</th>
<th>Max BC post-op</th>
<th>DP pre-op</th>
<th>DP post-op</th>
<th>Mean Follow-up (months)</th>
<th>Increased compliance (% patients)</th>
<th>Post-op continence status</th>
<th>Results for quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasan (1995) [18]</td>
<td>2</td>
<td>48 (13)</td>
<td>Ileum</td>
<td>307</td>
<td>588</td>
<td>NP</td>
<td>NP</td>
<td>38</td>
<td>69</td>
<td>Cured/improved: 92%</td>
<td>Good: 83%</td>
</tr>
<tr>
<td>Mast (1995) [77]</td>
<td>3</td>
<td>28 (24)</td>
<td>Ileum</td>
<td>235</td>
<td>511</td>
<td>72</td>
<td>46</td>
<td>30</td>
<td>95</td>
<td>Cured/improved: 95%</td>
<td>NP</td>
</tr>
<tr>
<td>McInerney [42]</td>
<td>3</td>
<td>100 (50)</td>
<td>Ileum</td>
<td>196</td>
<td>867</td>
<td>NP</td>
<td>NP</td>
<td>24</td>
<td>92</td>
<td>NA</td>
<td>NP</td>
</tr>
<tr>
<td>Singh (1995) [41]</td>
<td>3</td>
<td>78</td>
<td>Ileum, cecum, sigmoid</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>100</td>
<td>NP</td>
<td>Cured/improved: 93.6%</td>
<td>NP</td>
</tr>
<tr>
<td>Khoury (1992) [78]</td>
<td>3</td>
<td>100</td>
<td>Ileum, cecum, sigmoid</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>37</td>
<td>NP</td>
<td>Cured/improved: 91.7%</td>
<td>NP</td>
</tr>
<tr>
<td>Luangkhot (1991) [79]</td>
<td>3</td>
<td>21 (21)</td>
<td>Ileum, cecum</td>
<td>185</td>
<td>595</td>
<td>53</td>
<td>16</td>
<td>37</td>
<td>100</td>
<td>Cured/improved: 95%</td>
<td>NP</td>
</tr>
<tr>
<td>Robertson [80]</td>
<td>3</td>
<td>25 (19)</td>
<td>Ileum, cecum</td>
<td>122</td>
<td>659</td>
<td>23</td>
<td>7</td>
<td>14</td>
<td>Cured/improved: 40%</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>Hendren (1990) [81]</td>
<td>3</td>
<td>129</td>
<td>Ileum, stomach, sigmoid</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>Cured/improved: 94%</td>
<td>NP</td>
</tr>
<tr>
<td>Sidi [82]</td>
<td>3</td>
<td>12 (12)</td>
<td>Cecum, sigmoid</td>
<td>134</td>
<td>562</td>
<td>NP</td>
<td>&lt;30</td>
<td>1.3</td>
<td>NP</td>
<td>Cured/improved: 100%</td>
<td>NP</td>
</tr>
<tr>
<td>Lockhart [83]</td>
<td>3</td>
<td>15 (15)</td>
<td>Ileum, cecum, sigmoid</td>
<td>&lt;150</td>
<td>330-480</td>
<td>&gt;40</td>
<td>18-38</td>
<td>NP</td>
<td>NP</td>
<td>Cured/improved: 86%</td>
<td>NP</td>
</tr>
</tbody>
</table>
a cohort study (LOE2) focusing on this particular problem [31]. They report a high rate of intestinal transit disorders, affecting almost 50% of patients treated for neurogenic bladder. These complications distressed patients and nearly 10% regretted having undergone surgery. Although transit disorders cannot be imputed to surgery alone (patients with neurogenic bladder may have intestinal transit disorders unrelated to surgery), patients should be informed of this risk.

Since the gastrointestinal tract mucosa resorbs urine, water-electrolyte disorders may occur. Hyperchloremic acidosis is reported in up to 15% of cases (LOE 2-3). These water-electrolyte disorders may be accompanied by anomalies of calcium metabolism that do not appear to have any significant long-term effect, particularly on child growth, but the subject is still under debate (LOE 3) [32-35]. However, care must be taken when treating patients with a marked decrease in creatinine clearance, since metabolic acidosis is no longer compensated [4](LOE4).

In theory, diversions performed using the ileocaecal junction and the end segment of the ileum would expose patients to a risk of vitamin B12 deficiency (with possible onset of megaloblastic anemia). The fact that the intestinal segments measure less than 50 cm would explain why very few patients suffer vitamin B12 deficiency.

The risk of cancer development of the newly formed reservoir is particularly feared since neuro-urological surgery is often indicated in patients with long life expectancy, many being children. The general consensus today is that patients with a bladder reservoir are at higher risk of developing a tumour than is the general population, but this risk has not as yet been clearly defined. The figures usually given for the risk of tumour development range from 1 to 3% [36, 37]. (LOE 4). Most of the published cases concern adenocarcinoma at the junction of the intestinal mucosa with the urothelium. These usually developed long after the initial surgery (over 10 years in most cases). Some patients developed urothelial tumours with the typical risk factors. Two facts should be emphasised with regard to neurogenic bladder (augmented or not):

- The sensitivity and specificity of the routine bladder tumour diagnostic and monitoring tools (urinary cytology, BTA test, simple cystoscopy, etc.) are reduced. Patient monitoring can only be envisaged by regular cystoscopy with biopsy of suspect areas.
- Monitoring is essential, since many patients develop tumours without symptoms and may be not be diagnosed until late.
- The most serious and possibly life-threatening complication is cystoplasty perforation (LOE3). This can happen whichever gastrointestinal segment is used, but occurs more often after ileocystoplasty [38](LOE3). It is estimated to occur in 5 to 13% of cases [16](LOE3). Perforation usually occurs on the graft or at the junction of the bladder with the enterocystoplasty and often results from high pressure within the enterocystoplasty, or more rarely from traumatic catheterization or urodynamic investigations [39](LOE4).

**FUNCTIONAL OUTCOME**

The functional outcome of bladder augmentation by enterocystoplasty is given in Table 10-Table 10 ctd. Only series of patients undergoing bladder augmentation for neurogenic bladder were retained in our analysis. Given the wide range of indications, surgical techniques and enteric segments used, it is difficult to draw any clear conclusions from these studies. Furthermore, most were retrospective studies; however certain points should be noted.

All authors reported an improvement in bladder capacity and compliance (LOE2-3) [17, 18, 40-42]. Improved vesicorenal reflux has already been mentioned. More than 90% of patients achieved nocturnal continence, and between 91 and 100% achieved diurnal continence [17, 18, 40-42] (LOE2-3).

Two quality-of-life studies (LOE2) reported improvement rates exceeding 90% [18, 43]. However, we would draw attention to one potential bias due to the heterogeneous population in these studies. Some patients underwent augmentation for detrusor overactivity of neurological origin, and others for idiopathic overactive bladder. We may conclude that these results can be applied to the sub-population of neurogenic patients, since they have already accepted intermittent catheterization before surgery.

If the bladder compliance defect persists, exclusion or ischemia of the intestinal patch must be investigated [37, 42]. Sometimes urinary leakage is related to sphincter deficiency and may be treated by an artificial urinary sphincter [44] or other means of urethral pressure reinforcement [37, 45]. However most authors consider that this type of adjunctive treatment should not be performed routinely since most patients have a good functional outcome after bladder augmentation, and only those with marked sphincter deficiency prior to surgery require these measures.

**b) Possible alternatives to enterocystoplasty**

1. **GASTROCYSTOPLASTY AND URETEROCYSTOPLASTY**

The use of a pediculated segment of stomach (gastrocystoplasty) or ureter (ureterocystoplasty) as an alternative to enterocystoplasty has been reported mainly for children with a neurogenic bladder. In theory, its advantage lies in the absence of metabolic acidosis, but in adults this is very theoretical. Moreover, both these intestinal segments secrete less mucus than the small and large intestines [46-50]. Abdel-Azim et al.
utomation technique in adults (LOE3). In the light of their experience with children, they decided to use this technique in a set of young adults (mean age: 23 years, range: 4-32 years). Their paper records that the short-term results (3 years mean follow-up) of gastrocystoplasty were satisfactory, with increased functional bladder capacity and no impairment of the upper urinary tract (LOE3). However, two disadvantages are reported. First, a hematuria-dysuria syndrome requiring occasional use of antacids sometimes accompanied gastrocystoplasty. Second, the maximum bladder capacity was slightly lower than that observed in patients having undergone enterocystoplasty. This may have a benefit for easier bladder voiding but a negative effect due to the fear that in the long-term, the bladder may lose its capacity and further surgery will be required. The outcome in the very long-term for patients who have undergone laparotomy, can be performed by simple video-assisted gastrointestinal tract surgery (intra or extra peritoneal celioscopy) and/or perforation is poorly documented. An experimental animal study concluded that the bladder rupture pressure was slightly lower after enterocystoplasty, thus exposing the patient to an increased risk of rupture (LOE4). A retrospective study (LOE4) reported 20% complications for enterocystoplasty (infectious digestive and parietal complications) against only 3% for detrusorectomy [62]. The rate of secondary rupture and/or perforation is poorly documented. An experimental animal study concluded that the bladder rupture pressure was slightly lower after detrusorectomy than after enterocystoplasty, thus exposing the patient to an increased risk of rupture [68] (LOE4).


Bladder autoaugmentation without any associated gastrointestinal tract surgery as an alternative to enterocystoplasty was proposed as early as 1972 by Mahony and Laferte [51] who performed detrusorotomies (detrusor incision without resection) to increase bladder capacity and reduce incontinence. With Cartwright and Snow [52], the technique then evolved to detrusorectomy. This involves excising a thick segment of muscle from the dome of the bladder, leaving only the mucosal membrane in place. Bladder pressure gradually dilates the “demuscularized” area resulting in bladder augmentation.

The intervention, initially described by extra peritoneal laparotomy, can be performed by simple video-assisted surgery [53, 54] (intra or extra peritoneal celioscopy) or by robot-assisted surgery [55](LOE4). The detrusor can be dissected by laser [56](LOE3). The area around the detrusorectomy can be protected using the omentum [57] or a striated muscle [58] (rectus abdominus muscle) to prevent perforation and retraction(LOE4).

Techniques using free-graft or pediculated de-epithelialized gastric patches [59, 60] require gastrointestinal tract surgery and were therefore not included in the present work. Furthermore, most of the previously published studies concerned children. All the studies are retrospective and with few patients. For children, most authors [57, 61-65] report poor results after surgery, both symptomatic and urodynamic, together with a risk of upper urinary tract impairment(LOE4). Two authors recently reported better results with certain technical artefacts, namely an extensive detrusorectomy [66](LOE4) and rectus muscle hitch and backing [58](LOE4). The last technique supposes a large dissection of the rectus muscle. Urothelium is the sutured to this muscle in the theoretical objective to prevent its retraction and shrinkage.

Only three series are available for adults and all are retrospective studies. The first, published by Stöhrer et al in 1997 [67] (LOE3), reports interesting results for efficacy, with increased functional bladder capacity. However, the authors did not report mean follow-up and described a mixed population with 39 patients with neurogenic bladder and 11 patients without. The two other published series concerning adults [61, 62] did not confirm these findings but did confirm the marked superiority of enterocystoplasty with respect to both urinary symptoms and upper urinary tract impairment (LOE3). An analysis of the paper by Kumar [61] shows that the results of enterocystoplasty may differ according to the type of detrusor overactivity (DO). He reported good results for patients presenting idiopathic DO. Conversely, with a mean follow-up of 79 months, nearly all patients (5 of 6) with neurogenic detrusor overactivity were not improved (LOE3).

There is little information on specific complications, but detrusorectomy is simpler and seems to present less risk than enterocystoplasty. A comparative retrospective study (LOE4) reported 20% complications for enterocystoplasty (infectious digestive and parietal complications) against only 3% for detrusorectomy [62]. The rate of secondary rupture and/or perforation is poorly documented. An experimental animal study concluded that the bladder rupture pressure was slightly lower after detrusorectomy than after enterocystoplasty, thus exposing the patient to an increased risk of rupture [68] (LOE4).


It is not yet possible to use artificial bladders. However, bladder augmentation using porcine intestinal submucosa (SIS, Cook®) [69](LOE4) or an acellular matrix of porcine dermal collagen and elastin fibres (Pelvicol, Bard®) [70](LOE4) have been described. These biomaterials can only be used after performing clam cystotomy since the area to be colonized should not be too large. It also appears that the use of biomaterials is associated with higher incidence of bladder lithiasis. To date, the number of reported cases remains limited. Larger trials are necessary to evaluate routine use of biomaterials. The use of autologous tissue may also be envisaged. In 2006, Atala [71] has published promising preliminary results on a small prospective study of 7 young patient with a neurogenic bladder (LOE 2). In this article he describes his technique, which consists in seeding patient’s urothelial and muscle cells on a biodegradable scaffold. After 7 weeks, this engineered artificial bladder could be implanted in patients. Although the small number of patients doesn’t allow definitive conclusion, a trend to a better bladder capacity and compliance was observed. Future studies will have to confirm these very exciting results.
RECOMMENDATIONS

- Any segment of the gastrointestinal tract may be used for bladder augmentation, but the ileum seems to give the best results in terms of ease of use, risk of complications and efficacy (B). Few data are available concerning gastrecystoplasty and ureterocystoplasty in adults (D).
- When the bladder suffers a significant compliance defect, supratrigonal cystectomy is preferable to clam cystoplasty (B).
- Bladder augmentation may solve low-grade vesicorenal reflux. In the event of grade IV or V reflux, ureteral reimplantation may be necessary (C).
- Patient should be informed that the most frequent and serious complications are bladder calculi and perforation at the bladder/bowel junction, usually caused by the abdominal pressure (B).
- Bladder augmentation may have sequelae such as intestinal transit disorder, and patients should be informed of this before surgery (C).
- The body of evidence concerning detrusor myomectomy in neurological patients is controversial. Therefore, detrusor myomectomy should not be recommended in these patients with impaired bladder function (D).
- Bladder augmentation using biomaterials or tissue engineering is promising, but the preliminary results need to be confirmed by larger studies (D).
- Due to risk of complications regular follow up is needed (B).

6. CUTANEOUS CONTINENT URINARY DIVERSION

Keywords used for the medline research

Continent urinary diversion; vesicostomy; cystostomy; neurogenic bladder; spinal cord injury; spina bifida; myelomeningocele; multiple sclerosis

a) Introduction

For certain patients, urethral catheterization can be or become, unacceptable or even impossible. The following list is not exhaustive, but describes the more frequent reasons:

- Functional limitations of the upper limbs (Tetraplegia [1] unilateral or bilateral plexus problems, musculoskeletal trauma problems)
- Cognitive disorders (forgetfulness, lack of comprehension, refusal)
- Difficulties in terms of mobility and/or undressing (spasticity, upper spinal cord injury resulting in difficulty in maintaining the equilibrium of the trunk and or limited control of the upper limbs, obesity).
- Failure to reach the urethra independently (more common in women, compounded by the tilted pelvis and all other factors that cause mobility difficulties.)
- Urethral injuries (stenosis, fistulas, hyperesthesia), urethral pain.

In these situations, the realization of a continent cystostomy may be an option. The general principle is to permit the emptying of a full bladder, independently and easily, by intermittent catheterization through an efferent tube attached to the wall of the lower half of the abdomen. The absence of any leakage from the cystostomy is controlled by its own watertight system associated with the return process of a capacitive and compliant reservoir.

This will require careful selection of patient candidates especially when there is any function impairment of the upper limbs (trauma to the spinal cord) [2-4](LOE3).

A pre-operative assessment is indispensable and must include the motivation of the patient, capabilities for dressing and undressing, capability of catheterization in the planned stoma area, tolerance for the time and potential discomfort involved.

In the case of cognitive difficulties that are too significant, if a severe upper limb dysfunction exists [1] or if compliance of the patient remains an impossible obstacle, continent diversion is not indicated. Contraindication can also be a deteriorated renal function [5].

In neuro-urology, techniques for heterotopic continent neo-reservoir (derivation supra-bladder such as Koch pocket, Benckenhoun, Mainz, Miami…) are seldom used initially. They can be offered to patients with vesico-renal reflux, with incontinence through the native urethra despite bladder enlargement or when closure of the bladder neck will be needed (e.g. urethro-vaginal fistula).

b) Results of the different types of cystostomy:

The series are in the vast majority, retrospective (LOE 3) and frequently combine several techniques. This makes the analysis of the results difficult, but some major facts can be gleaned from them.

The catheterizable tube must be able to penetrate the intact or enlarged bladder and it must be able to reach the abdominal wall through a direct pathway with easy access for the patient that has already been predetermined by pre-operative research. The pathway...
of the tube must be direct in order to facilitate self-
catheterization. Two major families of techniques can
be used: simple tubes implanted with an anti-reflux
system and intestinal loop invaginations.

1. SIMPLE TUBES:
   a. Technique:

   Virtually any anatomical structure that is tubular or
   that can be tubularized and that is vascularized can
   be used to make a continent catheterizable tube
   [4](LOE4).

   The two structures that are the simplest to use are:

   The appendix: Transappendicular cystostomy
   according to Mitrofanoff's procedure [6] has long been
   the most used technique(LOE3). Different
   modifications have been proposed, especially to gain
   more length by removing a cecal cuff.

   A short, remodeled intestinal segment (small intestine,
   less frequently the sigmoid or right colon). Yang and
   Monti simple [7] (LOE3) or double technique and the
   Yang-Monti technique modified according to Casale
   in order to gain length by avoiding a double tube [8]
   (LOE3).

   Other structures that have been used in a more anecdotal
   manner, primarily in children: cecum and appendix
   monobloc [9] (LOE4), bladder [10](LOE4), stomach
   diverticulum [2, 13](LOE4), or the preputial or clitoral
   skin [14] (LOE4).

   For most authors, continence of the tube was
   guaranteed by implantation in the native bladder or
   in the augmentation via a submucosal path similar to
   that used in ureteral reimplantation for vesicorenal
   reflux. (LOE4). The submucosal path length must be
   at least 2cm, and is adapted to the bore of the tube
   (two to three times the diameter) [4] (LOE4). A posterior
   or posterolateral bladder flap (kept in case of a
   supratrigonal cystectomy) should allow a more solid
   implantation of the tube in the bladder [15](LOE2).
   Direct implantation into the digestive plasty has also
   been reported.

   The stoma's cutaneous anastomosis is made in the
   lower half of the abdomen, at the umbilicus, most
   frequently by principle, or in the right or left iliac fossa.
   Most authors recommend the interposition of a skin
   flap in the distal end of the tube in order to avoid
   frequent stenosis on the circular orifice scars. Several
   techniques have been proposed: flap in V, VOZ [16]
   (LOE3), and VR [17](LOE3). However, at present,
   the results published do not confirm that the risk of
   stenosis is avoided by any of the techniques.

   It seems essential that the site of the stoma would be
determined preoperatively in patients with functional
limitations of the upper limbs. The site is chosen based
on the patient's capabilities and the position during self-
catheterization (seated in a chair, supine, other). The
surgical technique used in this particular case must
allow access to any point on the lower half of the
abdominal wall [3, 18, 19].

b. Results:

Table 11 summarizes the results in terms of stoma
continence, utilization of the DUCC (carrying out ASPI
across the DUCC), and complications. We retained
only points specifically related to the continent stoma
in the articles. The necessity of reservoir augmentation
(80% of published cases) and techniques allowing
reinforcement of ureteral continence are addressed
in another chapter. Similarly, complications of the
upper apparatus were not detailed. They are in
essence found in the oldest series, in which bladder
augmentation was seldom proposed, and/or during a
ureteral reimplantation procedures (reflux treatment).

In adults as in children, techniques especially of
Mitrofanoff (or variations using the appendix) and of
Yang-Monti allow functional, continent stomas to be
obtained in 75 to 100% of cases (LOE3).

Seven studies indicate significant improvement in
quality of life after the procedure related to improved
autonomy in bladder evacuation, to continence, and
to improved sex life [3, 15, 19-23] (LOE2-3).

The rate of stoma complications (16 to 60%) is
dominated by the risk of stenosis, which is most often
treatable by a simple dilation [24] (LOE3). Many authors
emphasize the fact that this complication occurs most
often in the year following surgery. However, Liard's [25,
16] results (LOE3), which reported an elevated (65%)
intervention rate at 20 years of monitoring, must be
emphasized. For most authors the rate of complications
related to the tube continent was lower when the
segment used was the appendix or intestines remodeled
according to Yang-Monti (LOE3). However, these two
plasties seem to have equivalent complication rates.
Only Narayanaswamy et al [26] (LOE3) reported higher
rates for catheterization difficulty and reinvention
with the Yang-Monti tube in comparison to the appendix.
The Monti tubes in this study were double tubes in
68% (17/25) of cases, and the majority of the
complications were related to the junction area for the
two semi-tubes and not to stoma stenosis. Therefore
it seems that this lengthening method should be used
with caution. If there is a problem with tube length, the
method proposed by Casale [8] (LOE4) has the
theoretical advantage of avoiding an anastomosis on
the tube or a bent pathway at the junction of the two
tubes.

The umbilical anastomosis site for the stoma may be
related to an increased frequency of stoma stenosis
[10, 27] (LOE3). The poorer vascularization of the
umbilicus has been proposed as an explanation [27].
However, results on this point are contradictory with
more recent studies [15].
c. Other types of continent urinary stoma:

Techniques are extremely varied and are better described in the series on bladder cancer. Two technical approaches can be broadly outlined here:

Invaginated valves (Koch pocket, Benchekroun, Mainz) in which the continence mechanism is tied to the flattening of the invaginated valve by urine accumulated in the neo-reservoir;

Ileal-caecal reservoirs in which a portion of the ileum and the ileal-caecal valve are used as a continence mechanism (Indiana pouch, Charleston pouch, Miami pouch).

Data in the literature do not allow a determination to be made as to the superiority of one type of stoma over the others. However, the catheterization difficulties seem to be lower with stomas that use the appendix; the risk of lithiasis seems to be higher with the stomas which require the use of metal staples [28] (LOE4). Several authors have also specifically reported results in neurological patients [20, 29-34] (LOE3).

Continence rates for the stoma vary between 63 and 100%. Complication rates for the stoma are between 10 and 23%. The need to proceed systematically to ureteral reimplantation is aggravated to a certain degree by short term stenosis (0 to 18%), but, as in “simple” tube techniques, few long term follow ups of patients are available.

<table>
<thead>
<tr>
<th>Team</th>
<th>Year</th>
<th>LOE</th>
<th>n (neurogenic bladder)</th>
<th>Mean follow-up (months)</th>
<th>Technique</th>
<th>Functional continent cystostomy (%)</th>
<th>Stoma complication (%)</th>
<th>New procedure on the stoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mhiri [35]</td>
<td>2007</td>
<td>3</td>
<td>20 (28)</td>
<td>53</td>
<td>Mitrofanoff</td>
<td>100</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Karsenty [15]</td>
<td>2007</td>
<td>2</td>
<td>13 (13)</td>
<td>44</td>
<td>Mitrofanoff 7 Yang-Monti 6</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tsurma [23]</td>
<td>2007</td>
<td>3</td>
<td>12 (12)</td>
<td>33</td>
<td>Casale</td>
<td>100</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Franc-Guimond [17]</td>
<td>2006</td>
<td>3</td>
<td>12 (12)</td>
<td>18</td>
<td>Mitrofanoff</td>
<td>100</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Castelian [13]</td>
<td>2005</td>
<td>3</td>
<td>135 (100)</td>
<td>38</td>
<td>Mitrofanoff 74 Yang-Monti 45 Gastric tube 8 Bladder tube 2 Meckel tube 1</td>
<td>NP</td>
<td>23.5</td>
<td>8</td>
</tr>
<tr>
<td>Blaivas [31]</td>
<td>2005</td>
<td>3</td>
<td>98 (15)</td>
<td>108</td>
<td>Mitrofanoff 47 Yang-Monti 7</td>
<td>95</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>Chulamorkoti [36]</td>
<td>2004</td>
<td>3</td>
<td>54 (46)</td>
<td>30</td>
<td>NP</td>
<td>87</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>Barqawi [37]</td>
<td>2004</td>
<td>3</td>
<td>109 (60)</td>
<td>46</td>
<td>Mitrofanoff 114 Yang-Monti ileac 21 Ureter 11 Others 5</td>
<td>92</td>
<td>36</td>
<td>NP</td>
</tr>
<tr>
<td>Lemelle [38]</td>
<td>2004</td>
<td>3</td>
<td>46 (32)</td>
<td>64</td>
<td>Mitrofanoff 23 Yang-Monti 18</td>
<td>96</td>
<td>48</td>
<td>NP</td>
</tr>
<tr>
<td>Walsh [19]</td>
<td>2004</td>
<td>4</td>
<td>6 (6)</td>
<td>44</td>
<td>Mitrofanoff 3 Hemi Kock 2</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>De Ganck [27]</td>
<td>2002</td>
<td>3</td>
<td>53 (45)</td>
<td>32</td>
<td>Mitrofanoff 45 Yang-Monti 8</td>
<td>90</td>
<td>36</td>
<td>NP</td>
</tr>
<tr>
<td>Cain [10]</td>
<td>2002</td>
<td>3</td>
<td>31 (15)</td>
<td>41</td>
<td>Bladder</td>
<td>100</td>
<td>45</td>
<td>NP</td>
</tr>
<tr>
<td>Tekant [21]</td>
<td>2001</td>
<td>4</td>
<td>46 (11)</td>
<td>28</td>
<td>Mitrofanoff 38 Yang Monti 6</td>
<td>88</td>
<td>19.5</td>
<td>NP</td>
</tr>
<tr>
<td>Kochakarn [39]</td>
<td>2001</td>
<td>4</td>
<td>12 (12)</td>
<td>12</td>
<td>Mitrofanoff 10 Yang Monti 2</td>
<td>100</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Narayanaswamy [28]</td>
<td>2001</td>
<td>4</td>
<td>92 (21)</td>
<td>30</td>
<td>Mitrofanoff 69 Yang Monti 25 (17 double, 8 simple)</td>
<td>NP</td>
<td>Appendix 26 Yang Monti 60</td>
<td>NP</td>
</tr>
<tr>
<td>Liard [25]</td>
<td>2001</td>
<td>4</td>
<td>23 (22)</td>
<td>240</td>
<td>Mitrofanoff 20 Bladder flap 2 Ureter 1</td>
<td>75</td>
<td>38</td>
<td>65</td>
</tr>
<tr>
<td>Harris [40]</td>
<td>2000</td>
<td>4</td>
<td>31 (50)</td>
<td>51</td>
<td>Mitrofanoff</td>
<td>96</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Cain [41]</td>
<td>1999</td>
<td>4</td>
<td>69 (100)</td>
<td>48</td>
<td>Mitrofanoff 57 Yang Monti 22 Bladder tube 21</td>
<td>98</td>
<td>20</td>
<td>Appendix 21 Yang Monti 10 Bladder tube 29</td>
</tr>
<tr>
<td>Syora [18]</td>
<td>1997</td>
<td>4</td>
<td>7 (7)</td>
<td>NP</td>
<td>Mitrofanoff 5 Yang-Monti ileac 2</td>
<td>86</td>
<td>14</td>
<td>NP</td>
</tr>
</tbody>
</table>
7. NON-CONTINENT CUTANEOUS URINARY DIVERSION IN NEUROUROLOGY

a) Introduction

Non-continent cutaneous diversion refers to all methods used to divert urine, and where incontinence remains or where a system of extra-physiological continence is created, i.e. urine flow is continuous and requires a means of collecting urine attached to the skin.

In the context of neurogenic bladder, these diversions make it possible to obtain low bladder pressure and to preserve the upper urinary tract.

This type of surgery is a last resort for the many complications related to neurogenic bladder (and congenital anomalies of the lower urinary tract), in patients for whom other therapies have failed to help.

Four techniques are described for non-continent urinary diversions for patients with neurological vesico-sphincter disorders. In order of frequency these are: ileal conduit urinary diversion, ileovesicostomy, cystostomy and cutaneous ureterostomy.

b) Ileal conduit urinary diversion

Ileal conduit urinary diversion is the type of diversion most frequently performed on neurological patients with bladder dysfunction. It differs only slightly from the cystectomy performed for bladder cancer [1]. Pre-operative location of the intended stoma site is crucial and must be adapted to the patient’s main position (wheelchair or bed); the stoma site must be easy to access for management. The ileal segment must be as short as possible to prevent stasis [2](LOE3). There is a variant to this technique whereby a segment of jejunal loop is removed and a stoma made on the left hemi-abdomen. This technique can be proposed after irradiation of the pelvis minor, if the ileum has been impaired and a short loop must be used (about 10 cm) to avoid metabolic disorder (jejunal conduit syndrome: hyperkaliemia, hyponatremia, hypochloremia, acidosis) [3](LOE3).

In neurological patients, ileal conduit urinary diversion by laparoscopy and by robot-assisted laparoscopy have been described [4-7](LOE4). Patients seem to benefit from the procedure, though this remains to be confirmed in the medium and long-term [8] (LOE 2).

1. RESULTS IN NEUROLOGICAL PATIENTS WITH BLADDER DYSFUNCTION

Some series of neurological patients were evaluated to determine the onset of early and late complications [8-14](LOE2-3). Early series of children can be evaluated to determine the morphology of the upper urinary tract and renal function after urinary diversion over a long period (up to 20 years) [15-20](LOE3).

2. EARLY COMPLICATIONS

Mortality is estimated between 0 and 3.4% (LOE2-3) [8-14].

The commonest early complication is intestinal occlusion (4 to 12.6%), usually reversible after prolonged intestinal drainage [8-14](LOE2-3). The risk of gastrointestinal fistula should also be taken into account (0 to 3.3%). As for enterocystoplasty, the current trend is to try to reduce nasogastric tube drainage time to a few hours [21](LOE3).

The most frequent medical complications encountered (3 to 8%) are febrile urinary infections and thromboembolism (2 to 3%)[8-14](LOE2-3).

Other major complications include: urinary fistula in 0.3 to 3.4% of patients which may be prevented by placing a ureteral catheter for about ten days [8-14](LOE3). This complication could be a risk factor for later uretero-ileal anastomosis (LOE4).

3. LATE COMPLICATIONS

a. Gastrointestinal risk

The risk of long-term intestinal occlusion is difficult to evaluate. It ranges between 5 and 7% (LOE3) [9-14]. Even when a short intestinal segment is used, some patients can experiment transient constipation or diarrhoea, which could adversely affect their quality of life[22](LOE2).

b. Complications affecting the bladder left in situ
For the particular indication of neurological patients with bladder dysfunction, several authors have proposed not carrying out cystectomy so as to avoid potentially morbid surgery. At present, this is debatable for several reasons:

- First, there is a risk of pyocyst formation in the unused bladder (21-50%) [9, 10, 14, 23] (LOE3). Even where conservative treatments have been attempted (combining vesical irrigation with antibiotherapy) [24] (LOE3), secondary cystectomy is then necessary in 50 to 100% of cases [10, 15, 17]. For women, a surgical alternative is vaginovesicostomy, which appears to be effective [11, 17] (LOE4).

- Furthermore, the unused bladder is frequently infected and may become an "irritative thorn", especially in patients with spinal injury or multiple sclerosis (LOE4) [10, 25].

- A final argument in favour of cystectomy is that the risk of bladder neoplasia is higher in neurogenic patients, the principal risk factors being long-term indwelling catheterization (more than 8 years), bladder calculi and smoking [26-28] (LOE3). Moreover, screening by cystoscopy-biopsy is not effective [29, 30] (LOE3).

- Finally, improvement of the cystectomy technique (noticeably laparoscopic cystectomy) has considerably reduced related morbidity [8] [31] (LOE2-3). Supratrigonal cystectomy can be performed in men, preserving the prostate and preventing any genital and sexual sequelae.

c. Upper urinary tract complications

Stenosis of the uretero-ileal anastomosis may occur in the medium and long term. This is very damaging to the upper urinary tract and requires regular monitoring of the morphology. In contemporary series of neurological patients with bladder dysfunction, it occurs in 2 to 7.8% of cases within 10 years [9-14] (LOE3). For cases followed for more than 10 years, the finding of 16.5 to 50% stenosis is essentially that of early paediatric series [15-20] (LOE3). Impairment of the upper urinary tract and renal function seems to be correlated mainly with stenosis of the uretero-ileal anastomosis, but also with a long ileal graft and stomal stenosis leading to poor voiding and pyelonephritis [16] (LOE4). In the event of poor functioning of the uretero-ileal anastomosis, some authors suggest endoscopic dilation before further surgical repair of the anastomosis (LOE3) [13, 32-34]. Surgery however remains the reference treatment [32] (LOE3).

The risk of upper urinary tract lithiasis (3 to 31%) is always present in these patients (even without stenosis of the uretero-ileal anastomosis) [9, 10, 13, 14] (LOE3). Patient monitoring should include regular screening of the upper urinary tract to detect any lithiasis and to implement timely treatment (LOE 4).

Chronic bacteriuria is frequent but should not be treated if asymptomatic. Both patients and attending physicians must be informed so as to avoid the administration of unnecessary antibiotics. However, the risk of febrile infection persists over the long term and is logically favoured by uretero-ileal stenosis (12 to 34%) [9, 10, 13, 14].

d. Stoma complications

These are relatively frequent (18.6 to 30%) and varied [10, 13, 14]. The risk of peristomal eventration is the most frequently reported (between 7.7 and 10%). Stomal stenosis may also occur. Stoma complications appear to occur more often in obese patients (LOE3) [35].

Finally, it should be noted that some patient could ask for undiversion. These mainly concern adults who underwent surgery as children and who later wished to recover a continent system, or who have had complications with their non-continent urinary diversion [36-40] (LOE3-4).

\[\textit{c) Ileovesicostomy [41-50]}\]

This technique was first described by Cordonnier in 1957 for treatment of three children suffering from myelomeningocele [48] (LOE4). Its theoretical advantages are relative simplicity, the absence of dissection and suture of the ureter, thus preventing ureteral complications and the potential of "\textit{restitutio ad integrum}" of the bladder (only one case described) [47] (LOE4).

The surgery consists in removing a 10 cm ileal segment from about 15 to 20 cm above the ileocecal valve. One side of the segment is anastomosed to the dome of the bladder and the other to the skin halfway between the iliac spine and the umbilicus. A partial cystectomy is performed to reduce reservoir volume and possible urine stagnation. Surgical variants have been described with simple partial detubularization of the ileum before vesico-ileal suture [50], or the creation of a modified Boari flap on the bladder associated with partial detubularization of the ileum [42, 45-47, 49] (LOE3). These improve drainage by reducing the ileal segment. Laparoscopic ileovesicostomy seems to be feasible [41, 44] (LOE4).

One of the problems with this type of surgery, particularly in women, is the need for further surgery to prevent residual urinary leakage. All authors agree that this significantly prolongs surgery time. This further surgery may consist in closing the bladder neck or placing a suburethral tape [47, 49, 51, 52] (LOE3). Some authors propose performing this surgery later, where necessary [50] (LOE3).

1. \textbf{Early complications}

Early complications are related to the underlying condition of these patients, which is often poor. No case
of post-operative mortality has been reported in the published series [42, 43, 45-47, 49, 50, 52](LOE3). In some cases of poor drainage through the stoma, the drainage was prolonged to six weeks (instead of the usual three). Other early complications were related to poor results of the surgery performed to render patients continent (Table 12). Patients with this type of problem are the most likely to resort to cystectomy with ileal diversion (3 to 6%) [47, 51](LOE3).

2. Late complications

These are summarized in Table 10. No reported series to date has more than five years of follow-up. The most frequent problems appear to be poor voiding related to stenosis of the stoma or the ileovesical anastomosis. Only one report specifically mentions problems related to stoma equipment that occur in about 28% of patients [51](LOE3). The incidence of renal or vesicular lithiasis appears to be low, and several authors report that affected patients had history of lithiasis.

Renal function appears to be preserved with this procedure at least with a mean follow-up of five years (LOE 3) [16, 42, 43, 45-47, 49-51, 53]. No case of impaired renal function, or even post-operative ureterohydronephrosis was reported.

Finally, it should be underline that two patients in the series with the longest follow-up who developed a bladder tumor [45](LOE4).

d) Vesicostomy

Vesicostomy was described by Blocksom in 1957 [54] and detailed more recently by Lapides [55, 56].

The technique consists in constructing a bladder tube anastomosed to the skin by making a transverse suprapubic incision to reach the space of Retzius. The stoma is located half way between the umbilicus and the incision.

The principal benefits of vesicostomy are its simplicity and reversibility, particularly in children [57-63], making it possible to envisage temporary surgery to treat an acute urological problem. In pediatric series, an improvement in the symptoms of infection was reported, with 6 to 20% of patients suffering bladder calculi and 6 to 18% stomal stenosis. Hydronephrosis improved or stabilized in most cases. The rate of end-stage renal failure varied between 6 and 18% for mean follow-ups of 6-7 years.

Nowadays, it is rare to conserve a vesicostomy long term. The results of Lapides are therefore all the more interesting: after two years of follow-up, no urinary infection, 16% poor drainage and 12% calculi [56] (LOE3). Renal function was preserved. At 10 years of age, however, 9.6% of deaths due to end-stage renal failure, mainly due to calculi and repeated infection of the upper urinary tract, were reported [56] [64](LOE3). At 20 years, the rate of chronic renal failure is around 16.6%[54-65](LOE3).

e) Cutaneous ureterostomy

During this procedure, the ureters are placed in direct contact with the skin without using the gastrointestinal tract. There is no gastrointestinal resection/anastomosis which is a marked source of morbidity and mortality. Surgery via the retroperitoneal route is quick and simple.

The main inconveniences are: cutaneous stenosis if the stoma is left without catheter, upper urinary tract infections and calcification around catheters if stoma is equipped. Moreover, it is frequently necessary to construct a double stoma.

It is used in adults, usually in the context of palliative urinary diversion for those with obstructive pelvic cancer (bladder, uterus, rectum), and rarely in neurological patients [66-71].

Surgery is simple: in the absence of cystectomy, two short lateral incisions are made in the iliac fossa, at approximately 3-4 cm from the anterosuperior iliac

Table 12. Results for contemporary series of ileovesicostomy

<table>
<thead>
<tr>
<th>LOE</th>
<th>n</th>
<th>Mean follow-up (months)</th>
<th>Reoperation following primary surgery (%)</th>
<th>Stomal problems (%)</th>
<th>Kidney lithiasis</th>
<th>Bladder lithiasis</th>
<th>Continent (%)</th>
<th>Post-op hydronephrosis (%)</th>
<th>Symptomatic urinary infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan, 2007 [51]</td>
<td>3</td>
<td>50</td>
<td>26.3</td>
<td>54</td>
<td>38</td>
<td>2</td>
<td>6</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>Gauthier, 2003 [43]</td>
<td>4</td>
<td>7</td>
<td>37.4</td>
<td>NP</td>
<td>1/7</td>
<td>1/7</td>
<td>0/7</td>
<td>NP</td>
<td>0/7</td>
</tr>
<tr>
<td>Atan, 1999 [42]</td>
<td>3</td>
<td>15</td>
<td>23.2</td>
<td>NP</td>
<td>16</td>
<td>33</td>
<td>20</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>Gudziak, 1999</td>
<td>3</td>
<td>13</td>
<td>23</td>
<td>23</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>Leng, 1999</td>
<td>3</td>
<td>38</td>
<td>52</td>
<td>NP</td>
<td>13</td>
<td>10</td>
<td>5</td>
<td>NP</td>
<td>3</td>
</tr>
<tr>
<td>Mutchnik, 1997</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>1/6</td>
<td>1/6</td>
<td>0</td>
<td>0</td>
<td>6/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Rivas, 1995</td>
<td>3</td>
<td>11</td>
<td>24</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schwartz, 1994</td>
<td>3</td>
<td>23</td>
<td>45</td>
<td>NP</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>NP</td>
<td>0</td>
</tr>
</tbody>
</table>

860
spine. Direct retroperitoneal access is made and the two ureters located on the internal border of the psoas muscle or above the iliac vessels.

It is important that the peri-ureteral region be spared and the ureter sectioned as low as possible. The ureter is then catheterized and raised to the skin. The stoma is formed by attaching the ureter to the skin, or by spatulating the sutured ureter on a V-shaped cutaneous incision (separate sutures with fine resorbable thread).

Variants are described so as to obtain only one stoma: Y-transuretero-ureterostomy, implantation of both ureters in a single stoma, implantation of a single ureter (ureter ligated to the least functional kidney, or even nephrectomy). The use of cutaneous plasties may remove the need for ureteral catheterization [72].

Cutaneous ureterostomy was first performed in the 1960s, to treat children with spina bifida and severe upper urinary tract impairment [68, 71]. The technique was also developed to treat malformative uropathies (extrophy of the bladder and the posterior urethral valves) [66, 68-70].

Long-term results with a mean follow-up of 8 years are given hereafter: rates of stenosis between 8.7 to 11%, infections from 6.6 to 10% and calculi from 10 to 15.5%) [67, 70](LOE3).

Renal function was preserved for short follow-up times, but fatal end-stage renal failure occurred in up to 26.6% of children during long-term follow-up [69](LOE3).

This technique is almost never used for neurological patients with bladder dysfunction anymore because conservative treatments (intermittent catheterization, urological endoscopy) have improved and the number of children suffering from spina bifida or presenting with complex malformation of the lower urinary tract has gradually lowered. Moreover, new urinary diversion techniques have been developed.

RECOMMENDATIONS

- Utilization of a short intestinal segment (10 cm maximum).
- Minimal dissection of the ureters.
- There are several reports of good results for ileovesicostomy, but the medium-term results need to be confirmed in the long term. Quality-of-life studies should also be performed (C).
- Vescicostomy may be a useful transient solution, particularly for children (D)
- Cutaneous ureterostomy shouldn’t be used for non-continent urinary diversion in adult patients because of the rate of long term complications (B).

D. NEUROLOGICAL FAECAL INCONTINENCE

I. EPIDEMIOLOGY

• Summary from the previous edition [1]

There have been limited numbers of references giving data on prevalence of faecal incontinence (FI) following neurological diseases. Searching from Pubmed from 1964 to 2004, 36 papers were included and the prevalence and incidence of FI varied due to different definitions, severity and also causes/diseases.

The incidence of FI among spinal cord injury (SCI) patients after discharge from rehabilitation was reported between 11% and 75%; the prevalence of constipation and/or FI among multiple sclerosis (MS) ranged from 20% to 73%; and 30% to 50% of Parkinson’s disease (PD) patients reported bowel incontinent.

Regarding stroke patients, during acute admission 32% to 79% of the patients reported FI; the prevalence dropped to 25% to 28% at discharge and 12% to 19% at 6 months. New-onset FI in stroke survivors was transient. Modified risk factors for FI at 3 month after stroke onset were anticholinergic drug use and difficulty with toilet access. It was recommended that bowel dysfunction should be evaluated jointly with bladder dysfunction.

• Search strategy

To add new information to the previous edition, we searched from Pubmed from 2004 to 2008 with search words neurogenic bowel, faecal incontinence, prevalence, incidence, epidemiology, stroke, SCI, MS, PD. Relevant papers from Pubmed, non-Pubmed,
and also other relevant papers that were not cited in the previous edition were recruited and summarized as follows:

1. SPINAL CORD INJURY

During rehabilitation phase, Aya? et al (2006)[2] studied 24 traumatic SCI patients before applying abdominal massage and found that 45.8% had abdominal distention, 41.7% had FI and 25% had difficult intestinal evacuation. New PW (2007) [3] retrospectively reviewed 70 non-traumatic SCI consecutively admitted for initial rehabilitation, 5% of the patients (excluded who died) reported having FI, incontinent at least once per week before discharge.

According to the survey of the impact of secondary conditions after SCI reported in 2007 [4], 13.8% of 65 chronic SCI patients (mean current age 43.8 years, mean years since injury 13.7) rated bowel dysfunction (FI, constipation, diarrhea) as significant or chronic problem, equal to bladder dysfunction and circulatory problem.

Regarding chronic SCI, Tongprasert and Kovindha (2006) [5] studied 100 chronic traumatic SCI patients (duration from onset > 6 months, average 6 years) in Chiang Mai, Thailand and compared with 55 normal persons; 86% of the SCI patients reported constipation, 35% reported FI and 16% had hemorrhoids. The prevalence of constipation and FI were significantly different (P<0.0013) from the normal population (constipation 5%, FI 1.8%). However, prevalence of hemorrhoid between SCI and normal persons was not different (16% vs. 20%, p = 0.338). According to the study of Ng et al (2005)[6] done in 110 established traumatic SCI persons (> 12 months after injury, median 17 years) in Sydney, Australia, the prevalence, based on the Rome II Integrative Questionnaire, was as follows: 41% of FI, 22% abdominal bloating, and 46% constipation (including laxative use). Another prospective, multicentre follow-up observational study was reported in 2007 by the Italian Group for the Epidemiological Study of SCI [7], only 2.7% of 403 traumatic SCI persons (mean duration from discharge to follow-up 3.0+/−0.68 years) reported no bowel continence (= FI), 20.1% had partial, 77.2% had full bowel ‘continence’ (absence of unplanned bowel evacuations) and 70.5% had bowel autonomy (patient’s ability to perform bowel management without assistance). According to the survey in Canada reported in 2004 by Liem et al [8], the most common complication among 352 SCI volunteers for more than 20 years was bowel problems: 47.9% constipation and 41.8% diarrhea/bowel accidents.

FI was found to associate with higher level of anxiety (odds ratio, OR = 2.4, p =0.05) [6] and severity of injury [5] but not with the level of injury [5,6]. According to the study of Vallé et al (2006)[9], they found that in 54 patients with motor complete SCI (mean duration from onset 6 years), 67% presented with constipation (according to Rome II criteria) and 85% some degree of FI. They also found associations between bowel abnormalities i.e., constipation and FI and different neuropathophysiologic patterns. Those with SCI above T7 had frequent constipation (86%) and not severe FI; those with SCI below T7 with preserved sacral reflexes had not so frequent constipation (50%) and not severe FI; and those with SCI below T7 with no sacral reflexes had not very frequent constipation (56%) and greater severity of FI. When compared with those with spinal sacral reflexes, those with no such reflexes had significantly more severe FI (p < 0.005)[9].

According to Krog et al (2006)[10] who did a study in 424 SCI patients to develop and validate a symptom-based score for NBoD, those with daily FI had 10 times more impact on QOL than those with no FI (OR 10.0, p <0.05). Moreover, studies showed that NBoD had significant impact on QOL of chronic SCI patients [10] and they had significantly lower Gastrointestinal QOL score as compared with the normal persons (92.51 +/- 16.21 vs 118.33 +/- 14.17, p <0.001)[5]. From the Italian study [7], loss of bowel/bladder autonomy was correlated significantly with complications (OR 2.202; 1.357-3.574; p <0.001), re-admission (OR 2.097; 1.306-3.366; p < 0.002) and death (OR 5.457; 2.350-12.670; p <0.0001).

Regarding constipation, its association with level of injury was supported by many studies [5,6,9] i.e., upper motor neuron NBoD vs lower motor neuron NBoD (p =0.0013)[5]; cervical injury had more than 5 times more frequent constipation than lumbar injury (OR =5.6, p =0.02)[6]; lesion above T7 had more constipation than lesion below T7 (p <0.05)[9]. In addition, constipation was also associated with severity of injury [4] and taking bladder relaxants [5]. Moreover, it was associated with a 97% increase in the likelihood of needing more help with activities of daily living (ADL) [8].

2. STROKE

In 2006, Brittain et al [11] reported prevalence of isolate UI, FI and double incontinence (DI) in stroke survivors living in community of Leicestershire, United Kingdom. Those living in institutional care were excluded. Of 1,483 stroke survivors, the prevalence was as follows: 6.9% any FI, 4.7% major FI, 2.2% minor FI, 4.3% FI and UI (or DI) and 0.8% isolated FI. Major FI (soiling of underwear or more on a monthly basis) was 4.5 times as prevalent in stroke survivors as in the non-stroke population. DI (major FI and monthly urine leakage) was more than 4 times as high in stroke survivors than in the non-stroke population (4.3% was 0.9%, P < 0.001). Isolated FI as well as isolated UI was also significantly higher in the stroke population. According to the epidemiologic multi-centre study of the Thai Stroke Rehabilitation Registry [12], on admission to rehabilitation, 31.5% of 327 stroke patients (median 24 days; about 5%
admitted one year after onset) reported of bladder and bowel problems: 24.5% UI, 8.6% urinary difficulty and 11.9% FI.

Regarding factors related to FI in stroke, urinary incontinence (adjusted OR 8.1; 95% CI 6.62-9.69) and functional limitation (adjusted OR 4.02; 95% CI 3.27-4.95) were significantly related to major FI in stroke living in community [11].

3. MYELOMENINGOCELE

According to the Dutch study on the prevalence of incontinence in young adult spina bifida reported in 2007[13], of 179 participants (142 with spina bifida aperta and 37 with spina bifida occulta), 60.9% had UI and 34.1% had FI (defined as having accident once a month or more); 109 were diagnosed as having myelomeningocele, 13 as having meningomeningocele and 119 suffered from hydrocephalus. When classified by type of lesions, 40.8% of spina bifida aperta and 8.1% of spina bifida occulta; 46.2% of those with hydrocephalus and 10% of those with no hydrocephalus; and 39.7% of those having lesion at L5 or above and 13.2% of those having lesion below L5 reported FI (P <0.05). Moreover, about 2/3 of those with spina bifida aperta, hydrocephalus and lesion at L5 or above had UI as well; and most of them perceived FI and UI as problem.

4. PARKINSON’S DISEASE

Recently Krogh et al (2008) [14] did a study to compare bowel symptoms in PD with normal control subjects. Most of the cases had minor constipation-related symptom. However 7% of 416 PD but 0% of normal controls reported severe constipation; 27% and 23% with PD had bowel movements less than every second day and incomplete emptying every week, respectively. The severity of PD was associated with assisted defecation (p < 0.001) and unsuccessful attempts at defecation (p < 0.001). Regarding incontinence, 6% of PD patients reported incontinence to solid stool at least one per month, 6% to liquid stool at least one per month; 32% of PD patients had flatus incontinence at least one per week; these were no statistically significant difference to normal control group. They believed that the increase in obstructed defecation symptom but the less prevalence of FI are due to dystonia of the external anal sphincter but intact internal anal sphincter with normal anorectal sensibility.

5. TRAUMATIC BRAIN INJURY (TBI)

According to the report from the Traumatic Brain Injury Model Systems national database [15], the incidence of FI among TBI patients was 68% at admission to inpatient rehabilitation, 12.4% at rehabilitation discharge and 5.2% at 1-year follow-up; and FI was significantly associated with admission Glasgow Coma Scale score, length of coma and post-traumatic amnesia (PTA), length of stay (LOS), frontal contusion, functional independence measure (FIM) scores and urinary tract infection.

6. MULTIPLE SYSTEM ATROPHY (MSA)

Wenning et al (1994) [16] described the clinical features and natural history of 100 patients diagnosed as probable MSA. The most frequent autonomic symptom in men was impotence, and in women was UI. Moreover, Parkinsonism was the initial feature in 46%, but had subsequently developed in 91% of subjects at latest follow-up. According to the North American Multiple System Atrophy Study Group (2005) [17], UI occurred commonly. According to Sakakibara et al. (2004) [18], 93% of MSA patients showed neurogenic motor unit potentials in anal sphincter EMG and concluded that FI resulted from weak anal sphincter due to denervation.

CONCLUSIONS

- Faecal incontinence is prevalent among neurological patients, but less prevalent than urinary incontinence. (LOE 3)
- In spinal cord injured patients, constipation is more frequent than faecal incontinence; faecal incontinence is more severe in those without external anal sphincter responses/reflexes; and constipation is more frequent in those with higher level of injury. (LOE 3)
- The prevalence of faecal incontinence in stroke and traumatic brain injury survivors in community was lower than in hospital-based patients; and urinary incontinence, anticholinergic drug use and functional limitations were associated with faecal incontinence. (LOE 3)
- Faecal incontinence is commoner in spinal cord injured than in stroke patients. (LOE 3)
- Faecal incontinence is a significant problem of chronic neurological patients but not of multiple system atrophy patients. (LOE 3)

RECOMMENDATIONS

- Variation of definition of faecal incontinence as well as constipation should be minimized.
- More epidemiologic study on neurogenic bowel dysfunctions and its consequences in other neurologic diseases.
II. SPECIAL DIAGNOSIS OF FAECAL INCONTINENCE IN NEUROPATHIC PATIENTS

1. SEARCH STRATEGY

To add new information to the previous edition, we searched from Pubmed from 2004 to 2007 with search words of neurogenic bowel and faecal incontinence. There have been only 9 relevant papers and they are summarized as follows:

2. GENERAL PRINCIPLES

According to the previous section D2 in the chapter 17 of the 3\textsuperscript{rd} ICI on Neurologic Urinary and Faecal incontinence [1], 22 papers published from 1996 to 2004 were reviewed. Specific diagnostic tests for faecal incontinence (FI) are tests to assess anal sphincter including levator ani complex functions and structures, anal sensation, rectal sensation and rectal accommodation/compliance.

For neuropathic patients, comprehensive neurophysiologic or electrodagnostic tests – rectal mucosal electrical sensory threshold, thermal sensation, pudendal nerve latency, and needle EMG of the anal sphincter or puborectalis muscle, may be helpful to distinguish non-neurogenic from neurogenic causes of FI especially in those with lower motor neuron lesions (LMNL) including conus medullaris, cauda equina and peripheral nerve damage. For those with suprasacral or upper motor neuron lesions, electromyography (EMG) during straining and balloon expulsion test may show dyssynergic pattern. In addition, saline enema test has been suggested as patients with tethered cord lesion showed hyperactive rectum, diminished rectal saline retention ability and diminished maximal flow.

In spinal cord injured (SCI) patients, FI was not a common problem like constipation. However one should be reminded that constipation is one of the main causes of FI in SCI patients; and anal manometer and colonic transit time (CTT) were frequently selected to assess constipation. In addition endoanal ultrasound (US) or magnetic resonance imaging (MRI), and puborectalis and pelvic floor motion, assessed by dynamic MRI may be helpful to determine myopathic damage that may coexist in neuropathic patients. Moreover as FI has a strong impact on quality of life, QOL. Therefore QOL as well as patients' environment, physical disabilities and co-morbidity should be assessed in order to plan a comprehensive and appropriate management.

3. CLINICAL ASSESSMENT

Vallès et al. (2006)[2] studied and identified a comprehensive neurogenic bowel (NBo) pattern in 54 patients with motor complete SCI based on clinical assessment, total and segmental CTT quantification, anorectal function evaluation by manometry, intrarectal balloon distension, and surface EMG. They revealed 3 patterns: Pattern A, present in above T7 injuries, characterized by very frequent constipation (86%) with significant defecatory difficulty and not very severe incontinence (mean Wexner score 4.5); it was related to moderate delay in CTT (mainly in the left colon and recto-sigma), incapacity to increase the intra-abdominal pressure, and the absence of anal relaxation during the defecatory maneuver; Pattern B, present in below T7 injuries with preserved sacral reflexes, characterized by not so frequent constipation (50%) but very significant defecatory difficulty and not very severe incontinence (Wexner 4.8); the pathophysiological counterpart was a moderate delay in CTT, capacity to increase intra-abdominal pressure, increased anal resistance during the defecatory maneuver, and presence of external anal sphincter (EAS) contraction when intra-abdominal pressure increased and during rectal distension; Pattern C, present in below T7 injuries without sacral reflexes, characterized by not very frequent constipation (56%) with less defecation difficulty and greater severity of incontinence (Wexner 7.2); this was associated with severe delay in CTT (mainly in the left colon), capacity to increase intra-abdominal pressure, absence of anal resistance during the defecatory maneuver, and absence of EAS contraction when intra-abdominal pressure increased and during rectal distension.

Krogh et al. (2005)[3] did a cross-sectional questionnaire study to develop and validate a symptom-based score for neurogenic bowel dysfunction (NBoD). It included 39 questions about background parameters, FI, constipation, obstructed defecation, and impact on quality of life (QOL – no, little, some and major). Based on odds ratios for associations between items and impact on QOL, each item was given a corresponding number of points in the NBoD score; and 10 items met the criteria: frequency of bowel movements (0-6 points), headache, perspiration or discomfort before or during defecation (0-2 points), and drops against constipation (0-2 points each), time used for each defecation (0-7 points), frequency of digital stimulation or evacuation (0-6 points), frequency of FI (0-13 points), medication against FI (0-4 points), flatus incontinence (0-2 points) and perianal skin problems (0-3 points); and if the score is $>14$, NBoD is severe; if the score is 10-13, NBoD is moderate; if the score is 7-9, NBoD is minor and if the score is 0-6, NBoD is very minor.

4. ANORECTAL MANOMETRY

According to the study of Ito et al. (2006)[4], (Table 13) normal physiology of the lower urinary tract (LUT) and the caudal part of the lower gastrointestinal tract (LGIT) in 15 normal healthy volunteers by using the same videomanometry method revealing fluoroscopic images, subtracted bladder/rectal pressures, urethral/
anal sphincter pressures, sphincter electromyography, and urinary/fecal flow. Spontaneous phasic rectal contractions (SPRC) and abdominal strain are features of the LGIT, whereas micturition bladder contraction is a feature of the LUT. These features can aid in understanding the possible rectal ‘artifacts’ of videourodynamics and neurogenic pelvic organ dysfunction.

Li and Xiao (2006)[5] investigated the anorectal status by anorectal manometry in 26 patients with lumbosacral (LS) cord injury (2 AIS: A and 24 AIS: B-D; median age 43.7 years; median time since injury 59.1 months) with mixed symptoms of constipation and/or FI and 13 normal volunteers. The maximum anal resting pressure in the patients group was slightly lower than that in the control group (P=0.939). During defecation maneuvers, 23 of 26 (88.5%) patients and 1 of 13 (7.7%) normal volunteers showed pelvic floor dysfunction (PFD) (P<0.0001). Rectoanal inhibitory reflex was identified in both patients and the controls. The rectal volume for sustained relaxation of the anal sphincter tone in the patient group was significantly higher than that in the control group (P<0.0001). The mean rectal volume to generate the first sensation was 92.7 ml+/-57.1 ml in the patient group, and 41.5 ml+/-13.4 ml in the control group (P<0.0001).

According to the study of Sakakibara et al. (2004)[6], at the resting state, patients with multiple system atrophy (MSA) had a lower anal squeeze pressure (external sphincter weakness) and a smaller increase in abdominal pressure on coughing; during rectal filling, they showed smaller amplitude in phasic rectal contraction, which was accompanied by an increase in anal pressure that normally decreased, together with leaking in 3 patients; during defecation, most of them could not defecate completely and had larger post defecation residuals due to weak abdominal strain, smaller rectal contraction on defecation, and larger anal contraction on defecation (paradoxical sphincter contraction on defecation). They concluded that the responsible sites for these dysfunctions (constipation and FI) seem to be both central and peripheral nervous systems that regulate the lower gastrointestinal tract [6].

5. PELVIC FLOOR IMAGING

Adding fluoroscopy, Ito et al. (2006)[4] used the same videomanometry to reveal fluoroscopic images of the caudal part of the LGIT to help understand the possible rectal ‘artifacts’ of videourodynamics and neurogenic pelvic organ dysfunction in normal volunteers. During the last three years, there was no such study in neuropathic patients.

6. ELECTRODIAGNOSTIC TESTS

In 2006, there were two review articles. One was the study of Craggs et al. [7] who reviewed details of the interactions of somatic and autonomic lumbosacral pathways responsible for coordinating the bladder and sphincters, the nature of their aberration post-injury and those aspects of neural control of the pelvic organs that are amenable to neurophysiological examination in man; and the other was the study of Lefaucheur [8] who reviewed the neurophysiological techniques (Table 14) currently available to evaluate anorectal disorders.

To determine risk factors for development of FI, Dubravica and Demarin (2004)[9] examined the anal sphincters in 110 women with SCI and 91 women with spinal cord lesion (SCL) by means of standardized

Table 13. Shows normal values from manometry of the lower urinary tract (LUT) and the caudal part of the lower gastrointestinal tract (LGIT) derived from the study of Ito et al. (2006) [4] with 15 normal healthy persons

<table>
<thead>
<tr>
<th></th>
<th>LUT</th>
<th>LGIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sphincter pressure (cmH20)</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td><strong>Storage phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Volume at first sensation (mL)</td>
<td>170</td>
<td>129</td>
</tr>
<tr>
<td>- Maximum capacity (mL)</td>
<td>405</td>
<td>320</td>
</tr>
<tr>
<td>- Compliance (ml/cmH20)</td>
<td>99</td>
<td>65</td>
</tr>
<tr>
<td>- Spontaneous phasic contractions</td>
<td>not present</td>
<td>present</td>
</tr>
<tr>
<td>- Leakage</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Emptying phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Contraction pressure (cmH20)</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>- Abdominal pressure (cmH2O)</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td><strong>Urethral sphincter pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- during defecation (cmH2O)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>- during micturition (cmH2O)</td>
<td>-52</td>
<td></td>
</tr>
</tbody>
</table>

865
EMG technique with concentric needle electrode. The results demonstrated predominantly neurogenic lesion of the anal sphincters in SCL women and predominantly normal findings in SCI women. Sakakibara et al. (2004) [6] also studied anal sphincter EMG and showed neurogenic motor unit potentials in none of control subjects but in 93% of multiple system atrophy (MSA) patients; and FI resulted from weak anal sphincter due to denervation.

7. COLONIC TRANSIT TIME (CTT)

According to Sakakibara et al. (2004)[6], MSA patients had significantly prolonged CTT in the rectosigmoid segment and total colon. Constipation in MSA most probably results from slow colonic transit, decreased phasic rectal contraction, and weak abdominal strain.

8. QUALITY OF LIFE ASSESSMENT

According to the study of Krogh et al. (2005)[3], differences in NBoD score representing very minor, minor, moderate and severe NBoD groups of SCI patients reporting no, little, some or major impact on QOL were statistically significant (all P<0.001). In addition, frequency of FI, medication against FI and flatus incontinence were significantly associated with impact on QOL (OR 13.1, p < 0.0001; OR 3.6, p <0.01; OR 1.8, p < 0.05, respectively).

9. COMPREHENSIVE ASSESSMENTS

Bharucha (2006)[10] reviewed and summarized the indications, methods, strengths, and limitations of anorectal testing in clinical practice (Table 15). In patients with FI, diagnostic testing complements the clinical assessment for evaluating the pathophysiology and guiding management. When neurogenic sphincter weakness is suspected, anal sphincter EMG is recommended as the measurement of pudendal nerve latencies has several limitations [6,9,10].

<p>| Table 14. Shows electrodiagnostic tests that may help in diagnosis of FI suggested by Lefaucheur (2006)[8] |</p>
<table>
<thead>
<tr>
<th>Tests</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Concentric) needle EMG</td>
<td>External anal sphincter (EAS) denervation</td>
</tr>
<tr>
<td>Terminal motor latency (TML)</td>
<td>Anal motor nerve lesion, if latency is prolonged</td>
</tr>
<tr>
<td>Motor evoked potentials (MEPs)</td>
<td>Spinal or supraspinal lesion, if peripheral conduction is normal</td>
</tr>
<tr>
<td>Sacral anal reflexes (SARs)</td>
<td>Sacral cord or nerve lesion, if abnormal or absent</td>
</tr>
<tr>
<td>Somatosensory evoked potentials (SEPs)</td>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>Quantification of electrical/thermal thresholds (QSTs)</td>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>Sympathetic skin responses (SSR)</td>
<td>Autonomic neuropathy</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Greater severity of faecal incontinence was found in SCI individuals with no sacral reflexes due to absence of external anal sphincter contraction when intra-abdominal pressure increased and during rectal distension. (LOE 3)
- Anorectal manometry could show pelvic floor dysfunction during defecatory manoeuvres, impaired rectal sensation functions and abnormal cough reflex in those with lumbosacral cord injury. (LOE 3)
- Electrodiagnostic tests are complementary to other methods of investigation to establish the diagnosis and guide therapeutic management of neurogenic anorectal disorders. (LOE 3)
- Faecal incontinence in SCI individuals shows correlation to impact on QOL. (LOE 3)

RECOMMENDATIONS

- Perform electrodiagnostic tests, especially external anal sphincter needle EMG, in addition to anorectal manometry, to identify or confirm neurogenic cause of faecal incontinence. (C)
1. SUMMARY FROM THE PREVIOUS EDITION[1]

Bowel care is a procedure devised to initiate defecation and accomplish faecal evacuation. This can be achieved by bowel training with scheduled and stimulated defecation program consisting of cleansing the colon, normalizing of stool consistency with adequate fluid and fiber intake, and stimulating evacuation of stool on a regularly scheduled basis. Timing a bowel movement to take advantage of the gastro-colic reflex may be useful to achieve complete evacuation with the rectum free of stool, thus decrease the chance of faecal incontinence (FI).

Reflex-triggered bowel evacuation with mechanical stimulation – digital rectal stimulation and/or chemical stimulation – suppositories, enemas, can be helpful. In addition, Valsalva or manually-generated external pressure, oral medications – stool softeners, stimulant laxatives and prokinetic agents; diet modification; biofeedback; electrical stimulation and functional magnetic stimulations may be useful. However successful bowel care needs intensive patient education and training. If conservative bowel management fails, surgical management may be necessary.

2. SEARCH STRATEGY

Search from Pubmed 2004-2008 by using key words of faecal incontinence, neurogenic, neuropathic, neurologic, neurogenic bowel, bowel care, conservative treatment, and practice guideline. From such searches, there are 17 relevant papers of various levels of evidence as follows:

### 3. BOWEL PROGRAMME / BOWEL CARE

In 1998, the Consortium for Spinal Cord Medicine [2] published the “Neurogenic Bowel (NBo) Management in Adults with Spinal Cord Injury (SCI)” Clinical Practice Guideline (CPG). Later in 2005, to improve an adherence to the CPG recommendations through a targeted implementation strategy, Goetz et al [3] did a multi-site clinical trial study at 6 Veterans Affairs SCI centers. The CPG adherence was determined from medical record review for 3 time periods: before guideline publication (T1), after guideline publication but before CPG implementation (T2), and after targeted CPG implementation (T3). In focus groups before the intervention, the barriers were identified by SCI providers and then, two specific implementation strategies were chosen to address: the development and dissemination of a standardized documentation template and the development of a patient-mediated intervention to enhance guideline adherence. Because of the effective chart-based reminders, there was significant increase in overall adherence to recommendations related to NBo between T2 and T3 (P < 0.001) for 3 of 6 guideline recommendations: patient history, physical examination and documentation but the overall adherence of documentation was still low (40%). Moreover, it was found that other 3 recommendations i.e., functional assessment, education and competency, had high-rate of adherence in all 3 phases.

#### a) Mechanical stimulations for bowel movements

##### 1. DIGITAL RECTAL STIMULATION

Digital rectal stimulation (DRS), a gentle and slow rotation or circular movement of finger, is recom-
mended for reflex bowel as an adjunctive to facilitate bowel evacuation [2]. It dilates an anal canal and relaxes puborectalis muscle, thus decreases the ano-rectal angle and reduces outflow resistance to the passage of stool. Korsten et al (2007) [4] applied DRS, with a gloved finger fully inserted into the anal canal and distal rectum and contacted with the anal mucosa; each lasted for 1 minute with a 2-minute interval between successive DRS, to measure colonic motility by using a manometric catheter affixed endoscopically to the spleen flexure. In addition, evacuation of barium oatmeal paste was assessed simultaneously using fluoroscopic techniques. In 6 SCI patients, the results showed that the mean number (+/- SEM) of peristaltic waves per minute increased from 0 at baseline to 1.9 (+/- 0.5/min) during DRS and 1.5 (+/- 0.3/min) during the period immediately after cessation of DRS (P < 0.05). The frequency of contractions, as well as amplitude of contractions, during or immediately after DRS was not significantly different; peristaltic contractions disappeared 5 minutes after the cessation of DRS; and the manometric changes in response to DRS were accompanied by expulsion of barium oatmeal paste in every subject by the fifth DRS. This proved that DRS contributes to bowel evacuation in individuals with SCI in part by increasing left-side colonic motility.

However, mechanical stimulation may cause local trauma and induce autonomic dysreflexia (AD) in SCI individuals. Furusawa et al (2007)[5] studied the relationship between bowel manoeuvres and AD in cervical SCI patients and demonstrated that insertion of rectal medication induced a significant increase in systolic BP, which persisted during additional DRS; furthermore, the manual removal of stool induced AD, with maximal increases of systolic BP. However, after the end of stool flow the insertion of a finger into the anus did not cause a further increase in systolic BP which recovered to pre-program values within 5 min after defaecation. The combined effects of rectal and/or anal sphincter distension and uninhibited rectal contraction in response to the manual removal of stool are assumed to induce AD. According to the CPG [6], if the elevated systolic blood pressure is less than 150 mmHg, gently instill a topical anaesthetic agent into the rectum, wait for 2 minutes, gently remove the stool; if AD becomes worse, stop manual evacuation, instill additional topical anesthetic and recheck the rectum for the presence of the stool after 20 minutes

b) Chemical stimulants

According to the meta-analysis review done by Coggrave et al (2006)[7] to determine the effects of management strategies for faecal incontinence (FI) and constipation in people with neurological diseases affecting the central nervous system. Most of the ten trials were identified were small and of poor quality. Oral medications for constipation were the subject of four trials. Cisapride does not seem to have clinically useful effects in people with SCI (three trials). Psyllium was associated with increased stool frequency in people with Parkinson’s disease but did not alter colonic transit time (CTT) (one trial). Prucalopride, an enteroendocrine did not demonstrate obvious benefits in this patient group (one study). Some rectal preparations to initiate defaecation produced faster results than others (one trial). Different time schedules for administration of rectal medication may produce different bowel responses (one trial). Mechanical evacuation may be more effective than oral or rectal medication (one trial). The clinical significance of any of these results is difficult to interpret.

During the last 3 years there has been no research study on the effectiveness of such medications in patients with neurogenic bowel dysfunction (NBoD).

c) Assistive techniques for defecation

1. Abdominal massage

Another assistive technique usually applied to enhance bowel movement is abdominal massage in a clockwise motion up the ascending colon, across the transverse colon, and down the descending colon [2]. To investigate its effect on clinical aspects of NBoD and CTT, Aya? et al (2006)[8] did an uncontrolled clinical trial in 24 SCI patients whom were placed on a standard bowel program (phase I), after which abdominal massage was added to the regimen (phase II). In phase I, 45.8% had abdominal distention and 41.7% had FI; corresponding results for phase II were 12.5% and 16.7% (P = 0.008 and 0.031, respectively) and no significant differences between the proportions of patients with difficult intestinal evacuation or abdominal pain or in mean time required for bowel evacuation in phase I vs. phase II. The mean frequencies of defecation in phases I and II were 3.79 +/- 2.15 (2.75-4.55) and 4.61 +/- 2.17 (3.67-5.54) bowel movements per week, respectively (P = 0.006). Mean total CTT decreased from 90.60 +/- 32.67 (75.87-110.47) hrs in phase I to 72 +/- 34.10 (58.49-94.40) hrs in phase II (P = 0.035). According to this study, abdominal massage is an effective technique in enhancing bowel movement and defecation and thus reducing bowel accident, FI in SCI persons.

2. Anal stimulation with water streams (LOE 3)

In 2007, Uchikawa et al (2007)[9] reported the effectiveness of a newly modified washing toilet seat equipped with a CCD camera monitor and an electronic bidet to facilitate precise hitting of the anal area with water streams to stimulate bowel movement in patients SCI who were at least 5 months post acute injury, and could change their position on the toilet seat while watching the monitor. The stimulation was provided for a maximum of 30 minutes. Bowel movement was successfully induced in 15 of the 20 patients (75%) and success was not related
To evaluate the outcome of transrectal irrigation (TRI) significantly to injury level, ASIA impairment scale, or ability to voluntarily squeeze. Moreover, no complications were observed and time needed for successful bowel movement was shortened in 11 of 13 patients as they usually spent more than 30 minutes before stimulation.

3. TRANSCANAL / TRANSECTAL IRRIGATION

Christensen et al (2006)[10] did a prospective, multicenter, randomized controlled trial (RCT) involving 5 specialized European SCI centers, and 87 SCI patients with NBoD were randomly assigned to either transanal irrigation (TAI) using the Peristeen Anal Irrigation system with 750-1,500 ml of tepid water in 42 patients and conservative bowel management, scheduled bowel care at least every 2 days, at the same time of the day and after ingestion of food and liquid, diet modification, adequate fluid, regular physical activity; and laxatives or constipating medicine when necessary as recommended in the American CPG (2) in 45 patients for a 10-week trial period. Results showed that the TAI improved constipation, FI, and symptom-related QOL much better than conservative bowel management. In addition, urinary tract infection (UTI) was less in the TAI group than in the conservative group (5.9% versus 15.5%, P = .0052); AD tended to be less in the TAI group because the underlying faecal impaction was tested; and wheelchair users and those confined to be seem to have the highest benefit of the TAI. However, half from the TAI group discontinued due to failure of the TAI.

Later in 2008, Del Popolo et al (2008) [11] did a multi-center study in Italy to evaluate the effect of the Peristeen Anal Irrigation[10]. Twenty-four of 36 SCI patients with NBoD became less dependent on their caregiver; 28.6% of 32 who completed the study was able to perform it independently. All children were free of constipation; most (35/40) were also anal continent. Rectal volume and anal sphincter pressure improved, while plasma sodium values remained within the normal range. They concluded that TRI with tap water was a safe method to resolve constipation and FI in children with MMC and NBoD, but it did not help children to independence at the toilet.

4. APPLIANCE/ASSISTIVE TECHNIQUES FOR FAECAL INCONTINENCE

a) Anal plug (LOE 2)

Previous studies of an anal plug have yielded conflicting results. Bond et al (2007)[13] did a multi-centre RCT to evaluate the Conveen anal plug (Coloplast Limited) for the management of FI in congenital, acquired and neurogenic children and adults. It was used for 12 months. The main outcome measure was a condition-specific score on a 0 to 100 scale. Thirty-one intervention and 17 control patients were recruited. At baseline, patients managed their condition preemptively or protectively. Intervention patients used the plug as a complete management substitute or as an adjunct to existing management and majority retained the plug most of the time. Compared with control group, there was greater improvement from baseline in mean condition-specific score in intervention group but this difference was not statistically significant (t test p=0.053). Complete data analysis using analysis of covariance showed the mean difference between the intervention groups in condition-specific score of 9.9 (95% confidence interval-1.4, 21.1). Intention to treat analyses using imputation showed similar results.

b) Neuromodulation

According to Fowler’s review (2004)[14] on treatment related research in faecal and urinary incontinence, afferent innervation is important in sensing the degree of bladder fullness and in forming the input limb to involuntary detrusor contractions in neurogenic detrusor overactivity (NDO). It is likely that homologous mechanisms are involved in control of the bowel. Experimental evidence suggests that the “procontinence” reaction consists of an inhibitory effect on the detrusor and presumably the lower rectum resulting from contraction of the pelvic floor and the anal or urethral sphincter. Development of methods of enhancing the inhibitory reflex effect could lead to improved voluntary control of micturition and defaecation for patients with SCL.

1. INTRAVESICAL ELECTRICAL STIMULATION (IVES)

Han et al (2004)[15] retrospectively reviewed the effect of IVES on NBoD – controlling FI, in 9 boys and 15 girls (mean age 8.1 years) who completed a mean of 30.3 daily sessions of IVES. After IVES, the mean number of overall FI episodes decreased
significantly from 7.36 to 4.8 a week (p <0.05). Greater than 50% decrease in the episodes of FI was observed in 75% of the children but there was no significant change in the number of daily bowel movements before (1.8 daily) and after (1.55 daily) IVES.

5. QUALITY OF LIFE (LOE 3)

In 2005, there was one study of Luther et al [16] that compared patient outcomes and QOL for people with NBoD using either a standard bowel care program or colostomy. This study was part of a larger study that evaluated CPG implementation in SCI. The sample included 1,503 SCI veterans with the response rate of 58.4%. For comparison, a total of 74 veterans with SCI and colostomies were matched with 296 controls, using propensity scores. Seven items were designed to elicit information about the respondent’s satisfaction with their bowel care program, whereas 7 other items were designed to measure bowel-related QOL. No statistically significant differences in satisfaction or QOL were found between the responses from those with colostomies and those with traditional bowel care programs. Both groups had received training for their bowel care program, experienced relatively few complications, such as falls as a result of their bowel care program, and that their QOL related to bowel care was generally good. However, 55.7% of respondents with colostomies and 41.7% of those without colostomies reported that they were very unsatisfied with their bowel care program.

Zickler and Richardson (2004)[17] did a review on MMC and other neural tube defects children with NBoD and NBD, who had a physical inability to attain continence. However, they can attain continence when the appropriate modifications to the traditional routines are made. Enabling the child to attain continence would improve parental relationships and self-concept.

CONCLUSIONS

- Apart from relaxing the external anal sphincter, digital rectal stimulation increases peristaltic contractions by facilitating excitatory ano-colonic reflex and enhances bowel movement and evacuation in reflex bowel. (LOE 3)
- Abdominal massage has positive effects on some clinical aspects of neurogenic bowel dysfunction including defecation function and faecal incontinence. (LOE 3)
- Transanal irrigation seems to be a safe method to improve constipation and faecal incontinence in individuals with neurogenic bowel dysfunction. (LOE 3)
- An anal plug seems to benefit in controlling faecal incontinence in neurological patients but not better than control (without anal plug). (LOE 2)

- To increase adherence rate with bowel care programme/clinical practice guideline, implementation strategies should be addressed to care providers. (LOE 3)

RECOMMENDATIONS

- Apply appropriate mechanical stimulation - digital rectal stimulation, and/or assitive techniques – abdominal massage, transanal/transrectal irrigation to improve defecation and reduce faecal incontinence in neurological patients with neurogenic bowel dysfunction. (B)
- Be aware of autonomic dysreflexia when using mechanical stimulation and assitive techniques with neurologic patients with a high cord lesion. (B/C)
- Provide appropriate modifications to the bowel care program to improve bowel functions including defecation and continence. (B/C)

RECOMMENDATIONS FOR RESEARCH

- Further study to prove the existence of the excitatory ano-colonic reflex in response to digital rectal stimulation in individuals with lower motor neuron lesions.
- Further study to confirm that the newly anal stimulation with water stream is an appropriate method to facilitate bowel movements without complications.
- Well-designed controlled trials with adequate numbers and clinically relevant outcome measures of bowel management are needed.
- Larger and good quality randomized crossover trials are needed to confirm the effects of neuromodulation for controlling faecal incontinence and reducing constipation in neuropathic people.

IV. SURGICAL TREATMENT

- Methods

Using MEDLINE we identified English-language journal articles and reviews published from 2000 to April 2008, looking for the keywords neurogenic constipation and faecal incontinence, surgery, sacral nerve stimulation, ante grade, continent enema procedure, dynamic graciloplasty, artificial anal sphincter and colostomy.
Surgical treatment of faecal incontinence in the general population is overviewed in the Chapter on the Surgery for Faecal Incontinence. Therefore, this section focuses on specific aspects in neurogenic patients. Although traumatic lesion of external sphincter is treated by reconstruction of the external sphincter, functional impairment of anal sphincter without mechanical defect of the sphincter in neurogenic patients can not be treated by this simple surgical repair, and thus options for surgical treatment of neurogenic bowel dysfunction are limited. However, they consist of 1) sacral nerve stimulation, 2) ante grade continent enema procedure, 3) dynamic graciloplasty, 4) artificial anal sphincter, and 5) elective colostomy.

1. SACRAL NERVE STIMULATION (SNS)

Electrical stimulation of sacral nerve roots has been reported to restore continence in patients with intact muscle structure. The procedure is divided in three steps: acute percutaneous testing, temporary percutaneous nerve evaluation and permanent electro stimulation phase with an implantable neurostimulation device. An electrode inserted into the S3 sacral foramen provides low grade stimulation. Only when patients respond to acute and temporary percutaneous sacral nerve stimulation tested for 2 to 3 weeks, permanent stimulation via a chronic stimulator implanted under the anterior abdominal wall is applied or subcutaneously in the gluteal region. The first case report with this technique was published by Matzel et al [1] in 1995 who described a successful outcome in three patients with faecal incontinence. Since then, ten articles have been published [2-11] (Table 16).

Recently, Matzel et al [2] reported a multi centre, prospective trial with chronic sacral nerve stimulation in a series of 34 patients at a median follow-up of 23.9 months. At least 83 % of patients had a 50 % or greater improvement in total number of incontinent episodes per week and at least 71 % of patients a 50 % or greater improvement in total number of days per week with continence during the course of follow-up. Continence was fully restored in at least 12 (37%) patients. Quality of life improved in all four ASCRS (American Society of Colon and Rectal Surgeons) scales (p<0.0001) and in seven of eight SF-36 scales, though only social functioning was significantly improved (p=0.0002).

Although 12 patients had 19 device-related adverse events including pain (ten episodes in 9 patients), lead breakage in one patient, recurrent infection needing device removal in one patient and deterioration of bowel symptoms in three patients, resolution rate was 63.2 % and 100 % for all and severe complications, respectively. However, this study excluded patients with neurological diseases. Similar success rates (73-100 %) with this technique have been reported from other centres [3-5, 7-11]. Among these reports, only one case-series by Rosen et al [12] targeted mainly on faecal incontinence in patients with neurological lesions. In that study, 20 patients (15 neurogenic, 5 idiopathic) with severe faecal incontinence were initially treated by temporary external stimulation over a period of 10-14 days. Sixteen patients (11 patients with neurogenic causes including 5 spinal cord injuries, 4 post spinal cord surgeries, 1 myelomeningocele, 1 multiple sclerosis, and 1 Friedreich ataxia, and 5 idiopathic patients) who had shown a positive response to the temporary stimulation subsequently underwent permanent implantation. The median follow-up was 15 months (range, 3-26 months). All patients who had received a permanent implant revealed a marked reduction in their incontinent episodes as well as an increase in retention time. In the neurogenic subpopulation, the median numbers of incontinence episodes decreased significantly (p<0.01) from 7 (4-15) to 2 (0-5), and a median retention time significantly (p<0.01) increased from 2 minutes (0-5) to 7 minutes (2-15) after chronic stimulation. Assessment of QOL scales using ASCS questionnaire after 6 months treatment showed significant improvement on all scales. Three patients (2 neurogenic and 1 idiopathic) had severe infections needing explantation of devices and wound drainage 0-3 months after implantation. Another one patient had dislocation of the permanent electrode.

No complications were observed in the remaining 12 patients (60 % of total series). All of those patients with functioning systems have showed improved incontinence during the follow-up period. Although the mechanism of SNS to improve faecal incontinence is uncertain, rises in anal resting and squeezing pressures and changes in rectal sensitivity and motility have been proposed. Particularly in neurogenic patients, neuromodulation of sacral reflexes and regulation of rectal sensitivity appear to be the major reasons for the functional improvement [7].

Alternatively, the diagnostic stage can be performed as a staged implant, with a quadripolar foramen electrode (tined lead, Medtronic model 3886). This technique improves the results of the test period in the urological literature from a 50 % success rate with the wire electrodes up to 80 % using already the quadripolar foramen electrodes in the test phase Kessler et al., 2005 [13]. The tined lead has four active electrodes (compared with a single electrode used in PNE) and has self-retaining flanges, which prevent lead migration. Usage of the tined lead has the benefit of minimizing false-negative results. Recently, Jarrett et al (2005) [14] reported on their experience with sacral nerve stimulation for faecal incontinence in patients with previous partial spinal injury including disc prolapse; the spinal insults were disc prolapse (six), trauma (four), spinal stenosis (one) or occurred during neurosurgery (two).
Temporary SNS was performed in thirteen patients (median age 58, range 39-73 years). Twelve patients had successful temporary stimulation and proceeded to permanent implantation. The median follow-up time was 12 (range 6-24) months, the mean number of episodes of incontinence decreased from 9.33 (7.64 per week at baseline) to 2.39 (3.39) at last follow-up (p = 0.012). The number of days per week with incontinence and staining decreased significantly (p < 0.001). The ability to defer defecation improved from a median of not being able to defer (range 0-1 min.) to being able to defer 5-15 (range 0->15) mean (p = 0.022). The authors conclude that SNS can benefit patients with faecal incontinence following partial spinal cord injury.

Holzer et al (2007) [15] report on 36 patients included in a trial of SNS, 29 subsequently had a permanent implant. After a median follow-up of 35 (range 3-71) months, 28 patients showed a marked improvement: Incontinence to solid or liquid stool decreased from a median of 7 (range 4-15) to 2 (range 0-5) episodes in 21 days (p = 0.002). Saline retention time increased from a median of 2 (range 0.5-1) to 7 (range 2.1-19) min. (p = 0.002). The quality of life on all scales among patients who received the permanent implant increased at 12 and 24 months after operation. Also Holzer et al stated that SNS is of value in selected patients with neurogenic faecal incontinence.

CONCLUSIONS

RECOMMENDATIONS

2. ANTEGRADE CONTINENCE ENEMA (MACE)
has been applied mainly to paediatric population with neuropathic bowel dysfunction and anorectal anomaly, and successful outcome was achieved in 70-100 % [2-22] (Table 17). Overall, stoma stenosis is the most common complication, affecting 10-41 %. In a study of 62 children with median follow-up of 5.4 (3.25 to 8.25) years, 84 percent were completely continent or had soiling less than once a month [4]. There was a significant correlation between the level of continence and satisfaction with the procedure [4] Improvement of self-esteem and psychosocial function after the ACE procedure in children with myelomeningocele has been reported [6]. Several modifications have been reported including laparoscopic technique, left colonic continence stoma, etc [7-9, 11-13]. This procedure was also applied to adult neurogenic patients with faecal incontinence [3,12,14], and similar success rates (83-100 %) were reported. Casale et al (2006) [23] compared total continence reconstruction to staged-reconstruction of neuropathic bowel and bladder: In this retrospective chart review of all patients with Myelomeningocele who underwent went reconstruction with a cutaneous catheterisable urinary channel or Malone ante grade continence enema. The authors were unable to find any differences in the continence rate or stoma complications between total continence reconstruction or/and staged reconstruc- tion. However, because of shared pathology the authors believe that most patients benefit from intervention in the gastrointestinal and the genitourinary tract. Therefore, a major advantage of total continence reconstruction is avoidance of the morbidity of a second major surgical procedure (LOE 3).Recently, Herndon et al 2004 [24] reported on in situ Malone ante grade continence enema in 127 patients reflecting a 6-year experience: ACE in situ technique was performed in 76 females and 51 males, average patient age at the time of surgery was 9.6 years, diagnosis included myelomeningocele in 116 cases, lipomeningocele in 6, spinal cord injury in 2, posterior urethra walls in 1, sacral agenesis in 1 and functional constipation in 1. The mean follow-up was 26.9 months. Faecal continence was reported by 91 % of the patients, 13 stoma revisions (stenosis 10, prolapse 2 and leakage 1) were required in 11 patients. Major complications included a caecal volvulus requiring a right hemicolectomy in one patient, small bowel obstruction in two and a shunt infection and or malfunction in two. The authors conclude that the in situ MACE procedure has reliable long-term results for treating faecal incontinence associated with neuropathic bowel.

CONCLUSIONS AND RECOMMENDATIONS

• This procedure is effective for controlling faecal incontinence and constipation associated with neurogenic bowel dysfunction especially in neuropathic children (LoE 3; Grade B). Patients should be properly selected to determine appropriate motivation.

3. DYNAMIC GRACILOPLASTY

This procedure consists of transposition of the gracilis muscle around the anal canal and subsequent implantation of a pulse generator to stimulate the gracilis muscle. Before continuous stimulation is applied, the muscle is trained for 4 to 8 weeks according to a protocol. During a stimulation program the fatigable type 2 skeletal fibres are replaced by slow type 1 fibres, which are able to sustain a long lasting contraction. Satisfactory continence has been reported in 56% to 81% of patients [1–13] (Table 18). Recently, a prospective study of 200 consecutive patients with a follow-up of at least two years showed a 72% overall success rate [6]. Complication rate is rather high (42%-92%), especially infectious complications which occur in about one fourth of the patients. Impaired rectal emptying has occurred in 16% to 29%. A prospective controlled comparative study of single stage with the conventional two-stage procedure showed no significant difference in infection rates, continence rates, morbidity or quality of life between the two groups after a mean 521-day follow up [11]. A prospective controlled study comparing dynamic graciloplasty with artificial anal sphincter in 16 patients (8 in each group) showed that both of the two procedures had a high incidence of technical failures and complication requiring reoperation [12]. Chapman et al [13] reported a systematic review article of this procedure, where they searched articles published until November 1999, and found 40 articles met the inclusion criteria. Mortality rates were around 2% for both graciloplasty and colostomy. However, morbidity rates reported for graciloplasty appear to be higher than those for colostomy.

Rorgen et al [11] reported an 80% success rate with this procedure in 16 patients with neurogenic faecal incontinence. However, all studies presently available expect this report include quite small number of neurogenic patients, and there is no information on the outcome in neurogenic subgroup of patients.

CONCLUSIONS AND RECOMMENDATIONS

• Since dynamic graciloplasty seems to be associated with high complication rates, and outcome appears to correlate to surgeon’s experience, this procedure should only be carried out in specialist centres with a reasonably large number of patients, and should be reserved only for carefully selected patients with intractable faecal incontinence where other methods have failed (C).

• Further studies are needed to determine its role in the neurogenic subpopulation.
<table>
<thead>
<tr>
<th>Authors reference no., year</th>
<th>Level of evidence</th>
<th>No. of patients</th>
<th>Mean age (range)</th>
<th>Median follow up (range)</th>
<th>Success rate</th>
<th>Overall complication rate</th>
<th>Stomal stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malone et al [1], 1990</td>
<td>Level 4</td>
<td>5</td>
<td>(8-18)</td>
<td>(2-8 mos.)</td>
<td>100%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Teichman et al [2], 2003</td>
<td>Level 4</td>
<td>7</td>
<td>34</td>
<td>4,5 yrs. (all&gt;4 yrs.)</td>
<td>83%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Dey et al [3], 2003</td>
<td>Level 4</td>
<td>62</td>
<td>11,5 (3,8-17,6)</td>
<td>5,4 yrs. (3,25-8,25)</td>
<td>84%</td>
<td>66%</td>
<td>42%</td>
</tr>
<tr>
<td>Liard et al [4], 2002</td>
<td>Level 4</td>
<td>24</td>
<td>15</td>
<td>3,7 yrs.</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aksnes et al [5], 2002</td>
<td>Level 4</td>
<td>20</td>
<td>10,9 (6,8-17)</td>
<td>16 (9,5-23)mos.</td>
<td>80%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Liloku et al [6], 2002</td>
<td>Level 4</td>
<td>7</td>
<td>8-21</td>
<td>(1,5-18 mos.)</td>
<td>71%</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Tackett et al [7], 2002</td>
<td>Level 4</td>
<td>45</td>
<td>10,5 (3,8-25,8)</td>
<td>25,3 (4-65) mos.</td>
<td>87%</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>Perez et al [8], 2001</td>
<td>Level 4</td>
<td>12</td>
<td>14 (7-20)</td>
<td>15 mos.</td>
<td>92%</td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>Kajbafzadeh et al [9], 2001</td>
<td>Level 4</td>
<td>40</td>
<td>9,5 (4-22)</td>
<td>22 (8-48)mos.</td>
<td>100%</td>
<td>2,5%</td>
<td></td>
</tr>
<tr>
<td>Van Savage et al [10], 2000</td>
<td>Level 4</td>
<td>16</td>
<td>12 (4-21)</td>
<td>1,5 yrs</td>
<td>100%</td>
<td>50%</td>
<td>6,3%</td>
</tr>
<tr>
<td>Bruce et al [11], 1999</td>
<td>Level 4</td>
<td>7</td>
<td>33,6 (23-54)</td>
<td>22,4 (3-34) mos.</td>
<td>100%</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Robertson et al [12], 1999</td>
<td>Level 4</td>
<td>30</td>
<td>9,5 (5-16)</td>
<td>&gt;1yr. (3mos.-3,5yrs.)</td>
<td>90%</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>Teichmann et al [13], 1998</td>
<td>Level 4</td>
<td>7</td>
<td>32</td>
<td>11 mos.</td>
<td>100%</td>
<td>57%</td>
<td>28%</td>
</tr>
<tr>
<td>Meier et al [14 1998</td>
<td>Level 4</td>
<td>20</td>
<td>10 (4-18)</td>
<td>24 (9-45) mos.</td>
<td>90%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Driver et al [15], 1998</td>
<td>Level 4</td>
<td>29</td>
<td>10 (5-16)</td>
<td>28 (7-71) mos.</td>
<td>79%</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>Hensle et al [16], 1998</td>
<td>Level 4</td>
<td>27</td>
<td>16 (10-31)</td>
<td>(9-30 mos.)</td>
<td>70%</td>
<td>37%</td>
<td>18,5%</td>
</tr>
<tr>
<td>Levitt et al [17], 1997</td>
<td>Level 4</td>
<td>20</td>
<td>(3-27)</td>
<td>(1-29 mos.)</td>
<td>95%</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Goepel et al [18], 1997</td>
<td>Level 4</td>
<td>10</td>
<td>13,2 (6-26)</td>
<td>18,5 (8,5-36) mos.</td>
<td>100%</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Dick et al [19], 1996</td>
<td>Level 4</td>
<td>13</td>
<td>8 (6-14)</td>
<td>32 (24-60) mos.</td>
<td>85%</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>Ellsworth et al [20], 1996</td>
<td>Level 4</td>
<td>18</td>
<td>12 (5-31)</td>
<td>6,6 (2-24) mos.</td>
<td>96%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Koyle et al [21], 1995</td>
<td>Level 4</td>
<td>22</td>
<td>13 (5-26)</td>
<td>&gt;4 mos.</td>
<td>77%</td>
<td>36%</td>
<td>9%</td>
</tr>
<tr>
<td>Squire et al [22], 1993</td>
<td>Level 4</td>
<td>25</td>
<td>(3-18)</td>
<td>13 (2-61) mos.</td>
<td>88%</td>
<td>24%</td>
<td>20%</td>
</tr>
</tbody>
</table>
ARTIFICIAL ANAL SPHINCTER

Implantation of an artificial anal sphincter was first reported in 1987 [1]. The sphincter used was originally designed for treatment of urinary incontinence, but subsequently the device has been modified. The system consists of an inflatable cuff placed around the upper anal canal, a pressure-regulating balloon to maintain closure of the cuff placed in the subperitoneal space lateral to the bladder and a control pump accessible to the patient to empty the cuff for defaecation placed in the scrotum or labium. The system is left deactivated for 4 to 6 weeks. A multi centre prospective, non-randomized trial in 112 patients with one year follow-up showed 73 revision operations were required in 51 (46 %), and the infection rate necessitating surgical revision was 25 %. Forty-one patients (37 %) have had their devices completely explanted [4]. The reported success rates obtaining acceptable continence range were 41 % to 90 % [4-14] (Table 19). Explantation rates in the reported series were 20-40 %. One series with long-term follow-up (more than 5 years) showed that 7 of 17 patients had the system removed due to infection, malfunction or obstructed defaecation [13]. Technical complications like rupture of the cuff, which occurred frequently with the earlier modification of the device, are now rare. Emptying problems, without anatomical stenosis, as described for dynamic graciloplasty, have also occurred frequently (13 % to 45 %) in most series and have in some patients required explantation. Other complications leading to explantation have been erosion of the cuff through the skin or into the anal canal.

As shown in the Table, most studies have a small number of neurogenic patients or do not indicate the number of neurogenic patients included. In the study reported by Christiansen et al [10], 10 (59 %) out of 17 patients had neurological disorders, and the overall success rate was 47 %, which seems to be lower than the others. The authors mentioned that the result in neurogenic subgroup was clearly poorer than that in non-neurogenic subgroup.

In a prospective, randomized controlled clinical trial of placement of the artificial bowel sphincter for the control of faecal incontinence O’Brien et al (2004) [8] compared its effects to a program of supportive care and patients were followed for six months from operation or entry into the study.

The principal outcome measure was the level of continence, measured with the Cleveland Continence Score, representing perfect control through a total incontinence. Secondary outcome measures were peri-operative and late complications in the artificial bowel sphincter group and the changes in quality of life in both groups. In the control group (N = 7) the Cleveland Continence Score was not significantly altered. The artificial bowel sphincter group (N = 7)
<table>
<thead>
<tr>
<th>Authors reference no., year</th>
<th>Level of evidence</th>
<th>No. of patients (neurogenic)</th>
<th>Mean age (range)</th>
<th>Median follow up (month) (range)</th>
<th>Success rate (in neurogenic)</th>
<th>Explantation</th>
<th>Complication rates</th>
<th>Emptying problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parker et al [2], 2003</td>
<td>Level 4</td>
<td>45(2)</td>
<td>44(15-72)</td>
<td>51% (50%)</td>
<td>40%</td>
<td>34%</td>
<td>21/13pts</td>
<td>11%</td>
</tr>
<tr>
<td>Michot et al [3], 2003</td>
<td>Level 4</td>
<td>37(16)</td>
<td>51(22-73)</td>
<td>79%</td>
<td>30%</td>
<td></td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>Devesa et al [4], 2002</td>
<td>Level 4</td>
<td>53(9)</td>
<td>46(16-76)</td>
<td>26.5(7-55)</td>
<td>65%</td>
<td>19%</td>
<td>13%</td>
<td>26%</td>
</tr>
<tr>
<td>Wong et al [5], 2002</td>
<td>Level 3</td>
<td>112(ND)</td>
<td>49(18-81)</td>
<td>53%</td>
<td>37%</td>
<td>25%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Ortiz et al [6], 2002</td>
<td>Level 4</td>
<td>22(ND)</td>
<td>47(17-72)</td>
<td>26(6-48)</td>
<td>63%</td>
<td>44%</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Altomare et al [7], 2001</td>
<td>Level 4</td>
<td>28(4)</td>
<td>58(35-79)</td>
<td>19(7-41)</td>
<td>75%</td>
<td>32%</td>
<td>11%</td>
<td>57%</td>
</tr>
<tr>
<td>O’Brien et al [8], 2000</td>
<td>Level 4</td>
<td>13(1)</td>
<td>44(16-71)</td>
<td>77%</td>
<td>23%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehur et al [9], 2000</td>
<td>Level 4</td>
<td>24(4)</td>
<td>44(14-80)</td>
<td>20(6-35)</td>
<td>75%</td>
<td>29%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Christiansen et al [10], 1999</td>
<td>Level 4</td>
<td>17(10)</td>
<td>46(32-65)</td>
<td>7(5-10)years</td>
<td>47%</td>
<td>41%</td>
<td>18%</td>
<td>63%</td>
</tr>
<tr>
<td>Vaizely et al [11], 1998</td>
<td>Level 4</td>
<td>6</td>
<td>10(5-13)</td>
<td>83%</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehur et al [12], 1998</td>
<td>Level 4</td>
<td>13</td>
<td>30(5-76)</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehur et al [13], 1996</td>
<td>Level 4</td>
<td>13(2)</td>
<td>20(4-60)</td>
<td>90% (69%)</td>
<td>23%</td>
<td>15%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Wong et al [14], 1996</td>
<td>Level 4</td>
<td>12(3)</td>
<td>58</td>
<td>50% (75%)</td>
<td>33%</td>
<td>25%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Christiansen et al [1], 1987</td>
<td>Level 4</td>
<td>1</td>
<td>3</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
showed a highly significant improvement. One patient in the artificial bowel sphincter group had failure of healing and implantation of the device. There were major improvements in the quality of life for all measures in the artificial bowel sphincter group. The authors conclude that the placement of an artificial bowel sphincter is safe and effective when compared with supportive care alone. Peri-operative and late problems are likely to continue to occur and between 15% and 30% of patients may require permanent explantation. For the authors the device is easy and discrete to use, highly effective in achieving continence and able to generate a major improvement in the quality of life (LoE 3).

CONCLUSIONS AND RECOMMENDATIONS

- Implantation of the artificial anal sphincter may be done for the same indications as for dynamic graciloplasty except in patients with previous perianal infections or with a thin and scarred perineum where a muscle transplant is preferable. It should be emphasized that due to the relatively high risk of treatment failure and of complications requiring re-operation patient selection for both procedures should be very strict (C).

5. COLOSTOMY

Spinal cord injury (SCI) has a significant effect on bowel dysfunction, in terms of faecal incontinence, urgency, and toileting methods.

This results in a marked impact on quality of life [1-2]. Several retrospective studies on the effect of colostomy formation on bowel care and QOL in SCI patients showed a significant decrease in the average time spent on bowel care per week and improvement on QOL [3-13].

The early and long-term complication rates reported are 6 to 15%, and 15 to 37, 5%, respectively. The commonest long-term complication is mucus discharge per rectum. It should be noted that one of the frequent, persistent, problematic complication is diversion colitis [9-10]. Symptoms include hemorrhagic purulent rectal discharge, abdominal pain and tenesmus. This condition is thought to result from a deficiency of luminal short-chain fatty acids [11]. Steroid enemas, 5-aminosalicylic acid enemas or suppositories, or short-chain fatty acid enemas have been reported to be helpful [12].

CONCLUSIONS AND RECOMMENDATIONS

- Elective colostomy may be an option for some SCI patients with severe uncontrolled faecal incontinence (C).

E. SPECIFIC NEUROLOGIC DISEASES

I. DEMENTIA

1. DEMENTIA AND URINARY INCONTINENCE

- Methods

Using MEDLINE we identified English-language journal articles and reviews published from 2000 to April 2008, looking for the keywords Alzheimer’s disease, vascular dementia, Lewy bodies dementia, frontal-temporal dementia, urinary incontinence, bladder dysfunction, management.

The dementias can be categorized according to clinical presentation, neuropathology and/or etiology into four major dementia groupings, (I) Alzheimer’s dementia; (II) the vascular group (including large and small vessel disease); (III) the Parkinson’s group (including Lewy Body disease, dementia of Parkinson’s and Alzheimer’s dementia with Parkinson’s); (IV) the frontotemporal group (including Pick’s disease and Semantic dementia) [13]

a) Alzheimer’s disease

1. EPIDEMIOLOGY AND PREVALENCE

Alzheimer’s disease (ALD) is the most common type of dementia in clinical and autopsy surveys. AD affects mostly elderly people. The symptoms include worsening of the memory, impairment of language and other cognitive functions (analytical thinking, abstract reasoning). Ultimately, there is loss of self-hygiene, eating, dressing and ambulatory abilities and incontinence and motor dysfunction. The onset of incontinence usually correlates with the disease progression (LOE 3) [1]. The prevalence of incontinence is reported to be between 23% and 48% (LOE 3) [2-3].

2. PATHOLOGY AND DISEASE SPECIFIC LUT PROBLEMS

ALD at the outset was identified by its unique pathology, the plaques and tangles that Alzheimer referred to as “a clotting of fibrils…. in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex.”

The clinical hallmark of Alzheimer’s disease is memory impairment. A sense of memory failure, detected by the patient or a close relative, is usually the presenting symptom. Motor and sensory symptoms are absent until late in the course of the disease. However, other cognitive domains, such as language, praxis and recognition skills, are affected even early in the presentation.
ALD has a gradual and progressive course, typically 10 years from diagnosis to death. The advent of cholinesterase inhibitors has had some effect on the course of disease for individual subjects, though population trends have been harder to demonstrate (10, 11).

In a study by Del Ser et al (LOE 3) urinary incontinence was associated with severe cognitive decline in pure Alzheimer’s disease but usually preceded severe mental failure in patient with dementia due to diffuse Lewy body disease [4]. Nobili et al (LOE 3) performed quantitative EEG in Alzheimer’s patients, finding that incontinence was predicted by alpha power in the right side [5]. In another study by Nobili et al (LOE 3) the value of regional cerebral blood flow from a posterior temporal-inferior parietal area in each hemisphere predicted development of incontinence [6]. Brain computer tomography study done by Sugiyama et al (LOE 3) in Alzheimer’s disease patients showed that the degree of brain atrophy was more severe in those with detrusor overactivity than those without it [9].

Detrusor overactivity was found in 61% of their patients. Haddad et al (LOE 3) described two patients with vesicoureteral reflux, one of them showing buccosalivary, gastroesophageal, vesicoureteral, urethroprostatic and urethrovessicular reflux as a consequence of the neurologic dysfunction [8].

There is no systematic review of type and grade of LUT dysfunctions in Alzheimer’s disease, nor a study about progression of those dysfunctions as the disease progresses.

3. Disease Specific Diagnosis and Treatment

EEG and regional cerebral blood flow might predict when and if incontinence will occur during the course of the disease [5, 6]. Franssen et al (LOE 2) examined the occurrence of following developmental reflexes: the tactile suck reflex, the palmar and plantar grasp reflexes, and the plantar extensor reflex in healthy elderly, cognitively and functionally mildly impaired patients, and patients with Alzheimer’s disease [9].

Prevalence of all five reflexes was more than 6 times higher for those categories that comprised only permanently doubly incontinent patients as compared to those categories that comprised only continent individuals. It is interesting that the frequency of developmental reflexes rose sharply with the onset of progressive incontinence, suggesting its cortical origin. As demonstrated above, the development of incontinence in Alzheimer’s disease patients is associated with cognitive impairment and brain degeneration, suggesting its central nervous system origin. Therefore behavioural therapy, toilet training and prompted voiding would be most useful treatment modalities for this type of incontinence.

Hutchinson et al (LOE 3) suggested that caregivers of patients with Alzheimer’s disease should study the toileting behaviours. This would permit them to provide physical and cognitive assistance while attempting to avoid accidents and catastrophic events [10]. Tariot (LOE 4) stressed the necessity for taking into account different factors (like mobility, cognitive functions, general medical conditions), when planning treatment (also for incontinence) in Alzheimer disease patients [11].

Again the general guidelines should apply for choosing the best management of incontinence in Alzheimer’s disease patients. The treatment should be however tailored to individual patient needs and disease status.

There is still some controversy that the central Acetylcholinesterase (AcHE) inhibitors given by the neurologist might exacerbate urinary incontinence in those patients (18). Donepezil hydrochloride is a selective central acetylcholinesterase (AchE) inhibitor, which decreases degradation of acetylcholine in the brain, then increasing the concentration of acetylcholine in the synaptic cleft [21]. This drug is widely used to ameliorate cognitive decline in patients with Alzheimer’s disease [15; 20] which is thought to be due to a decrease in cholinergic innervation of the cerebral cortex and the basal forebrain [14]. Since the bladder is innervated by the parasympathetic cholinergic nerves [16] neurogenic lower urinary tract (LUT) dysfunction occurs in a subset of patients with AD [19; 22].

Although donepezil may facilitate cholinergic neurotransmission mostly in the central nervous system, common adverse effects of donepezil, such as nausea and abdominal discomfort, have been attributed to the peripheral nervous system (PNS) [15; 21]. Therefore, the increased bladder contraction is reasonably attributed to the PNS effects as seen with other cholinergic drugs. However, according to Sakakibara et al (2005) [12] the patients with AD showed a slight increase in the bladder capacity, which can not be explained by the PNS effects alone. Although it is unknown to what extent central cholinergic circuit may participate in the regulation of micturition, recent experimental studies showed that lesions in the nucleus basalis Meynert in the basal forebrain (central cholinergic nucleus projecting fibres to the frontoparietal cortex) give rise to decreased bladder capacity [19]. In addition, improved cognitive status and alertness may well lead to proper initiative to hold urine in the patients. Central AchE inhibitors including donepezil hydrochloride, therefore, may have complex effects on the LUT function. Although the number of the patients was small, it seems possible that donepezil could ameliorate cognitive function without serious adverse effects on the LUT function in patients with AD. This should be true also for other selective central AchE inhibitors.
4. Guidelines for further research

There is still no cure for Alzheimer's disease, which is progressive and a type of dementia associated disease. We are still lacking studies evaluating LUT disorders in Alzheimer's disease. No systematic review has been performed regarding the possibilities of medical management (both pharmalogical and behavioural) of incontinence.

An open issue also remains the question of aggressive surgery for LUT problems in these patients. Should we offer a surgical therapy for incontinence in female patients with stress incontinence and progressive Alzheimer’s disease? This is a question so far unanswered.

Conclusions

2. Diagnosis

Vascular dementia may be the result of a single strategic infarct, multiple cortical or lacunar infarcts, or a microvascular insult in which neither clinical symptoms of stroke nor infarcts by imaging are evident. There is an elevated risk for subsequent dementia in patients who have had a stroke in comparison to controls without any evidence of a stroke (LOE 2)[2]. Diabetes and hypertension are stronger risk factors for vascular dementia than for Alzheimer’s disease (LOE 3)[3]. The apolipoprotein e4 genotype is a risk factor for vascular dementia as well as AD (LOE 3) [4].

3. Pathology and disease specific LUT problems

Sakakibara et al (LOE 2) found that mainly the medial frontal lobe is responsible for urinary dysfunction in patients after stroke [5]. Griffiths (LOE 2) in his PET studies, shows that cognitive function was slightly more impaired in patients with genuine urge incontinence. But the strongest and most specific association was with impaired temporal orientation [6]. Genuine urge incontinence with reduced bladder filling sensation was associated with global under-perfusion of the cerebral cortex and more specifically, with underperfusion of the frontal areas of the brain, especially on the right. Jirovec et al (LOE 3) found that cognitive ability and mobility differ significantly between continent and incontinent patients [7]. When the variables were examined together, mobility emerged as the best predictor of the patient’s urine control, followed by cognitive impairment.

In a study by Resnick et al (LOE 2) performed in institutionalized elderly, detailed urodynamic studies in 94 of the 245 incontinent patients showed that detrusor overactivity was the predominant cause in 61 percent, with concomitant impaired detrusor contraction present in half these patients. Other causes among women were stress incontinence (21 %), underactive detrusor (8 %), and outlet obstruction (4 %) [11]. Among the relatively few men in this sample, outlet obstruction accounted for 29 % of the cases. Yoshimura et al (LOE 3) found a 47 % prevalence of detrusor overactivity which correlated with the prevalence of dementia [9].

4. Disease specific diagnosis and treatment

No specific diagnostic tests to evaluate dementia related incontinence were described. Since patients with dementia and incontinence usually have one or more concomitant diseases, the evaluation of the LUT functions should follow the general rules, bearing in mind that this is the population of frail elderly.

The treatment should start with modification of patient’s behaviours and general rehabilitation targeted at making patient more ambulatory, as it was demonstrated that movement limitations are strongly
related with incontinence. No other specific treatment in dementia have been described, however certain issues like prompted voiding, anticholinergic drugs and intermittent catheterization have been studied. In his review of trials where prompted voiding was implemented Eustice et al (LOE 1) found that prompted voiding increased self-initiated voiding and decreased incontinence episodes in the short-term [10]. A single small trial suggested that adding oxybutinin, reduced the number of incontinent episodes in the short-term. In a study by Suzuki et al (LOE 3) the best results were obtained with ambulatory patients with the use of a portable chamber pot and induced urination, while no improvement was seen in bedridden patients treated with anticholinergics [11]. Sugiyama et al (LOE 3) studied the effects of anticholinergics therapy in patients aged 65 years or older with and without dementia. The patients received anticholinergic agents for more than two weeks [12]. Urodynamic studies demonstrated significant increase of maximum bladder capacity in the dementia group and the non-dementia group. There was no significant difference in rate of objective improvement between both groups. On the other hand, rate of subjective improvement was significantly higher in the non-dementia group (40 %) than in the dementia group (15 %). Improvement of functional bladder parameters was not associated however with improvement of subjective symptoms in the demented patients. In case of emptying failure, like in other bladder diseases intermittent catheterization is a treatment of choice. Lieu et al (LOE 3) found that carer-assisted clean intermittent urethral catheterization is an effective and safe treatment option for persistent urinary retention in elderly female patients with cognitive impairment and other disabilities [13]. With this method of treatment, 54 % of the patients were able to void spontaneously and were continent after a median period of 6 weeks with a range of 1 to 40 weeks. Twenty-seven per cent had significant improvement in the symptoms of urinary incontinence and the residual urine volumes became progressively smaller. However, 19 % failed this treatment modality. The recovery of spontaneous voiding was found to be significantly influenced by the age of the patient, the carer performing the intermittent catheterization and the development of catheter-related urinary tract infection. Twenty-five per cent of the study patients developed symptomatic urinary tract infection which was associated with a delay in the recovery of spontaneous voiding. Its development was also found to be significantly associated with the presence of pre-existing diabetes mellitus, the person doing the catheterization, the presence of dementia and with more predisposing common medical conditions.

Another interesting issue is the surgical treatment in patients with dementia. Two major groups of surgical procedures could be identified: prostate surgery and incontinence surgery. Yonou et al (LOE 3) studied a group of 13 patients with dementia who underwent TURP procedure [14]. Six patients reported good urination, 3 reported some improvement in urination after surgery, although requiring intermittent catheterization and 1 developed mild incontinence. No specific study addressing the issue of incontinence surgery in woman with dementia was performed; however it seems that the incontinence surgery in patients with dementia should be reserved only for the cases with good ambulation and without concomitant functional disorders of micturition (overactive bladder, hypocontractile detrusor).

5. GUIDELINES FOR FURTHER RESEARCH
Since dementia is not a homogeneous disease a population study targeted at specific disorder of micturition is urgently needed. Also, a study evaluating different treatment modalities in patients with dementia (especially anticholinergic treatment for overactive bladder and surgical treatment for stress incontinence) is lacking.

CONCLUSIONS

- Dementia associated incontinence occurs in 30-100 % of patients with dementia (LOE 3).
- The degree of incontinence is strongly associated with patient’s general status and ambulation (LOE 3)
- There is no one major cause for incontinence in these patients; however overactive bladder is responsible for a significant portion of incontinence (LOE 3)
- LUT surgery is not contraindicated in this group of patients (LOE 3-4)

RECOMMENDATIONS

- The extensive and aggressive therapy of incontinence in dementia patients should be reserved for patients with good general status and ambulation (C)
- In case of ambulatory patients, prompted voiding, rehabilitation and oral anticholinergics seems to be treatment of choice (C).
- In case of significant post-void residual, intermittent catheterization is the treatment of choice (B); however in elderly non-ambulatory patients the recovery of LUT functions is not so good (C/D).

c) Dementia with lewy bodies

1. EPIDEMIOLOGY AND PREVALENCE
Dementia with Lewy bodies is thought to be the third most common type of dementia in the elderly,
accounting for 10 – 15% of cases at autopsy. In population-based studies of subjects aged 65 and older, the prevalence of dementia with Lewy bodies was found to be 0.7%, which is consistent with its rate of 10 – 15% of hospital-based cases at autopsy [3]. The epidemiology of dementia with Lewy bodies is sparse; age and gender distribution and potential risk factors have yet to be defined.

2. Pathology and Disease Specific LUT Problems

Dementia with Lewy bodies primarily affects the basal ganglia. Lewy bodies and Lewy neuritis are pathologic aggregations of alpha-synuclein, a ubiquitously expressed synaptic protein that has been implicated in vesicle production [1]. Lewy bodies also contain chaperone proteins and elements of the ubiquitin-proteasome system. Immunohistochemical staining for alpha-synuclein has been shown to be the most sensitive and specific method for detecting Lewy bodies and can be used in a semiquantitative grading of severity of Lewy related pathology [2].

In dementia with Lewy bodies (DLB), autonomic dysfunctions can occur and is actually included as a supportive feature for clinical diagnosis [8].

The essential feature for a diagnosis of possible or probable dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Fluctuations (waxing and waning of cognition, functional abilities and arousal from almost normal to markedly confused or hypsomolent) are a core feature of dementia with Lewy bodies.

Horimoto et al (LOE 3) found 97 % incidence of urinary incontinence amongst patients with Levy body dementia.

Many patients with dementia with Lewy bodies also have Alzheimer’s disease pathology, which alters the clinical presentation. Dementia with Lewy bodies’ patients who also have many neurofibrillary tangles display more core clinical features of AD [4]. Conversely, Lewy bodies also occur in more than half of all patients with sporadic and early-onset AD [5].

3. Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson and Alzheimer’s Disease – a Comparison

From the urological point of view patients with dementia with Lewy bodies (DLB) tend to develop urgency and urge incontinence more often than do patients with Parkinson (PD) or Alzheimer disease (ALD). Similar bladder capacity, detrusor pressure at maximum voiding, maximum urine flow, mean voided volume and post-void residual volume were found in these diseases, however detrusor overactivity, the major cause of urgency and urge incontinence, was more prevalent in DLB than in PD and in ALD [7]:

Urinary symptoms were recorded in 35 % of patients with DLB, compared to 70 % in MSA and 25 % in PD patients. Detrusor overactivity, the major cause of urge and urge incontinence was more prevalent in DLB and AD. No detrusor-sphincter-dyssynergia was observed. DLB patients with detrusor overactivity had significantly higher Hoehn and Yahr scores than did those without detrusor overactivity. Since the prevalence of frequency, urgency, urge incontinence and detrusor overactivity is markedly lower in AD than in Lewy Body disease, LUTS may contribute to the differential diagnosis of these two entities.

4. Disease Specific Diagnosis and Treatment

Since patients with Lewy Body disease and incontinence usually have one or more concomitant diseases, the evaluation of the LUT functions should follow the general rules, bearing in mind that this is most often the population of frail elderly (LOE3).

5. Guidelines for Further Research

Since dementia is not a homogeneous disease and can be classified in four main categories, further studies should aim whether there is a difference in LUT symptoms between these four groups and if yes, whether they could influence the urological treatment strategy.

RECOMMENDATIONS

- They do not differ from those in ALD and are very much dependent on the general condition of the patient (C).

d) Frontotemporal dementia

1. Epidemiology and Prevalence

Prevalence studies of FTD are inconsistent (LOE 3), giving ranges of 3,6-15,0 per 100,000 [1]. There is a high familial occurrence of FTD [2].

The distribution of FTD is equal between men and women. The mean duration of illness from onset to death is 4-6 years, with a range of 2-20 years. Progression to death in FTD is much more rapid than in ALD (average of 4,2 years and 6,0 years, respectively).

2. Pathology and Disease Specific LUT Problems

Frontotemporal dementia (FTD), also known as Pick’s disease, encompasses a diverse group of clinical and pathological disorders. There are several distinct clinical presentations, most commonly behavioral changes, but a language disorder, usually in form of a progressive non-fluent aphasia, can be the main presenting sign. The most common clinical presentation of FTD is characterized by profound changes in personality and social conduct, including a decline in manners and social skills that are incongruent with the patient’s premorbid behaviour. Affected patients lack emotional warmth, empathy and sympathy and are indifferent to others.
At autopsy markedly gross atrophy of the frontal and temporal lobes is seen in FTD. On histologic examination the salient features include neuronal loss, micro-vacuolization and astrocytic gliosis centered on cortical layer II.

MRI of patients with FTD often shows atrophy in the frontal and temporal lobes (LOE 2), which may be asymmetric [3].

There a no data on LUTS in patients with fronto-temporal dementia, however it is obvious that due to the cognitive state these patients have incontinence, either because they forget to take down clothes when they go into the toilet, or they have difficulty finding the toilet, they may urinate in inappropriate places and pass urine more often than usual. Moreover, they may be effected by constipation, diarrhoea or faecal incontinence.

3. DISEASE SPECIFIC DIAGNOSIS AND TREATMENT

No specific diagnostic tests to evaluate dementia related incontinence were described. There are no studies which show the significance of LUTS in fronto-temporal dementia.

4. GUIDELINES FOR FURTHER RESEARCH

As there are no studies which show the significance of LUTS in fronto-temporal dementia, such studies would be of value.

CONCLUSIONS

- There are no studies available which show the significance of LUTS in patients with fronto-temporal dementia.
- However, from the underlying pathology – gross atrophy of frontal and temporal lobes - autonomic dysfunction including LUTS should be present, but needs further investigation.

RECOMMENDATIONS

- The recommendations do not differ from those with other types of dementia

2. DEMENTIA, CONSTIPATION AND FECAL INCONTINENCE

- Methods

Using MEDLINE we identified English-language journal articles and reviews published from 1990 to April 2008. The key words included constipation, faecal incontinence and dementia. Special attention was given also to data regarding persons aged > 65 years.

- a) Prevalence

MEDLINE research detected only one paper related to the influence of dementia on the prevalence of urinary and faecal incontinence in an age group of 85-year-old men and women[1]. This is surprising, because patients with faecal incontinence experience anxiety, embarrassment, and social isolation.[2]

Hellström et al.[1] investigated the influence of dementia on the prevalence of urinary and faecal incontinence in 85-year-old men and women in the random sample n=485 of the total population of 85-year-olds from the city of Gothenburg, Sweden.

The prevalence of urinary and faecal incontinence and dementia were 38%, 17% and 29% respectively. Demented men (50%) and women (60%) were more often incontinent than non-demented men (18%) and women (36%). Also faecal incontinence was more prevalent in demented (34.8%) than non-demented subjects (6.7%); both urinary and faecal incontinence were more prevalent in demented women (43% and 20% respectively) than in men (27% and 11% respectively). The prevalence of urinary and faecal incontinence and dementia were higher in residents of a nursing home or hospital (74%, 51% and 92% respectively) than in subjects living at home (32%, 9% and 18% respectively): of the demented residents in an institution 78% were incontinent compared with 37% living at home.

- b) Management of faecal incontinence in demented people

No specific paper was found on the management of faecal incontinence in demented people; however it should not be too different from the management in frail elderly. Faecal incontinence in demented people can be negatively influenced by stool impaction, medications and neuro-muscular dysfunction.

Demented patients may benefit especially from a bowel habit training programme, which also includes management of constipation with non-pharmacologic (such as exercise and fibre) and pharmacologic measures.[3]

CONCLUSIONS

- Although the prevalence of faecal incontinence (as well as of urinary incontinence) in demented people is prevalent, no paper was found dealing with the disease specific management of faecal incontinence (LOE3).
- However this management should not be too different from that in frail elderly, focusing on bowel habit training programmes including management of constipation. (LOE 3)
RECOMMENDATIONS

- Studies on the prevalence of faecal incontinence in dementia are needed
- Studies should be undertaken to find out, which management is preferable for constipation and faecal incontinence in demented people.

II. MULTIPLE SYSTEM ATROPHY

Methods

Using MEDLINE we identified English-language journal articles and reviews published from 2000 to April 2008, looking for the keywords Multiple System Atrophy, Urinary Incontinence, Bladder Dysfunction, Bowel problems, Constipation, Faecal Incontinence, Management.

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Multiple system atrophy (MSA) is a rare, adult-onset degenerative disease of the nervous system of unknown origin. Autonomic failure (postural hypotension and urinary dysfunction) is fundamental to the diagnosis of MSA: it is diagnosed when the criteria of either postural hypotension (systolic blood pressure fall > 30 mmHg or diastolic > 15 mmHg) or urinary dysfunction (persistent, urinary incontinence/ incomplete bladder emptying) or both are fulfilled, along with poorly levodopa-responsive parkinsonism or cerebellar dysfunction.[1] Based on the major motor deficits MSA can be classified as MSA-P (parkinsonism - predominant) or MSA-C (cerebellar-predominant).


Urinary symptoms of incontinence are caused by neurologic detrusor overactivity and external sphincter weakness [3] (LOE 2). Sphincter electromyography (EMG) abnormalities were found in 91% of the patients with MSA [3] (LOE 2). Approximately 60% of patients with MSA develop urinary symptoms either prior to or at the time of presentation with the motor disorder [4] (LOE2). This indicates that many of these patients seek urological advice early in the course of their disease. Although postural hypotension was thought to be a marker for autonomic failure in MSA, Wenning et al [5] (LOE2) noted urinary incontinence in 71%, urinary retention in 27%; postural faintness in 53%, and syncope in 15% of 100 patients with MSA. Sakakibara et al [4] (LOE2) found that urinary symptoms (96%) were more common than orthostatic symptoms (43%) (p < 0.01) among 121 patients with MSA. Kirchhof et al [6] (LOE2), found that bladder symptoms preceeded symptoms of orthostatic hypotension in 76% of their 71 male patients. Sakakibara et al [4] (LOE2) also found that among 53 patients with both urinary and orthostatic symptoms, those who had urinary symptoms first (46%) were more common than those who had orthostatic symptoms first (29%), and some patients developed both symptoms simultaneously (23%).

b) Pathology and disease specific lut problems

Urinary dysfunction is divided to that of storage and voiding, respectively. Sakakibara et al [7] (LOE2) performed an extensive study of the urological symptoms in MSA patients. They found the following prevalence of different symptoms: difficulty of voiding in 79%, nocturia in 74%, sensation of urgency (recently called an overactive bladder) in 63%, urge incontinence in 63%, diurnal urinary frequency in 45%, enuresis in 19% and urinary retention in 8% of the patients. All of MSA patients presented with some kind of LUT symptoms. In addition, many of them had storage and voiding urinary symptoms together; suggesting altered storage and micturition functions in this disorder.

Among 245 urodynamic cases of MSA, Ito et al [8] (LOE2), found that average volume of post-void residuals as a marker of voiding dysfunction was 71ml at the first year, which increased significantly to 170ml at the 5th year (p<0.01) after onset of the disease. Patients were not always aware of their post-void residuals. The frequency of weak detrusor by a pressure-flow analysis was 20% at the first year, which increased to 53% at the 5th year (p<0.05). The frequency of detrusor-external sphincter dyssynergia was 12% at the first year, which increased to 39% at the 5th year (p<0.05). Therefore, detrusor underactivity seemed to contribute to voiding dysfunction in MSA more than detrusor-external sphincter dyssynergia did. The responsible sites of lesion (micturition facilitating area) for voiding difficulty and retention in MSA seem to be the locus coeruleus (pontine micturition center). The work of Bennaroch demonstrated, that in MSA there is severe depletion of catecholaminergic neurons of the CI and Al areas in the ventrolateral medulla, and this may contribute to orthostatic hypotension and endocrine disturbances in this disorder, respectively. Additionally loss of corticotrophin-releasing factor (CRF) neurons in the pontine micturition area may contribute to neurologic bladder dysfunction [9] (LOE 2). In addition, the sacral intermediolateral cell columns, where preganglionic neurons innervating the bladder are located, are affected in post-mortem MSA cases.

Regarding the storage abnormalities, the frequency of detrusor overactivity was 61% at the first year,
which increased to 75% at the 5th year (p<0.05) [8] (LOE2). The frequency of neurogenic pattern in the sphincter EMG was 52% at the first year, which increased to 83% at the 5th year (p<0.05) [10] (LOE2). Abnormalities in the videourodynamic study included open bladder neck at the start of filling in 53% of MSA patients, suggestive of bladder neck denervation [11] (LOE2). Similar results were reported by others [12]. The responsible sites of lesion (storage-facilitating area) for urinary urgency and incontinence in MSA seem to be the basal ganglia, cerebellum [13], lumbar intermediolateral cell columns where preganglionic neurons innervating the bladder neck are located, and sacral Onuf’s nucleus innervating the external sphincter, all of which are affected in post-mortem MSA cases, causing urinary stress incontinence.

Repeated urodynamic studies in MSA patients showed that the cystometrogram changed from detrusor overactivity to low-compliance or acontractile detrusor, and from negative to positive bethanechol supersensitivity [4] (LOE2). In fact, as the disease progresses, symptoms may change from urinary urgency and frequency to those due to incomplete bladder emptying. These findings suggest that the responsible sites of the bladder cholinergic disorder may change from the center to the periphery. Whereas in the midst of disease, the cystometrogram of patients with MSA often show neurogenic detrusor overactivity with impaired contractile function (DHIC), mostly accounting for urinary urgency / frequency and large post-void residuals, respectively. This condition presumably reflects lesions in both storage and voiding-facilitating areas in this disorder. [15]

Beside bladder disorders, patients with MSA may have nocturnal polyuria, which results in nocturia and morning hypotension. In normal children over 7 years and adults, the circadian release of arginine vasopressin from the posterior pituitary gland into plasma peaks at night. This leads to a nocturnal decrease in urine formation. The ratio of nighttime to daytime urine production is usually <1:2, which can be estimated by a bladder diary. A postmortem study of the brains of patients with MSA revealed the degeneration of arginine vasopressin neurons in the suprachiasmatic nucleus [16] (LOE 2), leading to impairment of the circadian rhythm of the plasma arginine vasopressin concentration in MSA [17] (LOE 2).

c) Disease specific diagnosis and treatment

Since LUT functional disturbances precede very often orthostatic hypotension and other autonomic nervous system symptoms in MSA patients, the diagnosis of lower urinary tract (LUT) symptoms is of paramount importance. Further discussion of the differentiation between MSA and Parkinson’s Disease is to be found in the section on PD.

Amongst different tests external sphincter EMG is the most sensitive one. Sphincter motor unit potential analysis showed neurologic motor unit potentials in 93% of those with MSA, suggestive of external sphincter denervation. Palace et al [18] (LOE 2) demonstrated abnormal sphincter EMG in 93% of MSA patients, which can differentiate this disorder from idiopathic Parkinson’s disease. Oertel et al [19] (LOE2) suggested that reduced genital sensation in females could be pathognomonic for MSA (with equal importance as erectile dysfunction in males). A total of 47% of the MSA patients and 4% of the control group had reduced genital sensation. Moreover, the appearance of reduced genital sensitivity in female MSA patients showed a close temporal relation to the onset of the disease. Hahn and Ebersbach [25] (LOE 2) investigated the value of sonography of the bladder to evaluate post-void residual urine (PVR) for the differential diagnosis between idiopathic Parkinson’s disease and Multiple System Atrophy. The positive predictive value of increased residual urine for MSA was 91.6% in the study, the negative predictive value was only 67.8%. They state, that bladder sonography is an objective, simple and safe tool that allows one to screen for urinary retention which is highly suggestive, but incompletely sensitive for MSA. Because sonography is easily accessible and rapidly performed, it is feasible for routine assessment of atypical Parkinson syndromes. Also Takashi et al 2006 (LOE 2) commented that urinary retention can be a major cause of morbidity in Multiple System Atrophy. The grand average volume of PVR was 140 cc in their patients, the average PVR volume increased from the first year from 71 cc to 129 cc in the second year and 270 cc in the 5th year.

When treatment of the voiding disorders in MSA is concerned, again the general principles of urodynamic based therapy should be used. However it is important to observe that aggressive surgical therapy is not recommended in MSA patients. Chandiramani et al [20] (LOE2) found that all MSA patients who underwent transurethral resection of the prostate (TURP) due to voiding problems were incontinent postoperatively, most probably due to pre-existing sphincter weakness. The same observations were done by Beck et al [3] (LOE2), who evaluated the results of TURP and stress incontinence surgery in MSA patients. They concluded that the results of surgery were unfavorable. Patients benefited from clean, intermittent catheterization (CIC), anticholinergic medication and desmopressin spray [21] (LOE 3), which improved continence in 82%.

A nearly half of the MSA patients suffer from voiding difficulties, its management by other means than CIC would be very attractive. Sakakibara et al [22] (LOE 3) compared different non-selective and alpha I A selective alpha blocking agents (prazosin and moxisylyte) in the treatment of LUT dysfunctions in MSA patients. The respective means for reductions in residual urine volume for the prazosin and moxisylyte groups were 38.1% and 35.2% and there was lessening of urinary symptoms. Side effects due to
orthostatic hypotension were seen in 23.8% of the prazosin group but in only 10.7% of the moxisylyte group. A more recent study showed that the effects of alpha blocking agents, as well as those of TUR-bladder neck, for lessening post-void residuals lasted for up to 2 years in MSA, although during that period patients benefited from the therapies [8] (LOE2). On the contrary, administration of amezinium, an adrenergic drug for ameliorating postural hypotension, may increase the risk of retention and post-void residual volume compared to that before treatment [23] (LOE2). Amezinium most probably stimulates the alpha receptors, both in the vascular wall (alpha1B receptors) and the proximal urethra (alpha1A/D adrenergic receptors).

Both postural hypotension and bladder dysfunction are common clinical features in MSA. Pyridostigmine, an acetylcholinesterase inhibitor, can be effective in lessening post-void residual volumes, since it stimulates muscarinic acetylcholine receptors on the bladder (M2/3-muscarinic receptors) that are innervated by parasympathetic cholinergic neurons. Pyridostigmine also lessens post-void residual volumes, since it may increase the risk of retention and post-void residual volume compared to that before treatment [23] (LOE2). Amezinium most probably stimulates the alpha receptors, both in the vascular wall (alpha1B receptors) and the proximal urethra (alpha1A/D adrenergic receptors).

Both postural hypotension and bladder dysfunction are common clinical features in MSA. Pyridostigmine, an acetylcholinesterase inhibitor, can be effective in lessening post-void residual volumes, since it stimulates muscarinic acetylcholine receptors on the bladder (M2/3-muscarinic receptors) that are innervated by parasympathetic cholinergic neurons. Pyridostigmine also lessens post-void hypotension, presumably by enhancing nicotinic acetylcholine receptor transmission in the sympathetic ganglia [24].

**RECOMMENDATIONS**

- The most sensitive test to detect multiple system atrophy associated LUT abnormalities is sphincter EMG (A), and post-voiding residual volume, especially when differencing from Idiopathic Parkinson’s disease.
- Due to progressive nature of the disease aggressive treatment and LUT surgery (e.g. TURP) are not recommended (A).
- Treatment of choice in case of increased post-void residual are alpha blocking agents and IC (B).

**CONCLUSIONS**

- LUT symptoms often precede the clinical manifestation of multiple system atrophy (LOE2).
- The most common LUT disturbances are detrusor overactivity, detrusor-external sphincter dyssynergia, sphincter and detrusor weakness (LOE2).
- Significant post void residual is observed in about half of the multiple system atrophy patients (LOE2).

**RECOMMENDATIONS**

- The most sensitive test to detect multiple system atrophy associated LUT abnormalities is sphincter EMG (A), and post-voiding residual volume, especially when differencing from Idiopathic Parkinson’s disease.
- Due to progressive nature of the disease aggressive treatment and LUT surgery (e.g. TURP) are not recommended (A).
- Treatment of choice in case of increased post-void residual are alpha blocking agents and IC (B).

**2. FECAL INCONTINENCE**

**a) Epidemiology and prevalence**

Lower gastrointestinal tract (LGIT) dysfunction is also common in patients with multiple system atrophy (MSA). Sakakibara et al [1] (LOE2) performed a bowel questionnaire in 15 patients with MSA and in 10 age-matched healthy control subjects. MSA group showed decreased bowel frequency (< 3 times a week) in 9, difficulty in expulsion in 11, and faecal incontinence in 3; whereas control group showed decreased bowel frequency in only 2, mild difficulty in expulsion in 2, fecal incontinence in none. Therefore, constipation is the major bowel dysfunction in this disorder; although in advanced stages faecal incontinence is not uncommon.

**b) Pathology and disease specific LUT problems**

Previous studies on the mechanism of bowel problems in this disorder are scarce. Stocchi et al [2] (LOE2) performed anorectal manometry in 16 patients with MSA; and 13 patients showed paradoxical anal sphincter contraction on fictive straining. Bardoux et al [3] (LOE3-4) reported a case of fecal incontinent patient due to MSA, who showed inability of anal squeezing. More recently, Sakakibara et al [1] (LOE2) performed colonic transit time, sphincter electromyography (EMG) and rectoanal video-manometry in 15 patients with MSA and 10 age-matched healthy control subjects. Compared with the control subjects, MSA patients had significantly prolonged colonic transit time in the rectosigmoid segment (p<0.05) and total colon (p<0.05). Sphincter EMG showed neurogenic motor unit potentials in none of control subjects but in 93% of MSA (p<0.01). At the resting state, MSA patients showed a lower anal squeeze pressure (external sphincter weakness) (p<0.01) and a smaller increase in abdominal pressure on coughing (p<0.01). During rectal filling, MSA patients showed smaller amplitude in phasic rectal contraction (p<0.01), which was accompanied by an increase in anal pressure that normally decreased, together with leaking in 3 patients. During defecation, most MSA patients could not defecate completely with larger post-defecation residuals (p<0.05). MSA patients had weak abdominal straining, smaller rectal contraction on defecation and larger anal contraction on defecation (paradoxical sphincter contraction on defecation, or anismus), though these differences were not statistically significant.

Therefore, constipation in MSA most probably results from slow colonic transit, decreased phasic rectal contraction and weak abdominal straining, whereas fecal incontinence results from weak anal sphincter due to denervation. The responsible sites for these dysfunction are still not entirely clear. However, as described in idiopathic Parkinson’s disease, they most probably reflect lesions of both central and peripheral nervous systems that regulate the LGIT.
**c) Disease specific diagnosis and treatment**

LGIT functional disturbance is often preceded by LUT dysfunction in MSA patients. Abnormalities in colonic transit time and rectoanal videomanometry in MSA were mostly similar to those in idiopathic Parkinson’s disease, except for the sphincter denervation and resultant fecal incontinence in MSA.

When treatment of the bowel disorder in MSA is concerned, use of objective parameters is recommended in order to clarify the action of drugs. A few such studies are available: Eichhorn and Oertel [4] (LOE3) gave polyethylene glycol 3350, an osmotic agent with high water binding capacity, in 2 patients with MSA, and found an improvement in stool frequency and difficult defecation in both patients. Similarly, Sakakibara et al [5] (LOE2) measured colonic transit time in 4 patients with MSA.

After administration of calcium polycarbophil, an osmotic and highly bulking agent, colonic transit time of total and the right segment shortened significantly. Liu et al [6] (LOE2) performed colonic transit time and rectoanal videomanometry in 7 patients with MSA. After administration of mosapride citrate, a novel selective 5-HT4 receptor agonist, the patients showed a shortened total and rectosigmoid segment colonic transit time; lessened first sensation and an augmented amplitude in phasic rectal contraction.

During defecation, mosapride augmented the amplitude in rectal contraction and lessened the volume of post-defecation residuals significantly. Similar results were obtained in a study by Sakakibara et al [7] (LOE2), in which dietary herb extract Dai-Kenchu-To, one active component of which is hydroxy-beta-sanshool (5-HT3 receptor agonistic action), was prescribed.

**d) Guidelines for further research**

MSA is a slowly progressive disease without any cure. More research is needed to evaluate the pathophysiology of LGIT dysfunction, and to evaluate the effects of different drug treatment modalities.

**CONCLUSIONS**

- Patients with multiple system atrophy have often abnormal bowel function (LOE2).
- The most common bowel disturbances are slow colonic transit, decreased phasic rectal contraction and weak abdominal straining, and faecal incontinence results from weak anal sphincter due to denervation (LOE2).
- Bowel dysfunction such as constipation is common and has significant impact on quality of life of patients with multiple system atrophy (LOE3).

**RECOMMENDATIONS**

- More studies on neurologic bowel dysfunction and management in patients with multiple system atrophy are needed before giving any recommendation.

**III. PARKINSONS DISEASE**

1. **URINARY INCONTINENCE**

   a) **Epidemiology and prevalence**

   Parkinson’s disease (PD) is a movement disorder due to degeneration of dopaminergic neurons in the substantia nigra and a loss of dopamine-containing nerve terminals in the basal ganglia. Degeneration of the nigrostriatal pathway is accompanied by decreases in corresponding biochemical markers, including dopamine, tyrosine hydroxylase, dopamine metabolites, and dopamine transporter. These central nervous system changes have also influence on autonomic functions, including voiding in affected patients. The most common are gastrointestinal (constipation), perspiratory (hypohidrosis) and urinary systems.

   Lower urinary tract (LUT) dysfunction in PD was estimated to occur in 37-71% in uncontrolled studies. Among these, in a study of Hattori et al [2] (LOE3) 60% of PD patients had urinary symptoms, which could be divided in the following categories: irritative in 28%, obstructive in 11%, and both symptoms in 21%. The frequency of urinary symptoms statistically correlated with severity of the disease, but not with the duration of illness. Gray et al [3] (LOE3) reported that LUT functional disturbances in PD are not disease specific and only correlated with age. In the more recent, control-based studies [4,5,6,7] (LOE2) the prevalence of LUT symptoms (LUTS) was found to be 27-63,9% using validated questionnaires [4,5,6], or 53% in men and 63% in women using a nonvalidated questionnaire that includes a urinary incontinence category [7], with all of these values being significantly higher than healthy controls. The majority of patients had onset of the bladder dysfunction after appearance of motor disorder. In one study, urinary incontinence in PD frequently occurred in conjunction with fecal incontinence, whereas no significant relation was observed between bladder and sexual dysfunction [7]. Also, it is of particular importance to note that that bladder dysfunction substantially affects the quality of life in patients with PD [7] (LOE2). There has been shown a correlation between bladder dysfunction in patients with PD and neurological disability [4] (LOE2), and a correlation to stage of disease [7] (LOE2), both suggesting a relationship between dopaminergic degeneration and LUTS. LUTS was more common in a group of PD patients with older age than that with...
younger age, as it is seen in healthy populations [7]. Among LUTS, nocturia (nighttime urinary frequency) is the most prevalent symptom reported by patients with PD (>60%) [4,5,6,7] (LOE2). Patients also complain of urinary urgency (33-54%), daytime frequency (16-36%), and urinary incontinence in 26% of their male and 28% of their female patients with PD [7].

Although less common than storage symptoms, PD patients also show voiding symptoms. In the study by Sakakibara et al [7] (LOE2), the PD patients had significantly higher rates of retardation in initiating urination (44% of men only), prolongation/poor stream (70% of men only), and straining (28% of women only) compared with the control group. However, despite the voiding symptoms, PD patients have low post-void residuals.

b) Pathology and disease specific lut problems

The net effect of the basal ganglia on micturition is thought to be inhibitory [8], whereas in PD, in which the basal ganglia is affected, the bladder becomes hyperactive. Functional neuroimaging during bladder filling resulted in activation in the globus pallidus of normal volunteers [9] (LOE2) and in the putamen in PD patients with detrusor overactivity[10] (LOE2). In contrast, dopamine transporter imaging (indicating brain dopamine neurons) was decreased in PD patients with urinary dysfunction than in those without it [11,12] (LOE2). The micturition reflex is under the influences of nigrostriatal dopamine[13] (both inhibitory in D1 and facilitatory in D2) and GABA (inhibitory). Deep brain stimulation in the subthalamic nucleus results in amelioration of motor disorder as well as increased bladder capacity and decreased post-void residuals [14] (LOE2). Therefore, urinary dysfunction in PD could reflect degeneration of the nigrostriatal dopaminergic cells associated with specific motor disorders. In addition to the nigrostriatal dopaminergic projection, the ventral tegmental area (VTA, the A10 cell group)-limbic cortex and the hypothalamic (the A11 cell group)-spinal cord dopaminergic projections are presumably involved in urinary dysfunction in PD.

In a study of PD and multiple system atrophy (MSA) patients, Sakakibara et al [15] (LOE2) found urinary symptoms in 72% of PD patients. They were mostly attributed to detrusor overactivity (81%) and external sphincter relaxation problems (33%). During micturition PD patients did not demonstrated detrusor-sphincter dyssynergia, however detrusor-hypocontractility was observed in 66% of women and 40% of men. In addition, patients with PD had mild outlet obstruction, e.g., mean Abrams-Griffiths number (outflow obstruction > 40) was 40 in women and 43 in men, respectively. Nevertheless, average volume of post-void residuals in PD was only 18 ml. Similar observations were done by Defreitas et al [16] (LOE2). The urge incontinence prevalence was around 54%, however no statistically significant correlation between the duration or severity of PD and urodynamic parameters was found.

c) Disease specific diagnosis and treatment

In voiding dysfunctions associated with presumed PD it is important to differentiate between PD and MSA. Chandiramani et al [17] (LOE2), suggested several criteria for distinguishing LUT symptoms caused by MSA from those caused by PD. Presence of the following features: urinary symptoms preceding or presenting with parkinsonism; urinary incontinence; a significant post-void residual urine volume; erectile failure preceding or presenting with parkinsonism, is strongly suggestive of MSA rather than PD. External urethral sphincter EMG is also helpful to distinguish between these two entities, since detrusor-external sphincter dysynergia was not seen in patients with PD but was present in 47% of those with MSA [15] (LOE2). This is also confirmed by studies of palace et al [18] (LOE2) who demonstrated abnormal sphincter EMG in 82% of MSA patients.

It is possible that levodopa and other antiparkinson medication may affect bladder function in PD. Aranda et al [19] (LOE3) studied the effects of apomorphine in 2 de novo PD patients (patients who have not had antiparkinsonian medication previously), and found that the bladder capacity increased. They gave oral levodopa to one of the patients, and the bladder capacity increased. In another study, after 3 months of treatment with levodopa, the storage urodynamic parameters were improved in de novo PD [20] (LOE3).

In contrast, in non-de novo patients, studies concerning the effect of dopaminergic drugs on micturition have produced conflicting results. Some reports have shown storage-facilitating effects of dopaminergic drugs as follows. A questionnaire study has shown that in non-de novo patients, voiding symptoms (intermittency and sensation of residual urine) were more common in those taking levodopa and bromocriptine (D2-selective agonist) than in those taking levodopa alone [7] (LOE2). In contrast, Kuno et al [21] (LOE3) showed that change of bromocriptine to pergolide (D1<2 agonist) brought lessening of nocturia, and Yamamoto [22] (LOE3) described improvement of detrusor overactivity by pergolide. Others have shown voiding-facilitating effects as follows. Christmas et al [23] (LOE3) have studied the effects of apomorphine in 10 parkinsonian patients, and found that anticholinergic bladder became normal in 2, and post-void residuals was ameliorated in 6 of these patients. More recent studies have shown that in early PD [24] (LOE2) and advanced PD with the on-off phenomenon [25] (LOE2), a single-dose of levodopa exacerbates detrusor overactivity in the filling phase, but also improves bladder emptying through increased detrusor contractility. We still do not know the exact reasons for the discrepancy.
There are several factors underlying the complex bladder behavior in non-de novo PD patients. Post-synaptic dopamine D1 (excitatory) and D2 (inhibitory) receptors have a millimolar affinity to dopamine, whereas dendritic D2 (inhibitory) autoreceptors have a picomolar affinity to dopamine [26]. Therefore, when levodopa is administered externally, it may first stimulate dendritic D2 autoreceptors, which might suppress the nigral cells and facilitate the micturition reflex. In cases of PD under long-term treatment with levodopa, dopamine receptors are down-regulated and potential hypersensitivity might occur [27]. Bladder overactivity might also involve an activation of D2 receptors in the spinal cord [28].

Detrusor overactivity should be treated according to the general knowledge of anticholinergic drugs. There are no specific studies on systematic anticholinergic drugs to treat neurologic detrusor overactivity in PD patients; however since anticholinergics were the first drugs available for the symptomatic treatment of PD and since they are still widely used today there is no reason to believe that they will produce any specific adverse events in these patients. A systematic review of anticholinergic use (centrally acting) to treat PD was recently done by Katschmacher et al [29] (LOE I).

For emptying failure the treatment of choice remains clean, intermittent catheterization (CIC); however PD patients rarely have post-void residual volume > 100ml [15] (LOE2). An interesting treatment option was suggested by Finazzi-Agro et al [30] (LOE3), who implanted subthalamic nucleus electrodes in patients with PD. They observed that during chronic subthalamic nucleus stimulation bladder capacity and reflex volume were increased for and the amplitude of overactive detrusor contractions was decreased (non significantly) in comparison with the studies performed when the stimulator was switched off.

As in MSA a very important issue in PD affected patients is the indication for pelvic surgery. Myers et al [31] (LOE2) found that women with PD and LUT complaints have a lower maximum cystometric capacity and a higher rate of detrusor overactivity at lower bladder volumes in comparison with non-neurologic control. Therefore surgery for stress incontinence in women with PD should be performed only when no significant detrusor overactivity is present, since it is well known that this type of surgery can evoke or aggravate detrusor overactivity and subsequent urge incontinence.

The issue of selecting the right patient for prostate surgery was described above. Staskin et al (LOE3) described the results of TURP in MSA rather than in PD patients. Since external urethral sphincter acontractility is extremely rare in true PD, prostate surgery should not be contraindicated in this group of patients.

d) Guidelines for further research

Despite there is no definite cure for PD, with the current knowledge we can slow down the disease process and bring patients to an almost normal live. Therefore it would be of extreme importance to introduce a validated scheme for LUT dysfunction therapy.

CONCLUSIONS

- LUT symptoms are associated in PD with degeneration of dopaminergic neurotransmission (LOE2).
- The most common LUT disturbances are detrusor overactivity, and detrusor hypocontractility (LOE2).
- The effect of levodopa on LIJT in PD patients remains to be elucidated (LOE3).

RECOMMENDATIONS

- Treatment of choice for detrusor overactivity in PD patients is antimuscarinics (B).
- For voiding failure in case of significant post void residual the treatment of choice remains intermittent catheterization (B).
- LUT surgery for patients with Parkinson's symptoms is an option as long as MSA is excluded. However stress incontinence surgery should not be offered to patients with significant detrusor overactivity (C).

2. FAECAL INCONTINENCE

a) Epidemiology and prevalence

Lower gastrointestinal tract (LGIT) dysfunction is common in Parkinson's disease (PD). It occurs in more than half of PD patients in uncontrolled studies. In the more recent, control-based studies [1,2,3] (LOE2), the incidence rate of decreased stool frequency (< 3 times a week) in PD patients ranges from 20% to 81%, that of difficulty in stool expulsion in 57-67%, and that of diarrhea in 21%. All of these values are significantly higher than in the normal population (range, decreased stool frequency, 0-33%; difficulty in stool expulsion, 26-28%; diarrhea, 10%). Fecal incontinence has been reported to be 10-24% in PD [2,4] (LOE2). Therefore, constipation is the most prominent LGIT symptoms in patients with PD. Indeed, PD is a risk factor for elderly nursing home residents to have constipation. Of particular importance is that bowel dysfunction affects the quality of life in patients with PD. Among three pelvic autonomic dysfunctions, the rate of dissatisfaction for bowel dysfunction (59%) is significantly higher than those for urinary (28%) or sexual dysfunction (29%) in PD, although the prevalence rate of all three dysfunctions
is almost the same (more than 60%). The rate of dissatisfaction for the bowel dysfunction in PD is also significantly higher than in healthy controls (16%) [2] (LOE2).

Difficulty in expulsion, and diarrhea are more common in the higher grade of Hoehn and Yahr staging [2,5] (LOE2), suggesting a relationship between dopaminergic degeneration and LGIT symptoms. Fecal incontinence in PD occurs commonly with urinary incontinence, whereas no significant relation has been seen between bowel and sexual dysfunction [2] (LOE2). Constipation in PD occurs commonly with a low coefficient of variation in electrocardiographic R to R intervals [6] (LOE3). The findings indicate that parasympathetic dysfunction might underlie these abnormalities.

A recent epidemiological study revealed an association between the frequency of bowel movements and the future risk of developing PD [7] (LOE1). This observation is in line with the pathological staging of PD by Braak et al [8] (LOE1), in which disease process in the central nervous system starts earlier in the dorsal motor vagal nucleus than in the substantia nigra in PD. From a clinical perspective, it is of particular importance that patients with PD see gastroenterologists or physicians first because of their bowel dysfunction, before they see neurologists and a correct diagnosis of PD is made. Therefore, constipation as the initial presentation of PD is akin to urinary dysfunction as the initial presentation of multiple system atrophy.

**b) Pathology and disease specific lut problems**

The enteric nervous system contains a program in order to generate the peristaltic reflex that promotes bowel transport within the LGIT [9]. The peristaltic reflex consists of two components: ascending contraction oral to, and descending relaxation caudal to the site of stimulus. Cholinergic receptors have a major role in the ascending contraction reflex. The strength of cholinergic transmission is regulated by opposing receptors; serotonin 5-HT4 receptor-mediating excitation and dopamine D2 receptor-mediating inhibition [10,11]. Postmortem studies of bowel in PD have shown decrease in dopaminergic myenteric neurons and the appearance of Lewy bodies along the proximal-distal axis, e.g., they were most frequent in the lower esophagus, but scarce in the rectum [12,13,14] (LOE2). These findings clearly showed that PD affects not only central, but also peripheral (enteric) nervous system.

LGIT function primarily consists of (1) colonic transport of the bowel content to the anorectum, (2) transient anorectum reservoir, and (3) defecation from the anorectum with the aid of strain. In PD, constipation results primarily from decreased transport and/or disturbed anorectal evacuation. Fecal incontinence may result from disturbed anorectal reservoir, or overflow secondary to constipation. Previous reports have shown that total colonic transit time (CTT) is increased beyond the normal threshold in 80% of PD patients, which translates into an increased average CTT ranging from 44 hours to 130 hours in PD [4,15,16] (LOE2), and in 89 hours in *de novo* PD patients [15] (LOE2), all of which are significantly longer than those of controls (range, 20-39 hours). Prolonged CTT has also been documented in PD patients without subjective constipation [17] (LOE2). Slow colonic transit is the major cause of decreased stool frequency. The slow colonic transit is likely to reflect a decrease in slow waves and spike activities of the colon [9].

In the resting anal manometry, the anal pressure of PD patients is low or normal [16,18] (LOE2). The resting anal pressure may reflect sympathetic innervation in the internal anal sphincter, since lesions or anaesthetic blocks at T12-L3 (where the sympathetic preganglionic neurons are located) substantially lessen the anal pressure [19]. Similarly, most PD patients have normal anal pressure increase on squeezing. This finding corresponds to a lack of neurogenic changes in the external sphincter EMG in this disorder. Nevertheless, the latent anal sphincter dysfunction may explain the fecal incontinence that occurs in most advanced cases.

In the slow-filling rectoanal videomanometry, PD patients had the same rectal volume at first sensation and a maximum desire to defecate, and the same rectal compliance as control subjects [16,18] (LOE2). In contrast to the bladder, the normal rectum shows spontaneous phasic contraction [20]. However, the amplitude of the spontaneous phasic rectal contraction in the PD patients is significantly less than that in control subjects [16,20] (LOE2). The decreased spontaneous phasic rectal contraction may share the same aetiology with the decrease in CTT.

During defecation, the healthy subjects utilized the final wave of spontaneous phasic rectal contractions for defecation [20] (LOE2). However, rectal contraction on defecation in PD patients is smaller than that in controls [16] (LOE2). In addition, in PD patients the abdominal straining is smaller [20] (LOE2). In PD patients paradoxical sphincter contraction on defecation (PSCD), or anismus, is observed in studies using sphincter EMG, radiography, and anal pressure measurement [16,18,21] (LOE2). The mechanism of the impaired straining in PD may include rigidity and reduced contractility of the axial muscles, and a failure of coordinated glottis closure [22] (LOE2). However, neuronal degeneration in the brain of PD patients relevant to straining is yet to be clarified. Mathers et al [21] consider PSCD a focal dystonia. PSCD also occurs in spinal cord-injured patients [23], suggesting that dysfunction in the suprasacral descending pathway to the external sphincter is a contributing factor. Apomorphine is shown to lessen PSCD [21] (LOE2). This effect was not antagonized by
domperidone, which did not penetrate the BBB, suggesting that the central nervous system pathology may produce PSCD.

c) Disease specific diagnosis and treatment

Insoluble dietary fibers produced an improvement in stool consistency and an increase in stool frequency in PD, which paralleled an improvement in levodopa absorption [24] (LOE3). More recently, dietary fibers such as psyllium [25] (LOE2) and polyethylene glycol 3350 [26] (LOE2), or bulking and highly hydrophilic agent polycarbophil [27] (LOE2), improve constipation in neurodegenerative disorders, including PD. Although psyllium does not alter CTT or anorectal parameters in PD patients, polycarbophil shortens the total CTT, particularly in the proximal bowel segments [27] (LOE2).

It is possible that levodopa and other antiparkinson medication may affect bowel function in PD. Endogenous dopamine is thought to inhibit intestinal motility via D2 receptors. However, no reports are available to see whether levodopa might change gut function in de novo PD patients.

Since levodopa is absorbed from the small intestine, bowel dysfunction in PD may interfere with levodopa absorption, worsen the motor disorder, or even lead to malignant syndrome [28] (LOE3/4). Domperidone, a peripheral D2 receptor antagonist that does not cross the blood-brain barrier, causes a mean 12% increase in peak plasma levodopa concentrations that occurs a mean of 10 min earlier than when levodopa is given alone [29].

After cisapride has been withdrawn in many countries due to cardiotoxicity, mosapride, a novel selective 5-HT4 receptor agonist, appeared in clinical use; it shortened total CTT (particularly the caudal segment), and augmented the amplitude in rectal contraction during defecation in patients with PD [30] (LOE2).

It is of particular importance that improvement of parkinsonism is more significant with pergolide-mosapride than with pergolide-domperidone, presumably reflecting better levodopa absorption (LOE3). Similar results were obtained in PD by dietary herb extract Dai-Kenchu-To, one active component of which is hydroxy-beta-sanshool (5-HT3 receptor agonistic action)[32] (LOE2).

d) Guidelines for further research

Despite there is no definite cure for PD, with the current knowledge we can slow down the disease process and bring patients to an almost normal live. Therefore it would be of extreme importance to introduce a validated scheme for LGIT dysfunction therapy.

CONCLUSIONS

- Patients with PD have often abnormal anorectal function (LOE2).
- The most common bowel disturbances in PD are slow colonic transit, decreased phasic rectal contraction and weak abdominal strain, and paradoxical sphincter contraction on defecation (or anismus) (LOE2).
- Bowel dysfunction such as constipation is common and has significant impact on quality of life of PD patients (LOE2).

RECOMMENDATIONS

- It seems possible that constipation in PD is treated by drugs acting on dopamine D2 receptors or 5-HT4 receptors in the bowel. (C)
- However, more studies on management of neurologic bowel dysfunction in PD are needed before giving any recommendation.

IV. CEREBRAL LESIONS AND CEREBRO-VASCULAR ACCIDENTS

Listing of terminology used for the searches: cerebrovascular accident, cerebral lesions, bladder dysfunction, urinary incontinence, faecal incontinence

1. URINARY INCONTINENCE

a) Epidemiology and Prevalence

Cerebro-vascular accidents are the third most frequent cause of death in industrialised countries after myocardial infarction and malignancies. Based on age-dependence of cerebro-vascular accidents (CVA) and the increase of the elderly in our population the importance of this disease enhances: currently one out of 200 inhabitants will suffer from a CVA, 80 to 90% of them above the age of 65. The 5-year-survival rate is 96 % in men and 64 % in women.

At the time of maximal impairment 41.1% of 4499 stroke patients (46.0% of females and 37.3% of males studied) had urinary incontinence [1]. An analysis of the symptoms of 532 patients seen within 7 days of their stroke found that the presence of urinary incontinence appeared to be a more powerful prognostic indicator for poor survival and eventual
functional dependence than a depressed level of consciousness in this period [2, 3]. It was suggested either incontinence was the result of a severe general rather than specific loss of function or that those who were incontinent were less motivated to recover from both continence and more general function. Outcome was so much better in those who remained or became dry that it seems possible that recovery of continence may promote moral and self-esteem which can actually hasten overall recovery. Urinary incontinence with impaired awareness of bladder sensation seem to be associated with poorer outcome than urge urinary incontinence with preserved bladder perception [4]. In Nayhama paper 20 % - 30 % of the patients still suffer from urinary incontinence six months after the CVA if no proper treatment has been instored [5]. Recently, it was shown that six months after stroke 16% of stroke patients experience urine loss, and that urinary loss was perceived as urinary incontinence when it occurred at least monthly [6].

b) Pathology and disease specific LUT problems

1. CEREBRAL LESIONS

Prior to the findings of PET-scan studies [7] all that was known about the cortical control of the bladder was based on clinical studies of patients with brain lesions. The most influential study was that by Andrew and Nathan, 1964 [8]. The typical clinical picture of frontal lobe incontinence they described was of a patient with severe urgency and frequency of micturition and urge incontinence, without dementia, the patient being socially aware and embarrassed by the incontinence. Micturition was normally co-ordinated, indicating that the disturbance was in the higher control of these processes. Nathan concludes his translation notes to the paper with a comment “this paper was written because people did not believe that there was such a thing as cerebral disturbance of the bladder”.

There have been a number of urodynamic studies of groups of patients who have had CVA's and subsequently developed urinary symptoms. The conclusions drawn from these groups of patients with disparate cortical lesions are that, in general, voiding is normally co-ordinated as no patients showed evidence of detrusor sphincter dyssynergia, and that the commonest cystometric finding is detrusor overactivity[9-11].

In 1996 Sakakibara et al. [12] reported on the bladder symptoms of 72 patients who had been admitted with an acute hemispheric stroke. When assessed at 3 months, 53 % were found to have significant urinary complaints. The commonest clinical problem was nocturia which occurred in 36 %, while urge incontinence affected 29 % and difficulty in voiding 25%. Urinary retention was seen in the acute phase of illness in 6 %. A significant positive correlation was found between the occurrence of a urinary disturbance and hemiparesis. Brain imaging techniques confirmed a more anterior location of brain lesions in these groups. Urodynamic studies on 22 symptomatic patients showed detrusor overactivity in 68 %, detrusor-sphincter dyssynergia in 14 % and uninhibited sphincter relaxation in 36 %. If this was really a detrusor-sphincter-dyssynergia, which should not occur in suprapontine lesions, or a hold-on manoeuvre to prevent urinary leakage, can not be clarified from the paper. There was some indication that lesion size was related to the occurrence of urinary symptoms. In contrast to the findings of Maurice-Williams [13] and Kuroiwa et al. [11] who found a correlation of urinary incontinence with lesions of the right brain hemisphere, Sakakibara et al. [12] could not find a preponderance of right sided lesions for incontinence. Their findings suggest that the damage to the antero-medial frontal lobe, its descending pathway and to the basal ganglia is mainly responsible for micturition dysfunction in stroke patients.

Urinary incontinence in stroke patients is usually interpreted as the loss of central inhibition, however also the loss of bladder perception as concomitant factor came recently into the focus of attention. Deficit of bladder sensation seems to be associated with poorer general outcome. Interestingly, those patients had more parietal lobe but less frontal lobe impairment than patients with urge urinary incontinence and preserved bladder sensation [12]. Another paper by Mochizuki and Saito [14], looking at patients with frontal lobe lesions (tumours) concluded the damage to the right superior bifrontal region was associated with temporary incontinence, whereas permanent incontinence was associated with bilateral damage.

Urinary retention has also been described in patients with brain lesions: Three case histories of elderly females with various forms of right frontal lobe pathology were described as urinary retention. In two, one with an abscess and the other with a haematoma, successful treatment brought recovery of bladder function [15, 16].

An experimental model for studying the effect of forebrain lesions and voiding dysfunction was recently developed in the rat by occluding the middle cerebral artery under pentobarbital or halothane anaesthesia. At thirty minutes after recovery from anaesthesia bladder capacity in animals with cerebral infarct was markedly decreased indicating an overactive bladder. The decreasing bladder capacity continued as long as four months after artery occlusion. Based on the effects of two different types of receptor antagonists on OAB induced by left middle cerebral artery occlusion, the authors Yokoyama et al. [17] conclude that the NMDA receptor (N-methyl-D-aspartate) has an essential role in the development of OAB after CVA. Therefore, a glutamate receptor antagonist can
be expected to be beneficial for treating overactivity caused by cerebrovascular disease, as the induced potentiation of bladder reflexes seems to depend on NMDA glutamate transmission (LOE 4).

2. BRAINSTEM LESIONS

Already in 1926 Holman [18] noted that voiding difficulty could be a sign of tumours in the posterior fossa. In a series of patients with brain tumours Ueki et al [19] reported voiding difficulty to occur in 46/152 (30 %) of patients with tumours in the posterior fossa, while urinary incontinence occurred only in 3 (1.9 %).

Renier and Gabreels [20] found urinary retention in 12/17 children with pontine glioma. There are a number of case histories published presenting difficulties with micturition in the presence of various brain stem pathologies [21-24].

Sakakibara et al. [23] reported the urinary symptoms of 39 patients who had brainstem strokes. Almost half the patients had urinary symptoms, nocturia and voiding difficulty in 28 %, urinary retention in 21 % and urinary incontinence in 8 %. The problems were more common following haemorrhage, probably because the damage was usually bilateral. Urinary symptoms did not occur in those with lesions of the midbrain, but they did in 35 % of those with pontine lesions and in 18 % of those with medullar stroke. Urodynamic studies in 11 symptomatic patients showed detrusor overactivity in 8/11, low compliance in 1/11 and detrusor acontractility in 3/11 three months, six months and 3 years after the occurrence respectively. A non-relaxing sphincter on voiding was found in 5/11 and uninhibited sphincter relaxation in 3/11 (LOE 3).

c) Disease specific diagnosis

Basic diagnosis comprises a targeted history and clinical investigation, urine analysis, postvoid residual urine and a bladder diary. In patients with significant residual urine of over 100 cc or more than 50 % of bladder capacity an urodynamic investigation is recommended to differentiate between detrusor weakness and functional or morphological outflow obstruction.

d) Disease specific treatment

Immediately after the stroke accident in the Stroke Unit, an indwelling transurethral or suprapubic catheter allows control of the urinary output. Diuresis should be monitored. Once the stroke situation is stabilised and diuresis is normalised the catheter should be removed and the patient put on intermittent catheterisation if voiding is unbalanced. In the early stage after the stroke, urinary incontinence can be managed by a condom catheter or by pads. Further treatment comprises, as the two main stays of management, behavioural therapy, initially toileting, later on micturition training and anticholinergic therapy, if the voided volumes are below 250 cc. The patient’s ability to squeeze voluntarily the anal sphincter is a good prognostic sign to achieve continence further on.

In the early phase, especially during catheter drainage, special care must be taken to avoid urinary tract infections with secondary complications. In diabetic patients low dose infection prophylaxis is recommended (LOE 4).

A recent systematic review on treatment of urinary incontinence after stroke in adults assessed the available knowledge on behavioural interventions (timed voiding and pelvic floor muscle training), specialised professional input interventions (e.g. continence nursing), compliment therapy and pharmacological/hormonal intervention (e.g. oxybutynin). It was concluded that data from the available trials are insufficient to guide continence care of adults after stroke and that better quality evidence is required concerning interventions for continence care after stroke [25] (LOE C).

e) Guidelines for further research

There is a need for further epidemiologic studies of the true incidence of LUT symptoms incl. incontinence after cerebro-vascular accidents in long term. There is a considerable lack of evidence concerning efficacy and safety of currently used therapeutic interventions. Controlled studies comparing behavioural therapy and anticholinergic medication alone and in combination should show which treatment regime is best.

CONCLUSIONS

- Incontinence after CVA is not only a distressing symptom but also a powerful prognostic indicator for survival and eventually functional dependence. (LOE 2)
- The commonest urological problems after stroke are nocturia (36 %), urge incontinence (29 %) and difficulty in voiding (25 %). (LOE 2/3)
- There is a positive correlation between the occurrence of urinary dysfunction and hemiparesis. (LOE 2/3)
- Urodynamic studies revealed detrusor overactivity in 68 %, sphincter relaxation problems in 36 % (LOE 4).
- Damage to the antero-medial frontal lobe and its descending pathway and the basal ganglia are mainly responsible for voiding dysfunction in stroke patients. With brainstem pathology symptoms of impaired voiding (urinary retention) predominate. (LOE 3)
RECOMMENDATIONS

- As the urological symptoms, especially incontinence are very distressing, urological care is mandatory for these patients (B).
- Prevention of early urinary tract infection, especially when during the acute phase an indwelling (Foley-) catheter is used. Thereafter, management with toileting, later micturition training, combined with anticholinergic therapy are the main stays (C).
- Rarely intermittent catheterisation is necessary due to unbalanced voiding mostly in men with pre-existing infravesical obstruction till general recovery allows surgical measures to relieve obstruction, if alpha-blockers and 5-alpha reductase inhibitors are not effective (C).

2. FECAL INCONTINENCE

a) Epidemiology – (LOE 3)

Brocklehurst et al. [26] observed that 14% of stroke patients with faecal incontinence became so beyond 8 weeks after the acute event, leading to speculation that constipation, immobility and dependence may be primary underlying causes. The incidence of incontinence was 51% (urine) and 23% (faeces) within one year. Faecal incontinence at onset is associated with measures of severity of stroke and of immobility.

In the Copenhagen Stroke Study, Nakayama et al. [5] did a survey of urinary and faecal incontinence using subscores of the Barthel Index during the hospital stay and at 6-month follow-up in 935 acute stroke patients. In the acute state, almost half of an unselected stroke population had urinary and/or faecal incontinence (40%). The proportion declined to one fifth for urinary incontinence and one tenth (9%) for faecal incontinence of the surviving patients at 6 months. By multivariate analysis, significant risk factors for both incontinences were age, severity of stroke, diabetes, and comorbidity of other disabling diseases. According to Harari et al. [27] prevalence of poststroke faecal incontinence was 30% (7 to 10 days), 11% (3 months), 11% (1 year), and 15% (3 years). New-onset faecal incontinence during acute state was associated with urinary incontinence (Odds ratio-OR, 19.96; 95% confidence interval -CI, 8.8 to 36.8), Glasgow Coma Score < 15 (OR, 2.84; 95% CI, 1.6 to 5.0), visual field defect (OR, 2.69; 95% CI, 1.6 to 4.6), dysphagia (OR, 2.16; 95% CI, 1.2 to 3.8) and age 65 years and over (OR, 2.16; 95% CI, 1.0 to 4.8). One third of patients with faecal incontinence at 3 months were continent by 1 year (suggesting the presence of a reversible underlying cause); conversely, 63% continent at 1 year had been continent at 3 months. Urinary incontinence (OR, 87.6; 95% CI, 41.6 to 184.4), anticholinergic drug use (including antipsychotics, tricyclic antidepressants, oxybutynin, or antihypertensives) (OR, 3.1; 95% CI, 1.1 to 10.2) and needing help with toilet use (OR, 3.5; 95% CI, 1.4 to 17.3) were significantly associated with faecal incontinence in stroke survivors at 3 months. Faecal incontinence at 3 months increased the risk of long-term placement (28% vs. 6%) and death within 1 year (20% vs. 8%). Modifiable risk factors for faecal incontinence 3 months after stroke are constipating drug use and difficulty with toilet access.

b) Conservative bowel management (LOE 3)

Venn et al. [28] performed a trial in persons with stroke and compared 4 bowel programmes based on the use of suppositories and scheduled bowel care. 85% of participants successfully achieved effective bowel training within a month. Those assigned to morning suppository schedules were more likely to establish a successful bowel regime than those assigned to evening schedules (P<0.01).

Munchiando and Kendall. [29] compared the effectiveness of two bowel training programs for patients with CVA and determined the length of time required to establish a regulated program. The sample of 48 CVA patients included 23 in the control group who had every-other-day digital stimulation and 25 in the experimental group who had daily digital stimulation. Demographic data showed no significant differences between the two groups. More subjects in the experimental group established regularity. However, the subjects in the control group who did achieve regularity took less time to do it. Subjects with right-side hemiplegia and less mobility required more time to become established. The routine protocol for bowel training in their rehabilitation unit was then changed to include daily digital stimulation.

Recently, a randomized controlled trial evaluated a specialised intervention (structured nurse assessment including history and rectal examination, targeted patient/carer education and treatment recommendations) versus routine treatment of constipation and faecal incontinence in stroke survivors. A single nurse intervention effectively improved symptoms of bowel dysfunction up to 6 months later, changed bowel-modifying lifestyle behaviors up to 12 months later, and influenced patient–GP interaction and physician prescribing patterns [30].

CONCLUSION (LOE2/3)

- Faecal incontinence after stroke is prevalent but declines over time.
- Faecal incontinence is associated with age, severity of stroke, urinary incontinence, co morbidity, using constipating drugs and functional difficulties.
- Suppository and digital stimulation may assist in regulating bowel evacuation.
V. MULTIPLE SCLEROSIS

1. EPIDEMIOLOGY

Even though there are few studies today to confirm it, the impact on the quality of life for patients with vesicourethral (VST) due to multiple sclerosis (MS) is probably significant. Moreover, in a recent cross-sectional study (LOE4), Notvedt et al [1] demonstrated that those patients with VST had distinctly lower quality of life scores on the SF-36 scale in comparison with the population of MS patients that is asymptomatic. The tools for evaluating quality of life that take into account VST in MS have been validated in a retrospective fashion or on a population of patients developing severe follow-on urological problems (LOE4) [15].

The prevalence of VST in the global population of patients who are suffering from MS is in the order of 30 to 96% [6-8, 10, 11, 13, 14, 16-32] (LOE 2b-4). The size of this interval manifests the differences linked to the type of MS, to the duration of the illness, and to the degree of handicap, as well as to a probable under-estimation of the population of MS patients that is asymptomatic. The tools for evaluating quality of life that take into account VST in MS have been validated in a retrospective fashion or on a population of patients developing severe follow-on urological problems (LOE4) [15].

The figures confirm the frequency of urinary disorders in the MS population: urinary frequency (28%), urgency (17%), urge incontinence (14%), and difficulty with bladder emptying (12.5%). Independent of the non-response rate, there are several elements that cause us to think that these figures are in actuality higher. Indeed, 65% of the patients complain of having at least 1 episode of urinary tract infection, and the majority of patients have not been treated or had a specific checkup. One can think of this very elevated rate of episodes, labeled “UTI”, as manifesting the underlying vesicourethral disequilibrium in numerous patients. Problems with emptying the bladder are particularly poorly evaluated by patients, with a large number of patients having a significant post-void residual amount without an evident clinical manifestation. In a cross-sectional study (LOE4) carried out in 2004, Kracht et al had also found a proportion of 16% of patients who had a post-void residual (PVR) greater than 100 ml but without any symptoms that were detected by the questionnaires that are normally used in evaluations of MS (EDSS, GI-Urological disability Scale (GU)).

The estimation of the global incidence of these disorders in the body of patients with MS underlines the frequency of VST in this population. In practice, it is therefore important that the tools that are used to evaluate these problems are the most appropriate ones possible, because, all of the authors agree that the fact that VST is often ignored by the doctors who take care of these patients is due to the fact that the patients under-report their symptoms (LOE5). What is more, a certain number of the patients will suffer from urological problems that develop progressively and slowly.

2. SYMPTOMATOLOGY OF VST IN MS

Urinary symptomatology in MS is polymorphic and, like its incidence, probably subject to change over time. The most frequent urinary symptoms are indisputably overactive bladder (OAB) symptoms: urinary frequency (32 to 99%), urgency (32 to 85%), and urge incontinence (19 to 80%) (LOE2b-4) [7-11, 13-15, 18-22, 24-34].

Obstructive urinary symptoms also exist to a lesser degree: difficulty of voiding and chronic or acute urinary retention. Dysuria was found in 6 to 79% of the patients, and acute episodes of urine retention were reported in 8 to 73% of the patients (LOE2b-4) [8-11, 13, 14, 18-22, 24-35].

All of these studies were carried out most frequently in a retrospective fashion or on a population of patients coming for a consultation for another reason, which can upwardly bias the estimated frequency of the disorders. There was a cross-sectional study from Marrie et al [5] (LOE4) of 16,858 patients. Of those patients, 9688 (57.5%) had responded to the two questionnaires that were posted (Bowel Control Scale (BWCS) and Urogenital Distress Inventory-6 (UDI-6)). The figures confirm the frequency of urinary disorders in the MS population: urinary frequency (28%), urgency (17%), urge incontinence (14%), and difficulty with bladder emptying (12.5%). Independent of the non-response rate, there are several elements that cause us to think that these figures are in actuality higher. Indeed, 65% of the patients complain of having at least 1 episode of urinary tract infection, and the majority of patients have not been treated or had a specific checkup. One can think of this very elevated rate of episodes, labeled “UTI”, as manifesting the underlying vesicourethral disequilibrium in numerous patients. Problems with emptying the bladder are particularly poorly evaluated by patients, with a large number of patients having a significant post-void residual amount without an evident clinical manifestation. In a cross-sectional study (LOE4) carried out in 2004, Kracht et al had also found a proportion of 16% of patients who had a post-void residual (PVR) greater than 100 ml but without any symptoms that were detected by the questionnaires that are normally used in evaluations of MS (EDSS, GI-Urological disability Scale (GU)).

The estimation of the global incidence of these disorders in the body of patients with MS underlines the frequency of VST in this population. In practice, it is therefore important that the tools that are used to evaluate these problems are the most appropriate ones possible, because, all of the authors agree that the fact that VST is often ignored by the doctors who take care of these patients is due to the fact that the patients under-report their symptoms (LOE5). What is more, a certain number of the patients will suffer from urological problems that develop progressively and slowly.

In a systematic review of the literature, De Sèze et al [17] found that the duration of the progression of MS was one of the principal factors that influenced the frequency of VST (LOE 2b-4). Thus, the majority of the studies that were carried out in patients who had a duration of the progression of MS of more than 13 years found a more homogenous frequency for the different symptoms that was in the high range in comparison with the other figures cited up until the present: urinary frequency (38.5 to 99%), urgency (44 to 85%), and urge incontinence (63 to 72%) (LOE2b-4). The frequency of obstructive disorders is
likewise markedly more elevated [36-79.5%] [7-10, 14, 18, 20, 25, 28]. A second important factor that is associated with the frequency of VST is the degree of the patient’s physical handicap as estimated by the EDSS (LOE2b-4) (Expanded Disability Status Scale) [1, 8, 20, 29, 36-40]. It is difficult to confirm from these studies whether this factor has a role in itself, however, on the other hand, clinical practice indicates this common sense observation. A person who can compensate for the urgency by going to the toilet beforehand will see the appearance of urge incontinence following the appearance of a new motor or visual handicap (LOE5). The appropriate management of this problem can allow the improvement of urinary disorders without any specific action on the bladder or the sphincter. As in those patients who have medullar injuries, the clinical examination does not always allow the discovery of the specific neurological insults that are associated with VST. Certain authors have found an association between the pyramidal syndrome and irritable VST [8, 14, 20, 29]. No neurological presentation has been found that is associated in a manifest fashion with bladder voiding disorders [10, 41, 42]. No correlation between radiological insults on the central nervous system (localization and intensity) and clinical VST has actually been found [36, 43-45]. The analysis of a series of autopsies that were done on patients who had a sacral and lumbar insult (autopsy series) did not find any correlation with clinical VST [46] (LOE5).

Other associations have been indicated, but they have all been controversial. The type of progression for the MS (progressive or by crisis), the age at which MS started, and the sex, the age, the geographical location where the patient lives, and the like do not thus appear to be associated with a more elevated frequency of VST [14, 20, 29, 36, 38-40, 47]. The age of the patient does not have impact anymore. On the other hand, older patients will have the same problems as the general population (benign prostate hyperplasia in men and stress urinary incontinence in women), and those problems will of course often be more difficult to treat than they are in the general population.

3. VST COMPLICATIONS IN MS

It is difficult to precisely establish mortality from urological complications. In a recent study of the causes of death in MS patients in the U.S. that was carried out using death certificates (LOE4), a symptomatic urinary tract infection was considered as a contributing cause to the death in 8.4% of the cases, which made it one of the principal causes that were associated with mortality [48]. In that study, terminal renal insufficiency was not found to be a notable cause of mortality.

a) Infectious complications

The reported frequency of lower urinary tract infections is elevated in the literature, ranging from 13 to 80% [7, 9, 10, 18, 21, 25, 29, 30, 38, 49-52] after at least 10 years of progression of the illness. In the study by Marrie et al, 64.6% of the patients indicated at least one annual episode of urinary tract infection. The diagnoses of symptomatic urinary tract infection is therefore very difficult in those patients who have a neurogenic bladder. Indeed, in close to half of these cases the symptoms that are related to neurogenic detrusor overactivity will be complicated by a lower urinary tract infection, as has been well demonstrated by Lisenmeyer et al (LOE 3c) in spinal cord injury patients (SCI) [53]. There is also an incompressible rate of asymptomatic bacteriuria in many neurological patients [54] (LOE4). The occurrence of febrile urinary tract infection (pyelonephritis, orchitis, or prostatitis) is estimated to be between 2 and 23% (9% on average). In addition to the risk of mortality from certain of these infections that has already been underlined, several retrospective studies (LOE5) report an aggravation of MS following an episode of this type [1, 55, 56]. Neurogenic detrusor overactivity is probably a significant factor in the occurrence of upper urinary tract infections. Game et al [57] have also reported a prospective open study in which the injection of botulinum toxin in the detrusor in patients with MS had allowed a significant reduction of symptomatic urinary tract infections to be observed (LOE3c).

b) Alterations of the bladder

Morphological alterations of the trabeculation, thickening of the bladder wall, and diverticulae type were found in 4 to 75% of cases according to the series (30% on average) [9, 10, 14, 19, 21, 25, 27-31, 34, 38, 49, 50, 52, 58, 59]. These alterations did not have pathological consequences that were different from those that are found in the general population (primarily increased risk of symptomatic urinary tract infections). The exact proportion of vesical calculus is difficult to estimate, because the majority of studies do not indicate the precise site of calculi events. It can be estimated to be in the neighborhood of 5%. Several factors are associated with the discovery of morphological alterations of the lower tract: post void residual greater than 100 ml and a progression of MS of more than 10 years in duration [19, 60]. There is no correlation between VST and the morphological anomalies that were found [14].

c) Bladder cancer

The data on the more elevated risk of a vesical tumor in patients with MS are controversial. Indeed, it known that those patients who have a neurogenic bladder have had a more elevated risk of developing a particular bladder tumor: epidermoid carcinoma (LOE2b-4) [61-64]. There are other factors that increase this risk in theory, such as tobacco use, indwelling urinary catheters, untreated vesical calculi, and chronic urinary tract infection. In patients with
of MS, the use of treatment by cyclophosphamide can be an additional risk. The risk is even further elevated in those patients who have an indwelling urinary catheter or who have been exposed to tobacco. The risk of bladder cancer appears to be slightly increased in those patients who suffer from MS, as a result of risk factors related to their neurogenic bladder as well as from medullar trauma: indwelling urinary catheter, vesicoureteral reflux was found in 2 to 15% of the cases (LOE 2b-4) [9, 10, 14, 18, 21, 25, 27-31, 34, 38, 49, 50, 52, 59]. Contrary to the case in medullar traumatization and in spina bifida, the incidence of terminal renal insufficiency is rare in patients with MS, and does not appear to be greater than what it is in the general population [68]. On the other hand, a certain degree of renal insufficiency is indicated in certain articles, and may be as high as 2 to 3% in those patients whose illness has progressed for more than 10 years [19, 25, 27].

e) Risk factors in urological complications

As we have specified previously, the great heterogeneity of the clinical signs of VST in MS leads to delayed diagnosis of urological complications. Simple clinical surveillance therefore exposes one to the risk of overlooking a complication that could significantly increase the risk of urinary tract infection, such as postmictional residue (LOE4) [42]. De Séze et al [17] looked at data based on the literature in an attempt to discern the principal risk factors for urological complications. Those results must be considered with prudence, because the majority of the studies that were used in that analysis were retrospective (LOE4). The duration of the progress of MS is the principal risk factor, with an increase in the frequency of disorders appearing after 6 to 8 years of progression of the illness. These data are consistent with two cross-sectional studies (LOE4) that report a duration of the progress of MS that is significantly more elevated in those patients who have alterations of the upper urinary tract [9, 49].

The second significant risk factor (especially infectious) is the method of urinary drainage. The indwelling catheter (LOE2b-4) [9, 25] has been associated with a number of known infectious complications [69]. The utilization of suprapubic catheters was associated with a reduced risk (LOE3c) [70, 71], however, the series that was published was mid-term [5 to 6 years) and not long term follow up. If one relies on the data that is available for the treatment of patients with SCI, then the best urinary drainage methods are intermittent catheterizations and voluntary voiding (when it can be done without residue) (LOE2) [72].

The third classic risk factor, independent of diagnosis with MS, is the occurrence of post void residual, which is associated with a more elevated risk of urinary tract infection, of vesicular calculus, and, over time, of the distention of the upper urinary tract.

The other risk factors, suggested by many authors, are more rarely reported and do not allow for a group analysis. The urodynamic risk factors will be addressed in the following chapter. The progression of MS and the patient’s sex are not associated with particular alterations of the upper urinary tract. Men were more disposed to have febrile urinary tract infections (LOE4) [8, 9, 25, 35]. Older patients were more susceptible to presentation with urological complications, due on the one hand to the occurrence of urological pathologies at their age, but also probably due to the longer progression since the start of MS [17]. The same factor could explain the data of certain authors who report more frequent urological complications in those patients who have a more severe handicap (LOE4) [9, 14, 15, 51].

4. THE ROLE OF THE URODYNAMIC EXAMINATION IN MULTIPLE SCLEROSIS

The clinical manifestation of vesicosphincteric disorder in MS is heterogeneous, and urodynamic examination is indicated in two situations. The first is in cases in which the patient requests treatment for urinary symptoms that bother him or her. The purpose of the examination is to understand the vesicosphincteric disorder that is causing the clinical symptom and to propose an appropriate treatment. The second situation is one in which the patient is considered at risk and for whom a search for additional urodynamic risk factors is to be carried out.

a) Urodynamic examination before the treatment of urinary symptoms

The most frequently found anomaly is detrusor overactivity, which is found in 34 to 99% of cases. It is defined by the presence of detrusor contractions outside of the bladder filling phase. The second anomaly was detrusor underactivity, which was found in 5 to 37% of the cases [6, 9-11, 18, 20, 22, 24-26, 28-30, 32-36, 38, 50, 52, 59, 73, 74]. In those patients who have urinary symptoms, a normal cystoma-
nometry was found in at the most 30% of the cases [21, 25, 33].

Regarding the sphincter, a vesicosphincteric dyssynergy (VSD) was found in 6 to 82% of the cases (35% on average). It is defined by the absence of relaxation or by the reinforcement of the electrical activity of the external sphincter during vesicular contraction miction, and is the object of needle electromyography of the anal sphincter [58, 75]. VSD is associated indifferently with detrusor overactivity or detrusor underactivity, although the association of detrusor overactivity with VSD (43 to 80% of cases [7, 18, 34, 50, 51]) is more frequent than that of detrusor underactivity with VSD (less than 10% [9, 73]). OAB syndrome seems to more often be the result of DO, especially urgency incontinence [20, 52] (one of the incontinence risk factors that was found was the female sex and the existence of low closure pressure [25]). Obstructive VST was as often associated with DO as it was with detrusor underactivity, and there is also often an associated VSD [10, 20]. VSD does not appear to correlate to the type of urinary symptom [20].

The urodynamic presentations progress through time in a manner that cannot be predicted, especially from the detrusor component. However, VSD, when it is demonstrated in a patient, most often persists without change [26, 59, 73, 76].

b) The urodynamic examination (UDE) in a patient who is considered at risk for urological complications

The role of UDE in this case is much more debated. Certainly, UDE is indicated because of the association of certain UDE anomalies with the possible occurrence of urological complications. The purpose of UDE is therefore the exclusion of an area of risk for the occurrence of complications. Even though this approach is today the most agreed upon, it is useful here to remember that, at least in the case of MS, it has never been evaluated in a strict fashion as part of a prospective protocol. This is explained in part by the fact that sometimes many years will pass before the urological complications occur, which makes the task of evaluation very difficult. The adversaries of preceding in this fashion propose a more pragmatic approach, with regular surveillance of simple criteria (postmictional residue, renal echography) and they propose a therapeutic approach only in those patients who present with a complication. This approach has the advantage of simplicity for the patient and for the doctor. The theoretical risk is that of the late diagnoses of a future complication (indeed, close to 50% of asymptomatic patients have urodynamic anomalies (LOE4)) [21] and of having to therefore propose a therapy to the patient that is more intensive than what could have been proposed had an earlier diagnosis been made.

The three elements of UDE that were strongly associated with urological complications were detrusor overactivity, bladder compliance failure, and VSD [9, 77]. The relationship between DO, bladder compliance failure, and the alteration of the upper urinary tract are classic in neurogenic bladders. The advent of the use of intradetrusor botulinum toxin reinforced the notion of causality between an elevated intravesicular pressure regime and the risk of alteration of the upper urinary tract, because certain authors indicated a disappearance of vesicorenal reflux after injection of botulinum toxin, at which time the intravesicular pressure regime normalized [57]. The relationship between urological complications and VSD is more debated [15, 29, 35]. The practical difficulties of researching this anomaly, the invasive nature of the electromyogram that is necessary for confirmation, and the absence of targeted therapeutic efficacy for VSD mitigate against this systematic search.

5. DIGESTIVE DISORDERS (BOWEL SYMPTOMS) IN MS

a) Epidemiology

Digestive disorders are very frequent in patients who have MS, and, like the urinary disorders that are to blame, when they are significant they have a significant impact on patients’ quality of life (LOE4) [1, 5, 78]. What is more, the patients seem to tend to be ashamed of these problems and seldom report them. The clinicians, for their part, have few tools at their disposal for evaluating this impairment. The het effect of these two observations is that it is the patients’ digestive disorders that are the most often hidden (LOE-4) [27, 34].

Taking into account the great diversity of definitions in the several studies that are concerned with this problem, one is obliged to regroup the digestive symptoms into two large groups: those symptoms that can be defined as “retentive”, including abdominal pain, flatulence, and constipation on the one hand, and those symptoms that can be defined as “irritant”, including false urges to defecate, diarrhea, and/or incontinence of stool and/or gas on the other hand. Digestive disorders of both types were found in 45 to 68% of the cases (LOE 4) [27, 78-82]. The frequency of the “retentive” symptoms was clearly the more elevated, ranging from 31% to 54% [27, 78, 80-82] [79]. The frequency of the irritant symptoms ranged from 6 to 20% [78, 80] [27, 79, 81, 82]. The authors who had sought to flush out the more exceptional episodes of incontinence found a frequency of at least one episode of that type in the months that preceded the interview in 29 to 30% of the cases [27, 79]. Finally, a proportion of about 20% of the symptomatic patients had a combination of irritant and retentive disorders [78, 80] [27, 79, 81, 82]. The figures were clearly more significant than in the general population, where the “retentive” disorders have a frequency that is
estimated to be around 2 to 20% and the “irritant” disorders have a frequency of 2% [83].

b) Risk factors for digestive disorders in MS

There was no factor that allowed the identification of a scalable type of MS that would be at greater risk of developing digestive disorders [78, 80] [27, 79, 81, 82]. Similarly, the duration of the progress of MS does not appear to be a factor that influences the frequency of digestive disorders.

The factor that seems to be the most important is the estimated degree of disability (LOE 3c-4) [82, 84]. Thus, Munteis et al [84] found in a case control study (LOE 3c) a frequency of digestive disorders that exceeded 21.2% if the patients had an EDSS between 0 and 1. This frequency exceeded 78% in those patients who had an EDSS that was greater than 4.5.

Other risk factors were suggested (LOE4), but they seemed to have an influence that was less clear, such as being of the female sex, the existence of related urinary disorders, age, and taking anticholinergic treatments [82, 84] [78, 80] [27, 79, 81].

c) Pathophysiology of the digestive disorders of MS

Few studies have been carried out specifically in patients who have multiple sclerosis. One of the difficulties is the frequent existence of related treatments that can themselves bring about the specific symptoms. The colic transit times can be extended or shortened in those patients who present with digestive disorders [85-87]. Several anorectal manometry anomalies were in evidence: reduced tone and compliance, a reduced sensation of filling and incoordination of the external anal sphincter during expulsion, with an onset of the phenomenon known as paradoxical anal sphincter contraction. In patients with faecal incontinence, a decrease in anal canal pressures and hyper-reactivity of the rectal wall have been shown manometrically. In the most recent of these studies, Munteis et al [84] has found that the anomalies that are found the most often are those of maximal sphincter pressure, of anal inhibitory reflex (which occurred later than in the control population), and the presence of paradoxical contraction of the puborectal musculature during straining. These anomalies might be able to allow the proposal of biofeedback reeducation in the concerned patients, however, at present the benefit of this approach has not yet been proven.

VI. SPINAL CORD LESION

1. URINARY INCONTINENCE
   a) Epidemiology and prevalence

Spinal cord injury (SCI) including cauda equina injury usually causes impairments of urinary functions such as urinary incontinence (UI) and/or difficulty in urination. During the past 3–4 years, there was no report on epidemiology of urinary dysfunction in acute or post-acute SCI but there were three studies on prevalence of bladder management in chronic SCI persons [1-3] (Table 20) and one study in patients with chronic cauda equina lesions [4]. About 8%–11% of chronic SCI persons had normal voiding [1,2], not different from the time after initial rehabilitation [2]; and more normal voiding in tetraplegics then paraplegics [2].

According to the study from Denmark [2], at discharge from the initial rehabilitation period of 233 traumatic SCI patients, bladder-emptying methods were as follows: 12% normal voiding, 57% suprapubic tapping, 19% abdominal pressure, 5% Crédé manoeuvre, 11% CIC, 2% SIC, 8% urethral indwelling catheter (IDC), 0.4% suprapubic catheter (SPC), 0.4% sacral-anterior-root-stimulation (SARS), and 5% use of condom-catheter or diaper. When dividing the patients by years of injury (before 1981 and after 1980), there was a decreasing trend of using suprapubic tapping (drop from over 60% to 45%), abdominal pressure (from over 20% to 15%) and Crédé manoeuvre (drop from over 12% to 1%) but there was an increasing trend of using CIC (rise from 0% to 26%). Over times, 37.5% to 46% of SCI persons changed their bladder-emptying management [2,3]; 28% found their bladder-emptying methods to be a problem; of these 58% were tetraplegic [2]; and the biggest bother bladder management to the subjects was in the compression or straining group (over 50% of the subjects)[1].

There was a statistically significant difference in the frequency of urinary tract infection (UTI) between the bladder management (P< 0.001) [1]; the frequency of UTI was high (about 70%) in the mixed group (65% used CIC with other methods) and the CIC group and less (less than 50%) in the groups with catheter free [1]. According to the study financed by Medicon Valley Academy and Coloplast A/S and done in Denmark, of those using CIC, 92% reported using hydrophilic-coated catheters [2] but there was no report about frequency of UTI. However there was a report of reused silicone catheter for CIC in 28 SCI men done in Thailand [5] with the average time of usage of each catheter of 3 years, 36% reported fever with cloudy urine and 64% of foul smell urine; however, where the frequency of CIC is higher, the abnormality of the urethra was lower (P, 0.05) [5].

In 2006, Podnar et al [4] studied 55 patients with chronic cauda equina or conus medullaris injury: 76% of the patients reported LUT dysfunction, 70% had urinary incontinence (UI) (56% of men and 71% of women); and a post void residual (>100 ml) was found in 40% of men and 17% of women. Perianal sensation was abnormal in 96%, electromyography (EMG) of the external anal sphincter (EAS) muscle in 88%, and sacral reflex in 84% of patients; using multiple linear
regression analysis, perianal sensory loss (P=0.0001) and female gender (P<0.02) had a significant positive effect on urinary incontinence score [4].

b) Pathology and disease specific LUT problems

1. Neuro- and bio-chemical regulation of the LUT

Pontari MA et al (2004)[6] analyzed 7 bladder specimens from 6 cervical SCI patients and 1 L1 congenital myelomeningocele (MMC); and compared with results from bladder specimens obtained from 8 organ transplant donors to determine whether the muscarinic receptor subtype mediating contraction shifts from M3 to the M2 subtype as in the denervated, hypertrophied rat bladder; and found that whereas normal detrusor contractions are mediated by the M3 receptor subtype, in patients with NBD, contractions can be mediated by the M2 muscarinic receptor subtype [6]. Haferkamp et al (2006)[7] evaluated the role of neuropeptide Y in 31 patients with NDO and 7 patients with stress urinary incontinence (SUI) and concluded that the reduction of neuropeptide Y-containing nerves, inhibiting the contractile response of the detrusor, may play a role in the development and persistence of NDO in SCI patients. Oner-Iyido?an et al (2004) [8] found that urine 8-iso PGF2alpha concentrations were significantly increased in SCI with hyperreflexic group (median value 0.89 pg/mg creatinine) compared to both normal control (0.52 pg/mg creatinine) and SCI with areflexic groups (P < 0.001); and the lowest concentrations of urinary 8-iso PGF2alpha were observed in the areflexic group (0.22 pg/mg creatinine) [8].

2. Neurophysiology of LUT

In patients with cauda equina lesion, on filling cystometry DO was found in 21% of men and 0% of women, reduced detrusor capacity in 9% of men and 15% of women, and during voiding phase an acontractile detrusor or detrusor underactivity were found in 59% of men and 85% of women [4].

According to the study of viscerosensory pathway of the lower urinary tract (LUT) by Schmid et al (2004)[9], after electrical stimulation (ES) of the posterior urethral mucosa (single square pulses of 0.2 ms, 2 to 3-fold sensory threshold, 60 mA in complete SCI patients), evoked skin sympathetic responses (SSRs) of the hand could be recorded in 14 of 15 sensory incomplete SCI patients with disturbed urethral sensation but not in 13 sensory complete SCI patients with loss of any urethral sensation. Electrically evoked urethral sensations resembled the subjective desire to void at full bladder reported by controls and patients [9].

Later in 2005, Schmid et al [10] did a comparative study of motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) in 9 healthy persons and 33 patients with neurogenic UI (15 SCL, 14 cauda equina lesion, and 4 multiple sclerosis). In healthy subjects the central latency was 19.0 msec, the peripheral latency was 4.25 msec, and the ratio between central and peripheral latencies was 4.4. In patients with

---

### Table 20. Prevalence of bladder management in chronic SCI

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Subjects</th>
<th>Methods of bladder management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahlberg et al (2004)[1]</td>
<td>129 traumatic SCI in Finland; mean time since injury 18 years (SD 13)</td>
<td>Normal voiding: 11%; Controlled voiding (assisted voiding or incontinence: 12% CIC: 12%; mixed (CIC with other methods):23%; Suprapubic tapping 24%; Compression or straining (usually with condom catheter): 12% Catheter or conduit: 5%</td>
</tr>
<tr>
<td>Hansen et al (2004)[2]</td>
<td>233 SCI in Denmark (82% males, 47% tetraplegics, mean age at the time of follow-up of 50.5 years and mean time since injury of 24.1 years)</td>
<td>46% changed bladder-emptying method Normal voiding: from 12% to 8% CIC: from 11% to 36% SPC: from 0.4% to 6% Suprapubic tapping: from 57 to 31% Crede manoeuvre: from 5 to 19%</td>
</tr>
<tr>
<td>Patki et al (2006)[3]</td>
<td>64 traumatic pediatric onset, ambulate SCI; mean follow-up 7 years; mean age 46 years</td>
<td>Spontaneous voiding: initial 62.5%; 47.5% of them deteriorated CSIC: initial 31.2%; 25% of them improved SPC: initial 6.3% 37.5% required a change in urological management 68.7% had abnormal urodynamics at the last follow-up</td>
</tr>
</tbody>
</table>
incomplete SCL, the central latency was significantly delayed (22.7 msec), whereas the peripheral responses were normal; and the ratio (5.5) was increased. Those with a complete SCL showed no UCM reaction after transcranial stimulation, whereas peripheral responses were normal. The increased ratio of 6.0 indicated a SCL. Ten patients with complete cauda equina lesions and UI had normal central latencies but prolonged peripheral latencies of 6.7 msec; the ratio of 3.4 indicated a lesion of the sacral caudal roots. In patients with complete cauda equina injury neither central nor peripheral responses could be evoked [10].

According to Dai and Xiao (2005) [11], the thresholds of stimulation on ventral root were 0.02 ms duration, 0.2-0.4 mA, (mean 0.3 mA+/−0.07 mA), compared with 0.2-0.4 ms duration, 1.5-3 mA (mean 2.3 mA+/−0.5 mA) for dorsal root (P<0.01) to cause evoked potentials and EMG. The continuous stimulation for about 3-5 seconds on S2 or S3 ventral root (0.02 ms, 20 Hz, and 0.4 mA) could resulted in bladder detrusor contraction, but the strongest bladder contraction over 50 cm H2O was usually caused by stimulation on S3 ventral root in 7 of the 10 patients [11].

3. URODYNAMIC STUDIES

Ockrim et al (2005) [12] found that in men with SCI, cystometric variables and detrusor overactivity (DO) remained consistent over sequential studies while in those with LUT symptom of urge, a significant decrease in the number and pressure of involuntary detrusor contractions (IDCs) in consecutive cystometries resulted in a reduction of observed DO from 72% to 63% and 48%, in the three studies. Chou et al (2006)[13] did a retrospective study on urodynamic studies to provide reference ranges for “normal” variability in urodynamic parameters that can be considered as “no real change” from one study to the next. Fifty consecutive individuals with SCI had 2 trials (trial 1 and trial 2) of urodynamic studies done 5 minutes apart, and the following data were collected:

- maximum cystometric capacity, opening pressure, maximum detrusor pressure, volume voided, and postvoid residual (Table 21).

Generao et al (2004)[14] did a retrospective review of SCI cases with 1-year minimum follow up to determine the effect of SCI on the developing bladder and kidneys using video-urodynamics, sonograms. In 42 children (average age at injury of 5.3 years and mean follow up of 5.5 years), 40 used CIC and 37 took antispasmodics. No patient had reflux, hydronephrosis or renal scarring. Safe bladder capacity, the pressure specific volume at 40 cm water or less, was less than the expected capacity in 80%, 58% and 50% of cervical, thoracic and lumbar injured patients but 100%, 76% and 67% of the respectively groups undergoing multiple urodynamics had increasing capacity with time.

Apart from the above-mentioned urodynamic/cystometric parameters, Ersöz and Akyuz (2004) [15] investigated bladder-filling sensation in 73 consecutive traumatic SCI patients to determine the quality of the preserved sensation and to determine the potential for sensation-dependent bladder emptying in this patient group. Bladder-filling sensation was present to some degree in all incomplete SCI patients, in 82.4% of the patients with complete lesions below T10, and 38.9% of the patients with complete lesions above T11. There were statistically significant differences between three groups with respect to bladder sensation category (P<0.001). About 86% of the patients with incomplete lesions, 53% of the patients with complete lesions below T10 and 22% of those with lesions above T11 had bladder-filling sensation before Pves reached 25 cmH2O and simultaneous bladder capacity of more than 150 ml was present in 61.2, 41.2 and 22.2% of the patients in the groups, respectively. Bladder-filling sensation investigations were reliable in terms of bladder filling sensation category in 36 SCI patients who had second cystometric examination.

Table 21. Shows ranges of variability in urodynamic parameters done in 50 SCI individuals from the study of Chou et al [13]

<table>
<thead>
<tr>
<th>Urodynamic parameters</th>
<th>Maximum</th>
<th>Maximum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5th to 95th percentile</td>
<td>10th to 90 th percentile</td>
<td>25 th to 75 th percentile</td>
</tr>
<tr>
<td>Mean</td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Cystometric capacity (mL)</td>
<td>234.63</td>
<td>+213.50</td>
<td>-158.05</td>
</tr>
<tr>
<td>Opening pressure (cmH2O)</td>
<td>54.56</td>
<td>+30</td>
<td>-18.00</td>
</tr>
<tr>
<td>Maximum detrusor pressure (cmH2O)</td>
<td>60.82</td>
<td>+17.35</td>
<td>-27.80</td>
</tr>
<tr>
<td>Volume voided (mL)</td>
<td>122.20</td>
<td>+177.25</td>
<td>-176.00</td>
</tr>
<tr>
<td>Postvoid residual (mL)</td>
<td>176.06</td>
<td>+197.25</td>
<td>-118.00</td>
</tr>
</tbody>
</table>

900
To quantitatively measure bladder mucosal sensory function, Ukimura et al (2004) [16] used neuroselective Current Perception Threshold (CPT) tests in 8 healthy volunteers and 38 patients with NBD. Standardized neuroselective CPT measures were obtained from the left index finger and the mucosa of the posterior bladder wall. The CPT values in the bladder could be determined using the neuroselective measures in all patients but three who had no sensory response (absence of sensation) caused by complete SCI. In the 8 patients with NDO due to incomplete supra-sacral SCI, the bladder CPT value (4.0+/-1.9) at 5Hz was significantly lower (p<0.01) than that in the controls (26.2+/-17.7). In the NBD determined to be underactive (n=11, including post pelvic surgery, post infra-sacral level SCI and diabetes patients), the higher CPT values of bladder mucosal sensory functions were found at 5Hz (p<0.05), 250Hz (p=0.07), and 2000Hz (p<0.05) compared to the controls. As described in the section diagnosis of neurogenic urinary incontinence, no fibre specificity has so far been found depending on frequency of current used or current type.

4. DETRUSOR (EXTERNAL) SPHINCTER DYSSYNERGY, D (E)SD

Schurch et al (2005) [17] assessed types of DSD (according to the Blavas classification during urodynamic examinations) in 105 chronic SCI males and evaluated the change in the DSD pattern over time. Results showed that those with an incomplete sensory and motor SCL presented with DSD type 1 whereas those with complete sensory and motor SCI lesion had DSD type 2 to type 3. A correlation was also found between the AIS and the DSD type but not between the DSD type and the level of lesion; and at medium to long-term follow-up, a significant change was found in the DSD type [17]. Generally, presence of DSD was determined by increased wire needle EMG activity and/or by dilated bladder neck and proximal urethra during detrusor contraction, in the absence of valsalva or attempt to inhibit voiding.

De et al (2005) [18] did a comparative study to explore the diagnostic congruence for DSD between needle EMG and voiding cystourethrogram (VCUG) in the neurogenic population. They found 60% agreement and 40% disagreement between EMG and VCUG for diagnosis of DSD. Binomial testing demonstrated significant disagreement (P < 0.000) in observed proportions [18]. By retrospectively analyzing clinical data consisting bladder and EAS EMG from 41 SCI individuals with NDO, Wenzel et al (2006) [19] found that the onset of bladder contractions was detected within 1 sec of the start of the EAS contraction for both synergic and dysynergic human subjects; and they concluded that this detection could be used as a control signal to deliver inhibitory ES to arrest nascent bladder contractions and maintain continence [19].

5. COMPLICATIONS RELATED TO URETHRAL INDWELLING CATHETERIZATION (IDC)

During 2004-2006, at least three papers reporting urinary complications related to prolonged urethral IDC such as follows: the catheter balloon of a Foley catheter inserted only half-way was inflated in the urethra distal to the stricture and a long-term IDC caused urethral erosion and a severe degree of hypospadias (Vaidyanathan et al, 2004) [20]; contracted bladder followed by autonomic dysreflexia (AD), gross hematuria and extravasation of contrast media due to improper technique of voiding cystourethrography (Kovindha et al, 2005) [21]; and continuously incontinent despite a catheter and low bladder compliance leading to a urinary diversion to achieve continence (Stoffel and McGuire, 2006) [22]. In chronic SCI, IDC was associated with higher mean levels of C-reactive protein (CRP) while intermittent catheterization was associated with lower levels of CRP when compared with other methods of bladder management (Frost et al, 2005) [23].

6. VESICOURETERAL REFUX (VUR)

VUR seems common among SCI patients with upper motor neuron (UMN) neurogenic bladder. According to the study of Linsenmeyer et al (2004) [24], there was an association of posterior position of ureteral orifices and reflux (p = 0.004) but no differences were found with regard to bladder capacity, bladder wall compliance, or voiding pressures between the reflux and nonreflux group.

7. STONE FORMATION

Linsenmeyer and Linsenmeyer (2004) [25] found that the majority of bladder stones were calcium phosphate (46.8%) or struvite (26.7%). According to the retrospective study in 32 patients with NBD, Matlaga et al (2006) [26] found renal stones were infectious in etiology in 37.5% (12 struvite/carbonate apatite) and metabolic in 62.5%. All with struvite calculi were infected with urea-splitting bacteria.

Stone formation is usually related to IDC. In 2006, there were five papers reporting on such. Ke et al [27] found bladder calculi with a nidus of hair that could have been introduced into the bladder accidently during the cystostomy catheter replacement. According to the retrospective study of Ku et al [28], over the 17 years 28% and 15% of 140 men were diagnosed with bladder and renal stones for a total of 59 and 25 episodes, respectively; bladder stone was more common in patients injured when aged > or = 24 years than in those injured when aged <24 years (OR 2.5; 95% CI 1.1-5.7; P = 0.03); patients with complete injury had a greater risk of renal stone formation than those with incomplete injury (OR 4.1, 95% CI 1.3-12.9; P = 0.016); renal stone was more common for patients with urethral catheterization than for those voiding spontaneously (OR 5.7, 95% CI 1.3-
individuals had no catheter encrustation; of these, for bladder stones 85% of the time. Thirty-six and 11 of them also had bladder stones i.e., a positive stones. Catheter encrustation was noted in 13 patients encrustation at the time of removal for cystoscopy prospective cohort study by examination of IDC for grew at concentrations of 10^5-10^8 cfu/L, but only a spp (19%), and Escherichia coli (12%); and bacteria incidence of bladder stone than CIC-dry (p<0.05). Linsenmeyer and Linsenmeyer (2006) [31] did a prospective cohort study by examination of IDC for encrustation at the time of removal for cystoscopy and found that 35% of 49 SCI individuals had bladder catheters. Catheter encrustation was noted in 13 patients and 11 of them also had bladder stones i.e., a positive result for catheter encrustation had a positive result for bladder stones 85% of the time. Thirty-six individuals had no catheter encrustation; of these, 16% were found to have bladder stones.

8. BACTERIURIA

According to the retrospective study, Jayawardena and Midha (2004) [32] suggested that healthy asymptomatic SCI patients who came for annual evaluations should not have routine urine cultures if they are at low risk for UTIs; that is, <6 WBC/HPF in the urine and/or nitrite negative [32]. Svensson et al (2004) [33] studied the occurrence of bacteriuria in SCI patients with NBD who used CIC. Of 344 cultured samples, there were 285 isolates: coagulase-negative Staphylococci (27%), Enterococci (25%), Klebsiella spp (19%), and Escherichia coli (12%); and bacteria grew at concentrations of 10^5-10^8 cfu/L, but only a few at 10^4 cfu/L. Levendoglu et al (2004) [34] prospectively studied in 27 SCI patients who applied CIC during the initial rehabilitation and 40 controls. E. coli was predominantly isolated from the urine and the urethral cultures of both female and male patients; there was concordance between urethra and urine cultures concerning the growth of E. coli (P=0.82); and Pseudomonas was colonized more in male patients [34]. Waites et al (2004) [35] found that among 77.1% of men with bacteriuria, uropathogens were shown to be present in the perineum in 57.4% and in the urethra in 85.2%; differences in the occurrence of uropathogens in men with and without bacteriuria were statistically significant, and organisms were present in higher numbers in men with bacteriuria.

9. EPIDIDYMO-ORCHITIS AND OTHER COMPLICATIONS

Over the 17-year follow-up study of Ku et al (2006) [36], of 140 male patients (24.3% complete, the average age at onset of 24.8 years old, the average time since SCI of 16.9 years), 27.9% were diagnosed with epididymo-orchitis; and in multivariate analysis, patients on CIC had a 7.0-fold higher risk (OR, 6.96; 95%CI, 1.26-38.53; P=0.026); however, a history of urethral stricture lost statistical significance (P=0.074). Nambiar et al (2005) [37] reported a C4 tetraplegia man presenting with a necrotic ulceration on the ventral aspect of the penis and scrotum of 2 days duration and diagnosed with fulminant Fournier gangrene. Vaidyanathan et al (2004) [38] reported cases of a perirenal haematoma due to warfarin and a tumor like of necrotic slough and debris in the bladder.

10. QUALITY OF LIFE (QoL)

Oh et al (2005) [39] conducted a prospective trial involving 132 SCI patients and 150 controls matched to age and sex to determine the psychological and social status of patients using CIC. According to health-related quality of life (HRQOL), the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) scores did not reveal any significant differences between the men and women in the patient group. When patients and controls were divided into two groups according to sex and age, the SF-36 scores of the patients were significantly lower than the controls across both sex and all age groups, other than the energy and vitality scale, the differences for which were not statistically significant in women and those younger than 50 years. Later Oh et al (2006) [40] used the Beck Depression Inventory (BDI) with SCI patients on CIC and control group and found that, the average total BDI scores were 20.3±1.0 in the patient group and 11.4/0.5 in the control group, respectively (P<0.001); 69.6% of 102 the patients reported severe depression; female patients had a 3.8-fold higher risk (OR 13.83; 95%CI 1.42-10.31; P=0.008) of depression than male patients; and those who were unable to perform catheterization independently had a 4.6-fold higher risk (OR 4.62; 95% CI 1.67-12.81, P=0.003) of depression than those who were able to perform self-catheterization.

c) Disease specific treatments

1. UROLOGICAL FOLLOW-UP PRACTICE

According to retrospective reviews [4,41], there was evolution of bladder management by time, outcomes and complications in both pediatric onset and adult onset SCI; and treatment was not modified during the entire follow-up in very few patients. Regular urodynamic follow-up is warranted for protection of the upper urinary tract (UUT) and maintenance of continence, however, urological follow-up practice varied: in Bochum, Germany, follow-up included urodynamic evaluation, sonography of the UUT and LUT, urine examination, and evaluation of renal function and treatment modifications were based on the urodynamic findings (Nosseir et al, 2007)[42]; in the Spinal Injuries Units of U.K., all units performed routine upper tract screening, ranging from annually to every 3 years (Bycroft et al, 2004)[43].
According to the retrospective chart review of Sepahpanah (2006) [44], the 24-hour creatinine clearance (CCr) was highly variable from one evaluation to the next and the within-subject standard deviation (SD) for CCr was 25.9 mL/min; for all comparisons of repeatability, variability, and reliability, serum creatinine was superior to CCr; and renal ultrasound results and post-void residuals were the major factors in changing medical management with regard to renal function preservation. To determine the accuracy of bladder stone detection by abdominal x-rays of individuals with SCI, 13/62 (20.97%) of stones found during cystoscopy were detected by the x-ray; the detection by x-ray was 33% for stones 1.0 cm to 1.49 cm, 33% for stones 1.5 cm to 1.9 cm, and 54% for stones > or = 2.0 cm; and 57% for volumes > or = 1.0 cm³ [25]. In addition, long-term SCI individual with aged 50 to 60 or more should be screened for prostate and bladder cancer [45,46]; however, PSA cannot be used in patients with IDC and diagnosis should be based on prostatic biopsies [28].

2. **INTERMITTENT CATHETERIZATION (IC)**

IC is recommended as the safest method of bladder emptying for SCI persons with NBD [47], especially for those who have sufficient hand skills or a willing caregiver to perform the catheterization [48]. Mizuno et al (2004) [49] reported a paraplegic woman using CSIC for 27 years who had no complications and absence of UI due to underactive and normal capacity bladder. However SCI men on CIC, according to the retrospective comparative study of patients on CIC had a 7.0-fold higher risk of epididymo-orchitis [28].

**• Techniques**

Previously, recommended bladder training with CIC was time-dependent, however; some experienced bladder over-distention, especially in those with polyuria that made an IC programme unmanageable [50]. Polliack et al (2005) [51] compared volume-dependent IC (VDIC) following bladder volume measurement by a portable ultrasound device in SCL patients with time-dependent IC (TDIC). After 12-30 days follow-up, the number of IC per patient per day, the time required to perform volume measurements and IC, and their total cost, were approximately 44, 49, and 46% lower in the VDIC group than in the TDIC group. UTI was found in three patients in the TDIC group and in none in the VDIC group.

**• Type of catheter**

In developed countries, there is a variety of urethral catheters available for SCI individuals.

However, by reviewing all controlled trials comparing methods of using catheters in people with NB, Jamison et al (2004) [52] could not draw any conclusions regarding the use of different types of catheter in managing the NB.

According to the multi-centre RCT of De Ridder et al (2005) [53], 57 SCI male patients completed the 12-month study; 64% of those using the SpeediCath hydrophilic-coated catheter experienced 1 or more UTIs compared to 82% of those using the uncoated polyvinyl chloride (PVC) catheter (p = 0.02); and twice as many patients in the SpeediCath group were free of UTI. According to another multi-centre study of Bjerklund Johansen et al (2007) [54], of 378 SCL (the mean duration of IC was 4.6 yr) who completed a 12-d trial of the novel hydrophilic catheter: LoFric Primo, 55.2% of the patients were happy to continue with the novel device, which was 74% of patients using standard PVC catheters and 36% of those using prelubricated PVC (p=0.04).

In a developing country, such as Thailand, Japanese reusable silicone catheters were reused and median duration of usage for each catheter was 2 years. Electron microscopic findings of the reused catheters for 2 years revealed encrustation but no obstruction in the lumens and 20% increase in stiffness. Demographic data, urinary management and complications did not have significant relation to the abnormality of the urethrogram or UTI [21].

3. **INDWELLING CATHETERIZATION**

As mentioned above, the long-term IDC caused significant complications in SCI patients and some applying CIC experienced incontinence in between catheterization. Therefore, Ozawa et al (2005) [30] applied a contemporary (reusable) balloon catheter at night time only. After a mean follow up of 41 months, the incidence of febrile episode was as follows: CIC-wet 3.36 times/100 months, IDC 2.96, cystostomy 1.11, the contemporary catheter 0.57, and CIC-dry 0.42. The incidence of febrile episode in CIC-wet and IDC were significantly higher than in CIC-dry (p<0.05). The incidence of bladder stone was as follows: IDC 1.11 times/100 months, cystostomy 1.05, the contemporary catheter 0.96, CIC-wet 0.61, and CIC-dry 0.21.

4. **BLADDER RELAXANTS**

Many SCI individuals with NDO experienced high detrusor pressure with incontinence and post-voiding residual, bladder relaxants – antimuscarinic drugs, usually are prescribed for those applying CIC as well as IDC. Tolterodine, 2 mg twice daily [55], controlled release oxybutynin (OXY-XL) [56], doubled dosage of tolterodine ER or Trospium [57] and self-selected dosages (SSD) of tolterodine and oxybutynin [55] showed reduction in degree of UI and increase in IC volumes, and cystometric capacity; but the side effect of dry mouth was differed significantly when comparing tolterodine SSD with oxybutynin SSD (P < 0.05) [55].

5. **INTRAVESICAL VANILLOIDS INSTILLATION**

According to a review article [58], currently available
intravesical treatment options either act on the afferent arc of the reflex such as local anaesthetics or vanilloids or on the efferent cholinergic transmission to the detrusor muscle such as intravesical oxybutynin or botulinum toxin. Later there were many clinical trials and case series done in SCI with NDO proved the efficacy of intravesical instillations of various concentrations of resiniferatoxin (RTX) by cystometric/urodynamic parameters and degree of UI [59-64]; intravesical capsaicin (CAP) also improved in symptoms and urodynamic parameters [57,61], without a significant difference between the CAP and the RTX groups [61]. When compared RTX with injection of 300 units botulinum A-toxin diluted in 30 ml normal saline, both treatments provided significant reduction in mean catheterization and episodes of incontinence, and a significant increase in mean first involuntary detrusor contraction and in mean maximum bladder capacity at 6, 12 and 24 months after therapy; while botulinum-A toxin significantly reduced also the maximum pressure of uninhibited detrusor contractions more than RTX at all follow-up time points [59].

6. Treatment of DSD

In those using reflex voiding to empty bladder, it is recommended to use non-surgical methods – alpha-blocker and botulinum toxin injection into urethral sphincter [48]. According to the study of Reitz et al (2004) [65], 12 male SCI patients with NDO and DSD received 10 mg of isosorbide dinitrate sublingually and found that nitric oxide significantly reduced external urethral sphincter pressures at rest (p < 0.05) and during dysynergic contraction (p < 0.05); and the mean post triggering residual volume was significantly reduced (p < 0.05).

7. Prevention of UTI

According to 2 double-blinded, placebo-controlled RCTs [66,67], to determine the effectiveness of cranberry supplement (400-mg cranberry 3 times a day for 4 weeks [66] and 2 g per day for 6 months [67]), at preventing UTIs in SCI individuals with NBD, bacterial count, white blood cell (WBC) count, bacterial counts in urine, urinary pH or episodes of symptomatic UTI did not differ between the placebo and cranberry groups. According to another RCT to determine the effectiveness of methenamine hippurate (MH) (1 g twice-daily) and of cranberry (800 mg twice-daily). MH as well as cranberry did not have a significantly longer UTI-free period compared to placebo Lee et al (2007) [68]. In addition, when taking phosphorus supplementation, there was no significant change in urine pH during the 2-week period compared to when the patient was off supplementation Schlager et al (2005) [69].

• Antibiotic prophylaxis

Some advocated antibiotic prophylaxis for recurrent UTI [43]. To determine the safety and efficacy of a weekly oral cyclic antibiotic (WOCA) regimen consisting of the alternate antibiotic administration of an antibiotic once per week over a period of at least 2 years to prevent UTI in SCI adult patients, symptomatic UTI dropped from 9.4 to 1.8 per patient-year; and no severe adverse events and no new cases of colonization with multiple drug resistant bacteria were reported (Salomon et al, 2006) [70].

• Bladder irrigation

Waites et al (2006) [71] conducted a randomized, double-blind comparison of twice daily bladder irrigation using 1 of 3 different solutions for 8 weeks with 30 mL of (a) sterile saline, (b) acetic acid, or (c) neomycin-polymyxin solution in community-residing persons with NBD who used IDC. Results showed that the 3 irrigants had no detectable effect on the degree of bacteriuria or pyuria; no significant development of resistance to oral antimicrobials beyond what was observed at baseline; but all groups had a significant increase in urinary pH.

8. Treatment of UTI

Bycroft et al (2004)[43] found few routinely treating asymptomatic UTI in SCI individuals using catheters; and the range of recommended duration of treatment for symptomatic UTI was 3-14 days (mean 6.3).

9. Electrical stimulation

Lavano et al (2004) [72] reported improvement in bladder emptying and continence in 6 neuropathic patients treated with sacral nerve stimulation (SNS) and results were unchanged during the follow-up (maximum 26 months) in all except 1 patient. Kutzenberger et al (2005) [73] reported a 17-years experience with sacral deafferentation (SDAF) and implantation of sacral anterior root stimulator (SARS). Of 464 paraplegics receiving a SDAF-SARS, complete deafferentation was successful in 94.1% and continence was achieved in 83%. With a mean follow-up of 6.6 years, 420 out of 440 paraplegics used the SARS for voiding (frequency 4.7 per day) and 401 used it for defecation (frequency 4.9 per week); UTI declined from 6.3 per year preoperatively to 1.2 per year postoperatively and kidney function presented stable. Hansen et al (2005) [74] applied automatic event driven ES of the dorsal penile/clitoral nerve triggered by Pdet exceed 10 cmH2O and reported during stimulated filling Pdet never exceeded 55 cm H2O and an average bladder capacity increase of 53% was achieved in suprasacral SCI patients.

d) Guidelines for further research:

Most of the papers relating to epidemiology and pathology of urinary incontinence in spinal cord lesion patients were case series; and few papers were clinical trials or RCTs relating to pharmacological treatments. As UTI is a common complication among SCI individuals, further RCT to prove whether a weekly oral cyclic antibiotic for UTI prophylaxis as well as optimal
dosage, effectiveness and safety of bladder relaxants including drugs for blocking nerves innervating bladder is beneficial in SCI with NBD should be done. Regarding types of catheter, RCT should be conducted to prove whether to reuse catheters is safe. In addition, to make an automatic, event driven electrical stimulation for the treatment of NDO suitable in a clinical setting further investigations are needed.

CONCLUSIONS

- Bladder contraction in neuropathic patients can be mediated by M2 muscarinic receptor subtype density. (LOE 3)
- The strongest bladder contraction was usually caused by stimulation on S3 ventral root.
- Skin sympathetic responses and motor evoked potentials seem to be a tolerated diagnostic tool to assess autonomic and somatomotor pathways of the lower urinary tract. (LOE 3)
- Over time changing of bladder-emptying method is common and usually depends on renal function. (LOE 3)
- Long-term urethral indwelling catheterization leads to bladder and urethral complications including continuously incontinent. (LOE 3)
- Encrustation of a catheter is predictive of bladder stones whereas abdominal x-ray is not adequate to detect bladder stones. (LOE 3)
- Hydrophilic-coated catheters seem beneficial regarding UTI. (LOE 3)
- A reusable silicone catheter may be a suitable and safe choice in developing countries if it is properly cleaned and applied to reduce infection. (LOE 3)
- Volume-dependent intermittent catheterization has economic and probably also clinical advantages over time-dependent intermittent catheterization. (LOE 3)
- Combined clean intermittent catheterization during the day time with indwelling contemporary balloon catheter used only at night time showed less urinary infection than clean intermittent catheterization with incontinence and permanent urethral indwelling catheterization. (LOE 3)
- Clean intermittent catheterization was a risk factor for epididymo-orchitis. (LOE 3)
- Increased dosage of Tolterodine or Trospium gave a better effect to control neurogenic detrusor overactivity with incontinence. (LOE 2)
- Oral administration of nitric oxide may reduce bladder outlet obstruction due to DSD as shown in one study. (LOE 3)
- Serum creatinine is reliable and superior to creatinine clearance. (LOE 3)
- Posterior position of ureteral orifices seems associated with vesicoureteral reflux. (LOE 3)
- Urethral flora was a significant source for the development of urinary infection. (LOE 3)
- Low bacterial concentrations in the urine \((10^5 \text{cfu/L})\) of patients who were on intermittent catheterization might be due to contamination. (LOE 3)
- Cranberry extract, methenamine hippurate or phosphorus supplements were not found to be effective in acidifying urine or preventing urinary tract infection. (LOE 2)
- Botulinum-A toxin injection seemed to provide better clinical and urodynamic benefits than intravesical resiniferatoxin. (LOE 2)
- A weekly oral cyclic antibiotic seemed efficacious in preventing UTI. (LOE 3)
- bacteriuria in persons with neurogenic bladder and using indwelling catheterization.

RECOMMENDATIONS

- Regular/annual urological monitoring to early detect complications and to adjust bladder management in patients with neurogenic bladder dysfunction. (A/B)
- Recommend urine culture only there is high risk of urinary tract infection. (C)
- Routinely observe catheter encrustation to early detect bladder stone. (C)
- Cystoscopy is necessary if bladder stones are suspected. (C)
- Change urinary treatment according to urological results and complications. (B)
- Combine EMG and VCUG to identify DSD. (C)
- Correct instructions about catheterization to prevent complications. (B)
- Increase bladder relaxant dosage to control neurogenic detrusor overactivity and incontinence; if side-effect cannot be tolerated, try botulinum toxin injection into the bladder. (B)
2. FAECAL INCONTINENCE

a) Epidemiology and prevalence

According to Dvorak et al, 2006[1], in patients with central cord syndrome, bowel and bladder continence was reported by 81% in those with American Spinal Injury Association (ASIA) motor score improvement from a mean of 58.7 at injury to a mean of 92.3 at follow-up. However, neurogenic bowel dysfunction (NBoD) is common among spinal cord injury (SCI) patients. From 2004 to 2007, there were 6 studies reporting epidemiology of NBoD in chronic spinal cord injured (SCI), from various countries [2-6] (more details see section D1 in this chapter). Apart from SCI [2-6], there were other spinal cord lesions (SCL) that causes NBoD such tumors (e.g. a conus medullaris ependymoma and filum terminale lipoma [7]; a clear cell meningioma along the thoracic and lumbar levels [8], neuroblastoma [9]); venous congestive myelopathy, mostly at thoracolumbar and/or conus medullaris levels [10]; transverse myelitis [11]; and iatrogenic [12,13]. Tanaka et al (2006) [11] 77% of 22 transverse myelitis (average age at onset 8.8 years, mean follow-up 7.1 years) had NBoD (Table 22).

b) Pathology and disease specific lower gastrointestinal (LGIT) problems

According to electromyography (EMG) of external anal sphincter (EAS), 18 and 22 of 64 patients with cauda equina or conus medullaris lesions had bilateral and unilateral EMG abnormalities [14]. In addition, it was found that those with no such reflexes had significantly more severe FI than those with spinal sacral reflexes (p < 0.005) [5] (see more details in section D2 – III Clinical assessment); FI was found to associate with higher severity of injury[4] whereas constipation was associated with a higher level of injury (cervical OR= 5.6 vs. lumbar) [3] which was due to incapacity to increase the intra-abdominal pressure, and the absence of anal relaxation during the defecation maneuver [5].

According to the anorectal manometry, the maximum anal resting pressure of a 26-lumbosacral SCI patients group with mixed symptoms of constipation and/or FI was slightly lower than that of a 13-normal volunteers control group (Li and Xiao, 2006)[15]. During defecation , 88.5% of the patients but 7.7% of the control group significantly showed pelvic floor dysfunction (PFD). Rectoanal inhibitory reflex (RAIR)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Countries</th>
<th>Subjects</th>
<th>Faecal incontinence</th>
<th>Constipation</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liem et al (2004) [2]</td>
<td>Canada</td>
<td>352 SCI (&gt; 20 years)</td>
<td>41.8% (including diarrhea)</td>
<td>47.9%</td>
<td></td>
</tr>
<tr>
<td>Ng et al (2005)[3]</td>
<td>Australia</td>
<td>110 SCI (duration from injury, median 17 years)</td>
<td>41%</td>
<td>46% (including laxative use)</td>
<td>Abdominal pain 33%; Abdominal bloating 22%;</td>
</tr>
<tr>
<td>Tongprasert &amp; Kovindha (2006) [4]</td>
<td>Thailand</td>
<td>100 SCI (duration from onset, mean 6 years)</td>
<td>35% (normal subjects: 1.8%, p = 0.0013)</td>
<td>86% (including uses of laxative, enema, etc)</td>
<td>Haemorrhoid 16% (normal subjects, 20%, p =0.338)</td>
</tr>
<tr>
<td>Vallès et al (2006)[5]</td>
<td>Spain</td>
<td>54 motor complete SCI (mean duration from onset 6 years)</td>
<td>85%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Vallès et al (2006)[6]</td>
<td>Spain</td>
<td>109 patients 83% had spinal sacral reflexes (SSR)</td>
<td>31%</td>
<td>27% more in tetra A,B,C</td>
<td></td>
</tr>
<tr>
<td>Pagliacci et al (2007)[6]</td>
<td>Italy</td>
<td>403 SCI (duration from discharge to follow-up, mean 3 years)</td>
<td>2.7% (20.1% partial)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 22. Shows prevalence of neurogenic bowel dysfunctions reported in spinal cord injury patients
was identified in both groups. The rectal volume for sustained relaxation of the anal sphincter tone in lumbosacral SCI patients group was significantly higher than the control group. The mean rectal volume to generate the first sensation was significantly higher in SCI patients than in the control group. Regarding constipation, its association with level of injury was supported by many studies [3-5] i.e., upper motor neuron vs lower motor neuron NBoD (p =0.0013)[4]; cervical injury had more than 5 times more frequent constipation than lumbar injury (OR =5.6, p =0.02)[3]; lesion above T7 had more constipation than lesion below T7 (p <0.05)[5]; it was also associated with severity of injury [4] and taking bladder relaxants [4]. In addition, decreased colonic pressure activity was found during sleep in SCI individuals and may contribute to delayed colon transit time after SCI [16].

Furlan and Fehlings (2006) [17] examined the characteristics of the top 100 most frequently cited articles (so-called “citation classics”) on traumatic SCI that were published between 1986 and 2003, and compared this selected professional literature with the consumers’ perspective on the key issues in SCI research. From a SCI consumers’ perspective, the areas of greatest interest included motor function, bowel and bladder control, sexual function, and pain. Motor function was the leading topic in the matching list between professional literature and consumers’ perspective. According to Anderson’s quality of life (QOL) survey of the SCI population (2004)[18], regaining arm and hand function was most important to quadriplegics, whereas regaining sexual function was the highest priority for paraplegics; and improving bladder and bowel function was of shared importance to both injury groups. Later, according to a web-based survey of 286 SCI population aged 18 years or older completed the survey, results showed that bladder and bowel concerns during sexual activity were not strong enough to deter the majority of the population from engaging in sexual activity (Anderson et al, 2007a)[19]; however, bladder and/or bowel incontinence during sexual activity was a highly significant concern in women with SCI; in addition, the occurrence of autonomic dysreflexia (AD) during typical bladder or bowel care was a significant variable predicting the occurrence and distress of AD during sexual activity. (Anderson et al, 2007b)[20].

Regarding chronic SCI individuals, FI had 10 times more impact on QOL than those with no FI and NBoD had significant impact on their QOL [21]. They had significantly lower Gastrointestinal QOL score as compared with the normal persons [22]. About one-third needed more help with activities of daily living (ADLs) [2]. There were no statistically significant differences in satisfaction or QOL between those with colostomies and those with traditional bowel care programs; however, 55.7% of those with colostomies and 41.7% of those without colostomies were very unsatisfied with their bowel care program [23].

c) Conservative bowel management

According to the “Neurogenic Bowel Management in Adults with Spinal Cord Injury” Clinical Practice Guideline published by the Consortium for Spinal Cord Medicine [24], rectal stimulations help assist elimination of the stool: mechanical stimulations — digital rectal stimulation (DRS) and manual evacuation; and chemical stimulations — suppository and mini-enema (liquid suppository). Korsten et al (2007)[25] used a manometric catheter to assess colonic motility at baseline, during DRS, and after DRS and evacuation of barium oatmeal paste in six subjects with SCI; and results showed that manometric changes in response to DRS were accompanied by expulsion of barium oatmeal paste in every subject by the fifth DRS. In patients with cervical SCI, a significant increase in systolic blood pressure (BP) was induced by insertion of rectal medications and persisted during additional DRS, and the manual removal of stool induced AD were reported; however, systolic BP recovered to pre-program values within 5 min after defecation[26].

Recently, Uchikawa et al. (2007) [27] reported a successful bowel movement in 75% of 20 SCI patients by using a modified washing toilet seat equipped with a camera monitor and an electronic bidet to facilitate precise hitting of the anal area with water streams to stimulate bowel movement for a maximum of 30 minutes. Regarding transanal irrigation, it showed improvement in constipation, FI and symptom-related QOL in SCI individuals [28].

According to the CPG, push up, abdominal massage and a forward-leaning position may aid evacuation by increasing abdominal pressure [24]. Aya? et al., 2006 [29] studied in patients with SCI and showed that abdominal message gave positive effects — increase in frequency of defecation per week, decrease in total colonic transit time and lesser FI. As contraction of the abdominal wall musculature plays a role in normal defecation, Korsten et al (2004)[16] assessed whether an abdominal belt with implanted electrodes would improve difficulty with evacuation in SCI individuals and demonstrated that neuromuscular stimulation of the abdominal wall improved defecation function, including time to first stool and total bowel care time.

Regarding medications to enhance bowel movement, Cisapride, oral does not seem to have clinically useful effects in people with SCI (Coggrave et al., 2006) [30]. Korsten et al (2005) [31] did a randomized, blinded design, to test the efficacy of neostigmine in SCI persons with defecation difficulty by infusing one of three intravenous infusates (normal saline, 2 mg neostigmine, or 2 mg neostigmine + 0.4 mg glycopyrrolate — to prevent neostigmine’s muscarinic effects) on separate days and determining on bowel evacuation of the barium paste, heart rate and airway resistance; and results indicated that both neostigmine and neostigmine + glycopyrrolate resulted in prompt bowel evacuation. Studies have shown that neo-
stigmine + glycopyrrolate intravenous administration is safe and well tolerated in persons with chronic SCI [31,32] and studies have been under way to assess the efficacy of neostigmine by other routes [32].

d) Guidelines for further research

Most of the studies reported were case series and used different definitions of faecal incontinence and constipation. Therefore further researches should base on internationally acceptable definitions so that they can be compared. In addition, RCTs on rectal or anal stimulations both mechanical and chemical as well as medications promoting bowel movement are needed.

CONCLUSIONS

- Constipation is more common than faecal incontinence among established SCI persons. (LOE 3)
- Constipation is more common in those with preserved sacral reflexes whereas faecal incontinence is more common in those without sacral reflexes. (LOE 3)
- Faecal incontinence has impact on QOL of SCI individual and is highly concerned by SCI women during sexual activity. (LOE 3)
- Digital rectal stimulations aid bowel evacuation in individuals with SCI in part by increasing left-side colonic motility. (LOE 3)
- Transanal irrigation with water improves constipation and quality of life in individuals with SCI. (LOE 2)
- Abdominal massage seems effective in enhancing bowel movement and defecation. (LOE 3)
- Anal stimulation by water stream seems effective in stimulating bowel movement and shortening bowel care time. (LOE)

RECOMMENDATIONS

- Encourage adherence to the clinical practice guidelines on neurogenic bowel management in adults with spinal cord injury. (A)
- Apply mechanical stimulation e.g. digital rectal stimulation to aid bowel evacuation especially in those with preserved sacral reflexes. (B)
- Use chemical stimulations when mechanical stimulations fail. (C)
- Beware of autonomic dysreflexia during bowel care especially in those with high lesion. (C)
- Consider transanal irrigation with water for those with severe chronic constipation and faecal impaction. (B)

VII. SPINAL CANAL STENOSIS

1. EPIDEMIOLOGY AND PREVALENCE

According to our previous extensive review of spinal canal stenosis (SCS) and incontinence published in the 3rd ICI (2005)[1], about half of the patients with intractable leg pain also had bladder symptoms – urinary difficulty with high post-void residual (PVR) and reduced flow rate and/or incontinence indicating cauda equina syndrome. Such symptoms including urinary incontinence (UI) may usually improve after surgical decompression.

Schkrohowsky et al (2007) [2], one third of patients with achondroplasia developed SCS, especially at lumbar level, requiring surgical intervention; and 77% had UI. According to Johnsson and Sass (2004) [3], in the County of South Jutland, Denmark during a 5-year period (1996-2000), the annual incidence of SCS was 272 per million inhabitants; and of 340 cases diagnosed with SCS during that period, only one patient presented with acute cauda equina syndrome: a 74-year-old woman with SCS from L2 to L4 appeared with urinary retention and fecal incontinence (FI) for the previous 24 hours; after an urgent operation and she recovered within 5 days from her anal sphincter paresis and within 5 weeks from her bladder paresis.

2. PATHOLOGY AND DISEASE SPECIFIC PROBLEMS

Goh et al (2004) [4] carried out a comprehensive retrospective review of the clinical features, radiological changes and outcome of 75 patients with radiologically diagnosed lumbar SCS; imaging of the lumbar spine showed that moderate to severe central spinal stenosis correlated with complaints of weakness and abnormal motor power on clinical examination; and the commonest symptom was numbness or tingling of the legs. According to the study of Inui et al (2004)[5], 58.8% of the 34 patients were diagnosed with positive neuropathic bladder; however there was no difference in the cross-sectional area of dural sac between those with and without neurogenic bladder dysfunctions (NBD) in patients with lumbar SCS; but the anteroposterior diameter of the dural was shorter in those with NBD; and a critical size for the dural sac of patients with NBD was revealed as 8 mm in this study.

Usually signs and symptoms of compressive neuropathy of multiple lumbar and sacral roots, so called ‘cauda equina syndrome’ is an indication for surgical intervention but relatively unknown as a postoperative complication following surgery [6]. Four years after diagnosis, 65% had undergone surgical decompression; a third of patients felt that their symptoms had improved while a quarter felt that they had worsened [4]. Imran and Halim (2005)[7] reported a 63-year-old man who developed acute cauda equina
syndrome due to fat graft compression after decompressive laminectomy, posterior instrumented fusion with pedicle screw fixation for spinal stenosis of L5 and S1 vertebral levels and free fat grafting to cover the exposed dura; three days postoperatively, gradual neurological deficit started with sensory loss and weakness of the affected dermatomes and myotomes, followed by FI on the 12th postoperative day; and immediate removal of the fat graft resulted in recovery from cauda equina syndrome.

Another case was reported by Tubbs et al (2005) [8]; a Caucasian girl who had idiopathic growth hormone deficiency and Klippel-Feil and Duane’s syndromes with symptomatic stenosis of the first cervical vertebra presented with episodes of loss of tone with subsequent falling, facial cyanosis, UI, hand weakness, and difficulties with swallowing; following suboccipital craniectomy and the removal of the posterior arch of the atlas, her symptoms were resolved and UI improved.

3. DISEASE SPECIFIC DIAGNOSIS AND TREATMENTS

To demonstrate narrowing of the lumbar canal with compression of the cauda equina, computer tomography (CT) or magnetic resonance imaging (MRI) is often recommended to reveal either bony or soft tissue compression [9].

Miyata et al (1998) [10] studied the relationship between bladder function and roentgenographic changes in the spinal canals of ossification of posterior longitudinal ligament (OPLL) patients. CO2-filling cystometry, uroflowmetry and PVR were measured and the vertical extent of OPLL and the degree of SCS was estimated by x-ray films and CT. The occurrence of abnormal detrusor activity had no relationship to the degree of canal stenosis, while the occurrence of an areflexic or underactive detrusor correlated with the vertical extent of OPLL [10].

Yamanishi et al (1998) [11] found detrusor overactivity in 14 lumbar canal stenosis patients (29%) and most of them had voiding symptoms and had storage symptoms which seemed to be caused by the irritation of sacral roots. Of 10 patients followed up after surgical decompression, detrusor overactivity disappeared in 5 patients, improved in 1 patient and remained unchanged in 4 patients [11].

Lee et al (1997) [12] did an expansive cervical laminoplasty in patients with nontraumatic cervical spondylosis with myelopathy and found that age greater than 60 years at the time of presentation, duration of symptoms more than 18 months prior to surgery, preoperative bowel or bladder dysfunction, and lower-extremity dysfunction were found to be associated with poorer surgical outcome.

CONCLUSIONS

- Patients with spinal stenosis, especially at lumbar level, may present with bladder and bowel involvements—which urinogenital and faecal incontinence (LOE 3/4)
- Lumbar canal stenosis may cause either detrusor underactivity/acontractility or overactivity. (LOE 3)
- Imaging helps diagnose spinal stenosis where as urodynamic study help diagnose neurogenic bladder dysfunction. (LOE 3/4)
- Acute symptom of incontinence or urinary retention may recover after decompression of spinal stenosis. (LOE 3/4)

RECOMMENDATIONS

- Surgical decompression is recommended in patients with spinal stenosis having acute symptoms of urinary retention/incontinence and faecal incontinence. (A)

VIII. GUILLAIN-BARRE SYNDROME

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Guillain-Barré syndrome (GBS) is the most common cause of acute, flaccid paralytic disease [1]. The term GBS defines a clinical entity that is characterized by rapidly progressing limb weakness and the loss of tendon reflexes. The disorder affects children and adults of all ages and both sexes. The following stages are observed: progression or acute phase, plateau phase and recovery phase. Despite intensive immunomodulating therapies such as intravenous immunoglobulin or plasma exchange, 4% to 15% of patients with GBS die from this syndrome and nearly 20% have a persistent disability [2]. Therefore, supportive care remains the mainstay of treatment. A recent consensus guideline in supportive care for patients with GBS covers airway problems and tracheostomy, pain, deep vein thrombosis, fatigue, cardiac problems, and bladder and bowel dysfunction [2]. Whereas cardiovascular autonomic dysfunction (mainly reflecting sympathetic adrenergic function) is recognized in up to 60% of GBS patients [3], lower urinary tract (LUT) function has only been studied infrequently in the acute phase of GBS. This is partly because most patients are catheterized as part of their general nursing care to maintain bodily hygiene or to monitor water balance [2].
Sakakibara et al [4] (LOE3/4) studied LUT symptoms in 28 patients with GBS (24 acute inflammatory demyelinating polyradiculoneuropathy, AIDP, 4 acute motor axonal neuropathy, AMAN) during the acute phase. They found that 25% of the patients showed micturitional disturbance. Voiding difficulties were presented by 86%, urinary retention by 43%, nocturnal urinary frequency by 43%, and urge incontinence by 28% of patients suffering from micturition problems. This figure is almost in accordance with the 25% found in the original reports of Guillain and colleagues.[5,6]. Urinary dysfunction in patients with GBS appeared after the occurrence of motor weakness in all cases [4]; whereas in two patients with axonal GBS, it is reported that voiding difficulty and motor weakness appeared almost simultaneously [7,8] (LOE3/4).

Sakakibara et al [4] (LOE3/4) indicated that urinary dysfunction increases with higher Hughes motor grade, although it did not reach statistical significance. Lichtenfeld [9] (LOE3/4) has also reported urinary retention in one-third of patients requiring ventilatory assistance. Even though up to 11% of GBS patients may develop urinary retention at the peak of motor weakness, it will mostly ameliorate along with other neurological signs after supportive patient management, with/without immuno-modulating therapies. In contrast, it is reported that urinary retention failed to recover for 10 months even after one patient (with axonal GBS) regained the ability to walk [8] (LOE3/4).

With regard to subtypes of GBS, it was found that heart rate and plasma noradrenaline concentrations were elevated in AIDP in 7 patients but not in 8 patients with AMAN [3]. This contrasts with the observation of bladder dysfunction in 21% of patients with classic GBS (AIDP) (n=24) but in 50% of those with axonal GBS (AMAN) (n=4)[4]. These findings may reflect the vulnerability of autonomic fiber among these variants, although it is too early to determine urinary function of axonal GBS since the number of such patients was too small.

b) Pathology and disease specific lutproblems

There is a lack of good systemic studies on micturition disorders in GBS during both acute and chronic phases. In a few reports,[10,11,12] detrusor areflexia and disturbed bladder sensation are common, and nonrelaxing urethral sphincter with neurogenic change in the sphincter motor unit potentials is another factor (LOE3/4). Among these, Grimvac et al [12] (LOE3/4) studied uodynamically 4 patients in the acute stage of GBS. All of them had complete urinary retention. They described both detrusor areflexia and detrusor overactivity, as well as detrusor-sphincter dyssynergia. One patient was followed during the chronic stage of the disease showing detrusor overactivity. The most extensive study was performed by Sakakibara et al [4] (LOE3/4) during the acute phase. They performed a urodynamic study on 4 symptomatic patients, and 2 of whom underwent repeated study. Disturbed bladder sensation was noted in one patient, detrusor areflexia in one and absence of the bulbocavernosus reflex in one. In contrast, cystometry also showed decreased bladder volume in 2 and bladder overactivity in 2, one of whom had urgency urinary incontinence and the other urinary retention. GBS primarily affects the large myelinated fibers, but pathology studies have revealed moderate to severe loss of small myelinated fibers and inflammatory cell infiltration in the lumbosacral spinal roots, sympathetic chain, and spinal cord [1,13]. Therefore, one mechanism is postulated for the urinary dysfunction in GBS: peripheral nerve damage and irritation in the sacral autonomic fibers, from either bystander inflammation or immune attack of the autonomic fibers [1,13]. Contrast enhancement in magnetic resonance imaging (MRI) of the cauda equina in GBS has also been reported [14].

Previously Wheeler and colleagues [11] (LOE3/4) found detrusor overactivity in 3 of 7 patients with GBS. However, they used carbon dioxide as a cystometry medium, which is not now recommended since it is an irritant to bladder mucosa. In addition, 2 of his patients with detrusor overactivity had extensor plantar responses, which raise questions regarding the diagnosis of GBS. However, water cystometry findings in the following studies showed detrusor overactivity with clinico-neurophysiologically definite GBS [4]. Whereas GBS patients do not have extensor plantar responses, some axonal GBS patients exhibited increased tendon reflexes [15]. Therefore, another mechanism is postulated for the urinary dysfunction in GBS: immune attack of the inhibitory spinal cord interneurons [15].

c) Disease specific diagnosis and treatment

Urinary dysfunction occurs in up to 25% of GBS patients including urinary retention in 11%, particularly in those with higher Hughes motor grade or those under mechanical ventilation. Therefore, in such patients, we should check post-void residual volume repeatedly by ultrasound echography. We then determine which supportive care is better; including the indwelling urinary catheter. Recovery of LUT function usually occurs along with the recovery of motor weakness in GBS. However, in rare cases it might take months. During the recovery period, not only voiding difficulty but also urinary urgency and frequency could occur. At this stage, urodynamic study is easily performed in order to optimize the therapy for the symptomatic patients. Clean, intermittent catheterization (CIC) is the treatment of choice to prevent over-distention bladder injury.

d) Guidelines for further research

There is only one study about the prevalence of LUT problems in GBS, which is however concentrated on the acute phase of the disease. Therefore a long-
term follow-up of these patients is needed. We still don’t know what are the long-term consequences of this disease for the LUT including urinary incontinence.

CONCLUSIONS

- In the acute phase of GBS, about 25% of patients demonstrate LUT functional problems (LOE3/4).
- Both storage and voiding dysfunctions are observed in GBS (LOE3/4).
- Recovery of LUT functions occurs along with the recovery of motor weakness. However, in rare cases it might take months (LOE3/4).

RECOMMENDATIONS

- Recovery of the LUT functions is expected in GBS; while supportive care including indwelling catheter and the following CIC is the treatment of choice in order to prevent over-distention bladder injury (C).
- During and after the recovery of paralysis a detailed functional evaluation of the LUT in symptomatic patients is needed in order to optimize the therapy (C).

2. FAECAL INCONTINENCE

a) Epidemiology and prevalence

Among various autonomic dysfunctions, whereas cardiovascular dysfunction occurs in up to 60% of Guillain-Barré syndrome (GBS) patients, [3,16] bowel dysfunction is less common, occurring in up to 15% [17,18]. In Burns’ study (LOE3/4) [17] in which adynamic ileus was noted in 17 out of 114 GBS patients, cardiovascular symptoms coincided with ileus in only 5 patients, suggesting a different pathomechanism may underlie in these two autonomic dysfunctions. Indeed, in 4 patients, mechanical ventilation and immobilization could be implicated. In 8 patients, preexisting conditions such as prior abdominal surgery or incremental doses of opioids could also be linked to ileus. However, three case reports by Gazulla Abio et al (LOE3/4) [19], Sawai et al (LOE3/4) [20] and Noew et al (LOE3/4) [21] have also shown that paralytic ileus can be the initial presenting symptom in GBS.

b) Pathology and disease specific lutproblems

There is a lack of good systemic studies on bowel disorders in GBS during both acute and chronic phases. However, there are some reports suggesting an involvement of bowel autonomic fibers in GBS. Sawai et al (LOE3/4) [21] performed a detailed bowel function test in a 47-old man with acute motor axonal neuropathy (AMAN) type of GBS who presented with ileus (also called intestinal pseudo-obstruction) by an abdominal X-ray. Sitzmarks showed prolonged total colonic transit time (86.4 hours; normal 16.0-48.0), suggesting slow transit constipation. As indicated in the bladder part, pathology studies of GBS have revealed moderate to severe loss of small myelinated fibers and inflammatory cell infiltration in the lumbosacral spinal roots, sympathetic chain, and spinal cord. Therefore, involvement of bowel autonomic fibers might also occur in GBS [21], as shown in an autopsy case of autoimmune gastroparesis [18].

c) Disease specific diagnosis and treatment

Adynamic ileus or intestinal pseudo-obstruction occurs in up to 15% of patients during a course of GBS, particularly in those with severe motor dysfunction or those under mechanical ventilation [17]. Supportive care remains the mainstay in the treatment of bowel dysfunction in GBS, including laxatives or enemas [22,23]. Recovery of bowel function usually occurs along with the recovery of motor weakness in GBS, after an intensive immune therapy including intravenous immunoglobulins.

d) Guidelines for further research

There is still a lack of a detailed functional evaluation of the bowel in GBS patients. Such studies are needed in order to optimize the therapy in the future.

CONCLUSIONS

- About 15% of patients demonstrate bowel functional problems particularly in the acute phase, but they can also be presenting symptoms (LOE3/4).
- Constipation and intestinal pseudo-obstruction are observed in GBS (LOE3/4).
- Recovery of bowel functions usually occurs along with the recovery of motor weakness.

RECOMMENDATIONS

- Recovery of the bowel functions is expected in GBS; while supportive case including laxatives or enemas is the treatment of choice (C).

IX. LUMBAR DISC PROLAPSE

Medline through Pubmed between 1966-2007

- Data base was searched for keywords:

Disc prolapse (or disc hernia), bladder dysfunction, neurogenic bladder, sphincter dysfunction, bowel dysfunction, fecal incontinence, and constipation

1. PATHOPHYSIOLOGY, EPIDEMIOLOGY AND PREVALENCE

Central lumbar disc prolapse compresses sacral nerve
fibers to and from the bladder, the large bowel, the anal and urethral sphincters, and pelvic floor resulting in so-called cauda equina syndrome. Cauda equina syndrome due to central lumbar disc prolapse has been reported to be relatively rare, the incidence being from 1 to 5% of all prolapsed lumbar disc [1-8]. Clinical features of the cauda equina syndrome include low-back pain, bilateral sciatica, saddle anesthesia, and urinary retention, loss of urethral sensation as well as constipation and erectile dysfunction [4,7,9,10]. Those patients with cauda equina syndrome usually have some sensory disturbance in the sacral dermatomes [4,10]. A Retrospective cohort study with prospective clinical follow-up showed that bowel dysfunction at presentation was associated with sexual problems at follow-up [11].

2. DISEASE SPECIFIC DIAGNOSIS AND LUT DYSFUNCTION PATTERNS

The most common urinary symptom associated with lumbar disc prolapse is acute urinary retention [12,13]. At the onset, acontractile detrusor with impaired bladder sensation is a typical urodynamic finding [4,10,12,13,14]. Severe denervation of pelvic floor [12] and external urethral sphincter [10] is also frequently demonstrated. Detrusor overactivity may occur through the irritation of the sacral nerve root [14,15,16]. Urinary disorders usually follow or accompany more obvious neurologic symptoms, such as lumbar pain and perineal sensory disturbances, that lead a proper diagnosis. However, sometimes voiding disturbances may be the only or the first symptom of this condition, which makes it more difficult to diagnose this disease [4,10]. Nevertheless, urgent MRI assessment is recommended in all patients who present with new onset urinary symptoms concomitantly with lumbar back pain or sciatica because it is impossible in a significant proportion of patients to exclude the diagnosis of prolapsed intervertebral disc in the context of referral with suspected cauda equina [17].

3. DISEASE SPECIFIC THERAPY

Emergency surgical decompression has been reported to be important to increase the chance of satisfactory neurological recovery in patients with cauda equina syndrome due to central lumbar disc prolapse [4,18,19]. In a meta-analysis of surgical outcomes, Ahn et al (2000) [7] reported that a significant improvement in sensory and motor deficits as well as urinary and rectal function occurred in patients who underwent the surgery within 48 hours compared with those who had the surgery more than 48 hours after the onset of the cauda equina syndrome. Although there is still a controversy [11], most of other reports support the concept that decompression performed within 48 hours of onset of this syndrome resulted in improved functional outcomes [3,8,20]. However, acontractile detrusor is usually irreversible even after immediate decompression [10,21,22], although many patients can empty their bladder postoperatively, but only by straining or changing their voiding postures [10,22]. In contrast to bladder dysfunction, urethral function shows a better recovery after surgery [10,13].

Please refer to the chapter on children. We have looked in the scarce literature on adult patients.

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Myelomeningocele (spina bifida) is one of the most common birth defects of the spine and brain. It occurs in 1-2 births per 1000, involving all levels of the spinal column (lumbar 26%, lumbosacral 47%, sacral 20%, thoracic 5% and cervical spine 2%). Associated Arnold-Chiari malformation is seen in 85% of children, often requiring ventriculo-peritoneal shunting of cerebrospinal fluid. Ingestion of folic acid prior to conception and during the first trimester of pregnancy has significantly reduced the incidence of this problem and other associated neural tube defects. The neurologic defect produced is quite variable and cannot be totally predicted by the vertebral level of the lesion. Additionally the fibrosis associated with myelomeningocele closure, may tether the cord. Subsequent growth of the infant or child will produce further neurologic problems, manifesting as changes in bladder, bowel and lower extremity function.

The incidence of urethrovaginal dysfunction in myelomeningocele is not absolutely known, but most studies suggest it is very high (>90%). Similarly, anorectal dysfunction is very common, but its exact incidence has not been reported. Congenital neurologic bladder dysfunction with spina bifida and sacral dysgenesis that manifested itself only at middle age in a 48-year-old male is reported by Kaneoya et al (LOE4)[1]. Yamamura et al reviewed the literature of tethered cord of adult onset and found 56 cases published.(LOE 3) [2].

b) Pathology and disease specific LUT problems

The two major consequences of the vesicourethral dysfunction are urinary incontinence and hydronephrosis which can occur early or later in life.

There are many studies documenting the urodynamic characteristics of the vesicourethral unit in myelomeningocele patients but almost all in children. Almodhen and colleagues examined myelomenigocele patients in postpubertal age and correlated these findings with upper urinary tract changes [3] (LOE 3). Of the 26 patients with urinary incontinence before puberty 12 achieved continence following puberty. Hydronephrosis remained stable in 4 patients, improved in 3 and was new onset in 3, whilst vesi-
c) Disease specific diagnosis and treatment

Urodynamics is the cornerstone in the diagnosis and management of vesicourethral dysfunction in myelomeningocele. As previously stated, urodynamic findings may predict the patients at risk of upper tract deterioration. Controversy continues as when to initiate these studies, either as soon as possible after back closure, at the first sign of upper tract changes or before considering management of incontinence. Studies supporting each position have been reported, although the preponderance of evidence suggests earlier diagnosis of hostile factors is advisable. Taskinen et al [4] examined 30 patients with anorectal anomalies mainly because of fecal or urinary incontinence. All patients underwent spinal magnetic resonance imaging and urodynamic investigation. Major lumbosacral abnormalities were detected in 57% of patients, including 13, 4 and 3 with a tethered cord, syringomyelia and caudal regression, respectively. Significant dysfunction of the LUT in 57% of the cases involved an overactive detrusor in 11, detrusor-sphincter dyssynergia in 4, distended bladder in 4 and lazy bladder in 1. When the spinal cord was normal, 54% of the patients had abnormal urodynamic findings but when the spinal cord was abnormal, 59% had abnormal urodynamics. When the bony spine was normal, 33% of the patients had an abnormal spinal cord but when the bony spine was abnormal, 69% had an abnormal spinal cord. (LOE3).

As hydronephrosis and vesico-ureteric reflux are a consequence of detrusor dysfunction, synchronous fluoroscopic evaluation of the urinary tract is advisable at the time of urodynamics. Similarly, renal ultrasound has become an invaluable routine serial evaluation in these patients, assessing renal growth, development of scarring and, most importantly, hydrouretonephrosis. Studies suggest a role for repeat urodynamics and ultrasound in this patient population, however, the timing and frequency of these studies still needs to be elucidated.

Although, renal scans are routinely used, especially in the myelomeningocele patient with hydronephrosis, the exact role of this study in these patients is not clear.

Urologic treatment depends on the age of the patient and the nature of the vesico urethral dysfunction as characterized by urodynamics. In a retrospective study urinary sepsis accounted for the majority of admissions (62%), while 38 of 62 patients required 60 surgical procedures[5]. Targeting the primary urological abnormality (the dysfunctional and usually poorly compliant bladder) allowed implementation of effective treatments, including regular intermittent bladder catheterisation (52%) in order to preserve upper renal tract function. Associated postural abnormalities complicated both conservative and interventional therapies.

The mainstay of treatment is clean intermittent catheterization and antimuscarinic medication. As continence is not at issue in the neonate and infant, treatment may be postponed, unless upper tract changes are present. Some evidence exists pointing to the fact that early initiation of treatment may prevent subsequent deleterious bladder changes. Recently botulinum toxin was suggested as a possibility to avoid invasive surgery in these patients [6].

Bruschini et al evaluated 104 patients who were not managed and followed-up adequately during their childhood [7] (LOE 3). Reflux and urinary tract damage were found in 30 patients, 6 patients presented signs of upper tract damage without reflux. The cystometry showed detrusor overactivity in 48% of patients, poor compliance in 49% of patients, increased bladder capacity in 2% and normal cystometry in 1%. Detrusor leak point pressure over 40 cm H(2)O was associated with upper urinary tract damage. Patients with a decrease of functional bladder capacity over 33% had more renal scars than their counterparts. Overall, 26 % of urological untreated myelomeningocele patients have kidney damage.

On the other hand there is a work by Olsson and colleagues, evaluating 175 Swedish myelomeningocele patients in adult age [8] (LOE 3). Clean intermittent catheterisation for bladder emptying was used by 85%, and 59% used enemas on a regular basis because of the neurogenic bowel dysfunction. Renal dysfunction was than seen only in 1.7% of the adolescents.

Management of incontinence and/or upper tract deterioration mirrors the treatment of neurologic bladder. Variations in this algorithm include the use of vesicostomy in the younger child who has failed conservative measures and has evidence of deteriorating upper tracts. External sphincterotomy
has no place in the management of these patients and the use of the appendico vesicostomy in continent LUT reconstruction (Mitrofanoff) has become very popular. Most studies on surgical management of the myelomeningocele bladder are descriptive (LOE 4) at best. Data from adult and paediatric surveys show renal damage to be the single most prevalent cause of morbidity and mortality; even in children, 30-40% exhibit evidence of renal damage. Additional factors such as chronic infection and stone formation will then render the kidney more vulnerable to progressive loss of renal mass and subsequent chronic renal failure. Renal transplantation is now considered the optimal treatment for end-stage renal disease in all age groups. Although more prone to complications, recent data on patients with meningomyelocele or severely abnormal LUTs demonstrate excellent patient and graft outcomes. [9] (LOE 3)

d) Guidelines for further research
Further clarification of the role of fetal surgery to repair the neural tube defect is required. Similarly the role of early intervention, conservative or surgical is required. The timing of surgical intervention needs further study as well as better quality of life assessments and risk/benefit analyses of LUT reconstructive procedures. The development of a tissue-engineered substitute for cystoplasty is being studied. Finally, the fate of the adult myelomeningocele patient, especially those who have undergone reconstruction needs to be documented.

CONCLUSIONS

- Myelomeningocele is one of the commonest birth defects (LOE 1)
- Incidence decreased by folate ingestion (LOE 2)
- Most have bladder dysfunction which can lead to incontinence and / or upper tract deterioration (LOE 3)
- Majority will derive significant benefit from conservative measures (LOE 3)

RECOMMENDATIONS

- Regular surveillance, from infancy, with urodynamics and renal ultrasound is mandatory. However the exact timing is not defined. One must observe the general rules for neurogenic bladder(B)
- Early initiation of conservative measures (clean intermittent catheterization, anti-muscarinic medication) generally provides protection of the upper urinary tract (B)
- Surgery is reserved for failed conservative treatment ( B)

2. FAECAL INCONTINENCE AND BOWEL PROBLEMS

• Methods
Using MEDLINE we identified English-language journal articles and reviews published from 2000 to April 2008, looking for the keywords myelomeningocele, fecal incontinence, management.

a) Pathophysiology
Voluntary control of defecation requires rectal sensation, peristalsis and adequate anorectal sphincter function. Neurological defects in patients with spinal lesions may affect one or more of these components resulting in different types of defecation disorders: fecal incontinence, chronic constipation or both. Incontinence is one of the major stigmas affecting patients born with myelomeningocele [1].

b) Prevalence
Bowel dysfunction occurs in most children with spinal cord impairment from disease or injury.

c) Management (LOE 3)
Although many different regimens have been used to manage this problem none has had universal success. Behavioural modification and laxatives failed to achieve an acceptable result because of the persistence of soiling. A small dose of laxatives alone accomplished nothing while administering a large dose to an incontinent patient only resulted in profound embarrassment [2]. Bearing in mind that none of these patients can resist the push of peristalsis, the most effective therapy is the emptying of the colon, which takes at least 24–48 h to refill again.

The main goal, to empty the colon as much as possible to achieve continence during the next 24–48 h, can be achieved nowadays by two ways, (A) by a retrograde colonic enema (RCE) using a special ballon catheter or (B) an operative procedure which allows an antegrade continence enema (ACE).

1. CONSERVATIVE
• The retrograde colonic enema (RCE)
In neurological fecal incontinence the standard enemas are difficult if not impossible to administer because there is inability to retain the enema which flows out involuntarily through the weak anus during its instillation.

Therefore a catheter system, which allows to perform the retrograde colonic enema, has been developed by industry, the application of which can easily be applied either by the parents or even by children over the age of 7–8 years. Not all children tolerate this procedure, in some of them colonic peristalsis creates pains. However the reported results are good according to Eire et al. [3], in 1998.
Shandling et al. [4] reported 100% success in using the enema continence catheter in the management of his patients with spina bifida.

These authors regard the RCE as one of the best conservative methods of treatment for relieving fecal incontinence originating from myelomeningocele and other neurological problems within intestinal dysfunction.

With intravesical electrical stimulation (IVES) also concomitant improvement in fecal incontinence was observed in children with myelomeningocele and IVES is regarded by some as another viable option for controlling fecal incontinence in these children [5].

Biofeedback was introduced for use in children with intact rectal sensation [6], but recent trials have reported less encouraging results [7]. “Digital disimpeachment” is unpleasant to perform and only succeeds in emptying the distal rectal ampulla.

2. Operative

• The antegrade colonic enema (ACE)

The impact of antegrade colonic enema (ACE) [8] in the management of patients with myelomeningocele was analysed recently by Lemelle et al [1]. 47 patients were treated with ACE, of whom 41 used the method at a mean time of 4.1± 1.9 years after the ACE operation: only six abandoned ACE for conventional management. With ACE, faecal incontinence was significantly improved compared with conventional management and neither retrograde rectal enema nor digital extraction were required.

In most cases, ACE was performed using the appendix or the caecum. Among the 47 patients operated with the ACE procedure, six patients (12.8%) stopped performing antegrade enema for various reasons, from conduit problems due to stomal stenosis or catheterization difficulties, lack of motivation or “too long time to empty the enema” in one case. Antegrade colonic enema was applied before, concomitantly or after urinary incontinence surgery in 5, 27 and 10 cases respectively. Antegrade enema was performed at most three times a week. Tap water was used in the majority of patients. Mean enema volume for ACE was 1.2 L (range 0.25–3.0 L). Mean enema time for colonic washout with ACE was 50 ± 19 min (range 15–90 min), however mean washout duration for ACE tended to be shorter with implantation of the conduit on the left-segment of the colon.

Casale et al. [9] were unable to find any differences in the continence rate or stomal complications between total reconstruction (ACE and continent urine stoma) or staged reconstruction. However, because of shared pathology the authors believe, that most patients benefit from intervention in the gastrointestinal and the genitourinary tract. Therefore, a major advantage of total continence reconstruction is avoidance of the morbidity of a second major surgical procedure (LOE 3).

Nevertheless, conventional treatment should be tested first, and the efficacy of retrograde enemas may be a predictor of the efficacy of ACE on bowel management. Moreover, percutaneous endoscopic insertion is fully reversible and does not present drawbacks and encountered with the catheterizable conduit [2]. Nevertheless, experience with the Malone procedure has proved that a suitable continent and catheterizable conduit can be obtained with an appropriate technique. In selected and motivated patients, and with the help of a specialist nurse providing close support in the postoperative period, surgical ACE procedure might be preferred according to the surgeon’s experience.

• Sacral neuromodulation has been recently described also in the therapy of these patients, but the persistence of continence control and tolerance of the patient need to be evaluated for a prolonged period of time(). Sacral neuromodulation may only be successful in a small selected number of patients, in whom preserved anatomy of the sacral nerves permits placement of the electrodes on the sacral nerves [10].

d) Quality of life – QoL (LOE 3)

As no absolute indication has been defined for ACE, other criteria should be used to evaluate clinical outcome of bowel management, including health – related quality of life (HRQoL). This assessment should be performed prospectively when ACE produce is planned and performed during pre and post-operative periods.

According to Eire et al. (1998) ACE procedure and RCE can be the best options for achieving the best social integration. For wheelchair users and other selected patients the ACE (being faster and easier) is better than the retrograde continence enema which needs some help in its use [3,6].

CONCLUSIONS (LOE 3)

• Neurologic bowel dysfunction and bowel problems incl. fecal incontinence and constipation are prevalent among myelomeningocele patients.

• Fecal incontinence and methods of bowel care affect the QoL and social activities of myelomeningocele patients.

• The main goal, to empty the colon as much as possible to achieve continence during the next 24–48 h, can be achieved nowadays either by retrograde colonic enema (RCE) using a special balloon catheter or by an operative procedure which allows an antegrade continence enema (ACE).
RECOMMENDATIONS B/C

- Colorectal problems deserve more attention in the treatment of myelomeningocele patients
- Appropriate bowel programme/management should be properly designed to each person after adequate counselling.

FURTHER RESEARCH

The development of a disease-specific HRQoL measure for use with myelomeningocele has been proposed by Parkin et al. [11]. In addition specific questionnaires should be designed to assess fecal incontinence.

XI. DIABETES MELLITUS

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Diabetes is one of the commonest causes of polyneuropathy. Amongst different types of polyneuropathies in diabetic patients “diabetic cystopathy” occurs in 43% to 87% of insulin-dependent diabetics, with no sex or age differences. It is also described in about 25% of diabetic patients on oral hypoglycemic treatment. A Scandinavian study showed that in patients who have had diabetes for 10 years, the prevalence of diabetic cystopathy in those who were insulin-dependent was 2 to 4 per 1000 and in those on oral hypoglycemic agents was 1 to 3 per 1000. The correlation between diabetic cystopathy and peripheral neuropathy ranged from 75% to 100%. Nephropathy was seen in 30% to 40% of cases [1] (LOE 3).

Diabetes duration, treatment type, peripheral neuropathy, and retinopathy were significantly associated with severe incontinence in multiple regression models adjusted for age, education, and history of UTI [2] (LOE 3). Lewis et al in a cross-sectional studies of 50-90 years old women found that insulin dependent diabetes was strongly associated with urinary incontinence, while non insulin dependent diabetes was not [3] (LOE 2).

b) Pathology and disease specific LUT problems

Van Poppel et al had neuropathological examination of bladder biopsies done on 14 patients with severe insulin-dependent adult-onset diabetes and compared with the acetylcholinesterase and S100 staining of 38 control specimens. A decrease in acetylcholinesterase activity, due to axonal degeneration was found in all cases. An increase in S100 positivity was found in the majority and is due to Schwann cell proliferation as a regeneration attempt after demyelination or axonal degeneration. When acetylcholinesterase activity decreases and an S100 density increase is found in a patient with diabetes, this combination is highly suggestive of diabetic cystopathy amenable to early symptomatic treatment [4] (LOE 2).

Since the peripheral nerves are involved, the clinical manifestations of diabetic cystopathy might be very different. Usually there is reduced sensation of bladder fullness, and decreased frequency of voiding. This is followed by slowing of the urinary stream and difficulty in voiding due to impaired detrusor contraction. Post-voiding dribbling may also occur. The impaired bladder emptying and urinary retention predispose to urinary tract infections. No prospective studies referring specifically to the problem of functional disturbances of the LUT in diabetic patients were performed.

Yamaguchi et al. recently studied 84 diabetic cystopathy [5]. In addition to large post-void residual and decreased sensation, urinary urgency, detrusor overactivity (DO), and increased bladder sensation were seen in 55%, 42%, and 14%, respectively. The frequency of DO in patients with increased bladder sensation was 58%. DO increased with age, but not with the duration of diabetes. A brain MRI was performed in 32 cases. The frequency of multiple cerebral infarction in patients with DO was 76.5%. They concluded that urinary urgency (overactive bladder symptom) is not uncommon in diabetic cystopathy. Both central and peripheral mechanisms are involved, e.g., MCI due to diabetic cerebral vasculopathy for the DO, and, to a lesser extent, peripheral nerve irritation for the DO and increased bladder sensation [5] (LOE 3).

c) Disease specific diagnosis and treatment

Since diabetic polyneuropathy occurs in most patients after prolonged insulin-treatment and in about a quarter of patients treated with oral hypoglycemic drugs, it would be interesting to know the patients who are at risk of developing diabetic cystopathy without performing extensive functional tests of the LUT.

Ishigooka et al [6] (LOE 3) described the results of the ice-water test in diabetic patients with and without cystopathy. 12.5% patients without cystopathy and 25% of patients with cystopathy did not feel the ice water sensation. Ueda et al [7], (LOE 2) performed studies evaluating sympathetic skin response in correlation with cystometry.

They found that patients without sympathetic skin responses had increased residual urine and decreased detrusor contraction pressure, while patients with a lower amplitude of sympathetic skin response and more prolonged latency than controls had a significant decrease in detrusor contraction pressure. The changes within the bladder functions were observed as early as within one year from the diagnosis of diabetes.
Beylot et al [8], (LOE 2) found that the presence of residual urine in diabetic patients, after exclusion of co morbidities, was strongly associated with peripheral neuropathy.

No specific treatment has been described in regards to the population of patients with diabetic cystopathy. Therefore general rules as for the other bladder conditions with impaired (absent) detrusor contractions should be followed.

d) Guidelines for further research

No good epidemiological studies of the true incidence of diabetes related functional disorders of micturition were performed. The same is true for the treatment of diabetic “neurologic bladder”. There are no studies referring to the theoretically effective prompted voiding, and intravesical electrostimulation

CONCLUSIONS

- Diabetic cystopathy occurs in up to 80% of insulin dependent diabetes mellitus (LOE3)
- Urinary incontinence is strongly associated with insulin dependent, but not with insulin independent diabetes (LOE 2)
- Patients with diabetic cystopathy generally have impaired detrusor contractions and increased post-void residual (LOE ?)
- Overactive bladder is not uncommon in diabetes, presumably reflecting both central and peripheral mechanisms (LOE 3)
- Recurrent urinary tract infections might be a long term problem (LOE ?)

RECOMMENDATIONS

- Post void residual and urine dipstick (optional culture) in all patients with insulin dependent diabetes mellitus should be performed yearly ( C)
- In case of increased post-void residual prompted voiding, intravesical electrostimulation might be useful ( C/D)
- Treatment of choice for acontractile bladder in this group remains intermittent catheterization ( B/C)

2. FAECAL INCONTINENCE

Caruana et al [1] (LOE 3) found that diabetes patients with faecal incontinence showed increased thresholds of phasic external sphincter contraction compared with controls (P<0.05) and had reduced resting and maximal voluntary anal sphincter pressures compared with controls (P< 0.05). Increased thresholds of conscious rectal sensation in some incontinent patients with diabetes may contribute to faecal incontinence by impairing the recognition of impending defecation. Nakayama et al [2] (LOE 3) found that age and diabetes have an independent negative influence on faecal incontinence after stroke. It could be due to an abnormal internal-anal-sphincter function in diabetes patients with faecal incontinence [3] (LOE 3).

Talley [4] (LOE 3) studied gastro-intestinal symptoms, frequent abdominal pain, bowel-related abdominal pain, reflux, dyspepsia, constipation, diarrhea, and fecal incontinence in diabetes patients. There was a clinically significant decrease in QoL scores in diabetics compared with population norms across all subscales. The impact on QoL in diabetes was predominantly observed in type 2 diabetics. For all the Short Form-36 subscales, GI symptom groups were significantly (all p < 0.0001) associated with poorer QoL in diabetes, independent of age, gender, smoking, alcohol use, and type of diabetes.

Russo found that acute hyperglycaemia inhibits external anal sphincter function and decreases rectal compliance, which could explain the ethiopathogenesis of faecal incontinence [5] (LOE 3)

CONCLUSIONS

- Faecal incontinence in diabetes patients may be due to impaired anorectal sensation and/or decreased anal closing pressure after hyperglycemic episodes (LOE 3)
- Gastro-intestinal symptoms impact negatively on health-related QoL in diabetes mellitus (LOE 3)

RECOMMENDATIONS

- Patients with diabetes and fecal incontinence should have anorectal manometry performed before introducing the therapy for fecal incontinence (C/D)
- More studies on neurologic bowel dysfunction and management in diabetes are needed before giving further recommendation (B).

XII. PERIPHERAL NEUROPATHY DUE TO IATROGENIC LESION (FOCAL NEUROPATHY)

1. EPIDEMIOLOGY AND PREVALENCE

LUT dysfunctions can occur from damage to the nerves innervating the pelvic organs, anywhere in the course of these nerves through the cauda equina, the spinal nerve roots, the sacral plexus, or to the various individual nerves that arise from the plexus
Most injuries to these nerves are iatrogenic. Extensive pelvic surgery as abdomino-perineal resection for rectal cancer, radical hysterectomy, and aortoiliac surgery are all likely to damage the pelvic parasympathetic nerves to the bladder and genitalia. Of course this listing is not complete and practically any surgery performed within the pelvis could damage some nerves e.g. adenomectomy, radical prostatectomy, prolapse surgery. Complications of these procedures are described elsewhere in this in the relevant chapters.

Additionally pelvic irradiation, apart from causing damage to the irradiated tissue could cause damage to the adjacent nerve fibers, resulting in altered functions.

A variety of types of voiding, erectile and fecal dysfunctions can result.

**a) Hysterectomy (simple and radical)**

It is difficult to attribute certain dysfunctions to neuronal damage alone, taking into account the altered, after hysterectomy, static and dynamic functions of the pelvic structures.

Parys et al [1] (LOE 3) studied 126 women after simple hysterectomy. The results show that 47.0% had detrusor overactivity, 36.7% had urethral obstruction, and 24.8% stress incontinence. Sekido et al [2] (LOE 3) described 9 women treated with radical hysterectomy more than 10 years before the study. Obstructive voiding symptoms and/or urinary incontinence were observed in 7 patients. Cystometry revealed impaired bladder sensation, detrusor acontractility, straining on voiding, and impaired relaxation of the sphincter in all assessable patients. In addition, decreased bladder compliance was observed in 5 patients. Axelsen [3] (LOE 2) studied 100 women after radical hysterectomy and found that these women who reported incontinence had lower urethral pressure. In a prospective study of over 1000 women Jackson et al found hysterectomy to be an independent risk factor of incontinence [4] (LOE 2). There is however significant lack of long term observations of patients after radical hysterectomy in terms of lower urinary tract neurogenic dysfunctions.

**b) Abdominoperineal resection**

Retrospective analysis of 52 patients after abdominoperineal resection was performed by Eickenberg et al [5] (LOE 3). Neurologic bladder dysfunction of various degrees was found in 50 per cent of all patients but represented a long-term problem in only 10 per cent.

Baumgarner et al [6], (LOE 3) studied 86 consecutive cases of abdominoperineal resection and described 11 cases of various functional problems of micturition. All these studies however lack specific tests of the LUT functions and are not prospective.

However curative total mesorectal excision can be done with high rates of preservation of such function: Pocard et al. [7] (LOE 3) investigated 20 patients, 13 men and 7 women following curative total mesorectal excision with autonomic nerve preservation for rectal cancer. There was no difference in preoperative and postoperative LUT function, International Prostatic Symptom Score or urodynamic results, nor in the results of the quality of urinary function questionnaire. Also sexual activity and potency were unchanged in these men. Therefore the authors conclude that autonomic nerve preservation is possible and does not impair urinary and sexual function. Also Kim et al [8] (LOE 3) showed relative safety in preserving sexual and voiding dysfunction with total mesorectal excision with pelvic autonomic nerve preservation. Evaluation was based on uroflowmetry, voided volumes and residual volume, symptoms were evaluated with the IPPS: There were significant differences in max. urinary flow rate and voided volume before and after surgery, however no differences in residual volume before and after surgery were apparent. The IPPS however increased after surgery from 6.2 +/- 5.8 to 9.8 +/- 5.9 (= < 0.05).

Similar results are reported by Turaldo et al. [9] (LOE 3) evaluating incidence and pathogenesis of LUT dysfunction after surgical treatment of rectal cancer in a series of 219 patients with normal urinary function preoperatively: in the immediate follow-up only 17 patients with dysfunction were observed, 14 stage II, 2 at stage III and 1 at stage IV according to Astler-Koller classification; six months later only 8 patients had claimed urinary dysfunction and 1 required catheterisation. However no urodynamic studies were performed. There was no correlation of those with LUT dysfunction with staging, radiotherapy, size of tumour, surgical technique, however worst functional results were observed in patients who underwent abdomino-perineal resection. Lim et al have found that not only surgery but also preoperative irradiation could cause lower urinary tract and anorectal dysfunctions. The maximum resting anal pressures were unchanged after chemoradiation, but the maximum squeeze anal pressures were reduced after chemoradiation. They concluded therefore that preoperative chemoradiation for rectal cancer carries a significant risk of pudendal neuropathy, which might contribute to the incidence of fecal incontinence after restorative proctectomy for rectal cancer [10] (LOE 3).

**2. PATHOLOGY AND DISEASE SPECIFIC LUT PROBLEMS**

Focal injury to peripheral innervation of the bladder and/or sphincter results in decentralization or denervation of the above mentioned organs. Therefore detrusor hypocontractility (acontractility) and/or sphincteric deficiency will be the result of such a damage. This in turn will result in impaired bladder...
emptying and/or stress incontinence. No prospective studies referring specifically to the problem of functional disturbances of the LUT in focal iatrogenic neuronal injury in patients after hysterectomy or colorectal surgery have been performed.

3. INFLUENCE ON FECAL INCONTINENCE

Iatrogenic faecal incontinence can be caused by sphincter damage caused by childbirth, anorectal surgery, trauma, fistulae and abscesses. Vaginal delivery can cause not only sphincteric, but also neuronal damage to the innervation of the anal sphincter [11] (LOE 3).

There is a significant paucity of the epidemiological data regarding fecal incontinence after pelvic surgery.

Studing of anorectal reflexes and performing anorectal manometry could predict function restoration.[12,13] (LOE 3)

4. DISEASE SPECIFIC DIAGNOSIS AND TREATMENT

The only test in this specific patient population was described by Nordling et al [14] (LOE 3). In patients after radical hysterectomy, those who had a completely denervated bladder had a greater rise in maximum urethral pressure during noradrenaline infusion (exceeding 20 cm H2O) than normal subjects (1 to 15 cm H2O). Therefore authors concluded that urethral supersensitivity to noradrenaline may be a promising test in diagnosing damage of the sympathetic nervous innervation of the LUT.

Since the major cause of focal neuropathy is surgical intervention, the best method is to avoid peripheral neuronal injury during surgery. The detailed knowledge of pelvis neuroanatomy and meticulous preparations of the structures adjacent to the possibly affected nerves was shown to be the best technique [15-19] (LOE 3). An interesting method of incontinence surgery is the feasibility of the use of the artificial urinary sphincter [11] (LOE 3). Preservation of parasympathetic nerves seems also to play a role in rectal cancer surgery. Kneist and Junginger studied 62 patients undergoing mesorectal excision. Pelvic autonomic nerve preservation (PANP) was assessed macroscopically and with the aid of intraoperative electrical stimulation of pelvic autonomic nerves.

In 46 patients preservation of parasympathetic nerves was confirmed and these patients remained unchanged in early and long-term urinary function opposite to the remaining patients without confirmed preservation of the nerves [23] (LOE 3).

Zanolla et al [24] (LOE 2) suggested that early implementation of rehabilitative treatment (prompted voiding) allows satisfactory functional recovery of the bladder activity in 91% of the symptomatic patients after radical hysterectomy. Another interesting issue is the feasibility of the use of the artificial urinary sphincter in patients after colorectal surgery, hysterectomy and or radiotherapy for the treatment of stress incontinence. Only one study on this subject was identified [25] (LOE 3), describing a series of patients after radical prostatectomy and amongst them a patient after abdominoperineal resection with adjuvant radiation [16].

Authors concluded that this method of incontinence therapy should be the method of choice, however there is a significantly greater risk of revision (38% versus 22% in the literature for low risk groups). Fecal incontinence after colorectal surgery, if not resulting from sphincter damage could be successfully treated by sacral neuromodulation [26] (LOE 3).

5. GUIDELINES FOR FURTHER RESEARCH

No good epidemiological, prospective studies of the true incidence of peripheral injury related functional disorders of micturition were performed. Neither the descriptive studies of the disorders were performed. No specific, injury related therapy was described. There is a strong need for registry database of urinary and fecal incontinence after different types of pelvic surgery in order to establish the true prevalence and prepare guidelines on treatment/prophylaxis.

CONCLUSIONS

- Injury to the bladder/sphincter innervation occurs in 30-50% of patients after extensive pelvic surgery (LOE 3)
- Pelvic irradiation could cause nerve damage attributing to the altered bladder/bowel functions (LOE 2).
- Fecal incontinence due to iatrogenic innervation damage could occur after complicated labor, anorectal surgery and pelvic irradiation (LOE 3)
RECOMMENDATIONS

- Focal injury results in impaired detrusor contractions and external urethral sphincter deficiency or detrusor/sphincter dyssynergy (LOE 3-4)
- The key issue in avoiding these complications are nerve sparing techniques and intraoperative nerve identification (LOE 3)

**c) Disease specific diagnosis**

Sakakibara et al. (LOE 4) [1] published the findings of 6 women and 2 men, mean age 23 years, suffering from SLE for 2-25 years under immunosuppressant therapy. All 8 patients had urodynamic abnormalities, 5/8 showed decreased urinary flow, 3/8 increased post-void residual urine, 2/8 increased max. urethral closure pressure, 5/8 showed detrusor overactivity, and 5/8 impaired detrusor contractility; furthermore detrusor-sphincter dyssynergia was found in 4/8, and neurologic motor unit potentials of the external sphincter in two of four patient studied. They found detrusor overactivity more common in patients with brisk deep tendon reflex (80 %) than in those without (33 %). Repeated studies during a follow-up period between 2 months and 8 years showed deterioration in 3/8 including loss of bladder sensation, development of a low compliance bladder and decreased bladder capacity (LOE 4).

Yu et al. studied 152 women with SLE and found a significant relationship between central nervous system involvement and the adapted AUA index score. The most common urodynamic finding was a small cystometric bladder capacity (<150 ml; n = 7 patients), followed by a a weak urinary flow rate (<12 ml/second; n = 6 patients). In 3 of 7 patients with small cystometric bladder capacities, imaging studies documented a contracted bladder with marked hydroureteronephrosis [2] (LOE 3)

CONCLUSIONS

- Half of the patients with systemic lupus erythematosi show nervous system involvement. In 30 % of them subacute and chronic encephalomyelopathy may cause LUT dysfunction with variable patterns including reduced bladder capacity, detrusor overactivity, impaired detrusor contractility, pathologic voiding pattern and increased post-void residual urine (LOE 4).

XI. SYSTEMIC LUPUS ERTHREATOSIS

As the literature contains only a case report of faecal incontinence, this will not be described here

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Nervous system involvement occurs in about half of patients with systemic lupus erythematosi (SLE). Seizures and psychiatric disorders are most common manifestations; spinal cord lesions are uncommon. Symptoms of LUT dysfunction can occur, however data on prevalence are not available.

b) Pathophysiology

Neurological manifestations of systemic lupus erythematosis are subacute encephalomyelopathy, subacute myelopathy (rarely) and chronic encephalomyelopathy.

XIII. SYSTEMIC LUPUS ERTHREATOSIS

- Patients after extensive pelvic surgery demonstrating functional disorders of micturition should be properly evaluated due to a variety of possible disorders (C)
- Early rehabilitation of the LUT and of the anal sphincter might improve voiding in a majority of patients (C)
- In case of increased post-void residual after prompt voiding, intravesical electrostimulation might be useful (C/D)
- Treatment of choice for acontractile bladder in this group remains intermittent catheterization (B/C)
- Surgeons should aim for autonomic nerve preservation when performing surgery for rectal cancer. Post-operative post-void residual urine measurements as well as a targeted history on micturition before and after are mandatory in order to avoid secondary myogenic damage of the detrusor by chronic urinary retention. (C)

RECOMMENDATIONS

- The dysfunction pattern may change over time, therefore urological follow-up is recommended. (C)
- Urodynamics are necessary to define the underlying pathophysiology of the urinary symptoms (C).
- Patients with SLE and voiding dysfunctions should be managed expectantly, accordingly to the urodynamic results (C).
XIV. HERPES ZOSTER

As the literature contains only a case report on faecal incontinence this will not be described here.

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Incidence of LUT dysfunction is as high as 28% if only lumbosacral dermatome-involved patients are considered. The overall incidence is 4% [1]. Despite such high prevalence only case reports are available.

b) Pathophysiology

Herpes zoster in the lumbosacral dermatomes may manifest according to Chen et al., based on 17 patients, as cystitis-associated (12/17), neuritis-associated (4/12) and myelitis-associated (1/17).

c) Disease specific diagnosis

Two case reports describe urodynamics findings in herpes-zoster patients. Usually patients develop complete urinary retention, with or without overflow incontinence due to detrusor acontractility and lack of bladder sensation. Repeated urodynamic studies at week 10 after the onset of the disease demonstrated a return of the detrusor contraction, which returned to normal after 14 weeks [2,3] (LOE 4).

Herpes zoster associated voiding dysfunction is a transient phenomenon and is not uncommon in patients with lumbosacral dermatome involvement. As long as voiding is unbalanced the treatment with intermittent catheterisation or indwelling catheter placement is recommended in order to avoid secondary damage to the LUT due to infection or chronic urinary retention. The disease usually is of a benign clinical course and almost every patient will either regain normal voiding or, at least balanced bladder function.

CONCLUSIONS

- P28% of patients with Herpes zoster in the lumbosacral dermatomes show LUT dysfunction with impaired voiding as the most common symptom (LOE 4)
- The most common symptom is overflow incontinence due to detrusor acontractility and lack of bladder sensation (LOE 4)
- Voiding dysfunction has a transient course and almost every patient will either regain normal voiding within 3-4 months or at least balanced bladder function (LOE 3).

RECOMMENDATIONS

- Till functional recovery takes place treatment with intermittent catheterisation or indwelling catheter are recommended (C).

XV. HIV

1. EPIDEMIOLOGY AND PREVALENCE

HIV virus belongs to the family of retroviruses. This family of viruses is known for latency, persistent viremia, infection of the nervous system, and weak host immune responses. HIV has high affinity for CD4 T lymphocytes and monocytes. HIV binds to CD4 cells and becomes internalized. The virus replicates itself by generating a DNA copy by reverse transcriptase. Viral DNA becomes incorporated into the host DNA, enabling further replication. HIV enters the nervous system early, at the time of initial infection, and may immediately cause symptoms, or may cause symptoms any time during the person’s lifetime.

All parts of the nervous system may be involved. Neurological disorders could be HIV-related, due to secondary infections, malignancies, metabolic or nutritional problems and to therapy.

It is estimated that without anti-retroviral treatment, up to 80% of patients are symptomatic in terms of nervous system and for 30%, neurological symptoms are the initial clinical problem.

Neurological syndromes may be the sole clinical problem or cause of death. The following brain symptoms were described: meningitis, dementia, stroke, seizures, degenerative disorders. For spinal cord both transverse myelitis and progressive myelopathy were observed.

Taking all these information together it is evident that nervous system involvement in HIV infection should be reflected to a various degree in the LUT [1].

Shin et al (LOE3) described a higher prevalence of incontinence in HIV-positive patients in nursing homes as compared to HIV-negative [2]. Whether this represents a true trend or is an observation related to the terminal stage of the disease and associated comorbidities remains to be elucidated.

Gyrtrup et al (LOE 3) found voiding problems in 12% of HIV-infected patients, mostly in advanced stage of the disease [3].
2. PATHOLOGY AND DISEASE SPECIFIC LUT PROBLEMS

As already described virtually all parts of the body could by involved in AIDS patients, either as the primary location of HIV infection or secondary to HIV-related complications.

Among these different manifestations particular attention should be paid to the primary locations as they develop early in the stage of the disease.

HTLV-I associated myelopathy (HAM) affects up to 3% of HIV positive patients and is manifested by slowly progressive spastic paraparesis, including deterioration of bladder problems [4](LOE 2). Another interesting primary demonstration of HIV infection is lumbosacral polyradiculopathy, described by Matsumoto et al (LOE 3)[5]. In this case report voiding difficulties and lower limb paresis were the primary manifestation of HIV infection.

Also Mahieux et al (LOE 3) described a case of acute myeloradiculitis due to cytomegalovirus as the initial manifestation of terminal stage [6].

Begara et al (LOE 3) performed urodynamic studies in 10 patients with AIDS and voiding disorders and found that the most common symptom was urge incontinence and the most common urodynamic finding was detrusor-external sphincter dyssynergia [7]. In 3 patients they found demonstrable functional disorders of the LUT (2 patients had detrusor overactivity: one of them had a history of encephalopathy from HIV and the other patient had polynéuritis; the third patient had myelitis and a urodynamically diagnosed sympathetic decentralization. Detrusor areflexia was described in 2 HIV-positive patients by Menendez et al [8](LOE 3). One of them had an ascending myelitis of probable herpetic origin, the other had a cerebral abscess caused by Toxoplasma gondii.

3. DISEASE SPECIFIC DIAGNOSIS AND TREATMENT

Since during the course of the disease all parts of the nervous system can be involved, either as the primary location or secondary to AIDS-related complications, no disease specific diagnosis or treatment can be proposed. It is important to observe that sometimes functional disorders of the LUT can be the first manifestation of the HIV infection.

When managing the patient with HIV infection one must bear in mind that both storage and voiding problems can occur and that both should be treated according to the results of urodynamic studies.

4. GUIDELINES FOR FURTHER RESEARCH

All rapports about HIV and voiding problems are rather anecdotal and no good prospective studies exist. The need for such studies is particularly important, when realizing that it takes up to 20-30 years from HIV infection to AIDS full manifestation and that new antiviral treatment modalities could prolong the life of a patient with HIV significantly.

Particular attention should be paid to primary nervous system involvement by HIV and to related voiding dysfunction as well as to the voiding dysfunctions that could be the side effects of HIV drug therapy.

5. FAECAL INCONTINENCE

As diarrhoea is common in HIV infected patients, the faecal incontinence can also occur, mostly due to anal sphincter weakness. Again the true incidence of HIV neuropathy related faecal incontinence is not known and further studies are needed [9], (LOE 4)

CONCLUSIONS

- HIV can influence the nervous system and the LUT functions in two ways: as primary infection site or secondary to AIDS related complications (LOE2/3)
- Nervous system manifestation of HIV infection can be the only sign and it is therefore important to take the possibility of HIV infection into consideration when facing unusual signs and symptoms from the LUT without any other obvious cause (LOE 3)
- HIV/AIDS is a progressive disease and dynamic changes to the LUT functions can occur during the evolution of the disease (LOE 2)
- Faecal incontinence in HIV/AIDS patients is usually associated with diarrhoea, however the true incidence is not known (LOE 4)

RECOMMENDATIONS

- Patients with HIV and nervous system pathological signs and symptoms should be evaluated towards functional LUT problems (B)
- Due to the variety of LUT functional damage in HIV patients urodynamic study is essential for tailoring the optimal therapy (C)
- No HIV specific therapy of LUT problems and faecal incontinence exist. Due to variety of functional damage therapy should be individually tailored, accordingly to the results of functional/imaging studies (C)
REFERENCES

A. INTRODUCTION


3. Fowler C J. The perspective of a neurologist on treatment-related research in fecal and urinary incontinence. Gastroenterology 2004; 126 S1: 172-174


B. PATHOPHYSIOLOGY

C. NEUROLOGIC URINARY INCONTINENCE


3. Fowler C J. The perspective of a neurologist on treatment-related research in fecal and urinary incontinence. Gastroenterology 2004; 126 S1: 172-174


C. I. EPIDEMIOLOGY NEUROLOGIC URINARY INCONTINENCE


27. Chandiramani VA, Palace J, Fowler CJ. How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol. 1997; 80: 100-104

69. Shapiro S. Medical realities of cauda equina syndrome


84. Chapelon C, Ziza JM, Piette JC, Levy Y, Raguin G, Wechsler M. Bowel and bladder dysfunction after spinal bupivacaine. Anesthesiology 2001; 95:1306. one page only


C. II. SPECIFIC DIAGNOSTICS NEUROLOGIC URINARY INCONTINENCE


37. Ko HY, Lee JZ, Park HJ, Kim H, Park JH. Comparison between conventional cystometry and stimulated filling


65. Mahajan ST, Fitzgerald MP, Kenton K, Shott S, Brubaker L Concentric needle electrodes are superior to perineal surface-patch electrodes for electromyographic documentation of urethral sphincter relaxation during voiding. BJU Int. 2006; 97:117-120.


82. Karaman MI, Kaya C, Caskurlu T, Guney S, Ergenekon E. Electrophysiological study of the striated urethral sphincter by using the UCM potentials (MEP) and evoked pressure curves (EPC) from cuff electrodes on extradural sacral roots in spinal cord injured patients. J Urol. 2005 ; 174:1482-1487


C. III. CONSERVATIVE TREATMENT
NEUROLOGIC URINARY INCONTINENCE

31. Chapple CR, Recherberger T, Al-Shukri S, Meffan P, Everaert K, Huang M et al. Randomized, double-blind placebo- and


67. Dalmose AL, Rijkhoff NJ, Kirkeby HJ, Nohr M, Sinkjaer T and Djurhuus JC. Conditional stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in


C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE

2. SURGERY FOR NEUROLOGIC URINARY INCONTINENCE ASSOCIATED WITH POOR BLADDER EMPTYING DUE TO DETRUSOR UNDERACTIVITY


C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE

3. DENERVATION PROCEDURES FOR TREATING REFLEX URINARY INCONTINENCE DUE TO NEUROLOGIC DETRUSOR OVER ACTIVITY


**C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE**

4. Surgery for Stress UI due to Neurologic Sphincteric Incompetence


C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE

5. SURGICAL ALTERNATIVES EXCLUDING DENERVATION PROCEDURES TO TREAT REFLEX INCONTINENCE DUE TO NEUROGENIC DETRUSOR OVERACTIVITY


937


C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE

6. CUTANEous CONTINENT URINARY DIVERSION


939


C. IV. SURGICAL TREATMENT NEUROLOGIC URINARY INCONTINENCE

7. NON-CONTINENT CUTANEOUS URINARY DIVERSION IN NEUROUROLOGY


D. NEUROLOGIC FAECAL INCONTINENCE

I. EPIDEMIOLOGY FAECAL INCONTINENCE


D. II. SPECIFIC DIAGNOSTICS FAECAL INCONTINENCE


D. III. CONSERVATIVE TREATMENT NEUROLOGIC FAECAL INCONTINENCE


D. IV. SURGICAL TREATMENT NEUROLOGIC FAECAL INCONTINENCE

I. SACRAL NERVE STIMULATION (SNS)


II. ANTEGRADE CONTINENCE ENEMA (MACE)


D. IV. SURGICAL TREATMENT NEUROLOGIC FAECAL INCONTINENCE

3. DYNAMIC GRACILISPLASTY


D. IV. SURGICAL TREATMENT NEUROLOGIC FAECAL INCONTINENCE
5. COLOSTOMY


E. SPECIFIC NEUROLOGIC DISEASES

I. DEMENTIA


E. I. DEMENTIA

b) Vascular Dementia


E. I. DEMENTIA

c) Lewy Bodies Dementia


E. I. DEMENTIA –

d) Frontotemporal Dementia


E 2. DEMENTIA, CONSTIPATION AND FECAL INCONTINENCE


E. II. MULTIPLE SYSTEM ATROPHY

1. URINARY INCONTINENCE MSA


E. II. MULTIPLE SYSTEM ATROPHY

2. FAECAL INCONTINENCE MSA


E. III. PARKINSON’S DISEASE

1. URINARY INCONTINENCE PD


E. III. PARKINSON’S DISEASE

2. FAECAL INCONTINENCE PD


2. Sakakibara R, Shinotoh H, Uchiyama T, Sakuma M,


E. IV. CEREBRAL LESIONS-CEREBROVASCULAR ACCIDENTS


E. V. MULTIPLE SCLEROSIS


27. Hennessey A, Robertson NP, Swingler R, Compston DA.
26. Goldstein I, Siroky MB, Sax DS, Krane RJ. Neurourologic
25. Gallien P, Robineau S, Nicolas B, Le Bot MP, Brissot R,
24. Eardley I, Nagendran K, Lecky B, Chapple CR, Kirby RS,
21. Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
18. Andersen JT, Bradley WE. Abnormalities of detrusor and
17. de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe
14. Sliwa JA, Bell HK, Mason KD, Gore RM, Nanninga J, Cohen
12. Strohbehn K, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
11. Stuntebeck M, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
10. Stuntebeck M, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
9. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
8. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
7. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
6. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
5. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
4. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
3. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
2. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE,
1. Talagala CM, Bemelmans BL, Hommes OR, Van Kerrebroeck PE.

---

**E. VI. SPINAL CORD LESION**

**I. URINARY INCONTINENCE SPINAL CORD LESION**


13. Aldrete JA, Ferrari H. Myelopathy with syringomyelia following

12. Post NH, Wisoff JH, Thorne CH, Weiner HL. Transient

11. Tanaka ST, Stone AR, Kurzrock EA. Transverse myelitis in

10. Rodriguez FJ, Crum BA, Krauss WE, Scheithauer BW, Giannini


E. V. SPINAL CORD LESION
2. FAecal INCONTINENCE SPINAL CORD LESION


E. VII. SPINAL CANAL STENOSIS


E. VIII. GUILLAIN BARRE


E. IX. LUMBAR DISC PROLAPSE


2. Tay ECK, Chacha PB. Midline prolapse of a lumbar


E. X. MENINGOMYELOCOELE

I. URINARY INCONTINENCE MENINGOMYELOCOELE


E. X. MENINGOMYELOCOELE

II. FAECAL INCONTINENCE MENINGOMYELOCOELE


E. XI. DIABETES MELLITUS

1. Urinary incontinence diabetes mellitus


E. XII. PERIPHERAL NEUROPATHY DUE TO IATROGENIC LESIONS (FOCAL NEUROPATHY)


E. XIII. SYSTEMIC LUPUS ERYTHEMATOSUS


E. XIV. HERPES ZOSTER


E. XV. HIV


Committee 11

Incontinence in the Frail Elderly

Chair-person

C.E. DuBEAU (USA)

Members

G.A. KUCHEL (USA),
T. JOHNSON (USA),
M.H. PALMER (USA),
A. WAGG (U.K)
## CONTENTS

<table>
<thead>
<tr>
<th>I. INTRODUCTION</th>
<th>VIII. URINARY RETENTION IN THE FRAIL ELDERLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. SEARCH STRATEGY</td>
<td>IX. NOCTURIA</td>
</tr>
<tr>
<td>III. DEFINING THE FRAIL ELDER POPULATION</td>
<td>X. MODELS OF CARE FOR THE FRAIL ELDERLY WITH UI</td>
</tr>
<tr>
<td>IV. AETIOLOGY</td>
<td>XI. RECOMMENDATIONS FOR MANAGEMENT</td>
</tr>
<tr>
<td>V. ASSESSMENT OF THE FRAIL ELDERLY WITH UI</td>
<td>XII. RECOMMENDATIONS FOR RESEARCH</td>
</tr>
<tr>
<td>VI. FACTORS IN MANAGEMENT</td>
<td>XII. ALGORITHM</td>
</tr>
<tr>
<td>VII. TREATMENT</td>
<td>REFERENCES</td>
</tr>
</tbody>
</table>

## ABBREVIATIONS USED

| ADE = adverse drug effect | ICS = International Continence Society |
| ADL = activities of daily living | IR = immediate release |
| ANP = atrial natriuretic peptide | ISC = intermittent straight catheterization |
| AVP = arginine vasopressin | LTC = long term care |
| BOO = bladder outlet obstruction | LUT = lower urinary tract |
| BPH = benign prostate hyperplasia | LUTS = lower urinary tract symptoms |
| CEI = cholinesterase inhibitor | NH = nursing home |
| CI = confidence interval | OAB = overactive bladder |
| CNS = central nervous system | OR = odds ratio |
| DHIC = detrusor hyperactivity with impaired contractility | PVR = postvoid residual volume |
| DO = detrusor overactivity | RCT = randomized controlled trial |
| ER = extended release | SUI = stress urinary incontinence |
| FI = faecal incontinence | UI = urinary incontinence |
| IADL = instrumental activities of daily living | UK = United Kingdom |
| ICI = International Consultation on Incontinence | US = United States |
| UTI = urinary tract infection | |
Older persons have the highest known prevalence of urinary incontinence (UI) of any group, other than persons with specific neurological disorders (e.g., spinal cord injury). The absolute numbers of older persons with UI is increasing exponentially worldwide with the global phenomenon of population aging [1]. In developed countries, the population of centenarians has doubled every decade since 1960, mostly as a result of increases in survival after age 80 [1]. As the baby boomers age, the number of persons aged 85 or older will rise steadily from just under 2 percent of the population now to nearly 5 percent by 2050. Thus, the absolute numbers of older persons will increase dramatically [2]. Even if the observed improvements in physical functioning among older persons continue, and research is able to demonstrate improved health and lower costs, the impact on future health care and long-term care costs will be profound [1].

Throughout the world, no matter how one defines “older” or “elderly,” this population is characterized by its variety, ranging from active, community-dwelling, working, healthy nonagenarians to bed-bound, chronically ill, functionally- and cognitively-impaired persons in their late 60’s. The former healthier group is closer in phenotype and physiology to middle aged persons than to frailer older persons. For these reasons, beginning with the Third Consultation, information about persons older than 65 years of age is organized by health status. Data regarding healthier older persons is integrated in the chapters covering anatomy, physiology, evaluation, and treatment, and this chapter focuses on frailer older persons, emphasizing not only the different aetiologies and treatment of UI, but the additional issues of disease burden, disability, altered responses to drug therapy, the role of caregivers, and goals and organization of care. This chapter is aimed at all types of providers who work with populations of frail elderly, and is also intended to be relevant to specialists who find standard approaches ineffective in this population. Faecal incontinence in frail elderly is now covered in the report of Committee ?.

UI in the frail elderly is uniquely different from UI in healthy older persons. The pathophysiology of UI in the frail requires a broader conception of “disease,” which centers on patient-level factors rather than just the lower urinary tract (LUT) and its neurological control. UI in the frail elderly constitutes a syndromic model of multiple interacting risk factors, including age-related physiologic changes, comorbidity, and potentially common pathways between them. Unlike UI in healthy older persons, the impact of UI in the frail elderly includes functional impairment, and extends beyond affected individuals to their caregivers, leading to outcomes of caregiver stress and institutionalization.

Therefore, the assessment of UI in frail persons requires a much broader medical and functional scope. Failure to address the multifactoral nature of UI limits not only clinical care and research regarding aetiology and treatment, but also important opportunities to improve function and quality of life [3]. Treatment must always be multicomponent, and must address the multiple associated factors and shared underlying impairments with other geriatric syndromes (for example, by combining lower extremity exercise with prompted voiding) [4]. Drug therapy must be placed in context of altered pharmacology, polypharmacy, and susceptibility to adverse effects. Effective management requires system-level approaches, with different models of care (e.g., for institutionalized persons).

A final challenge in providing a review of UI and FI in frail older people is the relative dearth of Level 1 evidence for interventions. This is not to say that existing studies are not robust, as the frail present multiple challenges for research (not the least of which is substantial trial drop-out due to intervening illness and death). What it does indicate is the continuing paucity of new clinical trials, despite the clear epidemiological imperative that the oldest-old are the fastest growing group of affected individuals. Reasons for this are myriad, including a lack of funding for multi-component interventions and “riskier” trials involving drug therapy. At the same time, one cannot assume that treatment outcomes from conventional therapy will be worse in the frail elderly than the healthy elderly without special data to so prove.
Intervention studies and outcomes need to be more broadly based, incorporating caregivers, a range of care settings, alternative models of care, and goals of care unique to this population [5].

II. SEARCH STRATEGY

Given the broad range of this report, we used multiple searches using the following MESH terms (in caps) and phrases, alone and in combination, using the PubMed and Ovid search engines: AGED, AGED OVER 80, ACTIVITIES OF DAILY LIVING, DEPRESSION, elderly, FALLS, frail, FRAIL ELDERLY, FRAILTY, function, geriatrics, LONG TERM CARE, MEDICATIONS, NURSING HOME, older, QUALITY OF LIFE, RANDOMIZED CONTROLLED TRIAL, and BLADDER, GYNAECOLOGICAL SURGICAL PROCEDURES, PELVIC FLOOR, PROSTATE, STRESS INCONTINENCE, SURGERY, URETHRA, URINARY INCONTINENCE, URINATION DISORDERS, UROGYNECOLOGY, UROLOGY, VAGINA, VOIDING DYSFUNCTION; Ovid Expert Search Filter; Publication years 2004-08. We included, where possible, information from non-English language articles where an English language abstract with sufficient information was available. References in retrieved articles were reviewed for additional relevant articles. We also searched the Cochrane Database and National Guideline Clearinghouse for relevant systematic reviews, meta-analyses, and evidence-based recommendations.

III. DEFINING THE FRAIL ELDER POPULATION

1. FRAILTY

Who, then, are the frail elderly? Consistent with increasing consensus in the geriatric literature, we define “frail older persons” as those over the age of 65 with a clinical presentation or phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including feelings of fatigue and exhaustion) [6-8]. Frailty is not, however, identical to disability and comorbidity. Among persons meeting strict phenotypic criteria for frailty, only 22% also had both comorbidity and disability, 46% had comorbidity without disability, 6% disability without comorbidity, and 27% had neither comorbidity nor disability [7]. Frail persons usually have multiple chronic medical conditions, take multiple medications, require care by other persons and assistance to perform some or all of the activities of daily living (ADLs) (e.g., bathing, dressing, toileting, and ambulation), are often homebound or in care institutions, and have a high risk of intercurrent disease, increased disability, hospitalisation, and death [1-6]. For example, in Japan, 10% of all persons over 65 require help or supervision with at least one ADL, [9] and the total prevalence of frail elders has been estimated at 6.1% [10].

Several studies suggest that the relationship between UI and frailty is not unidirectional. Incident UI in persons over age 65 has been associated with a two-fold increased risk of impairment in ADLs, instrumental activities of daily living (IADLs – e.g., transportation, finances, shopping, laundry, housekeeping), and poor performance on three physical measures, suggesting that incident UI may be an early marker of the onset of frailty [10]. In a population-based study of older Mexican Americans, incident but not prevalent UI was independently associated with functional decline in ADLs, IADLs, and physical performance [11]. Another population-based study found an association between UI and IADL decline, but not ADL decline, nursing home admission, or death, after adjustment for age and comorbidity [10A]. The authors suggest that the relationship between UI and adverse outcomes may be mediated by baseline illness severity and functional impairment [10A].

2. IMPACT OF UI ON MORBIDITY AND INSTITUTIONALIZATION

UI in frail persons can have much more severe consequences than in healthy older persons. Although one early study suggested that older persons with UI had a higher mortality risk, [12] subsequent studies that more fully adjusted for comorbidity and functional status have not found any association [10A, 10, 13, 14]. Several multivariate studies suggest that patients with new onset UI at the time of stroke have higher rates of death or disability at 2 years (OR 4.43; 95% CI 1.76 to 11.2) [15] and 6 months (OR 3.21 [95% CI 1.04 to 9.91]), [16] especially if UI persists (OR 7.47 [95% CI 2.29 to 24.42]) [16].

Given its association with frailty, it is not surprising that UI remains a risk factor for nursing home admission, despite global variation in services and temporal changes in elder care. Studies showing a significant association between UI and institutionalization have been done in: Finland (men [not women] with urgency UI); [17] Germany; [18] New Zealand (persons ≥ age 65); [19] US (men more than women), [20] after hip fracture, [21] among Hispanic elderly, [11] and patients attending a dementia clinic [22]); and Japan (men only) [23]. Two studies failed to find a significant association after controlling for comorbidity, using US [10A] and Canadian databases [24]. It is estimated that the fraction of US NH admissions attributable to UI in men is 0.10 (95% CI 0.08–0.13) and in women 0.06 (95% CI 0.05–0.09) [25]. The prevalence of UI at NH admission in the U.S. shows small area variation of almost 50% and differs by race, [26] suggesting that patient and caregiver factors and local resources affect the role UI plays in institutionalization. An important methodological issue for such studies is
the erroneously low prevalence of UI in administrative long-term care databases when UI is defined by physician diagnosis in the medical record [27,28]. Another issue, particularly in studies of institutionalization in persons with dementia, is the failure to include UI as a risk factor [29] or defining it only by a composite function score [30].

IV. AETIOLOGY

1. BACKGROUND

As noted above, the aetiology of UI in frail older adults is grounded in the concept of a classic geriatric syndrome, involving multiple interacting risk factors, including age-related changes, comorbidity, and potentially common pathways between them. This section addresses all of these components.

2. QUALITY OF THE DATA

The data on the aetiology of UI in the frail elderly population is limited, and the Consultation does not grade the level of observational studies, which constitute much of this literature. Moreover, longitudinal studies of large numbers of frail individuals are difficult to carry out. Despite the lack of such studies, many relatively large, careful descriptive studies and case series, as well as expert consensus processes, have made important contributions to our understanding of the aetiology of UI in this population.

3. UI AS A GERIATRIC SYNDROME

In older adults, especially those who are frail, UI is considered to be a geriatric syndrome, because many of its risk factors are not directly related to the genitourinary tract [31, 32]. Geriatric syndromes have been defined as “multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges [31]. Thus, large numbers of different baseline as well as precipitating risk factors may interact with each other in influencing the ability of an older individual to remain continent in the face of common daily challenges (Figure 1). This multifactorial complexity, combined with the fact that most individual risk factors typically account for only a small proportion of the overall risk, have greatly complicated the development of a pathophysiological framework for the study of common geriatric syndromes [31].

Nevertheless, because common risk factors (e.g. lower and upper extremity weakness, sensory and affective impairment) may be shared by different geriatric syndromes (such as UI, falls, and functional dependence), [33] they may represent particularly attractive sites for intervention development [31]. For example, as proposed by Kuo and Lipsitz, [34] the presence of brain white matter hyperdensities within critical periventricular and subcortical regions could represent key risk factors for the development of different geriatric syndromes such as falls, impairment in executive cognitive function, depressive symptoms, and UI. In fact, recent functional magnetic resonance imaging (fMRI) studies have begun to identify central nervous system areas that are particularly relevant to an individual’s ability to suppress urgency [35-37]. Therefore, failure of activation within orbitofrontal regions may contribute to individuals’ decreased ability to suppress urgency [37]. Connectivity pathways within the right insula and anterior cingulate gyrus may also play a role maintaining continence, [36, 37] supporting the concept that declines in connectivity [38] and coordination [39] between different brain regions represent early critical events in aging. These findings suggest the possibility that interventions to prevent the development of white matter hyperdensities, such as control of vascular risk factors, could also prevent UI.

4. AGE-RELATED CHANGES RELEVANT TO UI IN THE FRAIL ELDERLY

Age-related changes in the LUT can function as risk factors for the development, continuation, and worsening of UI in frail elderly persons (Table 1). At the same time, they rarely are alone sufficient to cause UI, and in some persons have no effect on lower urinary tract symptoms (LUTS) or UI. Furthermore, the literature on “normal” LUT ageing has many potentially confounding methodological limitations. Normal ageing changes are difficult to study, because longitudinal data including large numbers of individuals spanning many years are necessary to definitively separate “normal LUT ageing” from confounding factors and comorbidity. Cross sectional studies are subject to confounding by comorbidity and time-dependent cohort effects, such as change in labour and delivery practices. Thus, to date many studies actually describe “age-related” associations, as opposed to normal ageing. Other limitations include: derivation of much of the cellular and neurochemical data from animal studies; morphologic studies based on cadavers with unknown parity, comorbidity, and LUT symptoms; “age-effects” derived from studies of symptomatic persons; and use of surgical patients at tertiary centres as “normal” controls. Even the definition of “normal” can be difficult: is it continence, absence of LUTS, lack of comorbid disease, or normal physiologic testing? [40] The following sections focus on findings from more robust and, where possible, confirmatory studies.

a) Bladder

Understanding age-related changes in the bladder is complicated by a paucity of longitudinal data, variable definitions of “normal,” and use of potentially biased (and symptomatic) referral populations. It is difficult to isolate such factors as the role of decreased blood flow, poor voiding habits, comorbidity, central and peripheral
Table 1. Age-related changes that could potentially contribute to UI in frail elderly persons

<table>
<thead>
<tr>
<th>Age-Related Change</th>
<th>Potential Effects on Continence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder ultrastructure on electron microscopy</td>
<td></td>
</tr>
<tr>
<td>- Dysjunction pattern</td>
<td>Bladder overactivity and urgency UI</td>
</tr>
<tr>
<td>- Muscle and axon degeneration</td>
<td>Impaired bladder contractility, increased residual urine, and decreased functional bladder capacity</td>
</tr>
<tr>
<td>Bladder function</td>
<td></td>
</tr>
<tr>
<td>- Decreased capacity</td>
<td>Increased likelihood of urinary symptoms and UI</td>
</tr>
<tr>
<td>- Increased detrusor overactivity</td>
<td></td>
</tr>
<tr>
<td>- Decreased detrusor contractility</td>
<td></td>
</tr>
<tr>
<td>- Increased residual urine</td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td></td>
</tr>
<tr>
<td>- Decreased closure pressure in women</td>
<td>Increased likelihood of stress and urgency UI</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
</tr>
<tr>
<td>- Increased incidence of benign prostatic obstruction</td>
<td>- Increased likelihood of urinary symptoms and UI</td>
</tr>
<tr>
<td>- Increased incidence of prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Decreased oestrogen (women)</td>
<td>- Increased incidence of atrophic vaginitis and related symptoms</td>
</tr>
<tr>
<td></td>
<td>- Increased incidence of recurrent urinary tract infections</td>
</tr>
<tr>
<td>Increased night-time urine production</td>
<td>Increased likelihood of nocturia and night-time UI</td>
</tr>
<tr>
<td>Altered central and peripheral neurotransmitter concentrations and actions</td>
<td>Increased likelihood of lower urinary tract dysfunction</td>
</tr>
<tr>
<td>Altered immune function</td>
<td>Increased likelihood of recurrent urinary tract infections</td>
</tr>
</tbody>
</table>

Figure 1: Mechanistic Model of Geriatric Syndromes. Traditional pathophysiological models are based on a linear relationship proceeding from risk factors to early disease and then advanced disease (A), with prevention and treatment (red) directed at the causative risk factor. These models, while effective for many conditions, do not address the multifactoral nature of geriatric syndromes. Cancer researchers have used an alternative “concentric” model (B), in which a set number of risk factors (e.g., oncogenic pathways) lead to the clinical phenotype, and can become targets for therapy. This model also is insufficient for geriatric syndromes. Targeting individual RFs is unlikely to be effective because each RF accounts for only a small portion of the overall risk of disease. Geriatric syndromes are best described by an interactive concentric model (C), in which multiple risk factors likely interact with one another and (either common or separate) modulating factors. Interventions may be best targeted at those points that alter “downstream” risk factors [adapted from reference 31].
nervous system innervation, and reflex patterns as determinants of bladder function in older persons [41]. The research focus has been urodynamic function, neurohumoral responsiveness of detrusor smooth muscle, and ultrastructure. While the key role of the urothelium and afferent systems on micturition are increasingly appreciated (See Committee 2, Cell Biology; Committee 3, Neural Control; and Committee 4, Pathophysiology), there are only limited human data on urothelial changes with age.

Urodynamic changes associated with age typically include smaller voided volume, increased residual volume, smaller bladder capacity, and increased involuntary detrusor contractions (detrusor overactivity [DO]). Correlations with age are often small, suggesting that other factors are at least as important [42]. Urodynamic findings may not relate to symptoms: in a urodynamic study of community-based healthy persons over age 55, [40] DO was found in 42% of continent women, one-third of whom were totally free of LUTS. Within this older healthy cohort the prevalence of DO did not increase with age. Notably, completely normal urodynamic studies were found in only 18%. Nevertheless, in a cross-sectional study involving ambulatory, cognitively intact, community-dwelling older female volunteers, maximum urethral closure pressure, detrusor contraction strength, and urine flow rate all declined significantly with age, regardless of whether DO was present or not [43].

Detrusor contractility also declines in healthy older men who have no evidence of bladder outlet obstruction (BOO) or significant confounding disease [40]. A variety of different risk factors associated both with ageing and common comorbid conditions may contribute to age-related declines in detrusor contractility, which may ultimately lead to detrusor underactivity [44]. Decreased contractility during voiding in older persons is associated with lower urine flow rates and a small increase in postvoiding residual volume (PVR) (generally < 50 ml) [45]. Even in men with BOO, an elevated PVR may reflect decreased bladder contractility rather than obstructed voiding [46]. While some studies suggest a myogenic origin of impaired contractility, others suggest that impaired blood supply, with concomitant ischemic-reperfusion injury causing patchy denervation, leads to decreased contractility (see Committee 3, Neural Control). Incomplete bladder emptying from all causes can reduce functional bladder capacity, and thereby contribute to the urinary frequency and nocturia common in frail older persons [44].

The observation that bladder volume at the initial desire to void declines with age [48] may have been confounded by comorbid conditions and concurrent medications. Furthermore, unlike the positive association between detrusor contraction strength and DO found in younger subjects, older adults fail to demonstrate this DO-associated increase in detrusor contractility [49]. Moreover, many frail older persons with UI present with a combination of DO on filling and poor contractility during voiding, a condition termed detrusor hyperactivity with impaired contractility (DHIC) [44, 50]. In such cases, the bladder contraction does not empty the bladder fully, leaving a large PVR otherwise not explained by BOO. Because DHIC symptoms can include urgency UI, stress and mixed UI, dribbling, frequency, and nocturia, they may be mistaken for other conditions. At the same time, DHIC may be mistaken for DO with normal contractility because significant detrusor underactivity may be present in the absence of any relevant symptoms.

Ultrastructural studies demonstrate cellular changes associated with age-related changes in detrusor function. One series of such studies involved symptomatic and asymptomatic persons aged 65 to 96, using urodynamic testing and electron microscopy of bladder biopsy specimens, which were read in a blinded fashion using explicit protocols [45, 51-57]. A consistent, one-to-one correlation between specific urodynamic findings and bladder ultrastructure was observed. Patients with urodynamic DO had a “dysjunction pattern” with “protrusion junctions” and “ultra-close abutments.” The latter were postulated to be the anatomic explanation for the propagation of involuntary detrusor contractions in older patients. Patients with impaired bladder contractility had fibrosis with widespread degeneration of detrusor muscle and axons. A subgroup of patients had both types of pathology and urodynamic DHIC [50]. In the small number of asymptomatic patients with no DO, normal contractility, and no obstruction, detrusor muscle fascicles were largely intact, with two distinctive ultrastructural findings that may be related to ageing alone: muscle cell membranes characterized by numerous “dense bands” and markedly depleted caveolae, and slightly widened spaces between muscle cells with limited content of collagen and elastin. Depletion of caveolae may be related to de-differentiation of muscle cells, which could eventually result in the reversion of actively contractile cells to inactive, synthetically immature cells. A similar phenomenon has been reported in atherosclerotic blood vessels and postmenopausal myometrium, and may be related to reports of increased collagen in bladders from older women [45, 58]. Moreover, lack of oestrogen contributes to, and oestrogen replacement reverses, both caveolar depletion [59] and detrusor fibrosis [60]. Thus, both ageing and postmenopausal decline in oestrogen levels may contribute to bladder muscle cell differentiation and contractility [44].

The natural history of these ultrastructural changes remains largely unknown. From the ultrastructural studies described above, a subset of 23 patients was followed longitudinally [54]. The previously observed
one-to-one correlation between ultrastructure and function was maintained, but it was unclear whether urodynamic or ultrastructural changes occurred first in subjects who developed or had a change in LUTS. The pattern of dense-bands and nondisruptive muscle cell degeneration varied over time: the DO with dysjunction pattern developed in some subjects, and impaired detrusor contractility and the corresponding degeneration pattern was observed to progress in severity or develop. Other investigators have found similar results but without the one-to-one correlation (e.g., see Brierly et al [61]).

b) Urethra

Due to their common embryological origin, the urethra undergoes age-related mucosal and stromal changes similar to the vagina, and urethral changes in older women can be partially inferred from examination of vaginal tissue. Because of the difficulty of obtaining non-cadaveric urethral tissue, data on urethral smooth and striated muscle changes with age are complicated by confounding factors and definitions of controls.

Urethral closure pressure decreases with age [62, 63]. Based on a sample of 82 women aged 20-70, urethral closure pressure was found to decrease by 15 cmH2O per decade [64]. A number of anatomical and physiologic changes may account for this decline. Mucosal thinning and lack of proteoglycans reduce urethral wall apposition; this also may contribute to retrograde movement of perineal bacteria into the bladder causing urinary tract infections [65]. These mucosal changes may extend up to the bladder trigone, causing irritation of sensory afferent nerves, and possibly triggering DO [66]. The submucosal venous plexus in the proximal urethra loses its corkscrew shape, the number and volume of arterial vessels decrease, and vascular pulsations lessen [67]. Several studies, using different measurement techniques, have shown that urethral vascular density and blood flow decrease with age, but not vascular flow velocity [68-70]. However, age explained only 9% of the variability in vascular density in one study, [68] and none of the studies controlled for vascular risk factors such as hypertension and diabetes. The relative importance of decreased vascular volume versus hypoxia on urethral functional integrity is unclear. Other alterations in the urethral stroma are increased volume of connective tissue, decreased ratio of proteoglycans to collagen, and decrease in nerve density [71, 72].

Cadaver studies suggest that the number and density of urethral striated muscle fibres decrease with age, especially in the ventral wall of the proximal urethra [73, 74]. These authors estimated that striated fibers decrease by 1% per year. Large inter-individual variations were observed, with age and parity accounting for only a small part of the variability, suggesting that other yet to be defined factors are important. These studies also found that cross-sectional striated muscle fibre area decreased while fibre diameter was preserved. Another cadaver study by the same group found that circular smooth muscle width was 25%-50% higher in younger women (aged 20-39 years) than older (aged 70-89), and that younger women had higher fibre counts [75]. Smooth muscle loss in the older women correlated with loss of striated muscle in the anterior urethra.

Urethral sensation, measured as current perception thresholds, was significantly impaired in older women in two studies (by the same authors), one comparing 48 asymptomatic women and 13 with urgency UI, [66] and another in asymptomatic women [76]. The authors concluded that age-related LUT sensory neuropathy could contribute to the higher prevalence of overactive bladder (OAB) symptoms with age; however, urethral sensation thresholds were higher in women with urgency UI when controlled for age and parity, [66] and the “asymptomatic” older women may have had urodynamic DO [76].

With age, the urethral meatus generally moves toward the vaginal introitus, and may be difficult to see if there is considerable introital stenosis. Caruncles—benign violaceous soft swellings—often appear at the meatus, and are not problematic unless they cause discomfort or obstruction. Urethral diverticula can be a diagnostic challenge, especially in older women, because the symptoms (dysuria, pain, UI, frequency, urgency, dyspareunia) may be attributed to postmenopausal changes, age, OAB, or urgency UI [77]. Diverticula should be considered in women who have repeatedly failed “conventional” UI treatment. Diagnosis requires imaging by either voiding cystourethrography, ultrasound, or magnetic resonance scans.

Urethral obstruction is relatively uncommon in older women, and is nearly always secondary to other LUT dysfunction (e.g., pelvic organ prolapse) or is iatrogenic (from LUT/pelvic surgery or radiation).

In men, age-related decrease in striated sphincter muscle cell density occurs as well, [78, 79] and has been associated with increased muscle cell apoptosis [78]. While some investigations describe an increase in resting prostatic urethral pressure with age, [80] others note the increase occurs only to the sixth decade then subsequently decreases, along with a shortening of sphincteric urethral length [81]. These discrepancies may reflect differences in prostate volume and morphology.

c) Pelvic floor

Pelvic floor changes in normal older men have not been well studied. In women, the effect of age on pelvic floor structure and function is difficult to differentiate from the effects of hormonal status and parity. A number of studies are cross-sectional rather
than longitudinal, and focus on symptomatic women. For example, a questionnaire study of over 4,000 community women aged 25-84 found no association between age and stress UI (SUI), OAB, or anal UI, after adjustment for obesity, birth history, menopause, and hormone use [82]. Similarly, in a random sample of 343 Austrian women aged 18-79 years, impaired pelvic muscle contraction (graded by the Modified Oxford Scale) was weakly associated with parity and body mass index but not age [83]. Evidence of denervation and changes in pelvic striated muscle fibre number, type, and diameter have been found in asymptomatic and nulliparous women (see Committee 2, Cell Biology). For example, in a sample of 82 nulliparous women, neither levator function (measured by resting vaginal closure force and augmentation of vaginal closure force) nor pelvic organ support (on pelvic exam) showed an association with age [64]. A histomorphometric study, using levator ani muscle from 94 female cadavers (aged 15-58), 10 male cadavers (aged 23-35), and 24 women undergoing pelvic surgery, found that myogenic cell damage was associated with both parity and age (</> age 35), but there was no difference between nulliparous women, men, and women with pelvic organ prolapse and/or UI [84]. Total collagen content in pelvic muscle and fascia declines with age, with increased cross-linking and decreased elasticity, [85] but this association does not imply a direct causative effect of “ageing.” Constipation may independently contribute to pelvic floor dysfunction in older women [86, 87].

d) Vagina

The prevalence of age-related changes in the vagina varies with hormonal status, coexistent vascular disease, and the continuation or lack of sexual activity [88]. The postmenopausal decrease in oestrogen plays a part in many age-associated vaginal changes. Oestrogen is trophic for much of the LUT track in women, with oestrogen receptors found in the vagina, vestibule, distal urethra, bladder trigone, pelvic muscles, and ligamentum rotundum [89]. Yet, as the Women’s Health Initiative trial has shown, [90 91] one cannot assume that the association between low oestrogen levels and physiological changes implies that hormone replacement will reverse these changes, restore function, or reduce symptoms. Moreover, the data are equivocal whether and how LUT oestrogen receptors change in number, density, or function with age [67].

Following menopause, the vaginal epithelium loses the majority of its superficial and intermediate layers. Mucosal thinning may be associated with inflammation, evident as erythema, telangiectasia, petechiae, friability, and erosions. This may be responsible for urgency and frequency in some frail elderly women. In addition, there is loss of epithelial glycogen and lubrication, and mucosal pH increases from 4.5-5.5 to 7.0-7.4 [67]. These changes can lead to loss of normal adherent flora (lactobacillus), colonization with pathogenic organisms such as E. coli and enterococci, and the observed increase in bacteriuria and recurrent symptomatic urinary tract infections (UTIs) in older women [92].

Vaginal blood flow, which is important for mucosal integrity and submucosal fullness, decreases with age [67]. Whether this is oestrogen-related, and/or due to concomitant vascular disease is not known. Collagen and lipofuscin deposition in the stroma increases, and may be accompanied by invasion by lymphocytes and plasma cells [67]. The combined epithelial and stromal changes are associated with vaginal wall thinning and flattening of rugae [89]. The vaginal vault may shorten and narrow, and the introital opening decrease (and in severe cases become stenotic), which may make vaginal examination, intercourse, and use of pessaries difficult. However, it is not clear that vaginal shortening is clinically relevant: in one case series of over 3,000 women attending a general clinic, total vaginal length decreased by only 0.08 cm every 10 years [93]. Vaginal shape also may be altered by POP.

Because of the multiple potential confounding factors discussed above, a causal relationship between urogenital atrophy and urogenital symptoms/LUTS should not be automatically assumed. Very few randomized trials of oestrogen (oral or topical) for urogenital symptoms include women over age 75, use patient-defined outcomes in addition to physiological measures, or evaluate quality of life outcomes [94]. There are insufficient data to provide an evidence-based approach to symptomatic urogenital atrophy in older women. Oral oestrogen should not be used, but expert opinion supports topical oestrogen treatment (cream, intravaginal tablets, or oestrogen-impregnated pessary-like ring).

e) Prostate

Histological benign prostate hyperplasia (BPH) is strongly age-related, [95] and may lead to prostate enlargement (BPE) and outlet obstruction (BOO). While many LUT changes in women are associated with lower oestrogen levels, BPH results from the development of an oestrogen-predominant hormonal milieu in the prostate. The trophic prostatic androgen, dihydrotestosterone, is formed by the 5 - reduction of testosterone. Dihydrotestosterone levels decrease with age, while estradiol concentrations increase in the prostate stroma and remain constant in epithelial tissues, leading to an increase in the estradiol/dihydrotestosterone ratio [96, 97] and promoting stromal proliferation. Epithelial hyperplasia in turn is mediated by an array of stromal factors [98].

Histological BPH occurs in nearly 80% of men by age eighty [95]. Mean prostate volume increases with age but is very variable; its strongest predictor is prostate
specific antigen level of >1.4-2 ng/mL [99]. LUTS in men increase linearly over time, with the fastest increase during the seventh decade, such that by age 80 approximately one-third of men have received treatment for moderate to severe LUTS [100]. Natural history studies and randomized intervention trials, however, consistently demonstrate that symptomatic progression of benign prostate disease is not inevitable. LUTS remits in about one-third of symptomatic men without treatment [101]. Approximately one-third to one-half of affected men develop DO [102]. Thus, even in the presence of demonstrable BPE and/or BOO, the aetiology of LUTS is multifactorial, making prostate-related LUTS in older men a diagnosis of exclusion.

Although most patients are asymptomatic at the time of prostate cancer diagnosis, this is another possible cause of LUTS, including urgency UI, in older men. However, evaluation for prostate cancer in frail elderly men is rarely if ever indicated, given the high likelihood of limited remaining life expectancy.

The evidence is contradictory as to whether prostatic inflammation, either acute or chronic, contributes to urinary retention and LUTS in frail older men. In a single institution case series of 374 men undergoing TURP for acute urinary retention (AUR) or LUTS, pathological evidence of acute inflammation was significantly more common men presenting with AUR than LUTS (70% vs. 45%) [103]. However, in a much smaller case series of 70 men presenting with AUR, there was no association between inflammation from prostate infarction and AUR [104].

f) Other changes

The role of various neurotransmitters in the central and peripheral nervous system in UI is under active investigation (see Committee 2, Cell Biology). Nevertheless, age-related changes in the actions of these neurotransmitters, their receptors, or the cellular events they stimulate may contribute to the development of UI in frail older persons.

The prevalence of both asymptomatic bacteriuria and UTIs increase with age, [92] and the two are often found together in the frail elderly. Age-related changes in immune function, vaginal epithelium, faecal incontinence, and insufficient hygiene related to disability, cognitive impairment, and/or lack of caretakers may predispose the frail elderly to bacteriuria and recurrent UTIs. However, the role of otherwise asymptomatic bacteriuria (often found in association with pyuria), [105] in the aetiology of UI in frail elderly people remains unclear [106]. Treating otherwise asymptomatic bacteriuria in frail elderly patients with chronic, stable UI does not, in general, reduce UI severity [107]. UTI symptoms may be subtle and non-specific in this population, and include worsening of UI, altered mental status in patients with dementia, decreased oral intake, or a minor but important decline in functional ability [106]. At the same time, current consensus criteria for UTI are poorly sensitive and only fairly specific for UTI in frail elderly. In a prospective cohort of 340 nursing home residents, in which UTI was defined as pyuria (>10 white cells) with >100,000 colony forming units on culture, the McGeer, Loeb, and revised Loeb UTI criteria had sensitivities of only 19-30% and specificities of 79-89% [92].

5. FACTORS OUTSIDE THE LOWER URINARY TRACT CAUSING OR CONTRIBUTING TO UI

A hallmark of UI in the frail elderly population is the wide variety of factors and conditions outside the lower urinary tract that can cause or contribute to leakage (Table 2).

a) Comorbid medical illness

Numerous comorbid conditions are common in frail elderly with UI, and many patients have multiple such conditions. For example, in a large population-based observation study, [108] UI (defined as use of pads) was independently associated with one or more other geriatric conditions (cognitive impairment, injurious falls, dizziness, vision impairment, hearing impairment) in 60%, two or more conditions in 29%, and three or more in 13%. Comorbid conditions can affect continence through multiple mechanisms: e.g., diabetes mellitus, present in approximately 15-20% of frail elderly, may cause UI by diabetes-associated LUT dysfunction (DO, cystopathy), poor diabetic control (causing osmotic diuresis and polyuria), medications (see below), and/or diabetes-associated comorbidity (e.g., constipation) and impairment (amputation, vascular dementia).

b) Neurological and psychiatric disorders

Neurological and psychiatric disorders are highly prevalent in the frail elderly population. Stroke, dementia syndromes (most commonly Alzheimer’s disease, multi-infarct dementia, or a combination of the two [109]), and Parkinson’s disease can each contribute to UI through multiple mechanisms. First, these disorders may affect the brain’s pontine micturition centre and frontal lobes, and interfere with the normal ability to inhibit voiding. Second, each of these disorders can impair cognition. And third, each can impair mobility, and interfere with the ability to toilet independently. Frail older persons with these neurological conditions usually have multiple impairments and are at high risk for worsening disability. For example, in a UK cross-sectional survey of over 15,051 subjects, persons with cognitive impairment (MiniMental State Exam score ≤ 23, prevalence 18%), were significantly more likely to have UI (odd ratio [OR] 1.3), impaired hearing (OR 1.7), poor vision (OR 1.7), have had at least two falls in the previous six months (OR 1.4), and report poorer
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Comments</th>
<th>Implications for Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbid medical illnesses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Poor control can cause polyuria and precipitate or exacerbate incontinence; also associated with diabetic neuropathic bladder</td>
<td>Better control of diabetes can reduce osmotic diuresis and associated polyuria, and improve incontinence</td>
</tr>
<tr>
<td>Degenerative joint disease</td>
<td>Can impair mobility and precipitate urgency UI</td>
<td>Optimal pharmacologic and non-pharmacologic pain management can improve mobility and toileting ability</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>Associated cough can worsen stress UI</td>
<td>Cough suppression can reduce stress incontinence and cough-induced urgency UI</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Increased urine production at night can contribute to nocturia and UI</td>
<td>Optimizing pharmacologic management of congestive heart failure, sodium restriction, support stockings, leg elevation, and a late afternoon dose of a rapid acting diuretic may reduce nocturnal polyuria and associated nocturia and night-time UI</td>
</tr>
<tr>
<td>Lower extremity venous insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>May increase night-time urine production by increasing production of atrial natriuretic peptide</td>
<td>Diagnosis and treatment of sleep apnoea, usually with continuous positive airway pressure devices, may improve the condition and reduce nocturnal polyuria and associated nocturia and UI</td>
</tr>
<tr>
<td>Severe constipation and faecal impaction</td>
<td>Associated with “double” incontinence (urine and faecal)</td>
<td>Appropriate use of stool softeners Adequate fluid intake and exercise Disimpaction if necessary</td>
</tr>
<tr>
<td><strong>Neurological and psychiatric conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Can precipitate urgency UI and less often urinary retention; also impairs mobility</td>
<td>UI after an acute stroke often resolves with rehabilitation; persistent UI should be further evaluated</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Associated with urgency UI and less often urinary retention; also causes impaired mobility and cognition in late stages</td>
<td>Optimizing management may improve mobility and improve UI</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>Presents with UI, along with gait and cognitive impairments</td>
<td>Regular toileting assistance essential for those with mobility and cognitive impairment in late stages Patients presenting with all three symptoms should be considered for brain imaging to rule out this rare condition, as it may improve following a ventricular-peritoneal shunt</td>
</tr>
<tr>
<td>Dementia (Alzheimer’s, multi-infarct, others)</td>
<td>Associated with urgency UI; impaired cognition and apraxia interferes with toileting and hygiene</td>
<td>Regular toileting assistance essential for those with mobility and cognitive impairment in late stages</td>
</tr>
<tr>
<td>Depression</td>
<td>May impair motivation to be continent; may also be a consequence of incontinence</td>
<td>Optimizing pharmacologic and non-pharmacologic management of depression may improve UI</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>See Table 3</td>
<td>Discontinuation or modification of drug regimen</td>
</tr>
</tbody>
</table>
health (OR 1.9) [110]. Older persons with cognitive impairment have a nearly 6-fold increased risk of developing UI when they are hospitalized [111]. However, not all patients with neurological conditions causing cognitive impairment develop UI: in a six year longitudinal study, cognitive decline had only borderline association with UI, and only with UI that interfered with activities [112].

With the introduction of magnetic resonance brain imaging into routine clinical practice, radiology reports in older patients have increasingly emphasized the presence of structural abnormalities involving the white matter [113]. Terminology has also undergone a great change, moving away from subcortical atherosclerotic encephalopathy (a specific and relatively rare form of dementia), towards leukoaraiosis and, most recently, to the concept of white matter signal abnormalities (WMSA) [113, 114]. As noted above in Aetiology, recent fMRI studies [35, 37] demonstrate failure of activation within orbitofrontal regions in older persons with urgency UI, possibly contributing to a decreased ability to suppress urgency [37]. To date, there are no published studies of quantitative regional assessments of WMSA within these critical regions. While a dichotomous diagnosis of “cerebral white matter lesions” provided by a radiologist demonstrated no relationship to the presence or absence of UI, [115] a semi-quantitative measure of global WMSA appears to be associated with increased urgency UI and nocturnal frequency [116].

Normal pressure hydrocephalus should be a diagnostic consideration in any frail elderly patient who presents with new onset of UI in association with gait disturbance and cognitive impairment. A subset of these patients benefits from surgical implantation of a cerebrospinal fluid shunt [117].

LUTS, UI, and urodynamic DO are common in older persons with Parkinson’s disease, yet they may be related more to age and comorbidity than Parkinson’s-specific CNS pathophysiology [118-120]. The presence of UI in persons with Parkinson’s may in turn increase their risk for disability: in one series of patients with Parkinson’s, UI increased the risk of falling by nearly six-fold [121].

c) Depression

As in younger persons, frail elderly with UI have a higher risk of depression, a finding that has been replicated across cultures. Depression in older persons with UI may be under-diagnosed and under-treated: in one study of homebound adults with UI and severe depression, only 35% carried a previous diagnosis of depression and only 34% had been prescribed an antidepressant [122]. UI may add to the burden of depression by decreasing life satisfaction [123, 124] and self-rated health, [125] and by its association in frail elders with comorbidity [126].

Studies of the association of depression and UI in older persons are consistent across several depression measures. The validated Center for Epidemiologic Studies-Depression was used in two U.S. studies: a cross-sectional analysis of nearly 10,000 community-based persons (adjusted risk ratio for depression with UI 1.39 [95% CI 1.24, 1.55]), [127] and a large community-based study of older Mexican Americans (adjusted OR for depression 1.94 [95% CI 1.46-2.59]) [128]. Other multivariate studies finding significant associations between depression and UI in older patients used the Beck Depression index, [129] the

---

**Table 2. Comorbid conditions that can cause or contribute to UI in frail elderly persons (To be Continued)**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Comments</th>
<th>Implications for Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional impairments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired mobility</td>
<td>Impaired cognition and/or mobility due to a variety of conditions listed above and others can interfere with the ability to toilet independently and precipitate UI</td>
<td>Regular toileting assistance essential for those with severe mobility and/or cognitive impairment</td>
</tr>
<tr>
<td>Impaired cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environmental factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inaccessible toilets</td>
<td>Frail, functionally impaired persons require accessible, safe toilet facilities, and in many cases human assistance in order to be continent</td>
<td>Environmental alterations may be helpful; supportive measures such as pads may be necessary if caregiver assistance is not regularly available</td>
</tr>
<tr>
<td>Unsafe toilet facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unavailable caregivers for toileting assistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UI = urinary incontinence
emotional disturbances and social isolation subcales of the Nottingham Health Profile Questionnaire, [130] and have included studies in Asia [131]. Although no association between UI and depression was found in a Korean study, it used a higher cut-off on the Geriatric Depression Scale and, unlike many other studies, found no association between UI and mobility [132]. Self-report of sadness has [133] and has not been associated with UI [134]. Psychological distress, assessed by the General Health Questionnaire, was associated with UI in African Americans (adjusted OR 5.60 [95% CI 1.88–16.67]), but not in whites, in a cross-sectional study of community based older persons with mean age 67 [135]. However, a longitudinal analysis of the same population over 13 years found that persons with UI and psychological distress were more likely to report UI-specific functional impairment (e.g., avoidance of social activities, shopping, and physical activities) (adjusted OR 6.55 [95% CI 1.94–22.12]). Additionally, persons with UI and condition-specific functional loss were more likely to develop psychological distress (OR 3.66 [95% CI 1.61–8.33]).

The direction of the causal relationship between UI and depression in frail persons is unclear, as nearly all of these studies were cross-sectional. The results of the one longitudinal study suggested that it is not UI itself but UI-specific functional loss (e.g., avoidance of social activities, attending church, etc.) that is most closely associated with psychological distress, even after controlling for important covariates [122].

d) Medications

Older persons consume the majority of prescription medications and are therefore at greater risk of experiencing adverse events associated with their use. The risk of difficulty in controlling urination in community dwelling older women taking medications with LUT effects was about 30% higher compared to those who did not take such medications (OR 1.31 [95% CI 1.05–1.21]) [136]. UI was independently associated with antianxiety/hypnotic medications in one large sample of US nursing home residents [109]. Many classes of medications commonly prescribed for the frail elderly can cause or contribute to the development of UI (Table 3). The possibility that UI could be caused by a medication should be taken into account before prescribing drug treatment for UI in older persons.

e) Functional impairment

Impaired functional ability is a common pathway by which several medical and neuropsychiatric disorders cause or contribute to UI in frail elderly (see above). Impaired mobility can preclude a frail older person with urinary urgency from reaching the toilet in adequate time to prevent UI. The apraxia associated with moderate to severe dementia can interfere with independence in toileting and hygiene. Visual impairment is common in frail elderly, and may affect the ability to toilet independently.

Numerous studies support a close association between functional impairment and UI in frail elderly [33, 109, 137-141]. For example, UI was significantly associated with perceived limitations in usual role activities among community-based older persons [142]. In a longitudinal population-based study of older Mexican-Americans, prevalent UI was associated with an almost 60% increased risk of difficulty walking 8 feet (nearly 3 metres), and incident UI was associated with a two-fold increased risk for difficulty with ADLs and IADLs, as well as poor performance on three physical performance tasks [11]. Older women who experience a significant decline in physical performance over six years were more likely to report weekly UI (OR 1.31-1.40, depending on the physical measure) [112]. In the Health and Retirement Study, a population-based observational study of Americans aged ≥ 65 living in the community and nursing homes (n =11,093), UI sufficient to require pads was independently associated with multiple impairments, including toileting (OR 2.9 [95% CI 2.3–3.4]), transferring (OR 2.8 [2.4–3.2]), dressing (OR 2.3 [2.0–2.6]), eating (OR 2.1 [1.8–2.4]), bathing (OR 2.0 [1.8–2.2]), and dependency in one or more ADLs (OR 1.9 [1.7–2.0]) [108]. Among NH residents in one US state, both baseline UI and FI were associated with ADL loss over one year (for UI, adjusted OR 3.1; for FI, adjusted OR 2.9; combined UI-FI (adjusted OR 3.4) [143].

UI may have particular prognostic implications after stroke. Among Italian stroke patients admitted to home care program after post-acute rehabilitation, those with UI were more likely have a significant decline in physical function at one year (OR 1.64 [95% CI, 1.01-3.29]) [144]. Similarly, stroke patients admitted to a Spanish multidisciplinary geriatric rehabilitation unit who had UI on admission made less functional gains in mobility and self-care [16].

International studies demonstrate a bi-directional association between UI and falls, including those resulting in fractures. In a study of elderly women using day-care services in Japan, mixed UI (but not urgency or stress alone) was associated with falls over one year (RR 3.05 [95% CI 1.01-10.2]) [145]. Baseline UI was an independent risk for falls in longitudinal studies of frail elders in residential care in Australia, [146] long-term care in Germany, [147] and in the community in the Netherlands [148]. There is a significant association between UI and fractures as well. Supporting studies include: a secondary analysis of an observational study of community-dwelling women in the US (adjusted relative hazard ratio for non-spine nontraumatic fracture 1.34 [95% CI, 1.06-1.69]); [149] a cross-sectional analysis of the Canadian National Population Health Survey; [150] a cross-sectional analysis of older women attending a
Table 3. Medications that can cause or contribute to UI in frail elderly persons

<table>
<thead>
<tr>
<th>Medications</th>
<th>Effects on Continence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha adrenergic agonists</td>
<td>Increase smooth muscle tone in urethra and prostatic capsule and may precipitate obstruction, urinary retention, and related symptoms</td>
</tr>
<tr>
<td>Alpha adrenergic antagonists</td>
<td>Decrease smooth muscle tone in the urethra and may precipitate stress urinary incontinence in women</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Cause cough that can exacerbate UI</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause cognitive impairment and reduce effective toileting ability.</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause dependent oedema which can contribute to nocturnal polyuria</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Increase bladder contractility and may precipitate urgency UI</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Cause diuresis and precipitate UI</td>
</tr>
<tr>
<td>Lithium</td>
<td>Polyuria due to diabetes insipidus</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>May cause urinary retention, constipation, confusion, and immobility, all of which can contribute to UI</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>May cause confusion and impaired mobility and precipitate UI</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Confusion</td>
</tr>
<tr>
<td>Histamine1 receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin re-uptake inhibitors</td>
<td>Increase cholinergic transmission and may lead to urinary UI</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Can cause oedema, which can lead to nocturnal polyuria and cause nocturia and night-time UI</td>
</tr>
<tr>
<td>Glitazones</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory agents</td>
<td></td>
</tr>
</tbody>
</table>

UI = urinary incontinence
We could find no evidence-based guidelines for the optimal assessment and management. Professionals, and caretakers is usually necessary geriatricians, surgical specialists, nurses, other health collaboration among primary care physicians, identifying all potential contributing factors. A comprehensive assessment with the goal of the frail elderly is multifactorial, it is essential to conduct elderly persons with UI are summarized in the prevention of UI. Clothing also may be altered to make toileting easier (e.g., Velcro fasteners and pants with elastic waist bands rather than buttons and zippers).

Recommendations for the basic assessment of the frail elderly persons with UI are summarized in the Algorithm (see Summary Document). Because UI in the frail elderly is multifactorial, it is essential to conduct a comprehensive assessment with the goal of identifying all potential contributing factors. Collaboration among primary care physicians, geriatricians, surgical specialists, nurses, other health professionals, and caretakers is usually necessary for optimal assessment and management.

We could find no evidence-based guidelines for the assessment of UI in frail elderly. The United Kingdom (UK) NICE guidelines for UI in women do not address the assessment of frailer elderly women [155]. The US Agency for Health Care Policy and Research Clinical Practice Guideline on UI is significantly out of date (last revision 1996). The US government sets minimum quality standards for UI assessment and management in long term care, but these standards, along with basic fundamental principles of UI, are poorly understood by long term staff [156]. Two groups, the US Assessing Care of Vulnerable Elders (ACOVE) project and the UK Clinical Effectiveness and Evaluation Unit, have developed quality performance measures for UI care in frailler older persons, using structured literature review and expert panel review [157-160]. These measures are not guidelines per se, and in some instances lack sufficient detail. Unfortunately, both groups have demonstrated using their measures the poor quality of UI assessment and care by community practitioners in the US and the UK, including inadequate integration of continence services. Thus, there is an urgent need to re-establish the fundamentals of UI assessment and management for all personnel who care for frail older persons with UI.

1. COMPONENTS

a) Identification of frail older persons

Health care providers can screen older patients with UI for frailty using the Vulnerable Elders Survey, which can be administered in person or by phone (Table 4) [161]. Persons with a score of 3 or greater have four-fold increase in the risk of death and functional decline compared with persons with lower scores.

b) Primary care assessment

Geriatricians’ and primary care physicians’ (PCPs) UI assessments were compared in a randomized multicentre study involving 364 subjects, 42% of whom self-reported UI to the investigators. Geriatricians were significantly more likely to detect UI (59% of cases vs. 16%), regardless of the severity of UI, and were more likely to refer to Continence Programs (25%); all referrals by PCPs were to urologists [162]. An assessment strategy based on clinical evaluation, simple cystometry, and several criteria for referral was compared with urodynamic diagnosis. Approximately 25% of patients met criteria for referral, half of patients accepted urodynamic evaluation, yet urodynamics changed the treatment plan in only 12% of the patients who did not met the a priori criteria for referral [163].

Practice patterns and adherence to US UI guidelines were evaluated by retrospective chart review of 300 consecutive patients aged ≥ 65, seen by either an internist or geriatrician for UI at a tertiary care centre. Geriatricians ordered more testing, such as urodynamics, before referring patients to a surgical specialist [164]. Overall, primary care practitioners rarely follow the US Agency for Healthcare Research and Quality UI guidelines, [165] and nursing home practitioners rarely follow the Federal guidance for UI care regarding recommended physical examination, PVR testing, uranalysis, and identification of potentially reversible causes [166].

Systematic review of articles identified only 5 studies meeting eligibility criteria, and all were in women. None of studies found sufficient diagnostic evidence (defined as positive > 5 and negative likelihood ratios < 0.02) for different types of UI. The best was a general population study reporting the utility of history and exam for the diagnosis of SUI (positive and negative likelihood ratios 3.23 and 0.40, respectively) [167].
Table 4. Vulnerable Elders Survey (VES-13): see text for scoring

1. Age_____ (1 point for age 75-84, 3 points for age 85 or greater)

2. In general, compared to other persons your age, would you say that your health is:
   A. Poor (1 Point)
   B. Fair (1 Point)
   C. Good
   D. Very Good, or
   E. Excellent

3. How much difficulty, on average, do you have with the following physical activities: (SCORE 1 POINT FOR EACH BOLD RESPONSE, MAXIMUM OF 2 POINTS)

<table>
<thead>
<tr>
<th>Activity</th>
<th>No difficulty</th>
<th>A little difficulty</th>
<th>Some difficulty</th>
<th>A lot of difficulty</th>
<th>Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoopiong, crouching or kneeling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifting, or carrying objects as heavy as 10 pounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaching or extending arms above shoulder level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writing, or handling and grasping small objects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking a quarter of a mile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy housework such as scrubbing floors or washing windows</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Because of your health or a physical condition, do you have any difficulty: (SCORE 4 POINTS FOR ONE OR MORE YES RESPONSES IN THIS SECTION)

   A. Shopping for personal items (like toilet items or medicine)?
      o YES>> Do you get help with shopping? YES NO
      o NO
      o DON'T DO: Is that because of your health YES NO

   B. Managing money (like keeping track of expenses or paying bills)?
      o YES>> Do you get help with managing money? YES NO
      o NO
      o DON'T DO: Is it because of your health? YES NO

   C. Walking across the room? (USE OF CANE OR WALKER ALLOWED)
      o YES>> Do you get help with walking YES NO
      o NO
      o DON'T DO: Is that because of your health? YES NO

   D. Doing light housework (like washing dishes, straightening up, or light cleaning)?
      o YES>> Do you get help with light housework? YES NO
      o NO
      o DON'T DO: Is that because of your health? YES NO

   E. Bathing or showering?
      o YES>> Do you get help with bathing or showering? YES NO
      o NO
      o DON'T DO: Is that because of your health? YES NO
c) **Cough stress test**

Utility of the cough stress test was studied in 97 incontinent female long-term care residents using blinded comparison with single channel cystometry. Of the 77% in whom single channel cystometry diagnosis was congruent with the stress test (i.e., urodynamic DO with negative cough test, no DO and positive cough test), all were correctly classified; no woman with SUI was missed nor were any with DO misclassified [168]. An analysis 200 older women with UI found that provocative full-bladder cough test was as effective as radiographic or urodynamic pressure measurement in detecting SUI. Clinical diagnosis incorporating the cough test with leakage symptoms was 78% accurate, with only 6% false negatives for SUI, but was only 44% accurate with 45% false negatives for urgency UI [169].

d) **Postvoiding residual measurement**

We identified no studies evaluating the impact of PVR measurement on clinical diagnosis and treatment outcomes. Frail elderly may have a higher prevalence of elevated PVR, especially in association with DHIC. One study of 100 patients consecutively admitted to a geriatric ward found that 34% had PVR > 50 mL; these patients tended to have more UI (57% vs. 38%, p >.05), greater functional dependency, and a higher mortality rate (36% vs. 9%) [170].

However, the prevalence of elevated PVR in community dwelling frail elderly, especially those without associated disability or comorbidity, is not known.

e) **Urodynamic testing**

Urodynamic testing is feasible and safe, even in frail nursing home residents [171]. There is no evidence, however, that urodynamic diagnosis changes the outcome of treatment. Expert guidelines have recommended urodynamic testing before surgical or minimally invasive UI treatment in frail elders [172].

6. Urodynamic testing is feasible in frail elderly (Level 1) but it is unlikely change management or outcomes except in frail persons considered for surgical treatment of UI (Level 4)

### 3. RECOMMENDATIONS FOR EVALUATION (SEE ALGORITHM)

The essential first step is to screen all frail elders for UI, as the condition may be underreported across settings. The second is to identify treatable, potentially reversible conditions and other factors (medications, environment) that can cause or contribute to UI. Although UI associated with such factors has been commonly called “transient UI,” most frail elderly with UI have it as a chronic and often progressive condition. It is important to evaluate for such contributing factors because their amelioration may improve UI directly, make UI more amenable to other interventions, and overall improve the patient’s (and carer’s) quality of life [173].

Tables 2 and 3 list the common, treatable, potentially reversible conditions that can contribute to UI in frail older people. A mnemonic, “DIAPPERS” (delirium, infection [urinary tract], atrophic vaginitis, pharmaceuticals, psychological, excess fluid (in/out), restricted mobility, and stool impaction [and constipation]), has been commonly used to teach and remember these conditions [174]. However, treatment of two of these elements, atrophic vaginitis and UTI, may not improve UI (see Treatment section) and over-treatment of what is actually asymptomatic bacteriuria as UTI can lead to serious adverse outcomes (resistant organisms, secondary infections such as *Clostridium difficile*).

### VI. FACTORS IN MANAGEMENT

#### 1. BACKGROUND

This section, introduced in the 3rd ICI, highlights the issues that distinguish management of UI in frail elderly persons from that of healthier older adults. These include preferences for care, goals of care, determination of costs and benefits, special issues in drug treatment and issues unique to frail elderly men. They incorporate knowledge of physiological, psychological, sociological, and economic changes associated with frailty and advanced age, and reflect the importance of patient-centred goals and the role of caregivers in this population. These factors provide the context of continence care and should be incorporated into the management of all incontinent frail persons, *regardless* of the choice of specific treatment.
2. ROLE OF COMORBIDITY IN MANAGEMENT DECISIONS

Many frail elderly have concomitant disability and comorbidity, both of which can influence the clinical presentation and assessment of UI, as well as responsiveness to interventions. Frail older persons are not only at higher risk for unintended adverse effects from treatment (e.g., fulminate *Clostridium difficile* colitis from antibiotics used to treat otherwise asymptomatic bacteriuria in the setting of UI), but also may realize additional benefits in domains other than UI [173] from UI treatment that is aimed at underlying comorbidity and impairment (e.g., topical oestrogen for irritating atrophic vaginitis reduces recurrent UTIs; a nursing home exercise programme done in the course of toileting improves both physical function and UI [4]).

3. DEFINING OUTCOMES FOR TREATMENT

Outcome measures for frail older persons with UI must be fundamentally different from those used in healthy older persons, because of the heterogeneity of this frail population regarding comorbidity, remaining life expectancy (RLE), patient perceptions, personal values, and the involvement of caretakers and proxy decision makers. Unfortunately, intervention studies in the frail elderly remain focused on UI frequency and not these factors, and comorbidity is frequently used as an exclusion criteria in therapeutic trials. Also, there are no data on patients’ or carers’ expectations for the outcome of UI therapy.

Although quality of life (QoL) is a key concern for UI in all persons (see Committee 5, Initial Assessment Including Quality of Life), and has special relevance in the frail elderly with limited RLE, there are few validated QoL outcome measures applicable to this population. Only one validated UI-related QoL measure is derived specifically from patient-based data among persons older than 65, and these subjects were community-dwelling and relatively healthy [175]. None of the ICI-endorsed UI-related QoL measures have been validated in oldest-old or cognitively and/or functionally impaired persons. Traditional UI QoL domains—e.g., impact on IADLs, travel, sexual relations—are often not relevant to frail elderly, and there could be significant “floor effects” for social and role function domains. One alternative QoL domain for frail elderly is social interaction, especially for nursing home residents; [176] an analysis of cross sectional and longitudinal data from over 100,000 US nursing home residents found that prevalent and especially incident UI had negative impact on social interactions, particularly among persons with moderate ADL impairment [176].

The profound question when considering UI outcomes in frail older persons is, Is cure possible? The short answer is: it depends on patient factors, specific treatment(s), and the target outcome. While no geriatrician endorses “ageism” and therapeutic nihilism, research evidence suggests that complete dryness is unlikely for certain frail patients, particularly frail institutionalized persons with severe cognitive and functional impairment. Even “intractable” UI is amenable to interventions that may improve the patient’s urinary and bowel function and quality of life [3]. The Frail Elderly Committee of the Third ICI introduced an alternative continence paradigm for frail elderly (Figure 2), which subsequently was generalized for all persons with UI [177]. In this paradigm, persons with “dependent continence” are dry as a result of ongoing assistance, behavioural treatment, and/or medications. UI would return if the interventions ceased, a situation analogous to chronic disease models [178] such as “controlled hypertension” or “controlled diabetes.” Persons with “independent continence” are cured with or without need for ongoing treatment (e.g., dry after successful anti-incontinence surgery). For patients who are unable to achieve independent or dependent continence, “contained incontinence” should be possible by use of appropriate products such as pads, catheters, and appliances (See Committee 20, Management Using Continence Products), thus providing “social continence” or “accepted incontinence” [179, 180]. The balance between the types of continence achieved may vary as UI severity changes, and in conjunction with patient and caregiver preferences. All of the continence outcomes encompass a common need: to be both realistic and hopeful about UI in frail elders while avoiding nihilism and neglect, and maintaining comfort and dignity, and preventing avoidable complications of UI.

Although the ICS standardization document on outcomes in older patients is now 10 years old, little progress has been made and many of the identified needs still pertain (see Recommendations for Research) [5].
4. ROLE OF REMAINING LIFE EXPECTANCY IN TREATMENT DECISIONS

Remaining life expectancy (RLE) is a key yet often misunderstood concept in treatment decisions for frail older persons. RLE is not uniformly short in this population; moreover, there is a demographic trend of increasing RLE, with a smaller proportion of persons spending their remaining years living with disability [181]. Incorporation of RLE into treatment decisions in urology and gynaecology has been studied only in relation to cancer treatment. Only two studies, both in prostate cancer, examined specialists’ ability to estimate RLE. Canadian urologists were more accurate in estimating longer RLE: using scenarios based on actual patient data, 31% were accurate within 1 year, 67% within 3 years, and 82% in estimating greater than or less than 10 years in 82% of responses [182].

Walter and Covinsky [183] developed a graphical tool for estimating quintiles of RLE by age (Figure 3). Medical conditions most closely associated with shorter RLE are class III/IV congestive heart failure, end-stage renal disease, and oxygen-dependent chronic obstructive pulmonary disease. Estimates of RLE are significantly affected by frailty and cognitive and functional impairment [184]. Alzheimer’s dementia decreases RLE profoundly (by nearly 75%) among older persons who otherwise would be in the top quintile of RLE [185]. Compared to older persons with at most one IADL deficit, persons with more deficits have significantly higher 5-year mortality (with two deficit, adjusted RR 1.46 [95% CI 1.20 – 1.78] ; with three or more deficits, adjusted RR 1.64 [1.26 – 2.14]) [184].

5. PREFERENCES FOR CARE

Because there are multiple treatment options available for frail older adults with UI, and individualised care is emphasised, obtaining patients’ and carers’ opinions regarding preference is essential for quality care planning. It should not be assumed that persons with cognitive impairment are unable to make their care preferences known or participate in treatment decisions.

Three studies have directly addressed patient and caregiver preferences for UI care. Preferences for toileting and changing were studied in 111 nursing home residents with UI; residents preferred an average of 2 pad changes, 1.5 toilet assists, and 2 walking assists more than they actually received, yet even these levels were lower than guidelines recommend, suggesting that residents may have reduced expectations based on their experience [186]. In the second, residents of board-and-care facilities and two nursing homes, their family members, and facility nursing staff were given definitions of and information about five UI treatment options (indwelling catheter, prompted voiding, adult diapers [sic], electrical stimulation, and medications) [187].

Respondents were asked their preferences between pairs of treatment options (e.g., “diapers” versus prompted voiding). Most of the board-and-care respondents were continent, although some were undergoing UI treatment at an outpatient clinic. Patients and family members were evenly divided between “definitely” and “probably” preferring prompted voiding versus diapers. Almost 80% of nursing staff, however, preferred prompted voiding to diapers. Families perceived staff members as unwilling to perform prompted voiding, and some thought prompted voiding was degrading to the resident and that it was bothersome to be asked to go to the toilet frequently. Using a similar method, a German study with 117 geriatric hospital patients (mean age 85; 43% with UI), 72 staff members, and 71 family members, found that most patients preferred diapers (79%), medications (78%) and scheduled toileting (79%) over urinary catheters and 64% preferred scheduled toileting [188].

When choosing between diapers and medication, equal proportions preferred each option. Patients with greater functional dependence were more likely to
prefer catheters, and those with experience with diapers were more likely to prefer medications and toileting. Notably, spouses showed moderate to almost perfect agreement with patient preferences, but those of other family proxies had only slight to fair agreement.

6. COSTS AND BENEFITS OF UI TREATMENT IN FRAIL ELDERLY

An overall discussion regarding UI-related costs is covered by Committee 22, Economics of Incontinence. The following discusses UI cost issues specific to the frail elderly.

a) Estimating Costs

Successful ageing is a hallmark of modern society. For many populations, the greatest increase in population is occurring in the oldest old, those ≥ age 85. This group has the highest prevalence of UI, and accordingly their increased prevalence number will result in higher UI care costs. Such an increase has already been observed between 1992 and 1998 amongst US women aged ≥ 65 [189]. The costs of care for older persons has been estimated at double that for people under 65, but care for those older persons living in institutions was less than for community dwelling individuals [190]. Likewise, the cost of OAB in five European countries is estimated to rise by one billion Euros between 2000 and 2020, [191] and in the US it has been estimated that by 2030 the greatest increase in demand for UI care (81%) will be in older women aged 60-89 with OAB symptoms [192]. In one US study using of a community managed care population, the presence of OAB and comorbidity doubled the associated costs of UI care [193].

Costs can be expressed as direct costs, indirect costs, and intangible costs [194]. Previous estimates have focused on diagnostic costs, treatment (including routine care and pads), and consequence costs (skin irritation, urinary tract infection, falls, fractures, additional nursing home and hospital admissions, longer hospital length of stay). Direct healthcare costs are most often estimated but there is a lack of meaningful research into indirect costs and those related to comorbidity often present in the frail elderly. Intangible costs have not been considered in these estimates because of their subjective nature and the methodological difficulty of collection and estimation. Much of the evidence for the cost of UI in older persons has been gathered from either epidemiological surveys or analyses of claims from insurance databases, and have often involved many assumptions or complicated formulae to calculate final costs. There is a consistent theme that the cost of caring for older adults with UI will increase, but the estimated magnitude of this increase is variable.

For the frail elderly, especially those in long term care, cost calculation is especially complex. The greatest costs for UI care in nursing homes are by far nursing labour costs [195]. Extrapolated costs for nursing home admission due to UI was $6 billion (2000 US dollars), [25] with institutional costs of UI management and consequences of $5 billion (2000 U.S. dollars) [196]. In one small 6-month study, the mean daily cost of UI care, including direct nursing care, indirect nursing overhead, and supplies, was $9.09 (± $ 10.52 ) per resident (2003 U.S. dollars) [197]. The costs for UI pads alone in Dutch long-term care has been estimated at 160 million Euros [198]. In an Australian sub-acute care setting, the costs of daily UI care was $49 AU, with most spent on staff wages [199]. In Canada, researchers found that 1% increase in UI prevalence was associated with an 11-12% increase in costs [200]. The extra nursing time needed to maintain toileting programmes contributes to high costs [201]. Routine garment and laundry costs may be lower than estimated because in practice residents are not changed as often as needed. In addition, for prompted voiding to remain effective, such things as regular refresher education programmes for staff or wet sensors may be necessary, and thus are rarely considered in cost estimates.

Moreover, the time period over which the costs and benefit are calculated needs to be explicit because both benefit and costs will change, and patient morbidity and mortality need to be considered. The costs of correcting functional and medical causes of UI are rarely considered. Also, the potential differential in costs across the span of cognitive and functional impairment has seldom been assessed, [202] despite evidence that UI care costs are closely related to the degree of functional impairment [203]. Costs related to caregivers of frail persons with UI living in the community include lost wages, decreased productivity (both within and outside of the home), the additional number of caretaking hours when a frail person develops UI, [204] and the cumulative effect of increased strain and burden, along with any resulting illness. Overall, there are still limited data on costs of UI treatment in other residential (such as assisted living or rest homes) and acute care settings [205 204]. Costs may vary by access to care; because so many frail elderly are homebound or live in institutions, they often do not have the same access to the UI therapies as other populations. Their health care providers may be limited to primary care physicians, community nurses, and care assistants or aides with little to no expertise in UI management. Specialist consultation may be minimally available in home or long term care settings, leading to a focus solely on behavioural management and/or containment products.

Cost relates strongly to reimbursement, which varies considerably from country to country, depending not only on structure of the health system but special programmes for the aged and persons with UI (see Models of Care below). Within particular countries, there may be further variation based on insurance, co-
insurance, drug versus procedure coverage and incentives, access to care, programmes for vulnerable populations and urban/rural differences.

b) Benefit and effectiveness of treatment

The ability to define the benefit of UI treatment in frail older people is highly dependent on the individual, their caregivers, and the health care system. Outcomes research indicates that patients value quality of life, which encompasses many domains besides reduction in UI (See Committee 6, Symptom and Quality of Life Assessment). Even in cognitively impaired persons, one can still elicit treatment preferences, [188, 206] evaluate domains of quality of life (e.g., social interaction), [176] and assess treatment satisfaction directly or behaviourally. At the same time, we found no data on the value or utilities the frail elderly or their caregivers assign to varying degrees of UI (with or without treatment intervention) versus “dryness.” Standard outcomes such as quality adjusted life years (QALYs) may overestimate effectiveness in older people, [207] not just because of potentially different utilities but the altered importance of “years of life saved” in a population with variable and sometimes limited remaining life expectancy.

The above issues underline the need for novel and specific outcomes for use in both trials of UI interventions and clinical care of the incontinent frail elderly. Outcomes measured by single item tools of perceived benefit or satisfaction with treatment are unlikely to be generalizable across the heterogeneous frail elderly population. It should not be assumed that perceived benefit of treatment can be measured with the same tools across cultures and health systems, unless such tools are sensitive to differences in such things as reimbursement for continence services and supplies. Associations between expectations, preferences, and outcomes need to be prospectively studied. New approaches and tools to assess UI-specific quality of life in the cognitively-impaired frail elderly are needed, as well as better understanding of the interaction between functional impairment and the impact of UI [176]. When QALYs are included as an outcome in UI treatment trials in older persons, they should be specifically analyzed by age and also possibly health status.

7. ISSUES IN DRUG TREATMENT

a) Age-related changes in pharmacology

Specific age-related changes in pharmacokinetics, alteration in drug absorption, distribution, metabolism and clearance, and their potential effect on UI drugs, are shown in Table 5. Age-related pharmacokinetic changes are rarely if ever considered in planning the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age-associated Changes</th>
<th>UI Drugs Potentially affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Minimal quantitative change despite ↓ gastric motility, yet little known regarding effect on slow-release agents</td>
<td>Extended release preparations</td>
</tr>
<tr>
<td></td>
<td>Ø Skin thickness</td>
<td>Transdermal preparations</td>
</tr>
<tr>
<td>Distribution</td>
<td>Decrease in lean body mass leads to ↓ Vd / ↑ T 1/2 for hydrophilic drugs and ↑ Vd/↑ T 1/2 for lipophilic agents</td>
<td>Lipophilic agents, tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>Decreased protein binding in frail patients with low albumin, leading to higher concentration of free drug</td>
<td>Tolterodine</td>
</tr>
<tr>
<td>Hepatic metabolism</td>
<td>↓ Phase I reactions (oxidation/ reduction)</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>No change in Phase II reactions (glycosylation)</td>
<td>Oxybutynin</td>
</tr>
<tr>
<td></td>
<td>↓ Hepatic blood flow and ↓ hepatic mass, leading to reduced clearance for agents with first-pass metabolism</td>
<td>Tolterodine</td>
</tr>
<tr>
<td></td>
<td>Stereoselective selectivity in metabolism (hypothetical)</td>
<td>Solifenacitin</td>
</tr>
<tr>
<td></td>
<td>Cytochrome P450</td>
<td>Darifenacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enantiomers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxybutynin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solifenacitin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fesoterodine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darifenacin</td>
</tr>
<tr>
<td>Clearance</td>
<td>Decrease in renal clearance</td>
<td>Tolterodine</td>
</tr>
</tbody>
</table>

Vd = volume of distribution, T 1/2 = half life
duration of time off previous UI medications, placebo-
run in periods, and wash-out periods in UI drug trials
in older persons. The numerous factors potentially
affecting drug clearance in such patients, as well as
previous and/or cross-over compounds, may confound
observed drug effects. Age-related changes in
pharmacodynamics have been described for
benzodiazepines, beta-adrenergic agents, and opiates
[208, 209] but there are little available data concerning
changes in the frail elderly.

b) Availability of low dose agents

One effect of the under-representation (if not exclusion)
of frail older persons in UI drug studies is a lack of
knowledge regarding minimal effective drug doses
for this population. The age-related changes in
pharmacology noted above suggest that some UI
drugs may be effective at lower than standard doses
in frail elderly with concomitant decreased adverse
effects [210]. This issue is especially relevant for
extended-release preparations, which cannot be
divided into smaller doses. There are some data
supporting the effective use of low dose oxybutynin
in older persons, but such studies are exceptional
[211, 212].

c) Inappropriate polypharmacy

Approximately 60% of persons over age 65 take at
least one prescribed medication, and about one-third
take more than five prescribed drugs. In addition,
many take over-the-counter and naturopathic or herbal
agents, with the rate of use varying across countries
and cultures. The likelihood of adverse drug reactions
(ADRs) and drug interactions rises exponentially
as the number of medications increases. This has led to
the recommendation in geriatric prescribing to “subtract
before adding,” to consider whether target symptoms
might be due to medications before adding another
drug targeting those symptoms. This approach is
relevant in geriatric UI, as UI may have been
precipitated and/or worsened by medications (see
Table 3). Changes to existing drug regimens should
be considered in the management of UI in all frail
older people.

d) Adverse drug effects

ADRs are extremely common in older persons, [213]
with rates up to 35% among community-dwelling
persons aged ≥ 65 in the US, [214] to two-thirds of
long term care residents. [215]. In a recent UK study,
59% of ADRs requiring hospital admission involved
patients aged ≥ 60 [216]. Factors associated with
higher ADRs in the elderly are higher drug doses,
age-related pharmacological changes, polypharmacy,
comorbid conditions, and the interactions between
them. Older people are at higher risk of ADRs from
antimuscarinics because of age- and comorbidity-
related changes in muscarinic receptor number and
distribution, blood-brain barrier transport, and drug
metabolism [217]. Whereas antimuscarinic ADRs in
younger persons are bothersome, in the frail elderly
they can result in serious morbidity such as increased
heart rate, sedation, heat intolerance, delirium, and
falls with fractures [3].

A major antimuscarinic ADE of concern in frail adults
is cognitive decline, yet there are little data about its
actual incidence or prevalence. Cognitive effects may
be under-detected because they are clinically subtle,
neither asked about nor reported by the patient, or
mistaken for age-related diseases and ageing [218].
Persons with pre-existing cognitive impairment
(especially from conditions known to affect central
cholinergic pathways) may be at greater risk for this
ADE. Actual incidence rates of cognitive impairment
with antimuscarinic agents for UI are difficult to estimate
because of probable under-reporting, the different
measures used across studies, failure to specify the
measure in published trials, the use of proxy measures
(such as quantitative EEG), and differences in
psychometrics and clinical relevance of self-report,
physiologic and performance measures of cognition.

Antimuscarinic agents for UI also cause dry mouth
(xerostomia), which is already present in approximately
30% of persons over age 65. Most older persons take
at least one drug that causes xerostomia [219]. The
morbidty from xerostomia-dental caries, problems
chewing, poorly fitting dentures, dysphagia, and
sleeping difficulty should be included when assessing
the risks and benefit of antimuscarinics in frail older
persons. Another antimuscarinic ADE to which the
frail elderly may be predisposed is decreased visual
accommodation, yet this has been specifically
evaluated only in young healthy volunteers, [220] and
drug trials typically report only “blurred vision,” without
further characterization.

The incidence of increased PVR as an ADE is
seldom reported in clinical trials of antimuscarinics
for UI or OAB. When it has been reported, the
magnitude of increase is seldom of clinical significance.
The incidence of acute urinary retention with
antimuscarinics in general is low, but it has not been
systematically evaluated in frail elderly. There is no
consensus as to what constitutes a sufficiently high
PVR to preclude antimuscarinic treatment or to require
dose adjustment of an already prescribed agent. If
urinary frequency or UI worsens after an antimuscarinic
is started or increased, then PVR should be checked
because an increased PVR will lower functional
bladder capacity and worsen UI. PVR should be
monitored in frail older men treated with
antimuscarinics who may not reliably report change
in LUTS or voiding difficulty.

e) Drug interactions

Because frail older persons take higher numbers of
drugs and usually have several comorbid conditions,
Drug interactions are more common [221]. All antimuscarinic agents for UI will have additive side effects when combined with other anticholinergic agents. Antimuscarinics could potentially alter absorption of other drugs by slowing gastrointestinal motility.

**Drug-drug interactions** for oxybutynin, solifenacin, darifenacin, and tolterodine include potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, cyclosporin, vinblastine). Fesoterodine, a produg that is converted to tolterodine by non specific esterases, is also dependent upon CY3A4 for its excretion. There is one case report of interaction between tolterodine and warfarin in 2 older patients, [222] which has not been seen in healthy volunteers. Naturopathic/ herbal preparations should also be considered for potential interactions, especially in areas where these agents are used frequently.

There is still uncertainty regarding interactions between antimuscarinic agents for UI and cholinesterase inhibitors (CEIs) used for dementia. There is evidence CEIs can cause or worsen UI from a case report [223] and also a case series of 216 consecutive patients with probable Alzheimer’s disease attending a memory treatment center [224]. In the latter, CEI treatment was overall associated with 7% risk of new UI; the highest risk was observed in patients with more behaviour problems, and lower risk in patients who demonstrated positive cognitive and/or behavioural response to CEI. Evidence for an interaction between antimuscarinics and CEIs comes from a database study of nursing home residents in one US state [225]. Residents with dementia newly treated with cholinesterase inhibitors were subsequently more likely to be prescribed a bladder antimuscarinic than dementia patients not given CEIs, suggesting a classic geriatric “prescribing cascade” [226]. Concomitant use of antimuscarinic and CEIs in nursing home residents was associated with a decline in ADL function but not worsening cognition, possibly because the cognitive measure (MDS-COG) was inadequately sensitive [227].

Drugs also may interact with comorbid conditions (drug-disease interactions), such as diseases that affect hepatic or renal metabolism and clearance, slow gastric motility (e.g., advanced diabetes), predispose to delirium, or are associated with impaired central cholinergic transmission (Alzheimer’s and Parkinson’s diseases).

**f) Potentially inappropriate drugs for older persons**

Efforts at quality improvement for older populations have led to the development in several countries of expert consensus guidelines regarding inappropriate drugs for older persons, [228, 229] although the continuing relevance of these guidelines has been questioned and alternative systems suggested [230, 231]. These guidelines focus on drugs with lower risk-benefit ratios and higher potential for drug-drug and drug-disease interactions, and are used for nursing home regulation and quality performance measurement. Several UI drugs are included in the US guidelines (the “Beers criteria”): immediate-release oxybutynin (because of “high risk of anticholinergic adverse effects, sedation, and weakness”); oxybutynin (immediate- and extended-release), tolterodine, and flavoxate in the patients with BOO (because of “high risk of decrease[d] urinary flow, leading to urinary retention”); all anticholinergic drugs in patients with cognitive impairment (because of “high risk of CNS-altering effects”) or constipation (because of “risk of exacerbat[ing] constipation”); and tricyclic antidepressants in patients with stress UI (because of “high risk of produc[ing] polyuria and worsening of incontinence”). Whether or not one agrees with these recommendations, there is value in the concerns they raise, especially their emphasis on the level of thought needed for “best practice” prescribing for frail older persons.

**8. SPECIAL ISSUES UNIQUE TO FRAIL OLDER MEN**

Although their ranks thin into the ninth decade, men still comprise a significant portion of frail older persons. The prevalence of UI increases in men after age 80, going from about one-third of the rate in women to the same. Over the past ten years, the prevalence of UI in US male nursing home residents aged 65-74 has increased to a greater extent than in female residents (from 39% to 60%, compared with 45% to 59%) [232]. At the same time, frail men are under-represented in UI treatment trials, whether behavioural, pharmacological, or surgical (see also Committee 15: Surgery for Urinary Incontinence in Men).

This under representation is unfortunate, because results from treatment trials in frail women cannot be directly extrapolated to men for several reasons:

- Differences in comorbidity: frail older women have higher rates of functional impairment, [233] which may mean that frail men may be more likely to respond to behavioural interventions.
- Differences in caregivers: more older men have living spouses who can provide care, with a potential impact on the risk and type of caregiver burden associated with UI management.
- Differences in the relationship between UI and cognition: one systematic urodynamic study of nursing home residents with UI found a significant association between DO and more severe cognitive impairment in women, but not in men (although power was likely low, as the number of men was only 17) [171].
- Benign prostate disease: the prevalence of histological BPH, BPE, and BOO increase with age, and is associated with LUTS, UI, and DO. In the urodynamic study cited above, 29% of men had
BOO and 59% had DO as the predominant cause of UI, [171] versus 4% BOO and 61% DO in women.

- Prostate cancer: nearly all men in their ninth decade have histological evidence of prostate cancer. However, it is not clear that frail elderly men have an increased risk of prostate cancer-specific mortality, especially given that their RLE is primarily affected by comorbid conditions. The need to screen for and treat prostate cancer diminishes with functional status, comorbidity, and RLE [234]. At the same time, more men are living with the sequelae of prostate cancer treatment, particularly stress UI after radical surgery.

- Risk of urinary retention: because of age-related decrease in detrusor contractility and increased likelihood of BPE and BOO, it is often assumed that frail elderly men have a higher prevalence and risk of urinary retention. However, this has never been demonstrated. Among NH residents with UI, the prevalence of underactive detrusor was similar in women and men (38% and 41%, respectively), despite the higher prevalence of BOO in men [171].

Despite the issues noted above, evaluation and management of UI in most frail older men follows the same roadmap as for frail women (see Algorithm).

9. SUMMARY OF THE EVIDENCE

1. Patients and caregivers have clear preferences for the type of UI management, and they are often discordant between the two groups (Level 2)
2. Age-related changes in pharmacokinetics affect antimuscarinic drugs for UI and should be incorporated into treatment planning. (Levels 1-2)
3. Drugs may be effective at lower doses in frailer compared with healthier older persons (Level 3)
4. Polypharmacy increases the chance of adverse reactions to drug therapy. (Level 1)
5. Adverse drug events are more common in the frail elderly. (Level 2)
6. Drug-drug and drug-disease interactions are common in frail older persons (Level 1-3).
7. The economic burden of UI in frail elderly, as well as the cost-benefit, cost-effectiveness, and cost-utility of its treatment, has been incompletely characterized (Level 4)

VII. TREATMENT

1. LIFESTYLE INTERVENTIONS

As potentially treatable correlates of and risk factors for UI are determined, interventions that ameliorate their effects have been devised. Several lifestyle interventions have been evaluated in healthier older and younger women, including weight loss regimens, diet, fluid selection and management, smoking cessation, and constipation management (See Committee 12, Adult Conservative Management). Although many health care professionals advocate lifestyle interventions to treat UI, [196, 235, 236] we did not locate any studies of these interventions for the frail elderly. Several of these interventions may be inappropriate in frail elders (e.g., weight loss), yet advanced age alone should not preclude their use if assessment warrants. Inadequate fluid intake and dehydration are common in incontinent frail elderly in long-term care, in part because nursing assistants offer them less fluids in the belief that this will reduce UI [237]. Dehydration may actually increase the risk of UI in frail elders, because of the former’s significant association with constipation [238] and impaired cognition, [239] both known risk factors for UI.

a) Quality of data and results

We located articles addressing lifestyle interventions for UI in older women, but the number of oldest-old subjects was very small, few to none appeared to be frail, and no studies stratified results by age. Two very small older trials point to the possibility that increased hydration for incontinent frail elderly may actually decrease UI [240, 241].

b) Summary of the evidence (see Table 6)

No recommendations are possible regarding lifestyle interventions for UI in the frail elderly (Level 4)

2. BEHAVIOURAL INTERVENTIONS

Behavioural interventions have been especially designed for frail older people with cognitive and physical impairments that may affect their ability to learn new behaviours or to actively participate in self-care activities. These interventions evolved from classical behavioural change theory, using antecedent and/or consequent conditioning to shape the desired behaviour. Because behavioural interventions have no side effects, they have been the mainstay of UI treatment in the frail elderly [242]. Behavioural therapies used predominantly in frail adults, all of which require active caregiver participation, include:

- Quality of data and results
- Summary of the evidence (see Table 6)
- No recommendations are possible regarding lifestyle interventions for UI in the frail elderly (Level 4)
- Behavioural interventions have been especially designed for frail older people with cognitive and physical impairments that may affect their ability to learn new behaviours or to actively participate in self-care activities. These interventions evolved from classical behavioural change theory, using antecedent and/or consequent conditioning to shape the desired behaviour. Because behavioural interventions have no side effects, they have been the mainstay of UI treatment in the frail elderly [242]. Behavioural therapies used predominantly in frail adults, all of which require active caregiver participation, include:
Prompted voiding, involving prompts to toilet with contingent social approval, is designed to increase patient requests for toileting and self-initiated toileting, and decrease the number of UI episodes. It was first used in the 1980s for incontinent nursing home residents [243].

Habit training, which requires the identification of the individual's voiding pattern, involves pre-empting UI episodes. Habit training involves the identification of the individual's voiding pattern, and the use of a toileting schedule to prevent UI episodes [244, 245]. There is no attempt to alter an individual's voiding pattern.

Timed voiding involves toileting an individual at fixed intervals, such as every 3 hours. This is considered a passive toileting programme; no attempts are made at patient education or reinforcement of behaviours, or to re-establish voiding patterns [246]. Other terms used to describe timed voiding are scheduled toileting, routine toileting, and fixed toileting [247].

Combined toileting and exercise therapy involves strengthening exercises into toileting routines by nursing home aides [248]. Another combination intervention, administered by occupational or physical therapist, involves toileting and mobility skills [249].

Cognitive and functional impairments common in frail elderly and/or lack of caregivers may preclude the use of some of these interventions. Studies repeatedly show that, once a trial ends, indigenous long-term care staff rarely maintain the intervention at the same level, if at all (see, e.g., [4]). Outcome evaluation or even conduct the interventions. Studies repeatedly show that, once a trial ends, indigenous long-term care staff rarely maintain the intervention at the same level, if at all (see, e.g., [4]).

We identified a systematic review of prompted voiding (9 trials, 674 patients) [252] and a Cochrane review of habit training in nursing home and home care patients updated since the last ICI (4 trials, 378 patients) [253]. The majority of trials did not determine the type of UI, or sufficiently describe whether comorbidity possibly contributing to UI was evaluated or treated. Randomized trials in long-term care have overwhelmingly demonstrated that long-term care staff do not maintain interventions that are feasible in some frail older women.

Although pelvic floor muscle rehabilitation has not been studied extensively in frail elderly, age and frailty alone should not preclude their use in appropriate patients. Similarly, a combined cognitive and functional training programme involving pelvic floor muscle exercises, bladder training, and mobility skills [250].

Table 6. Lifestyle Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Authors</th>
<th>Study Design</th>
<th>Sample</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid management</td>
<td>Kincade et al, 2007 [236]</td>
<td>Two arm, randomized trial</td>
<td>224 community-dwelling women aged 18 years and older with UI</td>
<td>Self-monitoring was individualized and women were counselled on fluid consumption, quick pelvic floor muscle contraction, management of constipation and voiding frequency.</td>
<td>After adjusting for age, hormone status, and race women in the self-monitoring group had statistically significant less urine loss (average 13.3 g less urine loss) than women in the wait list group.</td>
</tr>
<tr>
<td>Caffeine reduction</td>
<td>Bryant et al, 2002 [466]</td>
<td>Prospective randomized controlled trial</td>
<td>95 consecutive adults with UI coming to two continence nurse advisors</td>
<td>Treatment group received education regarding caffeine reduction; control received no information.</td>
<td>Caffeine intake was significantly reduced in treatment group and frequency and urgency was significantly improved compared to control group one month post intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kincade et al, 2007 [236]</td>
<td>Two arm, randomized trial</td>
<td>224 community-dwelling women aged 18 years and older with UI</td>
</tr>
<tr>
<td>Bryant et al, 2002 [466]</td>
<td>Prospective randomized controlled trial</td>
<td>95 consecutive adults with UI coming to two continence nurse advisors</td>
</tr>
</tbody>
</table>

* Fluid management: Self-monitoring was individualized and women were counselled on fluid consumption, quick pelvic floor muscle contraction, management of constipation and voiding frequency.
* Caffeine reduction: Treatment group received education regarding caffeine reduction; control received no information.
* Combined toileting and exercise therapy: Functional intervention training incorporates strengthening exercises into toileting routines by nursing home aides [248]. Another combination intervention, administered by occupational or physical therapist, involves toileting and mobility skills [249].
* Combined toileting and exercise therapy: Functional intervention training incorporates strengthening exercises into toileting routines by nursing home aides [248]. Another combination intervention, administered by occupational or physical therapist, involves toileting and mobility skills [249].
luation is usually limited to “wet checks” (percentage of times the patient is found to be wet on a set schedule of checks) and not UI, and no studies report cure or patient-based outcomes such as satisfaction with treatment and quality of life. Little intervention research has been conducted with incontinent hospitalised and homebound frail elders.

Limitations in many studies include: small samples with low power to detect significant differences; variable terminology and operational definitions, making comparisons across studies difficult; little ethnic or cultural diversity; data limited to women, especially in nursing home trials; little focus on night-time UI; little consideration to the psychological impact of toileting programmes on patients and caregivers; [254] and no long-term follow up. Many studies excluded frail older adults with terminal illness, [255] inability to respond to an one-step command, [255, 256] or poor language ability [256-258]. Ethical concerns for human subjects prohibits withholding treatment, thus true “control” groups were nearly impossible to create. Two studies used delayed treatment as controls [257, 258]. The frequency of the intervention varied across studies as well, with toileting conducted every two hours over 12-hour, 14-hour, and 24-hour schedules [243].

b) Efficacy (Table 7).

Prompted voiding is more effective than no intervention for improving daytime dryness in nursing home residents and some home care clients (Level 1) [252]. Prompted voiding is not effective and should not be used for persons with end-stage dementia (unable to state name or point to one of two named objects), who are bedbound or require 2-person assist to transfers, or who have more than four UI episodes during a 12 hr daytime period; such persons should be managed by “check and change,” with the goal of dependent continence. Eligible persons should have a three-day trial of prompted voiding, and the intervention should be continued after only in those that achieve appropriate toileting rates (the number of times the resident voided into the toilet divided by the total number of voids) of ≥ 66% or a wet check rate (number of times the resident was wet when physically checked) of ≤20% [259]. All others should be managed by check and change. This approach allows prompted voiding to be targeted to only the approximately one-third of residents who are eligible for and respond to prompted voiding, and could help decrease the considerable time and labour costs now used for inappropriate, unsuccessful toileting [195]. The 2005 revised US guidelines for continence care in nursing homes approved this approach as quality care [260].

No data are available about the long-term effects of prompted voiding. Self-initiated toileting increased, as anticipated, in some trials but concern was raised about increased dependence on the caregiver for toileting assistance.

There is insufficient evidence to determine if timed voiding improves continence (Level 4) [246]. No additional intervention studies on timed voiding since the previous Consultation were located. Several of the studies included in a systematic review had only female subjects with cognitive impairment, and included use of additional interventions such as antimuscarinic drugs (propantheline or flavoxate), staff education, bedside commodes, and absorbent products.

There is insufficient evidence to determine if habit training improves continence (Level 4) [253, 254].

Functional Incidental Training (FIT) incorporates endurance and strengthening exercises (e.g., sit-to-stand, bicep curls) while an aide conducts prompted voiding with a resident [248]. FIT significantly improves physical endurance and UI (measured by wet check). Across several different long-term populations, FIT led to a 38% reduction in daily urine loss [4, 249] However, all FIT efficacy trials relied on trained research nursing stuff, FIT costs more than usual care, [4] and it may be difficult to implement in nursing homes without changes in existing staffing levels, [261] limiting its generalizability [262].

Operant behavioural strategies have shown some effectiveness in improving UI in long-term care residents (Level B) [243, 263]. The underlying principle is that behaviour is modified by its consequences, [264] even in frail adults. A balance must be struck, however, between encouraging self-care activities and patient functional status.

c) Summary of evidence

1. Prompted voiding is effective in the short-term treatment of daytime UI in nursing home residents and home-care clients, if caregivers comply with the protocol (Level 1).

2. Prompted voiding is ineffective and should not be used in persons who are unable to state their name or need the assistance of more than one person to transfer, and these persons should be managed with “check and change.” (Level 1).

3. Prompted voiding should not be continued in eligible persons who after a three day trial have less than a 20% reduction in wet checks (Level 1) or toilet successfully less than two-thirds of the time; these persons should be managed with “check and change.” (Level 1).

4. Interventions combining toileting and exercise decrease wet checks and improve endurance in nursing home residents, including those with psychiatric disease (Level 1).

5. Efficacy of behavioural interventions decrease when implemented by indigenous nursing home staff (Level 1) and the associated labour costs may be difficult to offset (Level 2).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Authors</th>
<th>Study Design</th>
<th>Sample</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prompted Voiding</td>
<td>Palmer, 2005 [243]</td>
<td>Systematic literature review</td>
<td>1 quasi-experimental. 1 repeated measures, 1 prospective case series, and 1 systematic (Cochrane) review</td>
<td>Sample, methods, and results were examined to address: Is prompted voiding effective in reducing wetness episodes and increasing requests for toileting?</td>
<td>Different prompted voiding protocols were used limiting comparison across studies. Sample sizes were small and mainly white elderly female long-term care residents participated. Staff adherence to the protocol was important to its success. Little evidence exists that self-initiated requests for toileting increased. Wetness episodes decreased in the short-term.</td>
</tr>
<tr>
<td>Habit Retraining</td>
<td>Cieslewicz, Chesterly &amp; Rose, 2006 [203]</td>
<td>Cochrane Review update</td>
<td>Nine trials included, N = 674 older adults.</td>
<td>Literature searched according to protocol (all randomized or quasi-experimental studies). Two reviewers evaluated studies for methodological quality; third reviewer proof-read the review.</td>
<td>Insufficient evidence to reach firm conclusions for practice. Suggestive evidence exists for short-term benefit from prompted voiding, longer effects are not known.</td>
</tr>
<tr>
<td>Timed Voiding</td>
<td>Cieslewicz, Johnston &amp; Roe, 2008 [246]</td>
<td>Cochrane Review</td>
<td>Four trials included, N = 378</td>
<td>Literature searched and evaluated per protocol. Trials too heterogeneous to for meta-analysis.</td>
<td>Adherence to habit retraining protocols is difficult for staff. Evidence is too limited to judge if improvements in continence make habit re-training protocols worth investment.</td>
</tr>
<tr>
<td>Mobility and Toileting Interventions</td>
<td>Oslolander, Griffth, McDowell, Flato, Kubnor &amp; Schnelle, 2005 [4]</td>
<td>Randomized controlled trial crossover design.</td>
<td>Two trials met inclusion criteria, N = 298 female subjects with reduced mobility and cognitive impairments.</td>
<td>Literature searched and evaluated per protocol.</td>
<td>Nighttime incontinence was significantly lower in intervention group. Data were considered too few to make a recommendation for or against timed voiding.</td>
</tr>
<tr>
<td>Prevention Interventions</td>
<td>Dijkstra et al, 2004 [251]</td>
<td>Randomized controlled trial comparing behaviour modification programme (BMP) to no treatment group.</td>
<td>Ambulatory post-operative continent volunteer women, N = 359.</td>
<td>Women in behavioural intervention group received educational sessions and individualized evaluations of knowledge, adherence and skills.</td>
<td>At 12 months follow up, women in behavioural intervention group had significantly better continence status, pelvic muscle strength and displacement score.</td>
</tr>
</tbody>
</table>
6. It is uncertain whether habit retraining reduces UI in frail older persons (Level 4).

7. It is uncertain whether timed voiding reduces UI in frail older persons (Level 4).

8. There are no proven interventions to reduce nighttime UI in frail elders (Level 4)

3. INTERVENTIONS WITH LONG TERM CARE STAFF AND CAREGIVERS

Many frail elderly persons must rely on family, caregivers, or residential and/or nursing staff for toileting assistance and personal care. These carers may not be available as frequently as necessary for the frail elder to maintain continence, and even if available they may not be able or willing to provide the needed assistance. Research has shown that the frequency of toileting assistance actually provided in US nursing homes is too low to maintain continence [265].

There is dissonance between nursing home surveyors, nursing staff, and nursing home administrators' knowledge and beliefs about UI and its management, which may be an important barrier to effective UI care [156]. One study suggests that nurses in the acute and long-term care settings continue to provide urine containment interventions rather than promoting continence [266 267]. Nursing staff preferences for UI management (toileting) are in conflict with those of residents and their families patient treatment preferences (medications and garments) [187, 188].

In long term care, a two-prong behavioural intervention to UI care, one geared towards the resident and the other geared towards staff members, appears necessary [268, 270]. Nursing assistants play a key role in the success of behavioural programmes, and organisational schemes need to be devised to create incentives for them to keep residents continent [271]. Direct care providers will be unlikely to implement programmes unless residents and their families advocate for them [272].

This advocacy, however, appears unlikely if, based on their experiences, nursing home residents have reduced expectations and do not anticipate receiving sufficiently frequent and prompt toileting, and therefore express no desire for more frequent toileting [265]. One documented barrier to toileting programmes in long term care is their labour intensity. Bladder training programmes are considered one of the three most time consuming activities for long-term care staff [197].

A specialty practice exemplar model has been proposed to improve continence care in long-term care, with a nursing faculty member with expertise in the assessment and treatment of UI having a clinical practice in a facility. Graduate nursing students, working with this individual, focus on the Minimum Data Set Resident Assessment Protocol for UI. Assessment and treatment skills ultimately are transferred to the facility nursing staff members through several mechanisms, including staff education and improved continence care systems [273]. Quality assurance programmes using incontinence quality indicators have also been proposed [157]. A clinical leadership model in the sub-acute setting in Australia used a staff empowerment and mentorship model to make evidence based changes related to continence care during patient's stay and on discharge [244].

a) Quality of data

Several authors point to the difficulty of conducting research in long-term care settings [268, 269, 274]. Factors such as staffing ratios, changes in administrative and regulatory policies, and fiscal issues are beyond researchers' control. Several investigators report that staff compliance was less than total, and some experienced problems with staff training. For instance, in one study several staff members did not attend group-training sessions and needed one-on-one training, and other staff members did not perform the protocol or document its use, especially when staffing levels were low [269]. Little staff intervention research to improve continence in older persons has been conducted in the acute-care setting.

b) Results

One group of researchers investigated the effect of a scheduled toileting programme on nursing home staff injury using a quasi-experimental design using a 75 bed unit and a similar comparison unit [275]. Fifty residents in the intervention unit were selected to participate based on an assessment indicating their eligibility for a toileting programme. Mechanical lifts were purchased for the intervention unit in anticipation of an increase in toilet transfers. Regular toileting increased from 12% pre-intervention to 67% in the intervention and 26% in the comparison unit. Staff injuries related to toileting did not increase in the intervention group, and the staff also noted less resident agitation. In-service classes on UI did not change staff knowledge and attitudes about UI, or improve resident toileting (only 70% of toileting assists were completed) [268]. The authors noted that staff members believed that toileting was “not worthwhile” for some residents. In a randomized study using advanced practice nurses (with post-graduate training) to work with staff to implement evidence-based protocols, residents in the intervention arm experienced significantly greater improvement in UI compared with those receiving usual care [276].

Several studies detail extensive barriers to UI care [166, 277, 278]. A staff survey revealed that nursing assistants believed prompted voiding was very helpful to residents in reducing the frequency and volume of incontinent voids, but that inadequate staffing, staff work load, turnover, and absenteeism were significant
barriers to prompted voiding. They believed that increased numbers of staff, improved communication, ongoing education, and alternative modes of care delivery were necessary to facilitate prompted voiding. Overall, staff believed toileting programmes improved resident quality of life but the realities of long-term care made them difficult to implement [279]. Nursing assistants believed that UI was a normal part of ageing and that nothing could be done for it, 99% of residents with UI in the study facility wore absorbent products and only 3% had received UI treatment [166].

When staff perceptions regarding completed toileting assistance were compared to research staff observations, staff over-inflated the percent of toilet assists they completed (stating 80-90% when the observed was 70%) [280]. Staff members also believed that residents were happier with a prompted voiding programme, yet only 52% thought the programme improved residents’ continence. In another study, long-term care facility residents reported a mean of 1.8 daily assists to the toilet, regardless of whether they were on a toileting programme or not [272].

Continence care creates additional needs for family caregivers. In a small pilot study, caregivers at home felt that the requirements of a behavioural protocol were more than they could manage [281]. Other family caregivers report embarrassment and social isolation as their most frequent emotional responses to UI, and a need for information about resources [282]. In contrast to long-term care staff, family caregivers were adherent with prompted voiding 89% of the time, and 93% were somewhat or completely satisfied with the decrease in UI [257]. A descriptive study found that caregivers of frail elders with UI report a high level of physical fatigue (70%) [282]. Caregivers dealing with different levels of UI (mild, moderate, catheter managed) have different educational needs and require different levels of support from healthcare professionals. For example, carers of frail persons with mild UI expressed the greatest need for different levels of UI (mild, moderate, catheter managed) have different educational needs and require different levels of support from healthcare professionals. For example, carers of frail persons with mild UI expressed the greatest need for professional care, but those of persons with moderate UI or catheters spent the highest number of daily hours providing care [283].

A computerised quality management programme for prompted voiding was tested in a convenience sample of 85 residents in eight US nursing homes [273]. Each facility was asked to identify staff members for the following roles: main contact person; quality control specialist; two licensed personnel who would conduct UI assessments; and two nursing/health care assistants who would implement the prompted voiding intervention. Information on the computer system included UI assessment and residents wetness rates. Research staff monitored the database and provided the nursing staff feedback by telephone consultation. The programme was effective in improving dryness for six months while research staff monitored the database, but only one facility continued the programme after the research ended [278]. The researchers noted that current incentives for nursing homes to maintain UI management systems are insufficient.

A scheduled toileting programme, designed to explore risk of injury to staff members and resident agitation and aggressive behaviour, required statistically significantly more staff time than “check and change,” with cleaning soiled patients while they were in their bed (slightly longer than 6 minutes to toilet versus slightly longer than 4 minutes to clean) [275].

Acute care patients have preferences for urinary incontinence treatment that is significantly discordant to hospital staff. For example, nurses and physicians preferred scheduled toileting over diapers more than did the patients [188]. The authors suggested that communication about treatment preferences should occur.

c) Summary of evidence

1. Although long term care nursing staff generally believe prompted voiding to be helpful, they fail to implement such programmes. (Level 2)

2. Interventions designed to maintain implementation of patient-focused behavioural interventions by long-term care staff are helpful in promoting continence care. (Level 2)

3. Family caregivers in the community setting can be adherent to behavioural interventions but experience fatigue and social isolation. (Level 2)

4. The use of computerised programmes to manage quality control for UI management does not persist after research studies have ended. (Level 2)

5. Toileting programmes including mechanical lifts may reduce staff injury and decrease resident agitation associated with toileting. (Level 2)

6. There is insufficient data to determine whether long-term care UI quality improvement efforts have an impact on costs related to UI (Level 4)

4. PHARMACOLOGICAL TREATMENT OF UI IN FRAIL ELDERLY PERSONS

a) Background

The pharmacological management of UI in healthy older persons is discussed in Chapter 10, Drug Treatment. This section deals with the management of frail elderly, using the definition at the beginning of the chapter. Specific treatments for bladder outlet obstruction and associated LUTS in frail elderly men are outside the scope of this chapter; special issues in the care of frail older men with UI are discussed above.

Frail persons with UI should be considered for drug treatment only following a comprehensive evaluation
of remediable causative factors, and if they are appropriate for and have had a trial of behavioural and lifestyle interventions. Drug treatment should not generally be used for persons who make no attempt to toilet when aided, become agitated with toileting, or are so functionally and cognitively impaired that there is no prospect of meaningful benefit. Even so, a recent study of US nursing home residents suggested that only a small proportion of incontinent residents potentially suitable for drug therapy ever received it [284]. There is still much to do, with potential benefit for many.

b) Quality of data

We located 17 randomised placebo controlled trials (RCTs) of antimuscarinic medication, predominantly involving subjects over the age of 80. The majority were of modest quality often reflecting their publication date (up to 40 years ago). The available RCTS were predominantly done in the US, with a small number in the UK, Germany, Taiwan and Japan. Approximately half of identified studies were conducted in long-term care facilities, whose residents are overwhelmingly female. All focus on antimuscarinic treatment of presumed urgency UI. UI diagnosis was overwhelmingly symptom-based; only three studies included urodynamic evaluation. The majority of newer studies including older persons but whom overwhelmingly appear to be “fit.” For most studies it was impossible to identify whether subjects were indeed frail, except where the study was performed in an institutional environment, in which it is reasonable to assume a high prevalence of functional and cognitive dependence.

Many older trials used a randomised cross-over design, which lessens power and increases the non-drug effect. The methods of blinding and randomisation in RCTs was seldom specified.

Other than those conducted by the pharmaceutical industry, most studies were generally small and under-powered, and others lost power because of high drop out rates due to illness and death (inevitable in trials with frail elderly persons). Because of these issues, many RCTs provide only Level 2 evidence. Some larger studies in older persons without clear frailty are included here, to recognise that, since the last consultation, there has been an increasing emphasis on including older persons in drug trials.

Precise descriptions of the target population—including the definition of “frail persons” and a comprehensive description of the degree of cognitive and functional impairment—were usually absent. Although some investigators included information on patients’ functional and cognitive status, as well as comorbid conditions, the descriptions were often only qualitative, and none addressed these issues adequately in the analyses. Explicit, concurrent behavioural therapy was used in most nursing home studies, yet may have occurred in many others. Combination therapy and high comorbidity could have attenuated differences between drug and placebo, and make it difficult to compare results directly with studies in healthy older and younger persons. Outcomes were universally assessed by UI frequency (pad-weighing, bladder diaries, and wet-checks), and none reported quality of life outcomes.

Treatment of some reversible causes of UI also may have affected the ability to detect drug effects. In at least six studies, investigators treated subjects with “urinary tract infection” (usually defined as pyuria and bacteriuria in the presence of UI) before initiating antimuscarinic therapy, and one study excluded such subjects. In another, investigators treated urogenital atrophy with oestrogen prior to antimuscarinic therapy, possibly leading to an additional amelioration of symptoms. However, no other reversible causes were addressed prior to entry or randomisation in most studies.

The generally low quality of these trials reflects not just study design, but the larger issue of the difficulty of doing large, prospective intervention trials in frail populations. Moreover, UI in frail elderly is universally a multifactorial problem involving a large number of factors beyond the bladder. Thus, the expectation that drug therapy targeted solely at urodynamic DO or SUI would markedly improve/cure UI in this population is unlikely to be realised.

c) Results

Results from randomised trials are summarised in Table 8; the following sections discuss specific drugs in detail, and include randomised trials as well as non-randomised trials in older persons.

1. **Oxybutynin**

The majority of studies in frail older persons used immediate-release oxybutynin (oxybutynin-IR). There are two studies of extended release oxybutynin (oxybutynin-ER), one examining cognitive effects in nursing home residents with dementia and urgency UI, [285] and the other involving community-dwelling women over age 65 [286]. Published trials of the efficacy of transdermal oxybutynin included subjects up to age 100 and in institutional care settings, but did not stratify results by age or comorbidity [287].

The pharmacokinetics of oxybutynin-IR and its active metabolite, N-desethoxybutynin, in one study tended to show greater plasma levels and bioavailability with increasing frailty and age [288]. Another found peak levels in 21 octogenarians similar to those reported in young normal males (12.5 ng/mL vs. 8.9 ng/mL) [289]. A study of the pharmacokinetics of transdermal oxybutynin showed no significant difference in plasma levels between young and old (up to 77 years) subjects [290].
<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Design</th>
<th>Setting and pts</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>Zorzitto 1989 [293]</td>
<td>8 day RCT; Oxy-IR 5 mg twice daily</td>
<td>Long term care residents (n=24)</td>
<td>No difference from PLC</td>
<td>Subjects tolerated 10 times daily, trial short</td>
</tr>
<tr>
<td></td>
<td>Oustadner 1986 [291]</td>
<td>RCT Oxy-IR vs. PLC vs. nil</td>
<td>15 long term care patients who failed prompted voiding</td>
<td>No difference in % of check ups, but 46% Oxy pts had ≤ 1 day per week UI episodes vs. 18% PLC (p&lt;0.005)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Szonyi 1995 [294]</td>
<td>2 mos RCT: titrated Oxy IR with bladder retraining vs. bladder retraining alone</td>
<td>Frail, community-dwelling</td>
<td>Significant drug effect on frequency (95% CI 8-27 fewer voids/2 wks but not on UI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zorzitto 1989 [293]</td>
<td>6 day cross over RCT; Oxy IR 5 mg twice daily</td>
<td>Long term care residents (n=24)</td>
<td>No difference from PLC</td>
<td>Subjects tolerated 10 times daily, trial short</td>
</tr>
<tr>
<td>Propiverine</td>
<td>Dorschner 2003 [327]</td>
<td>4 weeks RCT propiverine 15 mg three times daily</td>
<td>'Elderly' (mean age 65) with urgency or mixed UI (n=98)</td>
<td>54% decrease in UI episodes (p&lt;0.05 vs. baseline, PLC response not described)</td>
<td>Low AE (2% drug mouth on drug), no QT prolongation. Efficacy reportedly better for urgency than mixed UI.</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Caudal 1986 [343]</td>
<td>RCT titrated imipramine 25 mg/day, increased monthly by 25 mg</td>
<td>Older women referred to continence clinic (n=34) with urodynamc involuntary detrusor contractions</td>
<td>No statistical difference in continence rate (78% drug, 43% PLC) at trial and 26 months; concluded no benefit over the habit training that all subjects received</td>
<td>Subjects clinically well and could understand nature of the study. Type II error possible. AE 'frequent': dry mouth, constipation, one episode of confusion.</td>
</tr>
<tr>
<td>Emepronium</td>
<td>Williams 1981 [335]</td>
<td>Cross over</td>
<td>'Elderly' patients with urgency UI and urodynamc involuntary detrusor contractions</td>
<td>No significant effect on daytime or night-time UI</td>
<td>Subjects tolerated 10 times daily, trial short</td>
</tr>
<tr>
<td></td>
<td>Walter 1982 [336]</td>
<td>Cross over</td>
<td>'Elderly' patients with urgency UI and urodynamc involuntary detrusor contractions</td>
<td>Subjective cure/improvement rate 79% for drug and PLC; no change in urodynamc parameters</td>
<td></td>
</tr>
<tr>
<td>Emepronium and Fluoxate</td>
<td>Robinson 1983 [337]</td>
<td>RCT 14-20 days Emepronium 200 mg 4x/day plus Fluoxate 100 mg 4x/day vs. PLC with cross over</td>
<td>No significant change in UI episodes or urodynamc detrusor overactivity, but all subjects felt better on drug</td>
<td>Data presented only on 14 pts who completed trial; underpowered</td>
<td></td>
</tr>
<tr>
<td>Prepantheline</td>
<td>Zorzitto 1986 [338]</td>
<td>4 day cross over RCT Pre 15 mg 4x/day vs. PLC; non responders repeated cross over with doubled doses</td>
<td>43 long term care patients (42% female) with urodynamc involuntary detrusor contractions</td>
<td>Only 30 mg 4x/day dose statistically better than PLC</td>
<td>50% experienced ADEs (dry mouth, constipation); 1 pt at 30 mg dose developed retention and another bowel obstruction)</td>
</tr>
<tr>
<td></td>
<td>Dagouchers 1965 [341]</td>
<td>Cross over RCT, each period 10 day treatment with Prepanthline 15 mg 4x/day, or Vasopressin 5 units 2x/day or PLC</td>
<td>27 women in long term care</td>
<td>No differences in wet checks between the drugs and PLC. Patients who could use a bed pan had better response to vasopressin</td>
<td>No ADEs reported</td>
</tr>
<tr>
<td></td>
<td>Whithead 1967 [340]</td>
<td>2 week RCT Prepanthline 75 mg at bedtime vs. PLC, cross over at 1 week without washout all received habit training</td>
<td>40 long term care residents with severe dementia (50% female)</td>
<td>Prepantheline moderately yet significantly better than PLC, especially in women</td>
<td>Urinary retention in one man found in a related case series</td>
</tr>
<tr>
<td></td>
<td>Drag 1966 [339]</td>
<td>9 week RCT Prepanthline 15 mg 4x/day vs. PLC</td>
<td>31 'senile' long term care residents (71% female)</td>
<td>No difference between drug and PLC</td>
<td>AE: dry mouth (2 persons), hypersensitivity (1), transient blurred vision (1)</td>
</tr>
</tbody>
</table>
• Efficacy

An early, small (n=15) trial of oxybutynin-IR and habit training in long-term care residents showed no effect on UI episodes [291]. However, in a subsequent and larger study in long-term care residents who had failed prompted voiding alone, the addition of titrated oxybutynin-IR resulted in a significant but modest reduction versus placebo [292]. Wet-checks decreased from 27% at baseline to 20% on drug and 24% on placebo, leading the authors to conclude that the improvement was not clinically significant, especially given the continuing requirement for nursing intervention. However, their a priori definition of “clinically significant improvement” (one or fewer episodes of daytime UI) was achieved by 40% on drug but only 18% on placebo (p<0.05). The dose generally associated with improvement was 2.5 mg three times daily. In another controlled study of UI in long-term care residents (n=24), there was little effect of oxybutynin-IR 5 mg twice daily given for 8 days, but all residents were toileted 10 times daily, and the dose may have been too high and given too infrequently [293]. In a randomised two month trial in frail community-dwelling elderly, oxybutynin-IR plus bladder training was subjectively and objectively superior to bladder training alone in improving urinary frequency (95% CI 6-27 fewer voids per 2 weeks) but not UI [294]. Insufficient information was available regarding a Japanese study in 75 “elderly” patients to assess the population and outcomes [295]. A study in 416 community dwelling older persons, including the fitter elderly, found 68% reported a partial or complete symptomatic cure with 2.5 mg three times daily; 30% of subjects experienced ADEs, but only 10% withdrew because of them [211]. Only one of the two identified RCTs examined efficacy of oxybutynin-ER [286]. The other examined the effect on cognition [285] and is discussed below. No published RCTs of transdermal oxybutynin in the frail elderly were found, and post hoc sub-analyses of efficacy in subjects over the age of 65 has been published only in abstract form. In a small Japanese case series (n=13, mean age 75) in persons with urgency UI and cystometric DO, intravesical oxybutynin caused no significant increase in mean bladder capacity one hour after installation of 5 mg oxybutynin at pH 5.85 [296]. In four patients who continued twice daily installation, two had UI “disappear” and one “markedly decrease” (duration until effect not noted). No patient developed an “increased PVR” (not defined).

• Predictors of efficacy

Predictors of efficacy were studied in one study in
persons with urgency UI and urodynamic DO (n=41, mean age 79) treated with 2-4 weeks of oxybutynin-IR (5-15 mg/day) [297]. Factors associated with baseline urine loss (by pad weighing) were impaired cognitive orientation (on the Cambridge Mental Disorders of the Elderly Examination), number of daily voids, and fluid intake. Persistent urine loss after treatment was associated with impaired orientation, reduced sensation of bladder filling during cystometry, and most significantly global cortical under-perfusion on single photon emission computed tomography scan, suggesting that cortical factors are the main determinant of the severity of urgency UI before and after oxybutynin. In a study of 80 older patients (mean age 74), patients with dementia (by Hasegawa dementia scale) were less likely than cognitively intact patients to report subjective improvement in UI with antimuscarinic agents, despite similar objective outcomes [298]. However, these results could reflect treatment-associated cognitive effects.

• Adverse reactions

Cognitive side effects from oxybutynin have been reported in older persons. In one case series, four older men with Parkinson's disease and mild-severe cognitive impairment developed confusion, psychosis, hallucinations, behavioural disturbance, and/or paranoia after receiving oxybutynin-IR (5-15 mg/day), which resolved when oxybutynin was stopped [299]. Of note, each patient was also on L-dopa (co-beneldopa) and selegiline, and the observed effects could reflect drug-drug interactions. However, these results are belied by a large RCT in which oxybutynin-ER 5 mg daily did not cause more delirium than placebo in NH residents with UI and dementia [285].

There are case reports of reversible peripheral neuropathy confirmed by re-exposure in a 70 year old woman taking oxybutynin-IR 5-7.5 mg/day [300] and recurrent heat stroke associated with oxybutynin in one elderly patient [301]. Few studies have addressed cardiac effects. A small study of older persons in the community with UI (n=20, mean age 75) found no change in resting heart rate or electrocardiograph evidence of either prolonged PR interval or QTc, or QTc dispersion after 4 weeks of oxybutynin-IR (mean daily dose 7.6 mg [range 2.5-10 mg]) [302]. Using a large administrative utilization database, no association was found between antimuscarinics (oxybutynin, flavoxate, hyoscyamine) and ventricular arrhythmia and sudden death [303]. Post-marketing adverse events with extended release oxybutynin include tachycardia and hallucinations [304].

2. TOLTERODINE

Studies of tolterodine in “older patients” do not include frail persons. For example, “older” patients in one RCT of tolterodine-ER were all community-dwelling, able to complete a 7-day bladder diary, had a high prevalence of previous antimuscarinic treatment (53-57%), and a low prevalence of arthritis (15-18%), unlike most frail older persons [305]. Although several trials include elderly persons in their ninth and tenth decades, [305-307] mean age (~64 years) was much lower, persons with “[unspecified] disease which the investigator thought made the patient unsuitable” and/or “renal disease” were excluded, and results were not stratified by age. In a secondary analysis of a large, open label German trial of tolterodine-IR 2 mg twice daily, higher age was significantly associated with “less favourable efficacy” [308]. However, the absolute difference in odds was only 0.019, there was no association of tolerability with age, only mean age is described, and UI frequency was based on patient report, not bladder diaries, all of which fail to add up to a clinically meaningful difference. In a non-randomised study, tolterodine was given to 48 nursing home residents who did not respond to toileting alone; 31 of these patients had a 29% increase in dryness (versus 16% in residents on toileting alone) [309].

• Adverse reactions

There are no prospective systematic data on tolerability in frail patients. There have been case reports of hallucinations (73 year old woman with dementia [310]) and worsening memory, [311] including a 65 year old cognitively intact woman [312]. There is a case report of delirium when tolterodine was given with a cholinesterase inhibitor [313]. Analysis of prescription-event monitoring in the UK (mean patient age 63) found a significant association between age (>74 years) and psychiatric events and tachycardia (odds ratios not given) [314]. In a similar database study, the age- and sex-adjusted risk of hallucinations with tolterodine was 4.85 (95% CI 2.72-8.66) compared with 10 other drugs (acarbose, alendronate, famotidine, 3 proton pump inhibitors, finasteride, meloxicam, misoprostol, and nizatidine) chosen for presumed lack of antimuscarinic, cardiovascular, and CNS activity, and available in the database. Important confounders such as other drugs and comorbidity were not evaluated. Similar to oxybutynin-ER, post-marketing information on tachycardia and hallucinations was added to the tolterodine-ER package insert in 2003 [315].

3. FESOTERODINE

There are no published data in the frail elderly. Older, fitter subjects have been included in clinical trials, with persons over age 65 comprising approximately one-third of the total number of subjects studied, [316] yet no published results stratify by age.

4. SOLifenacin

Pharmacokinetics of solifenacin were evaluated in 23 older subjects (mean age 68); tmax was longer and a there was a higher maximum plasma concentration,
but the differences from results in younger patients were small and deemed by the authors to be clinically irrelevant [317]. There are no randomized controlled trials specifically examining its efficacy in frail elderly. A secondary analysis of pooled Phase III data in patients aged 65 and older (all community dwelling and fit, mean age 72) found similar efficacy to that reported for younger and middle aged persons [318]. However, direct comparison with subjects < 65 yrs from the same pooled trials was not done. Adverse effects in older frailer patients have not been specifically reported. However, data from an open-label, 12-week trial in patients treated by community urologists found that overall treatment-emergent adverse events were more likely in patients aged >80 years (OR 3.9 [95% CI 1.3-11.5]) and taking concomitant medications (OR 1.8 [95% CI 1.2-2.6]) [319]. Patients with concurrent medications were more likely to be male and on average about 12-14 years older, have comorbid disease, and be administered higher doses of solifenacin, yet had no observed increase in heart rate or blood pressure with solifenacin.

5. Darifenacin

We located one RCT of darifenacin for OAB in persons aged ≥65 (mean 72), in which there was no statistically significant difference between drug and placebo for the primary end point, UI frequency [320]. There were statistically significant improvements with drug for urinary frequency (-25.3% vs. -18.5% with placebo; p < 0.01) and quality of life, as measured by OAB-q and patient perception of bladder condition. Although subjects were not frail, this is the only prospective study of a more modern antimuscarinic in older persons.

- **Adverse effects**

Cognitive adverse effects of darifenacin have been prospectively studied in a series of trials. The first was a 3-period crossover RCT in 129 older subjects (mean age 71, 54% of those screened), 88% of whom had comorbid medical conditions and 93% were on other medications [321]. Cognition was assessed using a standardized computerized battery. Darifenacin at variable doses did not adversely affect cognition compared to placebo, but results were aggregated so that patients did not serve as their own controls. A subsequent study in cognitively intact older persons (n = 49, mean age 66) using a similar computer cognitive battery compared titrated darifenacin and oxybutynin-ER with placebo over 3 weeks [322]. Oxybutynin-ER but darifenacin or placebo adversely affected the primary endpoint, delayed recall on the Name-Face Association test. However, oxybutynin was titrated one week earlier than darifenacin, and to a final dose (20 mg daily) much higher than is commonly used in clinical practice. Also, there were no differences between the two drugs and placebo for many other domains of the cognitive battery.

6. Trospium Chloride

Although often promoted for use in the elderly because of the reduced likelihood that the drug crosses the blood-brain barrier, we found no studies that evaluated the agent specifically in frail older persons. All studies have included “younger elderly,” but even the most recent have not stratified results by age [323].

7. Propiverine

In 46 patients with dementia (mean age 81), there was a 40% decrease in urgency UI with propiverine 20 mg/day for 2 weeks, [324] similar to two small Japanese trials [325, 326] and a German trial in 98 patients [327]. The agent’s high protein binding, extensive first pass metabolism, 15-hour half life (in normal younger persons), and renal clearance [324] need to be considered if used in frail older persons.

8. Duloxetine

There was a statistically significantly reduced rate of clearance of duloxetine in patients over age 65, based on a study in 12 fit women aged 65-77 [328]. The authors felt the differences were not clinically significant given the “similar safety profile” of the drug in older and younger women. In three large RCTs in women (with SUI, aged 24-83 years, n = 494 [none frail]; [329] with OAB, aged 21-84 years [none frail], n = 306; [330] and with mixed UI, up to age 85 [331]), duloxetine decreased UI and urinary frequency, but none stratified outcomes or adverse effects by age. Duloxetine is not approved by the US FDA and is not recommended by the UK National Institute of Healthcare and Clinical Excellence.

9. Oestrogen

Oral oestriol 3 mg/day was compared to placebo for 12 weeks in 34 women aged 75 [65]. The group was highly self-selected; complete results were available for 11 with SUI, 12 with urgency UI, and 8 with mixed. Two-thirds of urgency UI and 75% of mixed UI patients reported improvement; there was no effect on SUI. Four patients reported metrorrhagia and mastodynia. A 10 week crossover trial comparing quinestradiol 0.25 mg four times a day with placebo in 18 women in long-term care (type of UI not reported) found a mean 12% decrease in UI episodes vs. 22% increase with placebo [332]. The combination of conjugated oestrogen 0.625 mg/day and progesterone 2.5 mg/day was evaluated in a 6 month, placebo-controlled trial in 32 female NH residents with predominantly urgency UI, who also received prompted voiding [333]. In the 21 women who finished the trial, there was no difference in wet checks between drug and placebo despite increased serum oestrogen levels and partial oestrogen effect on vaginal cytology and pH in the women on drug. Two women on the drug developed vaginal spotting, and 10% developed breast tenderness. Similar lack of efficacy despite vaginal
changes were found in a case series of 9 frail women (mean age 83) with urgency or mixed UI using an oestrogen-implanted vaginal ring (Estring®) [334].

10. MISCELLANEOUS MEDICATIONS

Most of these agents are not widely used in clinical practice, and are included here for primarily historical purposes. **Emepronium bromide** had no significant effect on daytime or nocturnal UI among patients with chronic “organic brain syndrome” or chronic “functional psychiatric illness,” [335] similar to another RCT [336]. In 20 frail patients seen in a continence clinic (only 14 completed the trial), treatment with both **emepronium and flavoxate** for two weeks had no effect on UI or cystometric DO, but did increase in PVR [337]. **Propantheline** (15 mg three to four times daily) had no effect on daytime UI [338] or nocturia [339-341]. When the dose was increased to 30 mg four times daily, useful clinical effects were overwhelmed by antimuscarinic side effects [338]. In a similar small NH study, nocturia but not daytime UI improved with **concomitant propantheline and flavoxate** [342]. Titrated **imipramine** was no different than placebo in a small trial in ambulatory older persons also treated with habit training [343]. **Flavoxate** 200 mg at bedtime reduced nocturia in a small uncontrolled trial (n=40, age 51-79) [344]. An even smaller trial (6 “elderly” patients with urgency UI and cystometric DO) found no cystometric or clinical effect of a loading dose of 100 mg intravenous followed by 200 mg orally four times daily for 7 days [344].

**Flurbiprofen** 50 mg 4 times daily for four weeks decreased UI by nearly 50% (vs. no change with placebo) in 37 older persons (median age 78) with “idiopathic detrusor instability,” yet complete data were available for only 11 subjects [345]. **Procaine haematoporphyrin** 200 mg/day had only borderline effect in an 26 week RCT among 65 residents (mean age 85) of UK care homes with clinical “urge UI due to neurogenic bladder.” [346]. No studies were identified that evaluated **bethanechol chloride** specifically for frail elderly with UI and impaired detrusor emptying.

11. COMPARATIVE TRIALS

We found no studies that compared antimuscarinic agents in frail older persons.

5. SUMMARY OF THE EVIDENCE

1. Short-term treatment with oxybutynin-IR has small to moderate efficacy in reducing urinary frequency and urgent UI when added to behavioural therapy in long term care residents. (Level 2)

2. Low dose oxybutynin-ER does not cause delirium in cognitively impaired nursing home residents (Level 1)

3. Oxybutynin-IR has been associated with cognitive adverse effects in persons with dementia and/or Parkinson’s disease (Level 3), although the incidence and prevalence are unknown (Level 4)

4. Oxybutynin has been associated with tachycardia (Level 3), but not associated with QTc prolongation (Level 3) or ventricular arrhythmia (Level 2).

5. Oxybutynin is less effective in persons with impaired orientation, cerebral cortical under-perfusion, and reduced bladder sensation (Level 2).

6. There is insufficient evidence to determine the efficacy, tolerability, and safety of the following agents in frail elderly (Level 4):
   a. Intravesical oxybutynin
   b. Trospium
   c. Tolterodine
   d. Fesoterodine
   e. Darifenacin
   f. Solifenacin
   g. Duloxetine
   h. Oral and topical oestrogen
   i. Bethanechol

7. Tolterodine is associated with cognitive impairment and tachycardia (Level 3), although the incidence and prevalence are unknown. (Level 4)

8. There is evidence for lack of efficacy in the frail elderly for:
   a.Emepronium bromide (Level 2-3)
   b. Propantheline (Level 2)
   c.Imipramine (Level 2)
   d.Flavoxate (Level 3)

9. Combination of propantheline and flavoxate reduces nocturia but cannot be recommended because of unknown tolerability and safety (Level 4)

10. Flurbiprofen, propiverine, and procaine haematoporphyrin cause a small reduction in UI (Level 3) but tolerability and safety are uncertain (Level 4).

6. SURGICAL TREATMENT

a) Background

Very little is known about surgical treatment of UI in the frail elderly, likely reflecting a bias toward conservative therapy in a group with high prevalence of comorbidity and functional impairment. There are still very few studies of gynaecological surgery in women, surgical treatment for post-prostatectomy UI in frail men, minimally invasive procedures, or peri-operative care (including prevention of common post-operative complications) in urological and gynaeco-
logical patients. We reviewed the available data and general issues regarding peri-operative care which could improve surgical outcomes in this group. Surgical treatment of UI in healthy older persons is covered in Chapter 15: Surgery for Urinary Incontinence in Men, Chapter 16: Surgery for Urinary Incontinence in Women, and Chapter 17: Surgery for Pelvic Organ Prolapse.

An exhaustive review of surgical management of UI in the frail elderly is beyond the scope of this chapter. Therefore, in providing an evidence-based summary on this topic, we have taken advantage of the recent literature review and research recommendations from the American Geriatric Society, New Frontiers in Geriatrics Research: An Agenda for Surgical and Related Medical Specialties [347]. This project involved systematic literature reviews that were used to generate summary statements and recommendations for research. Their findings and recommendations pertinent to the frail elderly regarding surgical treatment of geriatric UI, [348] geriatric gynecological surgery, [349] and general care of the geriatric surgical patient [350] are included in the summary statements below. Data supporting these conclusions are available in the monograph [351].

b) Incontinence surgery in frail elderly women

Data on surgery rates in older frail women are difficult to find and overall appear very low. Several studies have used U.S. national hospital discharge databases to examine surgery rates, but unfortunately they either age-adjusted results [352] or used relatively younger cut-points (e.g., <50 years) [353]. Even in series that specifically looked at elderly women (mean age 78, range 68-90), most patients were cognitively intact (95%) [354]. Cognitive impairment appears to bias against having surgery: in one study, only 0.11% of operations for UI were done in women with dementia, cerebrovascular disease, or hemiplegia combined [353]. While absolute numbers of ambulatory UI surgery cases in women increased from 1994-1996, the percent done in those aged ≥80 years remained the same (4-5%), [355] and the results were similar for pelvic organ prolapse surgery (5%) [356]. In the US, surgery rates in elderly women vary by region of the country and race [355, 356].

One single-centre, community-based series of 54 patients aged 70 years and over provides a picture of this surgical population [357]. Twenty-eight percent of patients were aged >80, four resided in a nursing home or assisted living facility, 82% had significant comorbidity, and 32% were classified as American Society of Anaesthesiology class III risk. Intra-operative complications occurred in 11% of patients; post-operatively, 11% required intensive care monitoring, 6% had serious complications, 7% became delirious, and 9% had slow return of bowel function [357]. The authors concluded that discharge planning is especially important for these patients, and recommend pre-surgery planning of place of discharge and likely care assistance needs [357].

Although higher complication rates generally reflect the comorbidity common in frail elders (10.4% complication rate with comorbidity vs. 5.8% without it, p<.001), [353] some studies have found age protective (in one, age ≥73 years was associated with lower risk of vaginal cuff infection and recurrent prolapse following vaginal sacrospinous fixation [358]). Overall, the morbidity and mortality for geriatric patients undergoing anti-UI procedures are similar to those of other major non-cardiac surgical procedures [348]. Mortality is inconsistently associated with increased age, and most strongly related to cardiac or cancer complications [349]. Many studies do not uniformly control for the impact of comorbidity on mortality [348, 349]. Pre-operative administration of oestrogen appears ineffective in promoting wound healing [350]. Patient-controlled analgesia provides adequate pain control and sedation and increased patient satisfaction compared with standard fixed-dose and time-administered medications in cognitively intact geriatric patients [350]. Choice of anaesthetic agent may affect postoperative cognition [350] and urinary retention. The use of methylaltrexone to treat opioid-related urinary retention may become an important adjunct to surgical care in frailer patients [359]. Very few age-specific data on outcomes are available, and no studies systematically examine quality of life, functional outcome, and discharge site.

With the advent of newer “minimally invasive” procedures, there has come some modicum of testing in older, albeit, not frail, patients. Injection of bulking agents in women appears to be effective in older women, and age does not appear to correlate with outcomes [348]. In a randomized controlled trial of tension-free vaginal tape (TVT) versus 6-month wait-list control, [360] at 6 months the intervention group had a statistically significantly greater improvement in mean I-QOL score, patient satisfaction score, and urinary problem score. There was no objective measure of cure. Peri-operative complications were not insignificant, with bladder perforation by needle in one-in-five (22.6%) which required 24 hours of indwelling catheterization, urinary retention (12.9%), and less than 5% with either a urinary tract infection or new urinary urgency (3.2%). In an uncontrolled case series examining the use of the suprapubic arch (SPARC) sling procedure, the outcomes in 43 older women (ages 65-91) were separately examined. Objective cure rate was evaluated by clinical and urodynamic examination and subjective cure rate was assessed using a visual analogue score and a global patient impression questionnaire, all at 3, 6, and 12 months. At a mean follow-up of 36 months (range, 12-54 months), objective and subjective cure rates with
surgery were 91% and 95%, respectively [361]. There were statistically significant improvement in pad weight and pad numbers (from a mean of 5 to 0) and the visual analogue score. No severe intra- or post-operative complications were observed, and no patient developed de novo urgency UI.

c) Incontinence surgery in frail elderly men

No specific conclusions can be drawn regarding surgical treatment of UI in frail men. Typical studies of anti-UI surgery in elderly men are very small or fail to stratify results by age and/or comorbidity (e.g., see references [362, 363]). One small study (n=46) found that advanced age was not a risk factor for poor outcome after collagen injection for post-prostatectomy UI, [364] while another (n=12, mean age 80 years) of trans-urethral resection prostatectomy (TURP) for obstruction-associated urgency UI found that cognitively impaired men had the greatest UI improvement [365]. In a single-institution case series of men aged > 80 years old undergoing TURP (68% of whom had urinary retention), 80% were satisfied with their outcome. Of the men with retention, 80% were able to void with a small PVR by six weeks. Complication rates were 41% (early) and 22% (late) [366]. Urodynamic evaluation of post-prostatectomy UI is recommended prior to surgical treatment (see, for example, reference [363]).

d) General issues in surgical care of the frail elderly

Important factors in the surgical care of frail patients include: pre-operative risk stratification (e.g., American Society of Anaesthesiology class, Charlson index, Modified Cardiac Risk Index, [367] Burden of Illness Score [368]); ensuring adequate nutrition, especially when patients cannot take oral feeding or become delirious; proactive management of comorbid heart disease, diabetes, and pulmonary disease; prevention, [369, 370] recognition, [371] and treatment of post-operative delirium; [370, 372] adequate pain assessment and treatment, especially in cognitively impaired persons; [373] recognition of the hazards of prolonged bed rest [374] and the prevention [375] and treatment of functional impairment; use of specialised care units for the elderly; [376] and discharge planning regarding rehabilitation, need for assistance, and site of discharge. These issues should be factored into any plan of surgical care of frail elderly persons.

e) Summary of evidence

1. No studies were identified regarding gynaecological surgery in institutionalized elderly women. (Level 4)
2. Exogenous administration of oestrogen is ineffective in promoting wound healing after gynaecological surgery in older women. (Level 3)
3. Injection of bulking agents appears to be effective in older women, and age does not appear to correlate with outcomes. (Level 3)
4. No studies were identified that evaluated functional or quality of life outcomes after UI surgery in frail older persons (Level 4)
5. Risks of morbidity and mortality for frail patients undergoing anti-UI procedures are similar to those of other major non-cardiac surgical procedures. (Level 2)
6. Surgical mortality risks are still low in elderly persons, and often due to cardiac or cancer complications. (Level 2-3)
7. Operative mortality is inconsistently associated with increased age, and many studies did not uniformly control for comorbid conditions. (Level 2-3)
8. Patient-controlled analgesia provides adequate pain control and sedation and increased patient satisfaction compared with standard fixed-dose and time-administered medications in cognitively intact geriatric patients. (Level 2)
9. Choice of agent for patient-controlled analgesia may affect postoperative cognition. (Level 3)
10. Some case series and waitlist-controlled trials suggest that minimally invasive surgical approaches may be useful in older adults, yet these trials may have little to do with whether surgical treatments are appropriate in the frail elderly (Level 3)

VIII. URINARY RETENTION IN THE FRAIL ELDERLY

The association of both detrusor underactivity and bladder outlet obstruction with age, comorbidity, and medications makes urinary retention (UR), either acute or chronic, a potential problem in frail older adults. Although bothersome in younger and middle-aged persons, in older frail persons UR and acute UR (AUR) carry significant morbidity, including delirium, [377] bradycardia (possibly related to alteration in the reflex loop involving the vagal and the sympathetic nerves), [378] higher mortality in the year following hip fracture, [379] and persistent UI. [380] UR and elevated PVR have [380] and have not been [381] associated with an increased risk of UTI in this population. Data from the UK NHS data base found that the 1-year mortality in older men without significant comorbidity presenting with AUR was 12% (age 75-84) and 29% (age > 85); in men with comorbidity, the respective mortality rates were 27% and 43%, and rates were even higher in men with “precipitated” retention (not associated with BPO) [382]. Of concern is the fact that UR may be asymptomatic in frail elders, particularly women.[383].
1. QUALITY OF THE DATA

Studies of the prevalence of UR among frail elders suffer from lack of standardization of the definition of UR, which ranges from inability to void to PVR cutoffs as low as 50 mL. PVR is usually reported as a volume and not percent of bladder emptying; results often are based on a single measurement; and whether or not the patient strained is rarely reported. Many studies do not exclude patients with medical reasons for impaired emptying, such as advanced diabetes mellitus and anticholinergic medications. There is also extensive heterogeneity in the populations studied, and there is a relative paucity of data on UR in women. The 1996 US Agency for Health Care Policy Research consensus guidelines on UI in adults suggested that PVR > 200mL is abnormal, <50 mL normal, and 50-200 mL intermediate [172]. Using data from symptomatic patients referred for urodynamics, Madersbacher et al estimated that, starting at age 40, PVR increased by 13 mL per decade in men and 4 mL per decade in women [42]. In two studies of postmenopausal women without DO, both with and without LUTS, Pfisterer et al found median PVR to be < 20 mL [43, 49]. Efforts to establish normative means for PVR in women only compared those less than age 65 versus those older; only 25 were aged > 65, and their mean PVR was 34± 31 mL [384].

2. RESULTS

Frail elders in hospital and rehabilitations units may be at special risk for UR and impaired bladder emptying. Amongst 100 consecutive patients admitted to a geriatric hospital ward (mean age 81), 34% had PVR >50 mL, and they had greater functional impairment and subsequent mortality than those with smaller PVR [170]. UR (defined as PVR ≥ 150 mL) was present in 22% of older patients on admission to a subacute, predominantly geriatric, rehabilitation unit; [380] patients with UR were more likely to be male and have poor mobility, neurologic disorders (e.g., stroke or multiple sclerosis), cognitive impairment, UI, previous prostate problems, previous LUTS, take anticholinergic medications, or have a UTI diagnosed on admission. Other risk factors for UR in this population include previous history of UR, [385] faecal impaction, [386] and several classes of medications. [44] UR is common after hip fracture: in consecutive series of patients admitted to hospital with hip fracture, a PVR >300 was present in 79-97% on admission. [379,387] 36% immediately pre-operatively, 56% post-operatively, and 22% during the recovery phase [379]. Randomized trials have shown both short-term indwelling and intermittent catheterization to be effective in restoring normal voiding in frail elderly [44, 388].

Impaired emptying is common among nursing home residents. In separate case series, 35% of residents had a PVR ≥100 mL (n=150), [381] 11% had PVR ≥150 mL, [386] and 59% had urodynamic evidence of detrusor underactivity [171]. Less is known about the prevalence of UR in frail elders in the community. In a case series of 167 frail elderly outpatients, 11% had UR (two consecutive ultrasound PVR measurements ≥150 mL), which was independently associated with advanced age, use of anticholinergic medication, diabetes, and faecal impaction [386]. Women attending a Female Pelvic Medicine Clinic who were found to have a high PVR (≥100 mL) were significantly older than women with normal emptying (62±14 vs. 59±13 years, p=0.005) [389]. Studies involving older men focus on AUR. Cathcart et al evaluated AUR among men in the UK NHS data base, defining AUR by ICD-10 coding; men with TURP, prostatic cancer, multiple sclerosis, or Parkinson’s disease were excluded. AUR incidence rose sharply with age, even amongst the oldest old, from 9.13/1000 person-years among men aged 75-84, to 16.8/1000 person-years among men aged 85-100 [390]. AUR incidence in older men (aged 70-83) was also evaluated in a prospective observational study of over 6,000 American male health professionals without baseline history of TURP, prostate cancer, or AUR. The estimated AUR incidence over 3 years was 7.9/1000 person-years among men with no or only mild LUTS at baseline, and 11.3/1000 person-years among men with moderate to severe LUTS [391].

Intermittent catheterisation (ISC) can be helpful in the management of patients with UR with or without UI. ISC can be carried out by either the patient or a caregiver, with the frequency based on PVR. The assumption that older patients are unwilling or unable to manage UR with ISC has not been borne out [392]. The ability to reliably and safely use ISC to manage UR in hospital and long term care settings is highly dependent on staff availability and training. In addition, using ISC in institutional settings (where multi-resistant organisms are common) may yield an unacceptable risk of nosocomial infections, and use of sterile catheter trays are very expensive. Thus, it may be extremely difficult to implement such a programme in a typical nursing home setting.

3. SUMMARY OF EVIDENCE

1. There is no consensus regarding a standardized definition of UR in frail older persons (Level 4)
2. UR is common in hospitalized frail elders and long term care residents (Level 2), but not in healthy, asymptomatic older persons (Level 2)
3. Hip fracture and orthopaedic surgery are associated with very high rates of UR in older persons (Level 2)
4. Risk factors for UR in frail elders include male sex, impaired mobility, cognitive impairment,
The prevalence of two or more episodes among men has been reported to be as high as 90% for one episode per night in persons over age 80 [398-402]. The prevalence of nocturia increases with age, and there are limited data on optimal diagnostic assessment, and treatment of nocturia in the frail elderly. Similar to UI, nocturia is usually multifactorial in frail elderly persons. Thus, diagnostic assessment must be comprehensive, and multi-component interventions may be necessary for successful treatment.

2. QUALITY OF THE DATA

There are good epidemiological data from multiple cultures and countries on the prevalence of nocturia, but limited data on associated factors and impact. Studies of the pathophysiology of nocturia in the elderly have generally been small and highly focused on one aspect of potential underlying causes. As with UI, there are limited data on optimal diagnostic assessment, and therefore recommendations are generally based on expert opinion [19, 393]. Data on treatment in elderly patients are very limited. Although there are some treatment RCTs, they are small, include few very elderly subjects, and have focused primarily on vasopressin. We located no data on the effectiveness of multi-component interventions for nocturia in the elderly.

3. PREVALENCE AND IMPACT

The prevalence of nocturia increases with age, and has been reported to be as high as 90% for one episode per night in persons over age 80 [398-402]. The prevalence of two or more episodes among men between 70 and 79 is nearly 50 percent [403]. This increasing prevalence is largely due to age-related conditions that underlie the pathophysiology of nocturia (see below). Nocturia is more common in young adult women than in men, but the gender ratio reverses after age 60 [403]. Nocturia has been variably associated with chronic medical conditions such as hypertension and diabetes, [404, 405] advancing renal failure, [406] and cardiovascular disease [407, 408]. Nocturia in the frail elderly can cause accidental falls [409]. Frail elderly persons with nocturia, who also have gait and balance disorders and other risk factors for falls, are clearly at increased risk for injury and consequent morbidity, yet no nocturia treatment trials have evaluated any impact on fall reduction. Nocturia also has adverse effects on quality of life, including an increased risk of depression and poor self-rated health, probably as the result of the impact on sleep [410, 411]. Adults with nocturia also complain that nocturia “makes them feel old” and they worry about falling at night [412].

4. PATHOPHYSIOLOGY

In elderly persons, the pathophysiology of nocturia is usually multifactoral and can be related to one or a combination of three primary underlying causes, all of which increase with age: low bladder capacity usually as a component of OAB, DO, urgency UI, or BOO in men; nocturnal polyuria; and primary sleep disorders [395-397]. The proportion of 24-hour urine volume produced at night increases with age, even among healthy older adults free of overt comorbid conditions [413, 414]. Studies of frail elderly have shown that the proportion of urine produced at night is close to 50%, rather than less than 30% as in young healthy adults [415-417]. Nocturnal polyuria is more common in older compared to younger nocturics [418]. In some elderly persons, this is due to mobilisation of excess volume caused by peripheral oedema, which may be due to venous insufficiency, medications, and/or heart failure. Some studies have suggested that there is an abnormality in the secretion and/or action of arginine vasopressin (AVP) or a loss of its normal diurnal rhythm (with inappropriately low values at night) in many elderly patients with nocturia [419, 420]. Another, however, failed to find an association between AVP deficiency (detected by water deprivation testing) and nocturnal polyuria in a series of elderly persons with nocturia [421]. Other research suggests that some frail elderly persons with nocturia have high atrial natriuretic peptide (ANP) levels at night; [422, 423] however, these investigators did not use echocardiography or brain natriuretic peptide levels to detect occult heart failure. Sleep disordered breathing and sleep apnoea also have been associated with nocturia and nocturnal UI in the elderly [422, 424-426]. Whether this relates to increased ANP production, [422] mechanical forces on the bladder generated during apnoea events, [424] or other mechanism(s) is unknown.
5. DIAGNOSTIC ASSESSMENT

The approach to the assessment of nocturia should be similar to that for UI described above. Special considerations include:

- A frequency-volume chart of at least 24 hours duration that includes timing and volume of each void at night as well as during the day, as well as a specific indication of when the individual went to bed with the intention of going to sleep at night and awoke in the morning. Some patients may find this difficult to perform, [427] but face-to-face explanation of the procedure, a receptacle to place in the toilet to measure volumes, and involvement of carers may improve compliance and accuracy.

- Additional questions in the history that focus on the possibility of a primary sleep disorder, such as asking about sleep quality, daytime sleepiness, snoring, and leg movements at night (this history is enhanced by questioning the bed partner).

- Additional history and focused physical examination related to volume overload (e.g., lower extremity venous insufficiency, heart failure); in some cases additional testing such as an echocardiogram or a brain natriuretic peptide level may be helpful in ruling out the latter diagnosis.

6. TREATMENT

Treatment of nocturia in elderly patients should be based on individualized identification of all potential underlying causes. The most commonly used measure of nocturia treatment efficacy is a reduction in nocturia episodes. However, studies have not related the number of nocturia episodes to the hours spent in bed, which may vary considerably in older persons. The impact of three episodes of nocturia is considerably different in someone in bed for seven compared with twelve or more hours. Cure, or the complete resolution of nocturia, is infrequently achieved in either clinical practice or in research. Some trials have reported percent of trial participants achieving a 50% reduction in nocturia or the percent of individuals reporting one fewer nightly episodes of nocturia. It is important to recognize that most reports of treatment have shown only a small reduction in episodes of nocturia, ranging from 0 to 0.8 fewer episodes of nocturia versus placebo. Patient-based outcomes are important and may include general satisfaction questions, nocturia-related bother, and nocturia-specific quality of life. Most trials examining nocturia as an outcome were performed prior to the validation testing of the ICIQ-NQOL instrument [428]. An additional important target for therapy is reduction in bother due to nocturia.

Although no specific data are available on multi-component interventions, elderly patients with nocturia may benefit from an approach to treatment that combines behavioural strategies, therapy for medical and sleep disorders, and nocturia-specific drug therapy.

a) Behavioural approaches and treatment of comorbidity

There are no specific data on the impact of behavioural strategies (e.g. altering fluid or sodium intake, leg elevation for oedema) on nocturia in older patients. Using bedside commodes or urinals, and minimising the distance necessary to reach a toilet and providing a safe, adequately lit path may be helpful in reducing the risk of night-time falls related to nocturia, especially in those with underlying gait instability and other risk factors for falls. Reducing volume overload associated with lower extremity venous insufficiency or congestive heart failure with a late afternoon dose of a rapid acting diuretic may be helpful in reducing nocturnal polyuria and nocturia in selected patients [429, 430].

Treating sleep apnoea with continuous positive airway pressure can reduce nocturia severity, but these trials have not usually included the frail elderly [431]. Treatment with very short-acting benzodiazepines for patients with primary insomnia, and with dopaminergic agonists for patients with restless leg syndrome, may improve sleep quality, but there are no data to support these approaches. There is one secondary data analysis of a RCT which demonstrated that behavioural therapy, with an emphasis on pelvic floor muscle exercises and urgency suppression strategies, reduced nocturia in women with urgency-predominant UI [432].

The median reduction of 0.5 episodes per night was significantly more effective than antimuscarinic (0.3 episodes) or placebo (no reduction). There are no trials of pelvic floor muscle exercises or urgency suppression strategies with nocturia as the primary outcome.

There are several approaches to drug therapy for elderly patients with nocturia. Most of the published guidelines suggest targeting a "primary" or "principal" causes of nocturia (e.g., nocturnal polyuria). Because most older adults with nocturia have multiple potential causes, treatment often will require combination treatment.

b) Antimuscarinic therapy

In general, if the history, bladder diary, and physical examination suggest that nocturia is related primarily or in part to OAB/DO/urgency UI, then treatment with an antimuscarinic agent should be considered (see Pharmacological Treatment above). There are several trials examining the effect of antimuscarinics for nocturia reduction, including trials of oxybutynin-IR, [432] solefenacin, [318] and tolterodine [433, 434]. Even when these agents have shown statistically significant reductions in nocturia, the net benefit of reduction in nocturia (above that effect shown with placebo) is only 0.0 to 0.3 episodes. There is evidence to suggest that these agents may be best used in combination with other therapies [433] rather than as single modality therapy.
c) **Agents for benign prostatic obstruction**

Alpha-adrenergic blockers used in patients with symptoms suggestive of BPO have a modest impact on nocturia, with a mean reduction of slightly less than one episode per night [421]. 5-alpha reductase inhibitors have mostly shown no statistical benefit for nocturia [421] except in one study among a subset of participants age ≥70 [435]. This statistical advantage did not persist beyond one year, and the net benefit compared to placebo was a difference of < 0.2 fewer nocturia episodes. Among postmenopausal women, one uncontrolled trial of estradiol in combination with a progestational agent showed a dramatic reduction in nocturia over 6 months, [436] but this was not replicated in another RCT [437]. There are few studies that have focused on treatment of nocturia with the use of medications for sleep. One RCT evaluated melatonin for treatment of nocturia associated with BOO in older men [438]. Melatonin showed only a trend towards reduction in nocturia compared to placebo (-.03 and -0.05 episodes from baseline 3.1 episodes, respectively) but did significantly reduce reported bother from nocturia.

d) **Anti-diuresis treatment: Desmopressin**

A large number of studies over the last 20 years have examined the potential role of exogenous AVP (desmopressin or DDAVP) for the treatment of nocturia in older patients [439-451] (Table 9). The majority have been uncontrolled case series involving relatively small numbers of subjects, and the inclusion criteria, outcome measures, and route, dosing, and duration of DDAVP treatment varied considerably. The two largest studies were RCTs of oral DDAVP using essentially identical designs, one conducted in men [449] and the other in women [450]. Although they included some patients older than 75, the mean age of the participants was closer to “middle” rather than “old” age (65 and 57, respectively). Both found significant reductions in nocturia and nocturnal urine volume, and increases in mean duration of self-reported first night-time sleep episode. However, the trials’ designs were unusual: the randomised controlled portion was preceded by a dose-titration run-in, with the subsequent exclusion of subjects who did not experience >20% reduction in nocturnal urine volume or who were intolerant to the medication. Although this approach may be useful for targeting therapy in clinical practice, it raises questions about selection bias and the generalizability of the results.

Most individuals in DDAVP trials were titrated up to an oral dosage of 0.4 mg, [449, 450] yet older patients can have a significant reduction in night-time urine with much lower doses of 0.1 or 0.2 mg orally [452]. A major concern related to DDAVP treatment in elderly patients is fluid retention (which can exacerbate underlying cardiovascular disease) and hyponatremia. Many older persons may have pre-existent hyponatremia due to a variety of medical conditions and drugs. A recent review [453] found the incidence of hyponatremia with DDAVP in older persons to be 0-9% (depending on definition), with the exception of the RCT in men discussed above, in which the incidence of any hyponatremia was 22% (4% with sodium < 130 mmol/L). Because so few frail elderly were included in these trials, the actually incidence of clinically significant hyponatremia from DDAVP is unknown. A further review of pooled trial results found that the incidence of hyponatremia in subjects with normal baseline sodium was <1% (3/336 subjects) in persons < 65 and 8% (22/2760) in those ≥65, and 75% (6/8) in older patients with a low baseline serum sodium [454]. Pharmacodynamic studies in younger older men (aged 55-70) found that DDAVP had a prolonged half-life which was in part responsible for hyponatremia [455]. DDAVP is not useful in frail older persons in nursing homes with nocturia and/or night-time UI because of the lack of efficacy for reducing night-time voids and the very high rate of hyponatremia [452].

7. SUMMARY OF EVIDENCE

- Late afternoon administration of a diuretic may reduce nocturia in persons with lower extremity venous insufficiency or congestive heart failure unresponsive to other interventions. (Level 2)
- If OAB, DO, and/or urgency UI is felt to be a major contributor to nocturia, antimuscarinic agents should be considered. (Level 3)
- If nocturia is due to insomnia alone, then a very-short acting sedative hypnotic may be considered. (Level 3)
- DDAVP should not be used in frail elderly because of the risk of hyponatremia. (Level 1)

X. MODELS OF CARE FOR THE FRAIL ELDERLY WITH UI

1. BACKGROUND

Throughout the world, frail elderly persons are cared for in a variety of settings using many different models of care. While there continues to be very few studies that examine these models in relation to UI management, a discussion of selected models is useful in identifying the challenges and opportunities to improve continence care in this population. This descriptive section briefly outlines four models of UI care particularly relevant to the frail elderly: home care, continence nurse advisors, collaborative practices between advance practice nurses and physicians, and long term institutional care. A
Table 9. Selected studies of desmopressin (DDAVP) for nocturia involving older patients

<table>
<thead>
<tr>
<th>Reference [No.]</th>
<th>Study Design</th>
<th>N</th>
<th>Sex</th>
<th>Age (Mean)</th>
<th>Nocturia Definition</th>
<th>DDAVP Dose</th>
<th>Outcomes</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seiler et al, 1992 [439]</td>
<td>Open label</td>
<td>9</td>
<td>M/F</td>
<td>73-90</td>
<td>_ nocturnal volume</td>
<td>10 µg</td>
<td>_33%</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 µg</td>
<td>_10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 µg</td>
<td>_50%</td>
<td></td>
</tr>
<tr>
<td>Asplund et al, 1993 [440]</td>
<td>Open label</td>
<td>21</td>
<td>M/F</td>
<td>(73)</td>
<td>_ nocturnal volume</td>
<td>40 µg</td>
<td>20-34%</td>
<td>4</td>
</tr>
<tr>
<td>Asplund et al, 1993 [441]</td>
<td>Open label</td>
<td>20</td>
<td>F</td>
<td>(71)</td>
<td>_ nocturnal volume</td>
<td>20 µg</td>
<td>_355 ± 205 mL</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2 nights)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olano et al, 1993 [442]</td>
<td>Open label</td>
<td>8</td>
<td>M/F</td>
<td>(64)</td>
<td>_ nocturnal volume</td>
<td>5-10 mg</td>
<td>4.6 / 2.5</td>
<td>4</td>
</tr>
<tr>
<td>Asplund et al, 1993 [443]</td>
<td>Open label</td>
<td>19</td>
<td>M/F</td>
<td>(73)</td>
<td>_ nocturnal volume</td>
<td>40 µg</td>
<td>_38%</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplund et al, 1998 [444]</td>
<td>Dose titration</td>
<td>23</td>
<td>M/F</td>
<td>60-74</td>
<td>nocturia ≥ 2, nocturnal volume ≥ 0.9 mL/min</td>
<td>0.1 mg</td>
<td>_31%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(68)</td>
<td></td>
<td>0.2 mg</td>
<td>_44%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4 mg</td>
<td>no further _</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplund et al, 1999 [445]</td>
<td>RCT</td>
<td>17</td>
<td>M/F</td>
<td>60-74</td>
<td>nocturnal volume ≥ 0.9 mL/min</td>
<td>10.40 mg</td>
<td>_36%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(68)</td>
<td></td>
<td>oral</td>
<td>1.7 / 1.1</td>
<td></td>
</tr>
<tr>
<td>Cannon et al, 1999 [448]</td>
<td>Double blind controlled trial</td>
<td>20</td>
<td>M</td>
<td>52-80</td>
<td>Nocturnal volume &gt; 33% of 24 hr volume</td>
<td>20 mg</td>
<td>_15%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 mg</td>
<td>_26%</td>
<td></td>
</tr>
<tr>
<td>Chanceller et al, 1999 [447]</td>
<td>Open label</td>
<td>12</td>
<td>M</td>
<td>&quot;Elderly&quot;</td>
<td>Nocturia &gt; 3, nocturnal polyuria</td>
<td>0.1 mg</td>
<td>20 patients responded 956 mL to 523 mL</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(oral)</td>
<td>5.2 / 2.2</td>
<td></td>
</tr>
<tr>
<td>Kuo, 2002 [448]</td>
<td>Open label</td>
<td>30</td>
<td>M/F</td>
<td>(75)</td>
<td>Nocturia ≥ 3, nocturnal polyuria</td>
<td>0.1 mg</td>
<td>20 patients responded 956 mL to 523 mL</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(oral)</td>
<td>5.2 / 2.2</td>
<td></td>
</tr>
</tbody>
</table>
Table 9. Selected studies of desmopressin (DDAVP) for nocturia involving older patients (Continued).

<table>
<thead>
<tr>
<th>Reference [No.]</th>
<th>Study Design</th>
<th>N</th>
<th>Sex</th>
<th>Age (Mean)</th>
<th>Nocturia Definition</th>
<th>DDAVP Dose†</th>
<th>Outcomes</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattiason et al., 2002 [449]</td>
<td>Initial dose titration then responders randomized to optimal dose vs. placebo for 3 weeks</td>
<td>115</td>
<td>M</td>
<td>18 – 88 (65)</td>
<td>Nocturia ≥ 2, nocturnal urine production greater than functional bladder capacity</td>
<td>0.1 – 0.4 mg (oral)</td>
<td>_36% vs. 8% in placebo</td>
<td>3.0 / 1.7 vs. 3.2 / 2.7 placebo</td>
</tr>
<tr>
<td>Lose et al., 2003 [450]</td>
<td>Initial dose titration then responders randomized to optimal dose vs. placebo for 3 weeks</td>
<td>144</td>
<td>F</td>
<td>21-89 (55)</td>
<td>Nocturia ≥ 2 and nocturnal urine production greater than functional bladder capacity</td>
<td>0.1 – 0.4 mg (oral)</td>
<td>_44% vs. 6% in placebo</td>
<td>2.9 / 1.8 vs. 2.9 / 2.4 placebo</td>
</tr>
<tr>
<td>Rembratt et al., 2003 [451]</td>
<td>Open label</td>
<td>72</td>
<td>M/F</td>
<td>66-90 (76)</td>
<td>Nocturia ≥ 2</td>
<td>0.2 mg oral (3 nights)</td>
<td>-306 mL mean reduction</td>
<td>-1 episode mean reduction</td>
</tr>
<tr>
<td>Lose et al. 2004 [469]</td>
<td>One year extension of Lose [451] and Mattiason [449] studies above</td>
<td>249</td>
<td>M/F</td>
<td>21-88 (65 men, 56 women)</td>
<td>Nocturia ≥ 2 and nocturnal urine production greater than functional bladder capacity</td>
<td>Men 3.1 baseline, 1.6 end Women 2.9 baseline 1.3 end</td>
<td>4 (as above)</td>
<td></td>
</tr>
<tr>
<td>Ho et al., 2005 [470]</td>
<td>Open label trial of man with bladder outlet obstruction on alpha blockers who failed antimuscarinics and had no nocturnal polyuria</td>
<td>28</td>
<td>M</td>
<td>43 – 91 (70.8)</td>
<td>Not defined</td>
<td>0.1 – 0.4 mg (oral) average dosage 0.104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Kerrebroeck et al., 2007 [471]</td>
<td>Initial dose titration then responders randomized to optimal dose vs. placebo for 3 wks</td>
<td>127</td>
<td>M/F</td>
<td>19-94 (62)</td>
<td>Nocturia ≥ 2</td>
<td>0.1 – 0.4 mg (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson et al., 2007 [472]</td>
<td>Double-blinded, RCT with titration</td>
<td>14</td>
<td>M</td>
<td>67 – 80 (74)</td>
<td>Nocturia ≥ 2 without evidence of bladder outlet obstruction</td>
<td>0.1 – 0.4 mg (oral), average dosage 0.31</td>
<td>-197 mL reduction from baseline vs. -126 mL reduction with placebo</td>
<td></td>
</tr>
</tbody>
</table>
comprehensive review of worldwide care models is outside the purview of this section. Of note, we located little new information since the 3rd ICI.

2. HOME CARE

Most care for the frail elderly who live at home is provided by spouses, children, other relatives, and in some cases neighbours or friends. Overall, there has been little research on UI interventions for this population. One trial found that behavioural interventions can be effective in selected frail homebound persons with UI and motivated caregivers [456]. Overall, however, the informal nature of care at home may lead to important barriers to effective continence care. First, caregivers may not be available 24 hours per day, and thus regular toileting assistance may only be intermittently available. Toileting programmes (e.g., prompted voiding) and intermittent catheterisation therefore may be impossible to implement consistently. Second, many caregivers for frail persons are in fact frail themselves. Spouses and even adult children may have medical illnesses and/or functional problems that make it physically difficult and stressful for them to provide continence care. Third, even among caregivers who are physically capable and available to assist with continence care, negative attitudes and lack of education may pose substantial barriers to providing the required care.

Trained, paid caregivers for frail elderly living at home are variably available throughout the world. Such services may include nurses to teach patients and caregivers UI care and management of intermittent or indwelling catheterisation; health aides who can assist with continence care; and provision of continence care supplies (e.g., pads and catheter supplies). In the US, for example, Medicare (health insurance for persons aged > 65) does not pay for ongoing UI care, only some catheter care and supplies period and need-based, home skilled nursing and physical therapy, and usually only on a limited basis and following hospitalisation... For patients who do not have access to continence home care and/or do not have an available and motivated caregiver, UI management remains pads and other protective products, which can be expensive if not provided or reimbursed through available health insurance. In these cases, some frail elders will devise homemade alternatives to pads, which are neither effective, comfortable, nor safe (especially for skin protection).

3. CONTINENCE NURSE ADVISORS

In many countries (e.g., UK, Australia, and Canada, among others), continence nurse advisors are available who can provide extremely valuable services for frail elderly with UI. Continence nurse advisors are highly trained in UI assessment and management. They are generally funded by the government and function as public health nurses for a region associated with one or more hospitals. They serve as advisors and provide education to physicians, nurses, and other health care professionals, as well as patients and their caregivers. They may also assist hospital staff in the assessment and management of UI in hospitalised frail elderly, and coordinate follow up care in the home or in an outpatient clinic. One Canadian study found that continence nurse advisors had a positive impact in improving management of UI in older persons [457].

4. COLLABORATIVE PRACTICES BETWEEN ADVANCE PRACTICE NURSES AND PHYSICIANS

In many countries, publicly supported continence nurse advisors are not available. However, other models have developed that generally involve collaborative practices between nurses with special interest, advanced training, and expertise in continence care and physicians (usually an urologist, gynaecologist, or geriatrician). These collaborations can be vital for providing optimal continence care for the frail elderly because of the multicomponent therapy required. Such nurses may provide reimbursable services in private offices and clinics; provide education, consultation, and/or direct services to nursing homes, other long term care facilities, and assisted living facilities; and assist with the assessment and management of UI for frail elders in their homes. Reimbursement for advance practice nurses and their ability to provide direct care independently of a physician varies across countries, and in some case within countries (e.g., in the US their scope of practice can vary by state). In some countries there are specialty organisations for this type of continence nurse (e.g., the US, Wound Ostomy Continence Nurses Society and Society of Urological Nurses and Associates). Although little data on the effectiveness of this model exist, it is becoming more widespread (e.g., Israel and Italy).

5. INSTITUTIONAL LONG TERM CARE

Long term care for the frail elderly is provided in a variety of types of institutional settings throughout the world. Continence care in these settings is dependent upon many factors, including: type of resident (only long-term care or also short-term rehabilitation post-hospitalization patients as well); physical environment; the organisational culture and leadership commitment to providing high quality care; the number, education, and motivation of direct care staff; access to physicians with interest and understanding of continence care; and financial and regulatory incentives to provide appropriate continence care. Nursing home staffing is a major barrier to translating research on prompted voiding and other interventions into practice (see Behavioural interventions above), and because resource constraints are stringent and will become more challenging with the rapid growth in the frail elderly population [267, 458].
The section on Interventions with Long-term Care Staff above reviews studies of interventions with nursing home staff to improve continence care. These interventions have generally met with limited success because they have not addressed the culture, staffing, and overall system of care in these facilities.

Three broad strategies have been employed to improve the quality of continence care for frail elderly nursing homes residents. The first are standardised approaches to identification, assessment, and management of UI. One is the Resident Assessment Instrument for nursing facilities, whose use is mandated in the US and other countries [460]. The Resident Assessment Instrument combines information from the Minimum Data Set (including data on individual resident demographics, medical conditions, function, cognition, and care needs) with Resident Assessment Protocols for specific conditions and impairments. The continence section of the Minimum Data Set is generally accurate in identifying incontinent patients, but not for determining the type or severity of UI or determining especially smaller changes in continence over time [459]. The original version of the Resident Assessment Protocol for UI was partially validated in a sample of approximately 100 frail, incontinent patients in one large academically-affiliated US nursing home [460]. Another approach is national guidance directives, such as that for surveyors who conduct yearly quality evaluations of all US nursing homes. A recent revision of the US guideline for UI attempted to replace the existing emphasis on nursing documentation of continence care plans with an emphasis on UI assessment and provision of patient-focused care [461]. However, a subsequent study found that both surveyors and nursing home staff did not understand this shift in emphasis, and that dissonance between these two groups in basic UI knowledge and elements of the guidance is a likely barrier to any change in quality of UI care [156]. The American Medial Directors Association (for nursing home physicians) publishes a clinical practice guideline for continence care, based on the US Agency for Healthcare Policy and Research guideline and the federal guidance mentioned above [462] yet its implementation and effectiveness has not been studied. However, despite the existence and dissemination of these approaches, several studies document an ongoing discrepancy between their recommendations and regulations and the continence care actually delivered in the US [166, 272, 463, 464] and UK [160]. The second strategy has been the use of principles of continuous quality improvement and total quality management developed for business management [465]. The key elements of these approaches are education and involvement of direct care staff, identification of a “continence champion” and team to implement the programme, and the continuous collection and analysis of quantitative outcome data using principles of statistical quality control. Quality assurance programmes using UI quality indicators have also be proposed [157]. One study successfully used a computerised assessment and quality improvement software programme and external oversight to maintain a 50% reduction in UI in eight diverse, geographically dispersed US nursing homes [273]. A second implemented a quality improvement programme in five diverse US nursing homes, but UI reduction was more modest (20-30%) in this effort to translate research into practice [309].

The third approach is a specialty practice exemplar model for continence care, with an academic nursing faculty member with expertise in the assessment and treatment of UI conducting a clinical UI practice in a long-term care facility (see Interventions with Long-term Care Staff, above). Graduate nursing students working with this individual focus on the Resident Assessment Protocol for UI. UI assessment and management skills are transferred to the facility nursing staff members through several mechanisms, including staff education and improved continence care systems [273].

Assisted living communities are social care residential models, in which older persons are provided primarily IADL assistance (meals, laundry, cleaning), are becoming more common (primarily in the developed world). There is substantial variation in the functional status and medical care needs of their residents, availability of nursing and physician care, reimbursement, regulation, and whether and how residents are allowed to age “in place” versus transferred to nursing facilities. In some countries and localities, assisted living residents may substantially resemble the nursing home population. There are no data on the quality of management of UI for frail elderly residing in assisted living facilities, or intervention trials specifically in this population. The US National Association for Continence (www.nafc.org) has published a “blueprint” for continence care in assisting living facilities, based primarily on expert opinion.

**XI. RECOMMENDATIONS FOR MANAGEMENT**

1. **BASIC ASSESSMENT** (SEE ALGORITHM FOR SPECIFICS)

   a. Active case finding for UI should be done in all older persons (Grade A).

   b. Screening for frailty is possible (Grade A) and encouraged (Grade C).

   c. The basic assessment of UI should focus on identification of potentially treatable conditions and factors that may cause or worsen UI, contribute to its burden, and impact management decisions (Grades A-C).
<table>
<thead>
<tr>
<th>Challenges</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete standard criteria of “frailty” for research</td>
<td>Provide specific definition of frailty.</td>
</tr>
<tr>
<td></td>
<td>Explicitly define variables in the domains of mobility, cognition, and nutrition.</td>
</tr>
<tr>
<td>Incomplete understanding of natural history of UI</td>
<td>Include control/placebo arms that consider time effects and measurement of primary and secondary outcomes of interest</td>
</tr>
<tr>
<td>Multifactoral nature of incontinence</td>
<td>Collect and describe measures to assess and address relevant comorbidity, e.g.:</td>
</tr>
<tr>
<td></td>
<td>• Medication changes</td>
</tr>
<tr>
<td></td>
<td>• Interval illnesses</td>
</tr>
<tr>
<td></td>
<td>• Interval bacteriuria</td>
</tr>
<tr>
<td></td>
<td>• Care setting</td>
</tr>
<tr>
<td></td>
<td>• Interventions affecting domains of continence (e.g., exercise programmes)</td>
</tr>
<tr>
<td>Complexity and expense of enrollment</td>
<td>Multistage selection process:</td>
</tr>
<tr>
<td></td>
<td>• Exclude robust/healthy</td>
</tr>
<tr>
<td></td>
<td>• Identify the frail</td>
</tr>
<tr>
<td></td>
<td>• Identify subset according to specific domain of frailty (e.g., need for toileting assistance).</td>
</tr>
<tr>
<td></td>
<td>• Prepare to contact family members or other proxy decision makers for consent [41]</td>
</tr>
<tr>
<td>High trial attrition rates</td>
<td>Plan for intention to treat analysis with explicit plans for dealing with drop-outs/deaths in the analysis.</td>
</tr>
<tr>
<td></td>
<td>Improve intervention adherence by:</td>
</tr>
<tr>
<td></td>
<td>• Designing interventions feasible for most, and incorporating caregivers/care setting in that consideration</td>
</tr>
<tr>
<td></td>
<td>• Allowing flexible time frame for follow-up assessments</td>
</tr>
<tr>
<td></td>
<td>• Prioritising safety</td>
</tr>
<tr>
<td></td>
<td>• Providing transportation</td>
</tr>
<tr>
<td></td>
<td>• Preplanning alternatives to clinic-based follow-up (e.g., home visit, telephone)</td>
</tr>
<tr>
<td></td>
<td>• Establishing good relationship and incentives to participate for family, caregivers, and/or care setting</td>
</tr>
<tr>
<td></td>
<td>• Understanding priority rank and definition of important potential outcomes to patients, caregivers, and care settings</td>
</tr>
<tr>
<td></td>
<td>Anticipated attrition rates should not preclude attempts at long-term follow-up.</td>
</tr>
<tr>
<td>Exclusions that decrease generalizability</td>
<td>Principle exclusion should be factors that prevent participation.</td>
</tr>
<tr>
<td></td>
<td>Avoid exclusions for comorbidity.</td>
</tr>
<tr>
<td></td>
<td>Exclude only those persons whose cognition is not compatible with the specific intervention.</td>
</tr>
<tr>
<td></td>
<td>Use explicit procedures for consenting participants; involve a surrogate/proxy when needed. Include discussion of ethical concerns and how they were addressed in the report.</td>
</tr>
<tr>
<td>Problems using self-report to assess outcomes</td>
<td>Supplement self-report of primary outcomes with “hard” measures, e.g. assist with toileting.</td>
</tr>
<tr>
<td></td>
<td>Collect “objective” measures of function and proxy information in parallel, e.g. percent of wet checks, hours of caregiver time.</td>
</tr>
<tr>
<td></td>
<td>Set outcomes to be less sensitive to random fluctuations (e.g., end point of “50% decrease in UI”).</td>
</tr>
<tr>
<td></td>
<td>Use outcome measures specific to the target population: e.g., for quality of life, use established measures of social interaction [42] rather than existing UI-specific scales; re-validate existing UI-specific scales; for community-dwelling persons, transfer to setting with higher level of care (e.g., from home to residential/institutional care)</td>
</tr>
<tr>
<td></td>
<td>Include measures related to caregiver time commitment, burden, costs, morbidity, quality of life, and satisfaction with intervention (regarding the patient and themselves).</td>
</tr>
<tr>
<td></td>
<td>Assess possible caregiver(s) preference(s) for care.</td>
</tr>
</tbody>
</table>
2. PRINCIPLES OF MANAGEMENT

a. Initial management should be individualized (Grade B).

b. Decisions on specific management of frail older persons with UI should incorporate:
   i. Most likely type of UI (Grade C)
   ii. Patient and caregiver preferences for care (Grade B)
   iii. Patient-centred care goals of care (Grade C)
   iv. The chance that a specific treatment will achieve the patient’s/’career’s goals within the patient’s expected remaining life expectancy (Grade C)
   v. Understanding of the potential direct and indirect costs and benefits of treatment for the individual, their caregiver(s), and health systems (Grade C)

c. Decisions to use drug therapy and choice of specific agent should incorporate:
   i. Age-related changes in pharmacology (Grade B)
   ii. Adding to pre-existent polypharmacy (Grade B)
   iii. Drug-drug interactions (Grade A)
   iv. Drug-disease interactions (Grade B)

d. Management of UI in frail older men should incorporate consideration of gender differences in:
   i. Comorbidity and functional impairment (less in men) (Grade C)
   ii. Caregivers (men more likely to have living spouses) (Grade C)
   iii. The relationship between UI and cognition (less strong in men) (Grade C)
   iv. Benign prostate disease (Grade C)
   v. Prostate cancer (Grade C)

  e. No recommendation is possible regarding gender differences in the risk of urinary retention from antimuscarinic therapy (Grade D).

  f. No recommendation is possible regarding the cost-benefit, cost-effectiveness, or cost-utility of specific interventions (Grade D).

3. LIFESTYLE INTERVENTIONS

a. Fluid restriction should be avoided in long-term care residents and other frail elders who may not have ready access to fluids or accurately sense thirst (e.g., persons with dementia) (Grade C).

b. No recommendation can be made regarding other lifestyle interventions (Grade D).
4. BEHAVIOURAL THERAPY

a. Prompted voiding should be offered to nursing home residents and homebound older adults with UI who: are able to state their name or point to one of two named objects; transfer with a maximum assist of one person; and have less than four UI episodes during the day (Grade A).

b. Prompted voiding should be continued only in those frail elders who, after a three-day trial, demonstrate at least a 20% reduction in leakage or toilet appropriately at least two-thirds of the time (Grade A).

c. Efforts must be made to increase and maintain caregiver compliance with prompted voiding (Grade B).

d. Combined toileting and exercise programs should be considered for frail elderly with UI who are physically inactive, when there are resources to conduct and continue the intervention (Grade A).

e. No recommendation can be made for behavioural treatment of night-time UI (Grade D).

f. No recommendation can be made for habit retraining in frail elderly (Grade D).

g. No recommendation can be made for timed voiding in frail elderly (Grade D).

5. PHARMACOLOGICAL THERAPY

a. Antimuscarinic treatment should be considered for those frail persons with UI who have symptoms of OAB, urgency UI, or mixed UI, and who have been assessed for contributing comorbid factors (including existing medications), and who are appropriate for and have had a trial of behavioural treatment (Grade C).

b. Choice of specific antimuscarinic should be based on:

i. Age-related changes in pharmacokinetics that could affect the metabolism and clearance of a specific agent

ii. Likelihood of the agent causing any adverse effects the patient already experiences, such as pre-existing constipation, dry mouth, and visual impairment (Grade C)

iii. Potential drug-drug and drug-disease interactions (Grade C)

c. Drugs should be started at the lowest possible dosage (Grade C).

d. There should be proactive monitoring and re-evaluation of drug therapy for achievement of explicit efficacy goals, any adverse drug effects, and appropriateness of continued drug therapy (Grade C).

e. Oxybutynin-IR can be considered for additional benefit for frail elders with OAB, urgency UI, or mixed UI in whom behavioural therapy is feasible, with careful monitoring for adverse effects (Grade C).

f. Topical oestrogens (cream, tablet, ring) may be considered for adjunctive treatment of urogenital atrophy in women (Grade B).

g. No recommendation can be made for the use of oral or topical oestrogen for the treatment of UI in frail elderly women (Grade D).

h. No specific recommendation can be made for use of the following agents for the treatment of UI in frail elderly (Grade D):

i. Tolterodine

ii. Topical or extended-release oxybutynin

iii. Darifenacin

iv. Solifenacin

v. Trospium

vi. Fesoterodine

vii. Bethanacol

viii. Duloxetine

ix. Propiverine

x. Flurbiprofen

i. The following agents should not be used in the frail elderly:

i. Emepronium bromide (Grade B)

ii. Propantheline (Grade B)

iii. Imipramine (Grade B)

iv. Fluoxetine (Grade B)

v. Procaine haemtoporphyrin (Grade C)

J. Combinations of bladder antimuscarinics should not be used (Grade C).

6. SURGICAL THERAPY

a. Age alone is not a contraindication to surgical treatment of UI (Grade C).

b. Urodynamic evaluation should be done before considering surgical treatment of UI in frail older persons (Grade B).

c. Pre-operative risk should be stratified using established indexes (Grade A).

d. Insure adequate post-operative nutrition especially in patients who cannot take oral feeding or who become delirious (Grade C).

e. Programmes to prevent post-operative delirium should be used (Grade A) along with proactive use of established measures to diagnose delirium (Grade A).

f. Pain assessment in cognitively impaired persons
should use measures specially-designed for this population and not general pain scoring tools (Grade B).

g. Proactive preventative approaches to hospitalisation-related functional impairment should be used (Grade A).

h. Specialised care units may improve selective outcomes for frail older patients (Grade A).

i. Discharge planning should begin before surgery takes place (Grade C).

j. Patient controlled analgesia can be used in cognitively-intact frail older persons (Grade B).

k. Analgesic agents associated with delirium (e.g., meperidine) should be avoided (Grade B).

7. NOCTURIA

a. Older patients with bothersome nocturia should undergo a diagnostic assessment that focuses on identifying the potential underlying cause(s), including nocturnal polyuria, a primary sleep disorder, OAB/DO/urgency UI, or a combination of these conditions (Grade C).

b. Treatment of elderly patients with nocturia should focus on the underlying causes:

i. For patients with OAB/DO/urgency UI, consider an antimuscarinic agent. (Grade B)

ii. Patients with nocturnal polyuria must be evaluated and treated for contributing factors (peripheral oedema [and its potential medical and drug aetiologies], congestive heart failure, and type and timing of fluids [all Grade C], and sleep apnoea [Grade B]).

iii. In patients with nocturnal polyuria unresponsive to treatment of contributing factors or of uncertain cause, afternoon dose of a rapid-acting diuretic can be considered with careful monitoring of efficacy, volume status, and electrolytes and renal function. (Grade C)

iv. Patients with a primary sleep disorder should be treated for the underlying cause(s), and the impact of treatment on nocturia monitored. (Grade C)

v. For patients without cognitive impairment and nocturia inadequately responsive to the above approaches who remain most bothered by inability to achieve sleep after an episode of nocturia, a low dose of short-acting hypnotic may be considered, (Grade C)

c. DDAVP should not be used in frail elderly with nocturia because of the risk of hyponatremia (Grade B).

8. INTERVENTIONS WITH LONG-TERM CARE STAFF

a. Long-term care institutions should implement staff development programmes to increase knowledge and skills about continence care and the efficacy of behavioural methods (Grade C).

b. Computerised databases may help caregivers determine the effectiveness of UI programmes (Grade C).

c. Family caregivers need monitoring for and resources to counteract fatigue, social isolation, and other burdens related to continence care. (Grade C)

d. Use of mechanical lifts may help to reduce staff injury and increase adherence to toileting programmes (Grade C).

XII. RECOMMENDATIONS FOR RESEARCH

1. AETIOLOGY

a. Racial and ethnic differences in LUT- and comorbidity-related causes of UI

b. Aetiological models and translational research in the causes of UI in frail older persons, incorporating principles of concentric, interacting, multiple risk factors models of geriatric syndromes

c. Relationship between emerging models of frailty and vulnerability and development of UI

d. Relative roles of lower urinary tract disorders, medical conditions, hormonal factors, sleep disorders, and other conditions in the pathophysiology of nocturia in frail older persons

e. Longitudinal studies incorporating basic science as well as clinical measures

2. EVALUATION

a. Efficacy and effectiveness of current evaluation guidelines and recommendations across settings (home, clinic, assisted living, long-term care)

b. Development and validation of consensus standards for the definition of elevated PVR and UR for both frail elderly men and women, in both clinical and research settings

c. Development and validation of consensus standards for evaluation of nocturia in frail older persons
3. TREATMENT

a. Proactive incorporation of frailer, older-old persons in all UI intervention trials

b. New outcome measures relevant to geriatric care, including quality of life, socialisation, need for institutionalisation, impact on comorbidity, caregiver burden, and alternatives to wet-checks for long-term care residents

c. Outcome measures that are sensitive to differences across cultures and health care systems, e.g., reimbursement for continence services and supplies

d. Association between expectations, preferences, and outcomes

e. New approaches and tools to assess UI-specific quality of life in cognitively-impaired frail elderly

f. Increased understanding of the interaction between functional impairment and the impact of UI

g. Investigation of the utilities frail elderly and their caregivers assign to varying degrees of UI (with or without treatment intervention) versus “dryness”

h. Multicomponent interventions

i. Development and validation of predictive models for guiding treatment decisions

j. Family caregiver characteristics associated with and optimum interventions to improve their effective use of behavioural interventions for UI in the home

k. Racial-ethnic differences in UI treatment efficacy, tolerability, and safety in frail older persons across care settings (home, assisted living, long-term care, hospital)

l. Racial-ethnic disparities in UI treatment in frail older persons across care settings

m. Efficacy and effectiveness of policy and regulatory approaches to improve UI care quality in long-term care

n. Efficacy and tolerability of antimuscarinics in older-old and frail persons across care settings

i. Include adequate numbers of patients (including those with cognitive and/or functional impairment, and comorbid conditions common in this population); use outcome measures specific for this population and include impact on caregivers; stratify outcomes by age, comorbidity, function, and frailty; specify diagnostic methods; and continue interventions for clinically-relevant periods

ii. Determine the characteristics of frail older persons who respond to drug therapy

iii. Incidence, prevalence, and risk factors for adverse cognitive and functional effects, and optimum research and clinical measures to detect them

iv. Cost-benefit, cost-effectiveness, and cost-utility studies of UI treatments, using models incorporating the special issues of patient and caregiver preferences, definitions of “benefit” in this population, and a comprehensive approach to costs across a range of care settings

o. Inclusion of older-old and frailer patients in surgical studies, with stratification of outcomes by age, comorbidity, oestrogen status (women), and urodynamic findings

p. Prospective studies to determine the magnitude and severity of common geriatric complications following anti-incontinence surgery

q. Develop and validate guidelines for identifying frail elders who would benefit from gynaecological/urological anti-incontinence surgery

r. Efficacy and effectiveness of specific devices and procedures to prevent complications from long term indwelling catheters in frail elderly

s. Efficacy and effectiveness of multicomponent treatment for nocturia, including interventions targeted at comorbidity and drug therapy

t. Compare the efficacy of specific models of UI care for frail elderly around the world.

u. Determine the factors associated with the effectiveness of care models in countries with different health care systems

XII ALGORITHM

1. URINARY INCONTINENCE IN FRAIL OLDER MEN AND WOMEN

Healthy older persons should receive the similar range of treatment options as younger persons, but frail older persons require a different approach addressing the potential role of comorbid disease, current medications (prescribed, over-the-counter, and/or naturopathic), and functional and/or cognitive impairment in UI. The extent of investigation and management should take into account the degree of bother to the patient and/or carer, goals for care, cooperation, and overall prognosis and life expectancy. Effective management to meet the goals of care should be possible for most frail elderly.

2. HISTORY AND SYMPTOM ASSESSMENT

Active case finding and screening for UI should be done in all frail older persons (Grade A). History
should include comorbid conditions and medications that could cause or worsen UI. The physical should include rectal exam for faecal loading or impaction (Grade C), functional assessment (mobility, transfers, manual dexterity, ability to toilet) (Grade A), screening test for depression (Grade B), and cognitive assessment (to assist in planning management, Grade C). The mnemonic DIAPPERS (see algorithm) covers some of these comorbid factors, with two alterations: 1) atrophic vaginitis does not itself cause UI and should not be treated for this purpose (Grade B); and 2) current consensus diagnostic criteria for urinary tract infection (UTI) are poorly sensitive and specific in nursing home residents. The patient and/or carer should be asked about the degree of bother of UI (Grade B), goals for UI care (dryness, decrease in specific symptom[s], quality of life, reduction of comorbidity, lesser care burden) (Grade B), likely cooperation with management (Grade C), and the patient’s overall prognosis and remaining life expectancy (Grade C). Urinalysis is recommended for all patients, primarily to screen for hematuria (Grade C); treatment of otherwise asymptomatic bacteriuria/pyuria is not beneficial (Grade D), and it may cause harm by increasing the risk of antibiotic resistance and severe adverse effects, e.g., *Clostridium difficile* colitis (Grade C). Utility of clinical stress test in this population is uncertain (Grade D). Wet checks can assess UI frequency in long-term care residents (Grade C).

Postvoiding residual volume (PVR) testing is impractical in many care settings, and there is no consensus for the definition of “high” PVR in any population. Yet, there is compelling clinical experience for PVR testing in selected frail older persons with: diabetes mellitus (especially longstanding), prior urinary retention or high PVR; recurrent UTIs; medications that impair bladder emptying (e.g., opiates); severe constipation; persistent or worsening urgency UI despite antimuscarinic treatment; or prior urodynamics showing detrusor underactivity and/or bladder outlet obstruction (Grade C). Treatment of contributing comorbidity may reduce PVR. Trial with catheter may considered for PVR > 200–500 ml if the PVR is felt to contribute to UI or frequency (Grade C).

Assessment of frail elders with bothersome nocturia should identify potential underlying cause(s) including nocturnal polyuria (by bladder diary [frequency-volume chart] or wet checks or oedema on exam) (Grade C); primary sleep problem (e.g., sleep apnoea); and low voided volumes (e.g., from high PVR).

3. CLINICAL DIAGNOSIS

The most common types of UI in frail older persons are urgency, stress, and mixed UI. Frail elderly with urgency UI also may have detrusor underactivity and high PVR (without outlet obstruction), called detrusor hyperactivity with impaired contractility (DHIC). There is no evidence that antimuscarinics are less effective or cause retention in DHIC (Grade D).

4. INITIAL MANAGEMENT

Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis (Grade C). In some frail elders the only possible outcome may be contained UI (managed with pads), especially for persons with minimal mobility (require assistance of ≥ 2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal UI.

Conservative and behavioural therapy for UI include lifestyle changes (Grade C), bladder training for more fit alert patients (Grade B), and prompted voiding for more impaired patients (Grade A). For select cognitively intact patients, pelvic muscle exercises may be considered, but there are few studies (Grade C). Antimuscarinics may be added to conservative therapy of urgency UI (Grade A-C, depending on agent). Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction (Grade C). All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable. DDAVP (vasopressin) has a high risk of severe hyponatraemia in frail persons and should not be used (Grade B).

5. ONGOING MANAGEMENT AND REASSESSMENT

Optimal UI management is usually possible with the above approaches. If initial management fails to achieve desired goals, next steps are reassessment and treatment of contributing comorbidity and/or functional impairment.

6. SPECIALIZED MANAGEMENT

If frail elderly have either other significant factors (e.g., pain, haematuria), UI symptoms that cannot be classified as urgency, stress, or mixed, or other complicated comorbidity which the primary clinician cannot address (e.g., dementia, functional impairment), then specialist referral should be considered. Referral also may be appropriate for insufficient response to initial management. Type of specialist will depend on local resources and the reason for referral: surgical specialists (urologists, gynaecologists); geriatrician or physical therapist (functional and cognitive impairment); continence nurse specialists (homebound patients). Referral decisions should consider goals of care, patient/carer desire for invasive therapy, and estimated remaining life expectancy.

Age per se is not a contraindication to UI surgery (Grade C), but before surgery is considered, all patients should have:
Discussion (including the carer) to insure that the anticipated surgical outcome is consistent with goals of care in the context of the patient’s remaining life expectancy (Grade C)

- Adequate trial of conservative therapy (Grade C)
- Evaluation and treatment for any comorbidity, medications, and cognitive and/or functional impairments contributing to UI and/or which could compromise surgical outcome (e.g., dementia that precludes patient ability to use artificial sphincter) (Grade C)
- Urodynamic testing, because clinical diagnosis may be inaccurate (Grade B)
- Preoperative assessment and perioperative care to establish risk for and minimise common geriatric post-operative complications such as delirium and infection (Grade A) and dehydration and falls (Grade C).

**REFERENCES**

8. Centers for Disease Control National Center for Health Statistics.
29. Tomlak, M., Berthelot, J.-M., Guimond, E. & Mustard, C.


103. Mishra, V. et al. Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? BJU International 100, 327-331 (2007).


406. Millier, M. Nocturnal polyuria in older people: pathophysiology
407. Hillier, P., Knapp, M. & Cove-Smith, R. Circadian variations
408. Blanker, M.H. et al. Normal values and determinants of
409. Stewart, R.B., Moore, M.T., May, F.E., Marks, R.G. & Hale,
410. Coyne, K.S. et al. The prevalence of nocturia and its effect
412. Mock, L., Parmelee, P., Kutner, N., Scott, J. & Johnson TM
414. B lanker, M.H. et al. Normal values and determinants of
417. Abraham L., Hareendran A., Mills I. and et al.: Development
418. Abraham L., Hareendran A., Mills I. and et al.: Development
419. Asplund, R. & Aberg, H. Diurnal rhythm of antidiuretic
420. Rembratt, A., Norgaard, J.P. & Andersson, K.E. Differences
421. Ouslander, J., Schnelle, J., Simmons, S., Bates-Jensen, B.
422. Ouslander, J., Johnson, T., Nasr, S., Schnelle, J. & Miller,
423. Ouslander, J., Johnson, T., Nasr, S., Schnelle, J. & Miller,
428. Pedersen, P.A. & Johansen, P.B. Prophylactic treatment of
430. Fantl, J.A., Bump, R.C., Robinson, D., McClish, D.K. &
431. Fitzgerald, M., Mulligan, M. & Parthasarathy, S. Nocturic
432. Johnson TM 2nd, Burgio, K., Redden, D., Wright, K. &
433. Rembratt, A., Norgaard, J.P. & Andersson, K.E. Nocturia and
434. Johnson TM 2nd, Burrows, P., Kusek, J. & et al Medical
435. Johnson TM 2nd, Burrows, P., Kusek, J. & et al Medical
437. Obara, K., Takahashi, H., Takeda, M. & Sato, S. [The effect of
desmopressin (DDAVP) in patients complaining of
nocturia]. Nippon Hinyokika Gakkai Zasshi - Japanese
Committee 12

Adult Conservative Management

Chairman

J. HAY SMITH (New Zeland)

Members

B. BERGHMANS (The Nederlands),
K. BURGIO (USA),
C. DUMOULIN (Canada),
S. HAGEN (U.K),
K. MOORE (Canada),
I. NYGAARD (USA)

Consultant

J. N’DOW (U.K)
Adult Conservative Management

J. Hay Smith,

B. Berghmans, K. Burgio, C. Dumoulin, S. Hagen, K. Moore,

J. N’dow, I. Nygaard

INTRODUCTION

Conservative treatment is any therapy that does not involve pharmacological or surgical intervention. It includes principally, lifestyle interventions, physical therapies, scheduled voiding regimens, complementary and alternative medicines (i.e. those not considered part of the traditional biomedical model), anti-incontinence devices, supportive rings/pessaries for pelvic organ prolapse (POP) and pads/catheters. In some countries a combination of the first three is called “behavioural therapy” (defined as an approach that seeks to alter the individual’s actions or their environment in order to improve bladder control). Conservative therapies are usually low cost, and managed principally by the person with urinary incontinence (UI) with instruction/supervision from a health professional. They differ from other forms of incontinence and prolapse management, in that they have a low risk of adverse effects and do not prejudice other subsequent treatments. Consequently conservative measures should be included in the counselling of patients who suffer from either UI or POP regarding their management options. As the prevalence of UI and POP is high, and with the current constraints on most healthcare economies, conservative treatment constitutes the principal form of management at the primary care level. It is also indicated for those patients for whom other treatments, in particular surgery, are inappropriate, for example, those who are unwilling to undergo or who are not medically fit for surgery and women who plan future pregnancies (as these may adversely affect surgery). Other indications include patients awaiting surgery or who wish to delay surgery and those whose symptoms are not serious enough for surgical intervention.

To date, however, only a relatively small number of intervention studies of adequate size have been carried out to assess the effectiveness of conservative management of UI and POP. This chapter reviews the main types of conservative management (excluding anti-incontinence devices and pads/catheters; see report of Committee 20: Management using continence products) with regard to their ability to prevent and treat UI and POP effectively. Comment is also made on the effect of conservative management on other lower urinary tract symptoms (in addition to UI) and also factors affecting outcome, in particular age. This information will assist in the counselling of neurologically ‘normal’ adults regarding these treatment options (readers are directed to the chapters on children, the frail elderly and neuropathic patients for discussion on the effect of conservative management in these specific groups). A systematic review of the literature has been carried out, principally of randomised controlled trials (RCTs), resulting in some recommendations for practice based on the level of evidence available (see preface) and suggestions for future research.

Notes to the reader: For ease, all studies are cited using the first author and year. Where summary statistics are presented, the raw data from which these are derived can be found in the trial reports and systematic reviews cited in the chapter. Readers who are interested in the conservative management of faecal incontinence are referred to the chapter on faecal incontinence.

A. UI IN WOMEN

Female UI is a distressing condition with significant social implications. It is common – the median level of prevalence estimates gives a picture of increasing prevalence during young adult life (prevalence 20-30%), a broad peak around middle age (prevalence 30-40%), and then a steady increase in the elderly (prevalence 30-50%) (see report of Committee 1: Epidemiology). Although the proportions of different types of UI are difficult to estimate, approximately half of all incontinent women are classified as stress incontinent, a smaller proportion as mixed incontinent and urge urinary incontinence is the smallest category. The various types most likely reflect different pathologies and aetiologies.
Stress urinary incontinence (SUI) is thought to occur due to a lack of bladder neck support and/or poor urethral closure. As a result the urethral lumen is not closed effectively during activities that increase intra-abdominal pressure with consequent involuntary leakage during effort, exertion, sneezing or coughing. If during urodynamic assessment there is involuntary urine loss synchronous with a rise in intra-abdominal pressure and in the absence of an involuntary detrusor contraction this is described as urodynamic stress incontinence. Urge urinary incontinence (UUI) can be due to a rise in intravesical pressure due to involuntary detrusor contraction, a condition known as detrusor overactivity (DO). This is further subclassified as idiopathic (cause unknown) or neurogenic (where there is a known neurological cause for detrusor muscle overactivity). Some women experience urgency with or without leakage, usually with urinary frequency and nocturia. This constellation of symptoms is called the overactive bladder (OAB) syndrome. Mixed urinary incontinence (MUI) is used when the person has evidence of both SUI and UUI. This chapter addresses the effect of conservative management in women and men with stress, urge (idiopathic), and mixed urinary incontinence, and OAB syndrome.

Where able, the authors of the chapter have differentiated the effects of interventions by diagnosis (such as SUI, UUI, OAB, and MUI). This diagnostic distinction was not made or not reported in some of the studies reviewed; where it was not possible to distinguish effect by diagnosis the more generic term urinary incontinence (UI) is used in summaries and recommendations.

### I. LIFESTYLE INTERVENTIONS

Various lifestyle factors may play a role in either the pathogenesis or, later, the resolution of UI. While published literature about lifestyle factors and UI is sparse, alterations in lifestyle are frequently recommended by healthcare professionals and lay people alike. However, to date, most studies about lifestyle report associations only and do not assess the actual effect on UI of applying or avoiding the behaviour in question. Currently, only a relatively small number of RCTs have been carried out to assess the effect of a specific lifestyle change on UI. This section will examine the evidence for the association and use of lifestyle interventions in the management of female UI. A summary of the search strategy and inclusion/exclusion criteria is given in the appendix.

#### 1. PREVENTION

No RCTs assessing the effect of lifestyle interventions on UI prevention were identified.

#### 2. TREATMENT

Where RCTs are available, these are reviewed. Where there are no RCTs for a particular lifestyle intervention, other types of evidence are considered.

##### a) Weight loss

Two RCTs were found that specifically recruited incontinent women [1, 2]. Another RCT focused on the effect of intensive lifestyle intervention in overweight women with diabetes [3]; the bulk of this intervention was weight loss. Four prospective cohort studies [4-7] evaluated the effect of weight loss. Other study designs were cross-sectional [8-14], retrospective cohort [15], or case-control studies [16].

#### 1. QUALITY OF DATA

Sample sizes for the intervention studies were 12 [5], 138 [6], 10 [4], 48 [1], 338 [2], 1,957 [3] and 101 [7]. Sample sizes for observational studies that assessed the association between obesity and UI ranged from 193 [15], 3536 [13], 27,936 [11] to 83,355 [14]. The case control study had a sample size of 108 cases and 108 controls [16].

Participant blinding was not possible in any of the three RCTs. Of 48 randomized in one trial, 40 remained in the study at the time of assessment [1]. Another trial [2] is in abstract form and full details have not been published. In the large RCT with diabetes as the primary focus, 2191 women were enrolled and 234 were excluded because data about UI were not available; the number that dropped out before the endpoint is not detailed for this subpopulation of women.

The outcome measure in most studies was subjective, determined by either validated or non-validated questionnaires. Studies by Bump (1992) and Subak (2002, 2005, 2007) also used objective measures including urodynamics, bladder diary and a standardised fluid loss quantification test.

Follow-up periods for the interventional studies were one year after gastroplasty surgery [5] and laparoscopic Roux-en-Y gastric bypass [7], six months after completion of weight reduction, either by means of low calorie liquid or reduced calorie solid diet [4], three months after completion of a very low calorie liquid diet and exercise [1], six months after completing an intensive group weight intervention programme that included lifestyle and behaviour changes [2], mean 2.9 years after beginning the intervention [3], and not stated [6].

#### 2. RESULTS

Many researchers [8-11, 13-20] have reported an association between increased weight, or increased body mass index (BMI, kg/m²), and UI. This association held after controlling for age and parity. In one multivariate analysis, Brown (1996) reported that the prevalence of daily UI increased by an odds ratio of 1.6 per 5 BMI units. In a multivariate analysis
of a different population, Brown (1999) found that the prevalence of at least weekly SUI increased by 10% per five units BMI. Similarly, Foldspang (1995) reported an OR of 1.07 for UI prevalence per BMI unit, after controlling for other factors [21]. Hannestad (2003) described a dose-response type relationship between BMI and severe UI. Compared to women with a BMI < 25, OR’s for the following groups were: BMI 25-29, OR 2.0 (95% confidence interval (CI) 1.7 to 2.3); BMI 30-34, OR 3.1 (95% CI 2.6 to3.7); BMI 35-39, OR 4.2 (95% CI 3.3 to 5.3); BMI 40+, OR 5.0 (95% CI 3.4 to 7.3). Danforth (2006) reported that in women with a BMI of 30 or higher, the odds of severe UI were 3.1 times that of women with a BMI between 22 and 24. Similarly, Melville (2005) found that women with a BMI of 30 or higher had a 2.3 fold risk of UI compared to normal weight women.

Three groups [5-7] reported resolution of UI in the majority of cases after massive weight loss in morbidly obese women undergoing surgical weight reduction procedures. While obesity is commonly considered a risk for SUI, in Bump’s (1992) study, women with UUI were as likely to experience post-operative continence as women with SUI. In the Burgio (2007) study, mean BMI decreased from 48.9 (standard deviation (SD) 7.2) pre-surgery to 35.3 (SD 6.5) at six months and 30.2 (SD 5.7) at 12 months post-surgery. Prevalence of UI decreased from 67% pre-surgery to 41% at six months and 37% at 12 months (95% CI for change 18.6 to 40.0%, p<0.001). Reduction in prevalence of UI was significantly associated with decreases in BMI (p=0.01). Among incontinent women who lost 18 or more BMI points, 71% regained urinary continence at 12 months. In a cross-sectional study of 1800 Swedish women [12], incontinent women were slightly more likely than continent women to report at least a five kg weight loss in the preceding five years (15% versus 11%, respectively; p=0.05). This may be secondary to intentional weight loss as a treatment for UI, rather than some effect of weight loss itself.

In Subak’s pilot study (2002) of 10 women, all six of the women achieving a weight loss of at least 5% had at least a 50% reduction in incontinent episodes compared to one out of the four women with <5% weight loss. In the 2005 RCT [1] reporting on 48 participants, median baseline weight (95 kg) and number of incontinent episodes (21 per week) were similar between the groups. Compared to controls (wait list) that did not participate in a weight loss programme, women in the weight loss (liquid diet) group lost 15kg (SD 7) (compared to 0kg (SD 4)) and experienced a 60% reduction in weekly incontinent episodes (compared to 15%). The Programme to Reduce incontinence by Diet and Exercise (PRIDE) [2] randomised 338 overweight incontinent women in a 2:1 ratio to an intensive 6-month group weight intervention programme or usual care, consisting of four information sessions. Women in the intervention group lost a mean of 8kg compared with 2kg in the usual care group. Forty one percent of women in the intervention group decreased the weekly number of incontinence episodes by at least 70% compared to 22% in the usual care group.

The RCT from the Diabetes Prevention Programme [3] reporting on 1957 participants found that overweight diabetic women assigned to intensive lifestyle therapy (consisting of low-fat diet, moderately intense exercise for at least 150 minutes per week and a behavioural and educational curriculum) were less likely to be incontinent compared to those assigned to placebo drug with standard lifestyle advice or metformin alone (38.3% versus 45.7% and 48.1%, respectively; p=0.001).

**Summary**

Obesity is an independent risk factor for the prevalence of UI. Massive weight loss (15 to 20 BMI points) significantly decreases UI in morbidly obese women. (Level of Evidence: 2). Moderate weight loss also results in decreased UI. (Level of Evidence: 1).

**Recommendations**

For morbidly and moderately obese women weight loss is a useful treatment to reduce UI prevalence (Grade of Recommendation: A). Based on the current evidence, maintaining normal weight through adulthood may be an important factor in preventing the development of UI. Given the high prevalence of both UI and obesity in women, the dual issues of weight loss and prevention of weight gain should receive high research priority.

**b) Physical forces (exercise, work)**

No RCTs exist in which UI prevalence is compared between subjects assigned to heavy work or high impact activity versus sedentary activities.

1. **Quality of data**

A case-control study compared the incidence of surgery for UI and/or prolapse between 28,619 population based controls and 1,652,533 nursing aids [22]. Be (1989) and Nygaard (1994) evaluated the difference in UI prevalence between 305 and 144 women, respectively, engaged in high versus low impact activities [23, 24] Be (2001a) compared 572 athletes ages 15-39 years with 574 controls [25]. In a retrospective cohort study, Nygaard (1997) reported UI prevalence in 104 high-impact and low-impact former Olympic athletes [26]. Caylet (2006) compared UI prevalence between 157 elite female athletes and 426 women from the general population between ages 18 and 35 [27]. Kruger (2007) conducted a case-
control study exploring mechanisms by which athletes might be more likely to experience SUI and compared pelvic organ descent and pubovisceral muscle volume between 24 elite nulliparous athletes and 22 age and BMI matched controls [28]. Eliasson (2005) compared UI at 36 weeks gestation and one year postpartum between 665 primiparous women participating in high-impact, low-impact or no activity [29].

Several small case series described UI in women doing specialised activities. Davis (1996) described a series of nine women who became incontinent after parachute jumping [30]. Larsen (2007) compared UI and POP in 37 soldiers that completed parachute training versus 79 that completed other summer military training [31]. Benjamin (2000) studied the prevalence of UI in 25 women aviators exposed to high gravitational forces [32].

Several cross-sectional studies compared the prevalence of UI with the self-reported level of physical activity. The Norwegian EPINCONT study compared both any and severe UI in 27,936 women according to three levels of high impact physical activity [11]. Kikuchi (2007) compared UI prevalence in 676 men and women age 70 years and older participating in three physical activity groups; physical activity was assessed by a single-item questionnaire [33]. Nygaard (2005) compared UI prevalence and severity in 3,364 women according to physical activity level as assessed by the International Physical Activity Questionnaire [34].

Using women enrolled in the Nurses Health Study, two prospective studies assessed the risk of incident UI according to physical activity level, reported as metabolic equivalent task hours per week, in 2,355 women ages 54 to 79 years [35] and 30,135 women 37 to 54 years at risk of incident UI [36]. Another study measured physical activity by questionnaire and electronic motion sensor in 69 women before and one year after successful treatment for UI [37].

2. RESULTS

Minimal SUI is common in young exercising women [23, 38, 39]. College athletes participating in high impact activities are more likely to report the symptom of SUI during exercise than those participating in low impact exercise [24]. Bø (2001a) found no difference in UI prevalence between elite athletes and controls. Caylet (2006) found that 28% of elite athletes reported UI compared to 10% of controls. There was no difference in UI prevalence between physically active and sedentary controls. In the prospective study of pregnant and postpartum women, high-impact physical activity before pregnancy was associated with more urinary leakage one year postpartum compared to low-impact activity [29].

There is little available information on whether strenuous exercise or activity causes the condition of UI later in life. In a study of 104 women who were Olympians approximately 25 years ago, those who competed in gymnastics or track and field were not more likely to currently report daily or weekly UI than Olympians who competed in swimming [26]. Certain provocations may cause SUI; one report described nine nulliparous infantry trainees who developed SUI and pelvic floor defects for the first time during airborne training, which included parachute jumping [30]. The precise number of total trainees is unknown but is estimated to be approximately 500. Larsen (2007) found no difference in UI prevalence between female paratroopers and women that completed regular summer training, but paratroopers were more likely to demonstrate stage II prolapse on examination (OR 2.7; 95% CI 1.4 to 5.4). In 25 women aviators, self-report of UI was not found to increase at high gravitational forces [28]. Compared to a control group, athletes that participated in high-impact, frequent intense training had a higher mean diameter of the pubovisceral muscle, greater bladder neck descent and a larger hiatal area on Valsalva manoeuvre [28].

The EPICONT study reporting on 27,936 women found no difference in either any UI (that is, mild or greater) or severe UI in women that reported high impact physical activity one to two hours per week or three or more hours per week compared to those that reported exercising less than one hour per week (after adjusting for age, BMI, parity, coughing and wheezing) [11]. In contrast, Nygaard (2005) reported that UI with physical activity was more common among highly active than less active women (15.9% versus 11.8%; p=0.01). Additionally, after adjusting for age, parity, comorbidities and other factors, women with very severe UI were more likely to be insufficiently active than continent women (OR 2.64). In Kikuchi (2007), compared to people in the lowest physical activity group, those in the middle and high level activity groups were less likely to report UI (adjusted OR of 0.71, 95% CI 0.47 to 1.09, and 0.58, 95% CI 0.35 to 0.96 respectively).

In older women enrolled in the Nurses Health Study, total physical activity (i.e. top versus bottom quintile of metabolic equivalent task hours per week) was significantly associated with a reduced risk of new UI (OR 0.81) in analyses adjusted for confounders. Walking constituted about half of the total physical activity among the participants and was related to a 26% lower risk of developing UI. Total physical activity was not related to the incidence of UUI [35]. These findings were mirrored in younger women enrolled in the same study [36]: the risk of at least monthly UI decreased with increasing quintiles of moderate physical activity (relative risk (RR) 0.80, 95% CI 0.72 to 0.89 comparing extremes of quintiles). Note that few women in either study did strenuous physical activity. Stach-Lempinen (2004) found no difference in exercise habits after successful treatment for UI.

Surprisingly little information is available on the
relationship between stressors in the workplace and UI. Danish nursing assistants, who are exposed to frequent heavy lifting, were more likely to undergo surgery for genital prolapse and/or UI than women in the general population (RR 1.6, 95% CI 1.3 to 1.9); the study did not control for parity [22].

**SUMMARY**

Strenuous exercise is likely to unmask the symptom of SUI during the provocation. There is currently no evidence that strenuous exercise causes the condition of UI although in a small number of women without other known risk factors, extreme provocations such as parachute jumping may cause UI.

There is good prospective cohort information suggesting that moderate exercise decreases the incidence of UI in middle-aged and older women; this effect may be mediated by weight control (Level of Evidence: 2).

There are scant uncontrolled data that suggests that women engaged in occupations with heavy lifting may be predisposed to genital prolapse and/or UI (Level of Evidence: 3). In spite of the fact that healthcare professionals commonly advise restricting exercise and heavy lifting following UI or prolapse surgery, there is no published evidence that this improves surgical outcome.

**RECOMMENDATIONS**

Given the large proportion of women who are employed in various occupations that require heavy lifting and the paucity of data about the association of such exertions and UI, this association should be investigated further. Specifically, research must establish whether heavy exertion is an etiologic factor in the pathogenesis of UI, and whether changing exertions can alleviate established UI.

c) **Smoking**

Understandably, there are no RCTs investigating the effect of smoking on UI. There are no trials of the effect of smoking cessation.

1. **Quality of data**

One case-control study compared incontinent smokers with incontinent non-smokers [40], while a second compared smoking behaviour between continent and incontinent women [41]. Seven large cross sectional studies evaluated multiple risk factors for UI, including smoking [8, 11, 14, 42-45]. One case-control study evaluated smoking as a risk factor for failure of SUI surgery [46]. One trial of women planning surgery for SUI assessed the association between smoking and severity of UI, defined by mean number of Incontinence episodes per day on a bladder diary [47]. An in vitro study assessed the effects of nicotine on bladder muscle contraction [48]. Sample sizes were 189 [40], 1761 [42], 160 [41], 199 [46], 7949 [8], 7338 [43], 1761 [42], 3302 [44], 5488 [45], 27936 [11], and 83355 [14].

2. **RESULTS**

Smokers were more likely to report UI than non-smokers in some studies [11, 14, 41, 43, 44], but not in others [8, 42, 45]. Amongst women with SUI, current smoking was positively associated with UI severity after adjusting for confounders [47]. After adjusting for age, parity, type of delivery, and pre-pregnancy BMI, smokers had a 1.3 fold higher RR (95% CI 1.0 to 1.8) of reporting UI at 16 weeks gestation than non-smokers [43]. The adjusted OR for moderate or severe UI among women reporting UI was 1.38 (95% CI 1.04 to 1.82) in current smokers, after adjusting for perimenopausal status, BMI, diabetes and ethnicity [44]. In the large population based study by Hannestad et al [11], smoking increased the odds of severe UI (OR 1.4, 95% CI 1.2 to 1.6) but not of mild UI. In the case-control study, after adjusting for confounders, smoking was a protective factor (OR 0.26, 95% CI 0.09 to 0.81) against recurrent UI after anti-incontinence surgery [46]. Incontinent smokers were found to have stronger urethral sphincters and lower overall risk profiles than incontinent non-smokers [40]; therefore, it was proposed that more violent coughing promotes anatomic defects, which allow UI.

In potential support of nicotine as a risk factor for UI, Hisayama (1988) and Koley (1984) found that nicotine produces phasic contraction of isolated bladder muscle probes in vitro [48, 49]. However, Milsom (1993) reported an apparent paradoxical local estrogenic effect of nicotine on the vagina, resulting in a decrease in vaginal pH and an increase in lactobacilli [50].

**SUMMARY**

Current data suggest that smoking increases the risk of more severe UI (Level of Evidence: 3). Smokers may have a different mechanism causing their UI than non-smokers.

**RECOMMENDATIONS**

Further prospective studies are needed to determine whether smoking cessation prevents the onset, or promotes the resolution, of UI.

d) **Dietary factors**

No RCT was identified that addressed dietary changes. In a prospective questionnaire study, Dallosso (2004a) studied the impact of dietary risk factors on the one-year incidence of SUI [51] and OAB symptoms [52,
53] in women. Participants completed a 130-item validated food frequency questionnaire. Anecdotal evidence suggests that eliminating dietary factors such as artificial sweeteners and certain foods may play a role in continence; however, no treatment trials have tested this hypothesis.

In a large postal survey, 6037 men and women responded to questions about tea, soft drink and alcohol consumption, as well as whether or not they had UI [54].

One RCT [55] assessed the effects of a caffeine reduction intervention upon frequency, urgency and UUI. Subjects were those with urinary symptoms who consumed more than 100mg caffeine daily. Those randomised to the experimental group received bladder training and a caffeine-fading method to decrease caffeine intake to less than 100mg per day, while the control group also received bladder training but no caffeine reduction information. Another RCT [56] used a crossover design to evaluate the effect of caffeine restriction and of increasing and decreasing fluid intake on urinary symptoms over a four-week period in women with urodynamic SUI or DO.

One study compared women with DO with continent women who received caffeine tablets [57], while another compared caffeine intake between women with DO and those without [58]. The effect of decreasing caffeine intake in a small cohort of incontinent women was examined in a prospective fashion [59]. Large epidemiologic trials using multivariate analyses assessed the effect of coffee drinking [8], alcohol consumption [9] and tea, coffee, and alcohol intake and UI [11]. A smaller cross-sectional analysis assessed the association between symptoms and lifestyle factors, including caffeine intake [60].

In one RCT, women with UI were randomly assigned to one of three groups: increase fluid intake by 500 cc, maintain fluid intake at baseline level, or decrease by 300 cc. Participants kept fluid intake and output diaries for five weeks [61]. Wyman (1991) analysed the correlation between mean daily oral fluid volume intake and mean daily voids and incontinence episodes in 126 women aged 55 and older that kept diaries for one week [62].

1. QUALITY OF DATA

It was not feasible to blind participants in any of the three RCTs, with dropout rates of 22% (26/58) [55], 37% (41/110) [56], and 45% (25/58) [61]. The numbers completing each study were 30 [57], 32 [61], 34 [59], 69 [56], 74 [55], 126 [62], 159 [58], 297 [60] 2764 [9], 6037 [54], 7949 [8], 27,936 [11], and 6,424 women [52] and 4887 men [63].

2. RESULTS

(a) Diet: After adjusting for age, physical functioning, SUI at baseline, obesity, smoking and certain dietary factors, the incidence of SUI at one year was increased in women consuming more total fat, saturated fatty acids and monounsaturated fatty acids, as well as those that consumed more carbonated beverages, zinc or vitamin B12 at baseline [51, 52]. The incidence of SUI was reduced in those that ate more vegetables, bread and chicken at baseline [52]. Higher intake of vitamin D, protein and potassium were associated with decreased risk of onset of OAB in women [53].

(b) Caffeine: One RCT found a clinical effect of decreasing caffeine, while the other did not. Bryant (2002) reported that women in the intervention group decreased daily caffeine consumption to a mean of 96.5mg, compared to 238.7mg in the control group. The experimental group had statistically significant reduction in urgency episodes (61% versus 12%); the number of incontinence episodes decreased as well (55% compared to 26% in the controls) but this was not statistically significant (p=0.219). In contrast, while Swithinbank (2005) found effect of decreasing fluid intakes (see below), changing from caffeine containing to decaffeinated drinks produced no improvement in symptoms.

Other study designs generally found mixed effects of caffeine on bladder function. Following caffeine intake, women with DO had increased detrusor pressure on bladder filling, while continent women had no such abnormality [57]. In a population of 259 consecutive women presenting for urodynamics, 131 women with DO had a significantly higher mean caffeine intake (484mg/day, SD 123) than women without this diagnosis (194, SD 123) [58]. This association persisted after controlling for age and smoking. In 34 women with symptoms of UI (mostly mixed) who decreased caffeine intake (from 900mg/day to 480mg/day), episodes of daily urine loss also decreased (from 2.3 to 1.0 per day) [59]. In a multivariate analysis, Brown (1996) found no association between coffee drinking or alcohol drinking and daily UI. In the Norwegian EPINCONT study, tea drinkers had a slightly higher odds for all types of UI (OR 1.2, 95% CI 1.1 to 1.2) for up to two cups per day compared to none and OR 1.3 (95% CI 1.2 to 1.5) for three or more cups per day compared to none, while no association was found between either coffee (at any dosage) or alcoholic beverages (three or more drinks per two weeks compared to none to two drinks per two weeks) and UI [11]. Bradley (2005) reported that, after adjusting for confounders, coffee drinking was associated with bladder symptoms of difficulty emptying (OR 8.6, 95% CI 1.4 to 55.0) and weak stream (OR 5.3, 95% CI 1.5 to 19.0).

(c) Alcohol: After adjusting for age and gender, no association was found between UI and consumption of alcohol [54]. After adjusting for age and fluid intake, consumption of wine, beer or spirits did not increase the incidence of either SUI or OAB (there was a trend...


**SUMMARY**

Fluid intake plays a minor, if any, role in the pathogenesis of UI. Caffeine consumption is pervasive in many societies and may play a role in exacerbating UI. The data on caffeine intake and UI are conflicting. While large cross-sectional surveys indicate no association (Level of Evidence: 3), small clinical trials do suggest that decreasing caffeine intake improves continence. (Level of Evidence: 2).

**RECOMMENDATIONS**

Given the fact that decreasing fluids may lead to urinary tract infections, constipation, or dehydration, this intervention should be reserved for patients with abnormally high fluid intakes (Grade of Recommendation: C).

A reduction in caffeine intake is recommended for those with incontinence symptoms (Grade of Recommendation: B). Larger RCTs to assess the effect of caffeine and other dietary factors are feasible and important.

e) Constipation

No published RCTs were found which assessed the effect of regulating bowel function on UI. An observational study compared the self-report of straining as a child with urogynaecological symptoms as an adult [64]. Population-based studies assessed multiple risk factors for UI [65, 66].

1. **QUALITY OF DATA**

Sample sizes range from 73 for the observational study [64] to 213 in a study correlating the surrogate measures of perineal descent and pudendal neuropathy [67] to 1154 and 1051 in the population-based studies [65] respectively.

2. **RESULTS**

In a small observational study, 30% of women with SUI and 61% of women with uterovaginal prolapse reported straining at stool as a young adult, compared to 4% of women without urogynaecological symptoms [64]. In a large population-based study of 1154 women over age 60 years, those with UI were slightly more likely to report constipation than those who were continent of urine (31.6% vs 24.7%) [65]. After adjusting for demographic and obstetric confounders, women who reported straining at stool were more likely to report SUI (OR 1.9, 95% CI 1.3 to 2.6) and urgency (OR 1.7, 95% CI 1.2 to 2.4) [66]. There appears to be an association between straining and pudendal nerve function. The mean pudendal nerve terminal motor latency increased after straining, correlated with the amount of descent, and returned to resting by four minutes after a strain [68]. Others found evidence of pudendal neuropathy in only 25% of women with abnormal perineal descent; in this large group of patients with defecating dysfunction no relationship was seen between neuropathy and pelvic descent, leading to the conclusion that pelvic descent and neuropathy may be two independent findings [67].

**SUMMARY**

There is some evidence to suggest that chronic straining may be a risk factor for the development of UI. (Level of Evidence: 3). There are no intervention trials that address the effect of resolving constipation on UI.

**RECOMMENDATIONS**

Further research is needed to delineate the role of straining in the pathogenesis of UI. If the association holds, public education, particularly of parents and paediatricians, is needed to make an impact on the common problem of straining due to constipation in children.

f) Other

There are many other lifestyle interventions suggested either by healthcare professionals or the lay press for the treatment of UI, including reducing emotional stress, wearing non-restrictive clothing, utilising a bedside commode, decreasing lower extremity oedema, treating allergies and coughs, wearing cotton underwear, and increasing sexual activity. There is no evidence to support these interventions for UI; support for these interventions is all anecdotal in
outside of the laboratory setting.

1. Quality of data

In the urodynamics laboratory, 65 women underwent a series of standing cough stress tests in each of four postures: standing, crossing the legs, bending forward from the hips, and a combination of crossing legs and bending forward [69].

2. Results

The mean loss was 12.3g (95% CI 8.5 to 16.1) in the standing position; this was significantly reduced to 1.3g (95% CI 0.5 to 2.1, P<0.001) with crossed legs and to 4.7g (95% CI 1.4 to 7.7, P<0.01) by the combination of crossing the legs and bending forward. Bending forward alone did not reduce fluid loss (10.2g, 95% CI 6.5 to 13.9). No study has evaluated whether postural changes are a satisfactory form of treatment outside of the laboratory setting.

SUMMARY

Crossing the legs and bending forward may reduce leakage during provocation, but this has not been tested in a clinical environment (Level of Evidence: 3). There is no evidence about whether many other recommended lifestyle interventions prevent or are effective treatments for UI.

RECOMMENDATIONS

Crossing the legs and bending forward might be useful in reducing leakage during coughing or other provocation (Grade of Recommendation: C). High quality studies evaluating the effect of many other lifestyle interventions on UI are warranted.

3. Other LUTS

Most published data on the effect of lifestyle interventions (in particular, dietary factors) on other LUTS pertain to males only, and thus, are not included in this review. In one study of a geriatric population (n=128), there was a strong relationship between evening fluid intake, nocturia, and nocturnal voided volume; this relationship was weaker for diurnal intake and voiding [70]. Bladder training combined with caffeine reduction significantly reduced the number of voids in 24 hours compared to bladder training alone (35% versus 23%) [55]

Future work should separately evaluate the impact of lifestyle interventions on nocturia, diurnal frequency, urgency and UUI to delineate whether certain interventions preferentially affect different areas of OAB.

4. Factors Affecting outcome

RCTs are sparse in this field of lifestyles advice, and none of those available specifically describe the impact of age or any other variable on outcome.

II. Pelvic Floor Muscle Training (PFMT)

One of the principal therapeutic uses of pelvic floor muscle training (PFMT) is the prevention and treatment of UI. Because pelvic floor muscle (PFM) integrity appears to play an important role in the continence mechanism (see report from Committee 4: Pathophysiology), there is a biological rationale to support the use of PFMT in preventing and treating UI.

PFMT has been part of exercise programmes in Chinese Taoism for over 6,000 years [71]. It first entered modern medicine in 1936; a paper by Margaret Morris describing tensing and relaxing of the PFM introduced the use of PFMT as a preventative and treatment option for urinary and faecal incontinence to the British physical therapy profession [72]. However, PFMT as a treatment for SUI did not become widespread until the 1950’s after American gynaecologist Arnold Kegel reported on the successful treatment of 64 cases of female SUI using PFM exercises with a pressure biofeedback perineometer [73].

• Biological rationale for PFMT for SUI

The biological rationale is three-fold. Firstly, an intentional, effective PFM contraction (lifting the PFM in a cranial and forward direction) prior to and during effort or exertion clamps the urethra and increases the urethral pressure, preventing urine leakage [74]. Ultrasonography and MRI studies have demonstrated the cranial and forward movement of the PFM during active contraction and the resulting impact on the urethral position, which supports this rationale [75, 76]. Miller (1998) named this counter-balancing PFM contraction prior to a cough the ‘knack’ and assessed its effectiveness in an RCT [77]; they demonstrated that a voluntary PFM contraction before or during coughing can reduce leakage after only one week of training. Other published research, employing the term ‘PFM functional training’, recommends pre-contraction of the PFM not only during a cough but for any daily task that results in increased intra-abdominal pressure [78].

Thus, research suggests that the timing of a PFM contraction might be an important factor in the maintenance of urinary continence. However, the optimal strength required to clamp the urethra and prevent urine leakage has not yet been determined. In healthy continent women, activation of the PFM before or during physical exertion seems to be an automatic response that does not require conscious effort [79-81]. There is some evidence that this PFM ‘reflex’ contraction is a feed-forward loop and might precede bladder pressure rise by 200-240 milliseconds [82, 83]. For incontinent women, learning to rapidly
perform a strong, well-timed PFM contraction may actively prevent urethral descent during an intra-abdominal rise in pressure [84].

Secondly, the bladder neck receives support from a strong, toned PFM (resistant to stretching), thereby limiting its downward movement during effort and exertion, preventing urine leakage [74, 85]. Bø has suggested that intensive strength training may build up the structural support of the pelvis by permanently elevating the levator plate to a higher position inside the pelvis and by enhancing the hypertrophy and stiffness of its connective tissues [85]. In line with and supporting this hypothesis, differences in the anatomical position of the PFM have been demonstrated between continent and incontinent women [86, 87]. Additionally, dynamometric studies have shown that SUI and MUI women demonstrate less PFM tone, maximal strength, rapidity of contraction and endurance as compared to continent women [88, 89]. Further, in an uncontrolled MRI reconstruction study, a significant reduction in the internal surface area of the levator ani was observed after PFMT suggesting an increase in passive stiffness of the levator ani, which is indicative of the state of PFM tone [90]. Griffin (1994), using a pressure probe inside the vagina, also showed a significant difference in subjects’ PFM resting pressure three to four weeks after starting PFMT and increased resting pressure after PFMT was completed [91]. Furthermore, Balmforth (2004) reported increased urethral stability at rest and during effort following 14 weeks of supervised PFMT and behavioural modifications [92]. Thus, there is a growing body of evidence to support the rationale that PFMT improves PFM tone and that it may facilitate more effective automatic motor unit firing of the PFM, preventing PFM descent during increased intra-abdominal pressure, which in turn prevents urine leakage [93].

Thirdly, PFM may be activated with a transversus abdominus (TrA) muscle contraction; this has implications for coordination of muscle activity in and around the pelvis/abdomen during everyday activity. An increasing body of evidence suggests that the active contraction of the TrA muscle is associated with co-activation of the PFM. This has been demonstrated by US, EMG and MRI studies [94-98]. However, a TrA muscle contraction does not appear to elevate the PFM in all women [99] and when it does, it does not appear to be as effective as a direct PFM contraction [97, 98]. Recent studies suggest that the relationship between PFM and TrA muscle differs between continent and incontinent women with the PFM being displaced less during a TrA muscle contraction in SUI women as compared to continent women [98]. More research is needed to better understand the relationship between the TrA and the PFM muscles as well as the effect on incontinence of rehabilitating the interaction between TrA muscle and the PFM.

Given the above biological rationale, for SUI the objective of PFMT is usually to improve the timing (of contraction), strength and stiffness of the PFM.

• **Biological rationale for PFMT for UUI**

PFMT can also be used in the management of UUI. The biological rationale is based on Godec’s observation that a detrusor muscle contraction can be inhibited by a PFM contraction induced by electrical stimulation [100], and Burgio (1985) has demonstrated that detrusor contraction can be inhibited by a voluntary contraction of PFM [101]. De Groat (1997) demonstrated that during urine storage there is an increased pudendal nerve outflow response to the external urethral sphincter increasing intraurethral pressure and representing what he termed a ‘guarding reflex’ for continence [102]. Additionally, Morrison (1995) demonstrated that Barrington’s micturition centre excitatory loop switches on when bladder pressures are between five to 25mmHg while the inhibitory loop is predominantly active above 25mmHg [103]. Inhibition involves an automatic (unconscious) increase in tone for both the PFM and the urethral striated muscle.

Thus, voluntary PFM contractions may be used to control UUI. After inhibiting the urgency to void and the detrusor contraction, the patient can learn to reach the toilet in time to avoid urine leakage. However, the number, the duration, the intensity and the timing of the PFM contraction required to inhibit a detrusor muscle contraction is not known. This focus on urge suppression by voluntary PFM contraction, combined with PFMT, is commonly called behavioural training.

• **Principles of skeletal muscle strengthening**

The aim of any strengthening programme is to alter muscle morphology by increasing the cross-sectional area, increasing the number and frequency of motor neuron excitations, and improving tone and stiffness. When muscles engage in intense, repetitive tasks that exceed the normal demands of daily activities this stimulates an increase in the muscle fibre size (hypertrophy), which in turn increases muscle bulk [104]. However, hypertrophy is not immediately evident as a training response. An increase in strength is evident long before visible hypertrophy. Early improvements in strength result from neural adaptation, including a greater number of activated motor units, an increased rate of motor unit excitation, more synchronised motor unit firings and more persistent activation of type II motor units [105-107]. Hypertrophy begins only after a minimum of eight weeks of regular and intense strength training [108]. With increased overload, hypertrophy may continue for some years.

There are four principles of strength training: specificity, overload, progression and maintenance [93]. Strength training is specific to the muscle(s) being trained and requires overload (that is, exposing the muscle(s) being trained to a gradual increase in resistance,
repetitions or repetition speed). Progression is the extension, through increased resistance, intensity and volume of training, of the initial exercise programme. Finally, maintenance refers to the extent to which the muscle is able to maintain a continued level of strength. In order to achieve an effective strength training programme, the American College of Sports Medicine recommends that all these elements be addressed [109].

**Terminology and method of review**

In this section, PFMT is defined as any programme of repeated, voluntary PFM contractions taught by a healthcare professional. This definition allows for variations in the end-goal of PFMT, the supervision (e.g. individual or group sessions) and the exercise programme (e.g. variations in frequency, intensity, number of contractions and duration of training). Thus, PFMT in the context of this chapter may also include the use of pelvic floor muscle contractions for urge suppression, and preceding changes in intra-abdominal pressure to prevent stress leakage; interventions that may also be called behavioural training. PFMT is used in preference to other previously used terms such as Kegel’s Exercises, pelvic floor exercises and PFM exercises. The term ‘Kegel’s Exercises’ is no longer appropriate because it refers to his original exercise programme of 500 contractions per day [73]. Advances in strength-training research (see above) indicate that fewer contractions, with a higher load are more effective, making current PFM programmes very different from that which was originally prescribed by Kegel (1948). Terminology that fails to include a reference to the muscle also seems inappropriate, as it is the muscular component of the pelvic floor that is the primary focus of the training. Ideally, it should also be clear that it is the PFMs, not pelvic muscles in general, which are the target of the intervention. Further, training is viewed as a more appropriate word than exercise. The term exercise is commonly interpreted as one training episode or a single muscle action, whereas, training means repeated exercises over time. Therefore, the term Pelvic Floor Muscle Training (PFMT) is used throughout this chapter.

PFMT was the primary intervention in the studies discussed in this section; however, some also included PFMT complemented by additional strategies related to urge and/or frequency. Trials that combined PFMT with urge and/or frequency strategies were included unless these were clearly part of a bladder (re)training programme or a timed or scheduled voiding programme. Trials were excluded if the primary intervention was clearly a combination of two or more treatments (e.g. PFMT with bladder training, PFMT with oestrogen). The exceptions were biofeedback (BF) and intravaginal resistance devices as these adjuncts are not stand-alone interventions.

This section will examine the evidence for the use of PFMT in the prevention and treatment of UI in women. Questions addressed are:

- Is PFMT effective in the prevention of UI?
- Is PFMT better than no treatment, placebo or control treatments for treatment of UI?
- Is one PFMT programme better than another in the treatment of UI?
- Is PFMT better than other treatments in the treatment of UI?
- Does the addition of PFMT to other treatments add any benefit in the treatment of UI?
- What factors might affect the outcome of PFMT in the treatment of UI?
- What is the effect of PFMT on other lower urinary tract symptoms?

**Evidence for PFMT for UI in women**

A systematic search of studies to November 2007 was carried out (see appendix). Only papers published in English or in a language for which a translator could be found were included. Relevant systematic reviews and reports of RCTs and quasi-RCTs were included. Therefore, only Level 1 evidence is considered in this section. Recommendations are based on the findings of existing systematic reviews, where they were up-to-date, or systematic reviews and more recent RCTs.

In this section, the pre-specified primary outcomes of interest were 1) self-reported UI (for prevention studies), 2) self-reported cure or 3) cure and improvement in UI symptoms (for treatment studies). Secondary outcomes of interest were 1) leakage episodes (treatment studies) and 2) quality of life (prevention and treatment studies).

With regard to assessment of study quality the Consort Statement Checklist was used [110]. Empirical evidence indicates that two elements of trial quality, allocation concealment and double blinding, are important in estimating treatment effect with precision. Trials with inadequate or unclear concealment of allocation appear to overestimate treatment effect by about 30% and trials that are not double-blinded overestimate effect by about 15% [111]. Therefore, trials that reported adequate allocation concealment have been noted. Although it is often difficult or impossible to blind patients to PFMT, trials that reported blinding of the outcome assessment were also noted. Readers may wish to consider these factors in their interpretation of the data.

1. **PREVENTION AND TREATMENT (PREGNANT AND POSTNATAL WOMEN ONLY)**

This subsection specifically considers PFMT for the prevention and treatment of UI in pregnant and
postnatal women (called childbearing women in this section). As the physiological changes of childbearing can affect PFM function, it is possible that the effect of PFMT might differ in this group compared to non-childbearing women. 

Five systematic reviews investigating the effect of PFMT on the prevention and treatment of UI in childbearing women have been published [112-116]. The review by Hay Smith (2002) did not separate data from childbearing and other women. Critical evaluation of the trials included in the four reviews reveals that women were often recruited to trials without regard to previous continence status.

Based on these prior reviews, three main groups of trials in childbearing women are of interest: 1) trials of PFMT for prevention of UI; 2) trials where it was not possible to differentiate prevention from treatment effects; 3) trials of PFMT for treatment of UI. Based on the latest Cochrane review [116], the primary outcome of interest was self-reported UI. The secondary outcomes of interest were condition specific quality of life (e.g. King’s Health Questionnaire, Incontinence Impact Questionnaire), or any other quality of life or health status measure (for example Short Form-36); symptom severity and number of leakage episodes.

a) Is PFMT effective in the prevention of UI in childbearing women?

There are three grades of prevention: primary, secondary and tertiary [117]. Primary prevention aims to remove the causes of a disease. Secondary prevention focuses on the detection of asymptomatic dysfunction and provides treatment aimed at stopping its progression. Tertiary prevention focuses on existing symptoms to prevent the progression of the disease through treatment. This subsection addresses the question of PFMT effectiveness for primary and secondary prevention of UI in childbearing women. Clinically it can be difficult to effectively screen trial participants to ensure that a disease process is altogether absent (for primary prevention studies) or present, although asymptomatic (for secondary prevention). In many cases, there are no reliable and valid clinical tests. Trials investigating prevention of UI usually enrol people purely on the basis of the absence of symptoms. Thus, in all likelihood the trials in this section probably represent a combination of primary/secondary prevention effects. No attempt was made to distinguish between primary and secondary prevention effects.

Five trials addressed prevention of UI in childbearing women [118-122]. Two of these studies were combined prevention/treatment studies, but published or unpublished data were available for women who were continent at recruitment [118, 121]. In the study by Sampselle (1998), 54 of 72 women were continent based on a standing stress test at 20 weeks gestation. After drop outs, unpublished data were available from 37 previously continent women (16 PFMT and 21 controls). Mørkved (2003) published data for 207 of 301 women who were continent before pregnancy and at 20 weeks gestation. After dropouts, data were available from 193 previously continent women (94 PFMT and 99 controls). Neither study was powered to detect differences in the previously continent subgroup; the subgroup sizes were small.

Four studies recruited nulliparous or primiparous women during pregnancy, and one “pregnant women” [120]. Reilly (2002) recruited primigravid women without a pre-pregnancy or current history of UI, but with bladder neck hypermobility at 18 to 20 weeks gestation. Sampsele (1998), Mørkved (2003) and Gorbea Chavez (2004) also recruited primigravidae, at 18, 20 and 28 weeks gestation respectively.

In all five trials, PFMT began during pregnancy while controls received the usual antenatal care, which may have included advice on PFMT from their maternity caregivers [118, 119, 121] or were asked not to do PFMT [120, 122]. There were some variations in the PFMT parameters (intensity and supervision):

- Eight to 12 near-maximal voluntary PFM contractions, held for six to eight seconds with a six-second rest, followed by three to four fast contractions at the end of each contraction, twice daily from 20 weeks gestation. Also a weekly exercise class from weeks 20 to 36 [121].
- Eight to 12 PFM contractions, held for six seconds with a two second rest, three sets twice daily, from 18 weeks gestation. Also individual PFMT with physiotherapist during monthly visit [119].
- Up to 30 near-maximal PFM contractions per day from 20 weeks of gestation [118].
- 10 PFM contractions; held for eight seconds each followed by three fast one second contractions; a six-second rest between contractions; for up to 20 weeks. PFMT taught one-on-one with physiotherapist. Weekly clinic appointments (one hour each) for eight weeks, then weekly phone calls [122].
- PFMT not described. Participants were seen twice monthly throughout pregnancy, and every three months postpartum for one year [120].

Mørkved (2003), Sampselle (1998), and Gorbea Chavez (2004) stated that a correct voluntary PFM contraction was checked prior to training.

1. Quality of data

Allocation concealment appeared adequate in four trials [118, 119, 121, 122] and the outcome assessors were blind in four of the five trials [118-121]. Dropout rates ranged from 4% [121] to 14% [119] and 36% [118]. Stothers (2002) did not report any losses to
follow up. Markved (2003) and Reilly (2002) measured outcomes at 34 and 36 weeks gestation then at three months postpartum. Sampselle (1998) assessed women at 35 weeks gestation, then postpartum at six weeks and six and 12 months; the primary endpoint was 12 months. Gorbea Chavez (2004) measured outcome at 28 and 35 weeks gestation, and six weeks postpartum. Stothers (2002) measured outcome at six and 12 months postpartum. Reilly (2002) was the only trial with long-term follow up, at four years.

2. Results

i) Late pregnancy (34 weeks or later): Pooled data from three trials [118, 121, 122] showed that women in the antenatal PFMT group were 56% less likely to report UI than the controls (RR 0.44, 95% CI 0.31 to 0.65). Statistically significant heterogeneity was observed in this comparison. While the point estimates in all three studies favoured PFMT these differed considerably between the trials (RR of 0.86, 0.46 and 0.03 in the studies by Sampselle 1998, Markved 2003, and Gorbea Chavez 2004 respectively). A possible reason why the difference between PFMT women and controls is more pronounced in the study by Gorbea Chavez (2004) is that the comparison group was asked not to do PFMT, whereas in the other two studies the controls had usual care that might have included PFMT.

ii) Early postpartum (up to 12 weeks): Pooled data from two trials showed that PFMT women were around 50% less likely to report UI, compared to the controls (RR 0.50 95% CI 0.31 to 0.80; [118, 122]).

iii) Mid postpartum (three to six month postpartum): PFMT women were statistically significantly less likely than controls to report UI, although the difference in risk had reduced to about 30% (RR 0.71 95% CI 0.52 to 0.97; [118-121]).

iv) Late postpartum (up to one year postpartum): Based on the data from a previously continent subgroup of participants in Sampselle (1998), there was no difference in prevalence of UI between PFMT women and controls at 12 months postpartum. This trial had not shown a statistically significant effect of PFMT at any of the three previous time-points (late pregnancy, early and mid-postpartum periods), and was not powered to detect a difference in the previously continent subgroup.

v) Long term (more than one year): At four year follow up, Reilly (2002) reported seven of 42 PFMT women and 26 of 58 controls had symptoms of SUI. This advantage for the PFMT group needs to be viewed with caution as less than half of the original sample was followed up.

Regarding secondary outcome measures, four of the five trials reported symptom severity data such as frequency or amount of urine leakage. None of the measures, or the ways in which they were reported, were common to the four trials. The data suggested that PFMT women with symptoms of UI might have demonstrated less severe symptoms than the controls. Only Stothers (2002) noted adverse events; two of the 43 PFMT women withdrew due to pelvic floor pain.

Only two trials reported treatment adherence data. Gorbea Chavez (2004) reported that 84% of PFMT women attended seven or eight of the eight physiotherapy appointments offered. In the study by Reilly (2002), nearly half the women in the PFMT group exercised for 28 days or more; postpartum similar proportions of women in the intervention and control groups were doing occasional or no PFMT (28% and 34% respectively).

Summary

Pregnancy and birth appear to be important factors associated with the development of UI in women. Therefore, all women who have had a child or children might be considered ‘at risk’ of developing UI at a later date.

Continent pregnant women having their first baby who participated in a more ‘intensive and supervised’ PFMT programme than the PFMT provided as part of usual care were less likely to experience UI from late pregnancy up to six months postpartum (Level of Evidence: 1). There was not sufficient evidence available to be sure whether this benefit persists 12 months or more. There was no evidence investigating the preventive effects of PFMT in pregnant, previously continent, multiparous women.

Recommendations

Continent pregnant women having their first baby should be offered a supervised (including regular health professional contact) and intensive strengthening antepartum PFMT programme to prevent postpartum UI (Grade of Recommendation: A). The usual or standard approach to PFMT in pregnancy (which is commonly verbal or written instruction without confirmation of correct contraction or supervision of training) needs to be reviewed.

Based on the long term findings of one trial [119] health providers with limited resources may wish to consider whether supervised intensive training would be best targeted at those women who are continent at 18 weeks gestation, but have increased bladder neck hypermobility.

Further, large, good-quality RCTs are needed to investigate the effect of antepartum PFMT on preventing postpartum UI in multiparous women.
b) Is PFMT effective in the mixed prevention and treatment of UI in childbearing women?

Eight trials contributed to this comparison. In all these trials, some women did and some women did not have UI at the time of recruitment, i.e. in these studies the effect of PFMT included a mix of prevention and treatment.

Four trials randomised nulliparous or primiparous women to either supervised antepartum PFMT or usual antepartum care [118, 121, 123, 124]. The other four trials randomised nulliparous women during pregnancy [125] or postpartum [126-128] to either postpartum PFMT or usual postpartum care or no PFMT.

i) Antepartum PFMT versus usual care: The interventions of the trials by Mørkved (2003) and Sampselle (1998) in pregnant women have been described section B.2.1a. Hughes (2001) recruited nulliparous women at 20 weeks gestation and women randomised to PFMT attended one individual appointment then, between 22 and 25 weeks gestation, a group PFMT session (maximum six women) with a physiotherapist. No details of the training parameters were reported. Women with no palpable voluntary PFM contraction or a flicker of contraction were randomised. Controls received the usual community antepartum care. In Dannecker’s (2004) study, women in the PFMT group were trained to use an Epi-No device (an inflatable vaginal balloon connected to a pressure gauge for visual feedback), 15 minutes daily; for three to six weeks. Controls received no device. This trial was primarily interested in improving the elasticity of the PFM for delivery rather than continence outcomes.

ii) Postpartum PFMT versus usual care or no PFMT: Chiarelli (2002) restricted inclusion to women who had had forceps or ventouse deliveries, or had delivered a baby weighing 4000g or more. Ewings (2005) restricted inclusion to women who had already experienced UI and who were at high risk of UI following childbirth in accordance with the SIFCRAFT risk scale. The control groups received the usual postpartum care, which included an invitation to postpartum classes taught by physiotherapists in Chiarelli’s (2002) study; standard ante and postpartum care in Sleep’s (1987) study, no PFM re-education from two to 10 months postpartum in Meyer’s (2001) study and verbal promotion of PFM exercises supplemented by a leaflet in Ewings’ (2005) study. In PFMT groups, women were visited by a midwife or physiotherapist on the postnatal ward and were advised to train as follows:

- PFMT exercises as often as remembered and contractions integrated with daily living activities, plus midstream urine stop. Correct PFM contraction was checked on a second visit at eight weeks postpartum [126]
- PFMT exercises with three to six-second holds, three times a day. A variety of adherence strategies were employed (e.g. red stick-up dots, home or hospital visit after eight weeks) [127]
- PFMT programme including 12 visits with a physiotherapist between two and 10 months postpartum, including a 20 minute BF training session and a 15 minute electrical stimulation session [125]
- PFMT taught one to one with physiotherapist in hospital in addition to an invitation to attend PFMT class at two and four months postpartum; 21 of 284 women participated in the first class (18%) and only 5 (4%) attended both [128].

1. Quality of data

i) Antepartum PFMT versus usual care: Two of the four trials had adequate random allocation concealment [118, 121]. In the other two women were allocated at random but it was not clear if allocation was adequately concealed [123, 124]. Assessors were blinded in two of the four trials [118, 121]. Mørkved (2003) [121] randomised 301 women, Sampselle (1998) 72, Dannecker (2994) 144 and Hughes (2001) 1169 women. Dropout rates were 4% [121] at three months postpartum and ranged from 24% [124] to 34% [123] at six to seven months post-partum. At 12 months, the drop-out rate was 36% [118].

ii) Postpartum PFMT versus usual care or no PFMT: Random allocation concealment was adequate in the trials by Chiarelli (2002), Sleep (1987) and Ewings (2005), but inadequate in Meyer (2001) where alternate assignment was used. Blinding of outcome assessment was adequate in Chiarelli (2002). Sleep (1987) randomised 1,800 women; Chiarelli (2002) 720; Ewings (2005) 234, and Meyer (2001) 107. Both the Sleep (1987) and Chiarelli (2005) trials measured outcome at three months, with the loss of 191 (11%) and 44 women (6%) respectively. Ewings (2005) measured outcome at six months, with a loss to follow-up of 19%. Finally, Meyer (2001) measured outcome at 10 months with no withdrawal or loss to follow-up.

2. Results

i) Antepartum PFMT versus usual care: Pooled data from three trials [118, 121, 123] showed that women who were randomised to antepartum PFMT had about 10% less risk of UI in late pregnancy (RR 0.88, 95% CI 0.81 to 0.96). Statistically significant heterogeneity was observed in this comparison. While the point estimates in all three studies favoured PFMT these differed considerably between the trials (relative risks of 0.67, 0.81 and 0.93 in the studies by Mørkved 2003, Sampselle 1998, and Hughes 2001 respectively); the study by Hughes (2001) carried considerable weight in the pooled analysis; most likely because it was the largest study. One of the differences between the studies by Mørkved (2003) and the other two in this comparison was the PFMT intensity and
supervision as reported previously, being more ‘intense’ in the former.

Prevalence of UI was not statistically significant between PFMT and control groups in the early (RR 0.82, 95% CI 0.48 to 1.40; [118]), mid (RR 0.89, 95% CI 0.78 to 1.02; [118, 121, 123]) or late postpartum period (RR 0.96, 95% CI 0.70 to 1.32; [118, 124]).

Three trials reported data on symptom severity such as frequency or amount of urine leakage, but none of the data suggested that PFMT was superior to control or vice versa at the primary endpoint for each study [118, 123, 126].

ii) Postpartum PFMT versus usual care or no PFMT: There was no statistically significant difference in the prevalence of UI in women randomised to postpartum PFMT or control in the mid (RR 0.97, 95% CI 0.85 to 1.09 [126-128]) or late postpartum period (RR 0.94, 95% CI 0.75 to 1.16 [125, 127]). Statistically significant heterogeneity was observed in the combined data for the mid postpartum period, with one study favouring PFMT [127], one neither PFMT nor control [126] and one favouring the control condition [128]. Some potentially important clinical differences were noted between the studies. Firstly, Chiarelli (2002) recommended a PFM strength training programme; neither of the other two studies described their PFMT programme, so it is not possible to determine whether the latter studies could have had an effect or how different the PFMT and control conditions were. Further, Sleep (1987) found only a moderate difference in the proportion of PFMT women and controls doing some PFMT at three months postpartum (58% and 42% respectively) while at three month postpartum Chiarelli (2002) found that about half the controls were doing PFMT (58%) but an even greater proportion of the PFMT group (84%) were exercising. A second difference was that, Chiarelli (2002) recruited women at potentially increased risk of postnatal UI, such as those who had a large baby or a forceps delivery.

SUMMARY

The effect of antepartum PFMT or postpartum PFMT, in groups of women where some did and some did not have prior UI symptoms, varied by study with some studies showing a benefit of PFMT on UI prevalence whereas others did not (Level of Evidence: 2). The characteristics of the two studies, both methodologically robust, that demonstrated some effect were:

a) For antepartum PFMT: Mørkved (2003) recruited pregnant women having their first baby and used an intensively supervised strengthening PFMT programme; PFMT reduced UI prevalence in late pregnancy and three months postpartum but this was not evident six years after the index delivery.

b) For postpartum PFMT: Chiarelli (2002) recruited primiparous and multiparous women at potentially greater risk of postpartum UI after a large baby or forceps delivery, and used a strengthening PFMT programme; PFMT reduced UI prevalence at three months postpartum but not at one year.

RECOMMENDATIONS

Health providers should carefully consider the cost/benefit of population based approaches to health professional taught antepartum or postpartum PFMT; that is, health professional instruction to all pregnant or postpartum women regardless of their current or prior continence status (Grade of Recommendation: B).

Where a population approach is used, the ‘best’ evidence to date suggests the following: (a) an intervention comprising a daily home PFMT and weekly physiotherapist-led exercise classes for 12 weeks, starting from 20 weeks gestation for pregnant women having their first baby, and (b) an individually taught strengthening PFMT programme that incorporates adherence strategies for postpartum women who have had a forceps delivery or a vaginal delivery of a large baby (4000g or more) (Grade of Recommendation: C)

c) Is PFMT effective in the treatment of UI in childbearing women?

Four studies addressed the treatment of existing UI after delivery [129-132]. One study recruited incontinent women during pregnancy [132], while the other three recruited women three months or more after delivery. All four studies recruited a mix of primiparous and multiparous women.

The control groups in three studies [129, 130, 132] received standard care, which included ante and postpartum advice on PFMT, whereas the control group in Dumoulin’s (2004) study received, in lieu of training, relaxation massages at the same frequency as the PFMT treatments.

The PFMT interventions varied as follows:

- Wilson (1998) randomised women in the intervention group to either PFMT, or PFMT with vaginal cones, or vaginal cones (VC). PFMT comprised 80 to100 PFM contractions per day (a mix of fast and slow), with three home visits by a nurse, healthcare visitor or continence advisor. The VC group received 15 minutes per day of cone therapy while the combined PFMT/VC group received both interventions [129].
- The PFMT programme in Glazener (2001) was the same as Wilson (1998), supplemented by instruction from a physiotherapist on four occasions [130].
• In Dumoulin’s (2004) study PFMT included electrical stimulation (ESstim) with or without deep abdominal training. PFMT comprised weekly sessions supervised by physiotherapists for eight weeks with 25 minutes of PFMT and 15 minutes of ESstim (bi-phasic rectangular form; frequency 50Hz) [131].
• Woldringh’s (2007) study included four one to one and half hour sessions with a physiotherapist (three antepartum and one at six weeks postpartum) but details of the PFMT programme were not given [132].

1. Quality of Data

Random allocation concealment was adequate in three of the four trials [129-131] and outcome assessors were blind in two [130, 131].

There were 85 losses to follow-up in the trial by Wilson (1998) with high attrition rates noted in all intervention groups (20/39 PFMT, 24/38 PFMT/VC, 15/36 VC). Glazener (2001) reported 223 (30%) losses to follow-up and Woldringh (2007) 38%. In contrast, Dumoulin’s (2004) trial (which included weekly contacts with a physiotherapist for eight weeks) reported a 6% loss to follow-up. Wilson (1998) and Glazener (2001) measured outcome 12 months after delivery, and then 24 to 44 months post-delivery, and six years after the index delivery [133]. Dumoulin (2004) reported outcome nine weeks after intervention began. However as women were recruited at varying lengths of time following delivery (all more than three months postpartum) the data are presented alongside those from Glazener (2001), and Wilson (1998), as long-term post-natal data.

2. Results

In the one study of antepartum PFMT for treatment of UI, Woldringh (2007) did not find any statistically significant difference in the prevalence of UI between PFMT and control groups at 35 weeks, eight weeks postpartum, six months and 12 months postpartum. Pooled data from the three trials of postpartum PFMT found women were about 20% less likely to have UI after treatment compared to the controls (RR 0.79, 95% CI 0.70 to 0.90). Statistically significant heterogeneity was observed. The treatment effect in the study by Dumoulin (2004) was much greater than that in the other two studies. Possible reasons are that the controls in the study by Dumoulin (2004) were asked not to do PFMT, whereas controls in the other two studies received usual care and both interventions and control groups were also doing PFMT (a mean of 20 versus five PFM contractions per day in Glazener 200), and 86 versus 35 in Wilson 1998). Another difference was the intensity and supervision of the PFMT intervention; Dumoulin (2004) used a more intensive PFMT programme with adjunctive electrical stimulation and BF and physiotherapy appointments once a week for eight weeks, whereas in the other two studies [129, 130] women had three or four appointments with health professional over approximately six months and were asked to do PFMT on their own.

All four treatment trials reported some data on symptom severity such as frequency or amount of urine leakage. None of the measures, or the ways they were reported, was common to the four trials. The data suggested that PFMT women with symptoms of UI might have less severe symptoms than the controls, but this was not a consistent or clear-cut finding. Dumoulin (2004) stated that none of the women in the PFMT group reported any adverse events.

Three trials reported some data related to treatment adherence, one for antepartum PFMT [132] and two for postpartum PFMT [129, 130]. In the antepartum study, at 36 weeks gestation 37% of the PFMT women were exercising intensively compared to 14% of the controls [132]. Glazener (2001) and Wilson (1998) both reported the mean number of PFM voluntary contractions per day at 12 months postpartum. Respectively, the mean number of contractions was 20 (SD 29) and 86 (95% CI 69 to 104) per day in PFMT women, and 5 (SD 15) and 35 (95% CI 30 to 40) per day in the controls.

Glazener and colleagues followed up women six years after the index delivery. The effect of PFMT on UI was not sustained. At six years, 100 out of the 263 in the intervention group and 99 out of the 253 in the control group experienced UI at least once per week [133]. However, the women had had an average of 1.5 deliveries since the index delivery.

Summary

To date, only one trial has investigated the effect of PFMT for the treatment of UI in pregnant women [132]. This was a moderate-size study that did not report on allocation concealment or blinding of the assessors, and did not describe the type of PFMT programme employed. In the absence of any detail on the PFMT programme it is impossible to judge if the intervention had the potential to be effective. Postpartum women with UI who were randomised to PFMT taught and supervised by a health professional were less likely to be incontinent than controls (standard care or relaxation massage) six to 12 months following delivery (Level of Evidence: 1). Of the three trials, the one that used an intensively supervised strength training programme demonstrated the greatest treatment effect. It is unclear if the benefit of PFMT is maintained over time or with subsequent deliveries (Level of Evidence: 2). For women who have persistent symptoms of UI at three months postpartum PFMT is a more effective treatment than standard postnatal care or relaxation massage;
effects might be greater with supervised and intensive strengthening PFMT (with the addition of EStim). It is not clear if the effect can be sustained over the long-term; there is also no data on the effect of short periodic refresher sessions on long-term effect.

Recomendations

PFMT should be offered as first line conservative therapy to women with persistent UI symptoms three months after delivery (Grade of Recommendation: A); an ‘intensive’ PFMT programme (in terms of supervision and exercise content) is likely to increase the treatment effect (Grade of Recommendation: B).

There is a need for at least one large, pragmatic, well-conducted and explicitly reported trial with long term follow-up (five plus years) of postpartum PFMT that investigates the effect of ‘intensive’ treatment followed by periodic refresher sessions.

2. PREVENTION (OTHER WOMEN)

Hay-Smith and colleagues have previously reviewed trials of PFMT and other physical therapies for the prevention of UI [112]. Three main groups of trials were found. The first included trials that investigated the effect of PFMT on PFM activity in women, but did not measure continence related outcomes as so were not relevant for this chapter. The second recruited only childbearing women; these trials were considered in section B.2.1a, which addressed the prevention of UI in childbearing women. The third group included trials for prevention of post prostatectomy UI and these trials are considered in Section C.2.1.

No trials investigating the primary/secondary prevention effects of PFMT for UI in non-childbearing women were found.

3. TREATMENT (OTHER WOMEN)

a) Is PFMT better than no treatment, placebo or control treatments?

Recommendations in this section are based on the updated but as yet unpublished findings (Dumoulin and Hay-Smith 2008, personal communication) of a Cochrane systematic review [134]. Primary outcomes of interest were 1) patient-reported symptom cure or improvement and 2) symptom bother and incontinence specific quality of life assessment. Secondary outcomes of interest included the number of leakage episodes and other quality of life measures (not UI-specific, e.g. Short Form 36).

Seventeen RCTs comparing PFMT with no treatment for women with UI were found, of which five were excluded. Two were excluded because they compared supervised with unsupervised PFMT [135, 136]; for these trials see B.2.3b. One trial, reported only as a conference abstract, was excluded because it was unclear if it was a RCT and it lacked adequate data [137]. Finally, two more trials were excluded because the PFMT versus sham PFMT comparison was considered to be confounded by the choice of sham PFMT [138, 139]. In both trials, sham PFMT consisted of strong isometric hip abductor contractions and according to EMG, dynamometric and MRI studies, both hip abductions and external rotations result in a synergic contraction of the PFM [80, 97, 140]. These two trials probably compared a direct versus an indirect approach to PFMT; for this comparison see B.2.3b.

Of the 12 included trials, nine recruited women with SUI only [77, 141-148]. One included women with SUI, with or without UUI. However, the proportion with MUI was small (9%) and it was thus analysed with the SUI studies [149]. One included older women with UUI with or without SUI (with urge as the predominant type) [150]. The remaining study recruited women with a range of diagnoses [151].

Four studies gave no details about the PFMT programme used [142, 143, 146, 148]. Of the eight remaining trials, five stated that a correct voluntary PFM contraction was confirmed prior to training [77, 141, 145, 147, 150] and in all cases PFMT was taught by a health professional. Based on the description of training programmes, two trials had PFMT programmes that clearly targeted coordination [77] or strength training [145]. It was more difficult to categorise the other PFMT programmes, because they were either a mixed (i.e. strength and endurance) programme or did not provide enough information on the exercise parameters.

The ‘control’ groups received no treatment, [77, 141, 142, 146, 147, 149] placebo drugs, [150] sham EStim, [143], sham PFMT with placebo drug [148] or a non-active control intervention such as the use of an anti-incontinence device [149] or advice on incontinence pads [143].

The potential to consider the combined results from individual studies was limited by: 1) lack of consistency in the choice of outcome measures chosen by the researchers and because many did not use any of the pre-specified outcomes of interest for the review; and 2) poor reporting of outcome data (i.e. mean reported without a measure of dispersion) which meant the data could not contribute to a pooled analysis.

1. Quality of Data

The brevity of the reporting in three trials, which were published as conference abstracts, made it difficult to assess the quality [142, 146, 148]. Only Bø (1999) reported adequate random allocation concealment. Seven trials reported using blinded outcome assessors [77, 144-146, 149-151].

1042
2. Results

Twelve RCTs, involving 670 women, compared PFMT (353 women) with no treatment, placebo, sham or other non-active control treatments (317 women). In the six trials contributing data, the two comparison groups comprised 175 and 184 women, respectively. Two trials reported data on cure and both found that PFMT women were statistically significantly more likely to report cure [145, 150]. The size of effect was quite different in the two trials; SUI women receiving PFMT were about 17 times more likely to report cure compared to controls (RR: 16.80, 95% CI 2.37 to 119.04) [145], whereas PFMT women in the study with urge predominant UI were about two-and-half times as likely to report cure (RR: 2.34, 95% CI 1.11 to 4.94) [150].

With regard to patient-perceived cure or improvement the two trials in women with urodynamic SUI [143, 145] suggested more likelihood of cure or improvement than the single study in women with UUI with or without urodynamic SUI [150].

Two trials in women with urodynamic SUI used psychometrically robust questionnaires for the assessment of symptom impact. Be (1999) used the Bristol Female Lower Urinary Tract Symptoms Questionnaire (B-FLUTS), but only the lifestyle and sex-life domains were reported. Fewer women in the PFMT group reported that UI symptoms interfered with activities or were problematic. Schagen van Leeuwen (2004) reported a mean change in Incontinence Quality of Life score (I-QoL), but it was not clear if the difference in favour of the PFMT group was important as the means were presented without a measure of dispersion.

Four studies used urinary diaries to count leakage episodes. Effect size was greater in the Lagro-Janssen's (1991) trial (MD -2.92, 95% CI-3.74 to -2.10); a possible explanation may be inadequate random allocation concealment, with a resulting overestimate of treatment effect. The point estimates in the other three trials (MD -1.29, 95% CI-2.24 to -0.34) [149], (MD -0.77, 95% CI-1.22 to -0.32) [150], (MD -0.80, 95% CI-1.60 to -0.00) [145] were similar and all were statistically significant. PFMT women experienced, about one less leakage episode per 24 hours compared to the controls.

Few trials had long-term follow up. In all trials, supervision of PFMT stopped at the end of the treatment period except where the controls were then offered supervised training. Because of this ‘crossover’ of controls to training, follow up data were usually presented for all women in the trial, rather than by group allocation. Three trials have published long-term follow up results, at three and six months [149], nine months [141], and one and five years [152]. Burns (1993) found that those experiencing mild leakages were more likely to have a return of symptoms in contrast with those experiencing moderate to severe leakages, who were more likely to continue to improve with PFMT. At nine months Henalla (1989) reported that three of the 17 women (from the 25 originally allocated to PFMT) had recurrent symptoms. Lagro-Janssen reported data from 88 women of an original 110 [152]. The proportion of continent women was the same after five years (25%), but more had severe UI (increased from 3% to 18%). Leakage had also increased significantly (p = 0.009), with a mean increase of 2.7 episodes per week (95%; CI 0.7 to 4.6). Two thirds (67%) remained satisfied with the outcome and did not want further treatment, although women with UUI or MUI were less likely to be satisfied and SUI women were less likely to report that their condition had worsened. Nearly half (43%) who had done PFMT were no longer training at all, while 39% were training daily or “when needed”.

Summary

PFMT is better than no treatment, placebo drug or inactive control treatment for women with SUI, UUI, or MUI (Level of Evidence: 1). Women treated with PFMT were more likely to report cure or improvement and have fewer leakage episodes per day than the controls. Condition-specific quality of life might also be better after PFMT, but this finding needs confirmation through further studies. The trials suggested that treatment effect might be greater in SUI women who tended to be younger (in their 40s and 50s) and participated in a supervised PFMT programme for at least three months. These hypotheses need further testing. The limited evidence from follow up after treatment means that the long-term outcomes of PFMT are less clear, although continued treatment effect is probably associated with continued training.

It seems likely that treatment effect will be enhanced if PFMT is based on sound muscle training principles: such as, specificity, overload and progression, correct contraction confirmed prior to training, and if women are supported to maintain treatment adherence (Level of Evidence: 4).

Recommendations

Supervised PFMT should be offered as first line conservative therapy for women with stress, urge or mixed urinary incontinence (Grade of Recommendation: A).

b) Is one PFMT programme better than another?

A number of factors may influence the outcome of the PFMT programme, such as the way in which it is taught and supervised, the exercise parameters, and adherence to training. In this section, different
Twenty-eight trials were identified, and three were excluded for the following reasons. In one study, electrical stimulation (EStim) was added to the biofeedback arm only, and in a second study EStim was added to both treatment arms. In both studies the addition of EStim rendered the trial ineligible for inclusion [137, 153]. Another study reported outcomes by diagnosis and not by intervention group [154]. The included trials compared:

- Health professional supervised PFMT versus self-directed PFMT [135, 136, 155];
- Direct versus indirect (such as PFM contractions facilitated through abdominal or gluteal muscle work) PFMT [138, 139, 156, 157];
- Different exercise parameters (such as strength versus endurance training) [158-160];
- PFMT with repeated episodes of BF versus PFMT without BF [147, 149, 161-167].
- PFMT with intravaginal resistance versus PFMT without resistance [168];
- PFMT with adherence strategy (such as alarm or diary) versus PFMT without strategy [169, 170];
- PFMT with more versus less health professional contact [171-173].

i) Health professional (HP) supervised PFMT versus self-directed PFMT: Three trials made this comparison. Burgio (2002) compared written instruction on PFMT and urge suppression strategies (no HP contact) versus HP taught and supervised PFMT with urge strategies and anorectal BF versus HP taught and supervised PFMT with urge strategies but without BF. Treatment duration was eight weeks for all three treatment arms with four HP visits in the supervised arms. Goode (2003) compared written instruction on PFMT versus HP taught and supervised PFMT; treatment duration was 10 weeks in both arms with four HP visits in the supervised arm. Williams (2006) compared written instruction on PFMT along with fortnightly nurse visits versus HP taught PFMT with fortnightly visits for 10 weeks.

ii) Direct versus indirect PFMT: Four trials compared direct with indirect approaches. One arm of each trial was PFMT. The other arm was hip abductor contractions in two trials [138, 139]; Pilates in one trial [157] and ‘Paula method’ in another [156]. The ‘Paula method’ focuses on strengthening the circular muscles (such as the pubococcygeal muscle, the anal sphincter, and grip) based on the hypothesis that all sphincters in the body work simultaneously. Thus, exercising circular muscles in one area of the body might strengthen other sphincters. Treatment duration was 12 weeks in both arms of all four trials.

iii) Different exercise parameters: Three trials made this comparison; each comparison was different. Johnson (2001) compared near maximal (10 minutes three times a day at 90% of maximal PFM) versus sub-maximal PFMT (15 minutes three times a day at 60% of maximum contraction intensity) for six weeks. Hay-Smith (2003) compared motor relearning PFMT (being PFM contractions in different body positions, preceding and sustained during different provocative activities) versus motor relearning with strengthening PFMT programme (10-12 near maximal PFM contractions, six to eight second hold with equivalent rest, three times a day, at least three days a week). Both groups trained for 18 to 20 weeks. Borello-France (2006) compared 12 weeks of twice daily PFMT in supine versus the same programme performed in supine, sitting and standing.

iv) Addition of BF (Figures 1 and 2): Studies used either home or clinic based BF. Potentially, home based BF offers women more opportunity to make use of this adjunct and it might be expected that any BF effects would be greater in these studies. Clinic and home based BF trials were therefore considered separately.

Five trials used clinic based BF. In four of them the home PFMT programme was the same in both groups, with the addition in one arm of clinic BF once a week [149, 163], twice a week [167], or three times a week [162]. Treatment durations in both arms were four weeks [162, 163], eight weeks [149] and 12 weeks [167]. In the fifth trial there were some differences in the PFMT as well as the addition of clinic based BF in one arm. Pages (2001) compared PFMT (group PFMT five times per week for four weeks and daily home PFMT) versus daily home PFMT and clinic BF five times per week for four weeks; in both groups this was followed by eight weeks of home PFMT. flewind (1996) had a greater amount of supervisory HP contact with the BF group than with the PFMT alone group.

Four trials used home-based BF. In all of them the home PFMT programme was the same in both groups, with the addition in one arm of home BF. Treatment durations in both arms were six weeks [161], eight weeks [147], 12 weeks [164], and six months [166].

v) Addition of intravaginal resistance (IVR): One trial compared daily home PFMT versus PFMT daily at home with intravaginal balloon device for resistance; treatment duration was six weeks in both arms [168].

vi) Addition of adherence strategy: Two trials investigated the use of adherence strategies. In both trials the daily home PFMT programme was the same in both groups, with the addition in one arm of an
adherence strategy or device. These were a device that beeped in the rhythm that contractions were to be performed and participants pressed a button on this device to record their PFM contractions [170], or audiotape of exercise instructions, counting aloud 25 consecutive PFM contractions [169]. Treatment duration was four to six weeks [169], or eight weeks [170].

vii) More versus less health professional (HP) contact: Three trials contributed to this comparison. In all three studies both groups did the same daily home PFMT programme with the addition in one arm of a weekly 45 minute group exercise sessions [171], weekly supervised training session in groups of five [173], or twice weekly phone calls from a registered nurse monitoring progress [172]. Treatment duration was four to six weeks [169], or eight weeks [170].

1. Quality of data

i) HP supervised PFMT versus self-directed PFMT: One trial reported adequate random allocation concealment [155]. Outcome assessment was blind in Burgio (2002). The number of women allocated to each group was between 60 and 80 in all three trials. Dropouts were 7/75 for the self-directed group, 11/73 and 9/74 in the HP led groups in Burgio’s (2003) study. In Goode’s (2003) study, 25/67 in the self-directed group and 12/66 in the HP led PFMT group withdrew. In Williams’s (2006) study, 3/79 in the self-directed group and 3/79 in the HP group withdrew.

ii) Direct versus indirect PFMT: Two of the four trials reported adequate random allocation concealment [139, 157] and two reported blind outcome assessment [139, 157]. The number of women allocated to each group was less than 10 [157], between 20 and 30 [138, 156] and between 40 and 50 [139]. Losses to follow-up were less than 10 % in three trials [138, 156, 157] and was 20% in one [139].

iii) Different exercise parameters: One trial reported adequate allocation concealment and blind outcome assessment [159]. Two trials randomised less than 25 women to each group [158, 160] and Hay-Smith (2003) randomised about 60 per group. Four percent of women withdrew from the trial by Hay-Smith (2003), while14% dropped out from Johnson’s (2001) trial and 18% in Borello-France’s (2006) trial.

iv) Addition of BF: Of the five clinic based BF trials, two had adequate random allocation concealment [162, 167] and two had blinded outcome assessors [149, 162]. Two trials randomised between 25 and 50 women to each comparison group [149, 167] while others randomised less than 25 women per group [162, 163, 165]. There were no withdrawals or losses to follow up in one trial [162] less than 10% in one [149], less than 15% in two [163, 167], and 22% in the other [165]. In the latter trial all the dropouts were from the BF group [165]. All women were assessed post-treatment; further follow up was conducted by Burns and co-workers [149] at three and six months, and by Glavind (1996) at three months and two to three years.

Of the five home based BF trials, random allocation concealment was adequate in just one [166], and outcome assessors were blind for some or all of the outcomes in three trials [161, 166, 174]. The number of women allocated to the comparison groups was 20 or less in three trials [147, 161, 174]. Laycock (2001) randomised women in a ratio of 2:1, so there were 40 women in the BF group and 20 in the PFMT only group. Mørkved (2002) randomised 50 women or more to each group. Three trials had complete data sets on trial completion [147, 161, 174], Mørkved (2002) reported 9% withdrawal, and 33% dropped out of the trial by Laycock (2001). One trial reported a one-year follow up [175].

v) Addition of IVR: It was not clear if allocation concealment was adequate or outcome assessors were blind. There were 10 women in each intervention group and it seemed there were no dropouts. Women were assessed post-treatment and followed up at 12 to 24 months [168].

vi) Addition of adherence strategy: Both trials had inadequate allocation concealment, and neither stated if outcome assessors were blind to treatment allocation.
There were no statistically significant differences between the groups for self-reported cure/improvement (RR 0.25, 95% CI 0.03 to 2.21), cure/improvement (RR 0.88, 95% CI 0.59 to 1.31), or the number of leakage episodes in 24 hours (MD −0.2, 95% CI −0.55 to 0.15). Nor were there consistent differences in the nine domains of the KHQ. Johnson (2001) compared near maximal PFM contractions (strengthening programme) with sub-maximal PFM contractions (endurance programme) for women with urodynamic SUI. After six to seven weeks of training there was no statistically significant difference between the groups in the number of leakage episodes per day (MD −0.36, 95% CI −1.85 to 1.13). Borello-France (2006) compared PFMT in lying versus lying and upright positions for SUI women. There was no statistically significant difference in improvement in Incontinence Impact Questionnaire (IIQ) scores between the two groups, or differences in the weekly reduction in leakage or amount of urine lost during the pad test.

For the home BF trials, it was difficult to interpret or combine the data, principally because data were not reported in useful ways. Pooled data from Shepherd (1983) and Mørkved (2003) found no statistically significant differences between the groups for self-reported cure (RR 1.54, 95% CI 0.95 to 2.50) or self-reported cure/improvement (RR 1.17, 95% CI 0.93 to 1.47). Both trials recruited women with urodynamic SUI. Interestingly, at one-year, cure/improvement was 68% in the home BF group compared to 53% in the PFMT group; this difference did not reach significance.
[175]. Markved (2003) did not find any statistically significant differences between the groups on the Social Activity Index post treatment. Markved (2003) stated that no women reported an adverse event, while Aukee (2004) found that a small number of women could not use a vaginal probe due to discomfort or reported discomfort with PFMT without a probe.

v) Addition of IVR: The single trial did not collect any data for the pre-specified outcomes of interest.

vi) Addition of adherence strategy: Sugaya (2003) found that SUI women who used an electronic device to cue PFMT were more likely to be satisfied with treatment outcome (RR 3.17, 95% CI 1.02 to 9.88), but there was no difference between device and no device groups for the number of leakage episodes per day post treatment (MD –0.50, 95% CI –1.55 to 0.55). Gallo’s (1999) study did not measure any continence outcomes although an interesting finding was that SUI women who used the audiotape of exercise instructions were more likely to be performing the PFMT exercises twice daily as per instruction (RR 7.05; 95% CI 2.78 to 17.88).

vii) More versus less HP contact: Be (1990) found no statistically significant difference in the proportion of SUI women reporting cure (RR 6.25, 95% CI 0.31 to 124.10). Pooled data from two trials found SUI women having more HP contact were more likely to report cure/improvement (RR 1.80, 95% CI 1.34 to 2.43) [171, 173]. Konstantinidou (2007) found that SUI women in the more contact group had significantly fewer leakage episodes in 24 hours (MD -1.39, 95% CI -2.04 to -0.73) and were less likely to report high scores on a study specific UI quality of life score (RR 0.55). Gallo’s (1999) study did not measure any urinary outcomes of interest although an interesting finding was that SUI women who used the audiotape of exercise instructions were more likely to be performing the PFMT exercises twice daily as per instruction (RR 7.05; 95% CI 2.78 to 17.88).

SUMMARY
Considering the number of trials that compared one approach to PFMT versus another it is disappointing there were so few data for analysis. Many trials collected no data for the pre-specified outcomes of interest, collected data for only one of these outcomes, and/or did not report the collected data appropriately (e.g. presented mean without measure of variance).

With regard to HP supervised PFMT versus self-directed PFMT women were more likely to report cure/improvement, fewer leakage episodes and better quality of life if PFMT was taught and supervised by a HP (Level of Evidence: 1). Although women in self-directed PFMT programmes reported improvements, improvements in the HP led group were greater.

The four trials that compared direct versus indirect PFMT methods made different comparisons; none found an indirect method better than direct PFMT (Level of Evidence: 2).

Three trials also compared different exercise parameters, but none made the same comparison. For SUI women there may be no difference in the number of leakage episodes per day after six weeks of strength versus endurance PFMT; the training period was probably not long enough to be sure about the lack of difference (Level of Evidence: 2). For SUI women, combination strength/motor relearning PFMT versus motor relearning PFMT alone as well as supine versus a combination of supine, sitting and standing exercises seemed equally effective (Level of Evidence: 2). With regard to clinic based BF it seemed that there were no statistically significant differences between BF assisted and non-BF groups for self-reported cure, cure/improvement, or leakage episodes per day or quality of life (Level of Evidence: 1). This pattern appeared to be consistent across trials that recruited SUI women only, women with urodynamic SUI, MUI, or OAB. There were a similar number of trials addressing the effect of home BF, but fewer data. In a single robust trial, there were no statistically significant differences between home BF and non-BF groups for self-reported cure, cure/improvement, or quality of life for women with urodynamic SUI (Level of Evidence: 2).

Based on a single poor quality trial, SUI women might be more satisfied with the outcome of PFMT if accompanied by an exercise cue, this may not be reflected in differences in number of leakage episodes (Level of Evidence: 2).

Self-reported cure or cure/improvement in SUI women was more likely with more HP contact during PFMT (Level of Evidence: 1). More contact also appeared to lead to better quality of life and fewer leakage episodes for UI women. Based on follow up from a single trial, the initial benefit of intensively supervised PFMT may not be maintained 15 years later when training adherence is low.

RECOMMENDATIONS
Clinicians should provide the most intensive HP led PFMT programme possible within service constraints because HP taught and supervised programmes are better than self-directed programmes, and more HP contact is better than less (Grade of Recommendation: A). There does not appear to be any benefit of adding clinic (Grade of Recommendation: A) or home based BF (Grade of Recommendation: B) to a PFMT programme.
There are many hypotheses that need further testing, such as:

- Whether any indirect method of PFMT (Paula method, transversus abdominus training, hip abductor or adductor exercise) might be as effective as direct PFMT, or add benefit to a direct PFMT programme.
- Different types of PFM exercise (strengthening, endurance, co-ordination, functional training) may be as effective as each other.
- BF may benefit certain women, such as those with a weak PFM or with difficulty contracting the PFM in isolation.
- IVR adds benefit to PFMT. Given the evidence for the effect of vaginal cones on UI (see B.3) and the fact that PFMT most commonly aims to strengthen the PFM, there seems to be some biological rationale for the use of IVR devices.
- Cues to exercise are useful.

**c) Is PFMT better than other treatments?**

Trials were considered for inclusion in this section if they compared PFMT with another stand-alone intervention, e.g. vaginal cones, bladder training, drug therapy. Thirty RCTs comparing PFMT with another stand-alone treatment were found. Four trials were excluded. Two were reported as conference abstracts and contained no useable data [177, 178], one was reported in two conference abstracts with inconsistent data [179], and the fourth compared PFMT and vaginal cones versus electrical stimulation [180].

The 26 trials addressed the following comparisons:

- PFMT versus vaginal cones (VC) [129, 145, 155, 164, 177, 181-183]
- PFMT versus electrical stimulation (EStim) [141, 143, 145, 167, 184-187]
- PFMT versus bladder training (BT) [151, 188, 189]
- PFMT versus drug [139, 141, 142, 150, 190, 191]
- PFMT versus surgery [192]

**i) PFMT versus VC:** Eight trials compared PFMT with VC in women with SUI [129] or urodynamic SUI [129, 145, 155, 164, 177, 181-183]. Three trials recommended using VC once a day for 10 minutes [164] 15 minutes [181] and 20 minutes [145]. Four trials asked women to use cones twice a day for 15 minutes [129, 177, 182, 183]. The remaining trial suggested using cones two to three times a day for 10 to 15 minutes at a time [155]. All the VC programmes asked women to retain the heaviest cone possible, and programmes were progressed by increasing the cone weight. The lightest cone weights were 10g [155], 20g [129, 145, 177, 183] or 50g [181, 182] progressing to 60g [155], 70g [145, 177, 182], 80g [181] or 100g [129, 183]. Laycock (2001) did not describe the cone weights or progression. One study also asked women to perform 20 maximal PFM squeezes with a 65g weight once a day, progressing after two months to 100g [181].

The PFMT programmes varied too, as follows:

- 50 maximal PFM contractions per day [183].
- 10 daily sessions of five PFM contractions [177].
- 10 brief forceful PFM contractions and 10 sustained PFM contractions for 10 seconds, repeated as able [182].
- 100 fast and slow PFM contractions daily [129].
- eight to 12 near-maximal PFM contractions with six second hold and six to eight second rest, with three to four fast contractions at the end of every contraction, thrice daily, and a weekly group session [145].
- 20 maximal PFM contractions, 15 sub-maximal PFM contractions, and one static two minute sub-maximal contraction, twice daily [181].
- 10 minutes of personalised fast and slow PFM contractions [164].
- personalised individual PFMT four times a day [155].

Treatment duration was the same in both arms of all studies, and ranged from four weeks [183], to 10 weeks [177], 12 weeks [155, 164, 182], four months [181], six months [145] and 12 months [129]. The number of HP contacts was the same in both groups in Arvonen (2001), Laycock (2001), Haken (1991), Wilson (1998), greater in the VC than PFMT groups in Peattie (1988), Cammu (1998), but greater in the PFMT than VC group Be (1999) and Williams (2006).

**ii) PFMT versus EStim:** Eight trials compared PFMT with EStim in women with UI [186], SUI [145, 184, 185], urodynamic SUI [141, 143], mixed UI [187] or OAB [167]. There were different PFMT and EStim protocols in each study.

Two trials used interferential current. Laycock (1988) compared interferential (two to three times weekly, 30 minutes, 10-50Hz) to PFMT (weekly PFM exercise courses and daily home exercises), for four to six weeks. Henalla (1989) compared interferential (20 minutes weekly for 10 weeks, 0-100Hz, at maximal tolerated intensity) to PFMT (five PFM contractions with five second holds, hourly, every day for 12 weeks). Another trial used external (extra-vaginal and lumbar) electrodes to deliver an unknown type of current (10 minutes, three times weekly, intensity increased until noticeable PFM contraction and patient added voluntary PFM contraction) versus PFMT (no details given), for six weeks [143].
The remaining trials all delivered the stimulation using a vaginal electrode. The comparisons were, in approximately ascending order of duration of EStim:

- 20 minutes, twice weekly, biphasic symmetric intermittent current at 10Hz, pulse duration 400 microseconds, duty cycle 10 seconds on and five off, maximum tolerated intensity, versus PFMT (no details given), for 12 weeks [167].

- 30 minutes, three times weekly, biphasic intermittent current at 50Hz, pulse duration one millisecond, two second contraction, duty cycle one to two, at maximal tolerated intensity up to 100 mA (for predominant SUI) or the same stimulation at 20Hz (for predominant UUI), versus PFMT (no details given), for eight weeks [186].

- 30 minutes daily, biphasic intermittent current at 50Hz, pulse duration 0.2 milliseconds, individualised duty cycle depending on ability to hold PFM contraction, at maximal tolerated intensity up to 120mA, versus PFMT (three times daily, eight to 12 near-maximal PFM contractions with six second hold and six to eight second rest, with three to four fast contractions at the end of every contraction in addition to weekly exercise class), for six months [145].

- up to 60 minutes, twice daily, symmetric balance biphasic intermittent current at 12.5 and 50Hz, pulse duration 300 microseconds, five second contraction time with two second ramp up and one second ramp down, duty cycle one to two, intensity to 80mA, versus PFMT (daily, 60 slow and quiet PFM contractions), for four months [187].

- six to eight hour per night, intermittent current at 12, 20 or 50Hz, versus PFMT (six to eight times daily, five to 10 maximal PFM contractions with five second hold and five seconds rest, and one sub-maximal contraction with 30 to 40 second hold), for six months [184].

Amount of HP contact was the same for both groups in one trial [141], greater for EStim in two [143, 185], and greater for PFMT in another [145]. Any differences were not clear in the other four trials.

**iii) PFMT versus BT:** Three trials compared PFMT with BT in women with SUI [189], SUI and/or DO [188] or UI [151]. BT was not described in the conference abstract of the study by Sherburn (2007); in both the other trials BT comprised a voiding schedule with weekly progression. Wyman (1998) also included urge inhibition techniques (affirmations, distraction and relaxation).

Sherburn (2007) did not describe PFMT. In the other two trials BT was compared with:

- PFMT with clinic based BF, and a twice daily home PFMT programme of five fast (three second holds) and 20 sustained (10 second holds with 10 second rests) PFM contractions, PFM contraction for urge suppression and with increases in intra-abdominal pressure [188].

- PFMT with clinic based BF, and daily home PFMT of 30 PFM contractions for strength and endurance (12 second holds) [151].

Treatment duration, and amount of HP contact, was the same in both arms of all three trials, with treatment duration ranging from eight weeks [151], to 12 [188] and 20 weeks [189].

**iv) PFMT versus drug therapy:** Six trials compared PFMT to drug therapy in women with UUI [150], SUI [139, 141, 142, 190, 191].

The trials by Henalla (1989, 1990) compared Premarin (conjugated equine oestrogens) 2g per night for six [142] or 12 weeks [141] versus PFMT. In Henalla (1989) the PFMT comprised a daily home programme of five PFM contractions with five second holds per hour, but in Henalla (1990) PFMT was not described. All the other trials used different drugs.

Wells (1991) compared phenylpropanolamine hydrochloride (50mg qd for two weeks, increasing to bid for two weeks if leakage continued) for four weeks versus six months of PFMT (90 to 160 PFM contractions with 10 second hold and 10 second rest distributed throughout the day). Ishiko (2000) compared clenbuterol (20mg bid) versus PFMT (10 minutes daily), for 12 weeks.

Ghoniem (2005) compared duloxetine (4mg bid, plus sham PFMT) versus PFMT (four times weekly, three sets of 10 six to eight second contractions and two sets of 10 one to two second contractions), for 12 weeks. Burgio (1998) compared oxybutynin chloride (2.5mg tid, progressed to maximum 5mg tid) versus PFMT (15 PFM contractions thrice daily, 10 second hold, plus PFM contraction with increased intra-abdominal pressure and urge strategies), for eight weeks.

Four trials had the same amount of HP contact in drug and PFMT groups [139, 141, 150, 190]; in Henalla’s (1990) trial, this was not clear. Wells (1991) assessed treatment effect after four weeks in the drug group, and six months in the PFMT group.

**v) PFMT versus surgery:** Only one trial compared PFMT and surgery. For women randomised to surgery, Klarskov (1986) chose a surgical technique based on the type of defect identified; Burch colposuspension for anterior suspension defects and vaginal repair for posterior bladder descent.

Women with both defects had a combined Burch and vaginal repair procedure. No details on the PFMT parameters were provided; women had five or more group sessions with a physiotherapist.
1. Quality of data

**i) PFMT versus VC:** Bø (1999), Cammu (1998), Wilson (1988) and Williams (2006) reported adequate allocation concealment. Bø (1999) stated that outcome assessors were blind, and in the trials by Wilson (1988) and Williams (2006) some but not all outcome assessment was blind. Bø (1999), Cammu (1998) and Williams (2006) randomised 29, 30 and approximately 80 women per comparison group, while Wilson randomised 39 to the PFMT group and 36 to the VC group. There were dropouts from both PFMT and VC groups in all trials except Cammu (1998), where all the dropouts were from the VC group. Drop out rates were higher in the VC group for Arvonen (2001), Cammu (1998), Haken (1991) and Laycock (2001) but higher in the PFMT group for Bø (1999), Peattie (1988), Wilson (1988) and Williams (2006). None of the trials reported follow up beyond the post treatment evaluation.

**ii) PFMT versus ESTim:** Of the eight trials, two reported adequate random allocation concealment and blinding of outcome assessors [145, 167]. Three trials randomised approximately 10 women per comparison group [143, 184, 187], and the remaining trials between 20 and 35 women per group. Four trials appeared to have no dropouts [141, 143, 184, 187], with 5% [186], 12% [145], 13% [167] and 19% [164] reported in the others. All women were assessed post treatment; Henalla (1989) and Hahn (1991) also followed-up longer term, at nine months, and one to four years respectively.

**iii) PFMT versus BT:** Sherburn (2007) reported adequate random allocation concealment. Yoon (2003) and Sherburn (2007) reported blinding of outcome assessors while Wyman (1998) stated that outcome assessors were not blinded. Sherburn (2007) randomised 43 women to PFMT and 41 to BT, and Wyman (1998) randomised nearly 70 women per group. The trial by Yoon (2003) was smaller with approximately 15 to 20 women per group. Dropouts were approximately 4% for Wyman (1998) and 12% for Yoon (2003) and not mentioned by Sherburn (2007). All women were assessed post treatment, and Wyman (1998) followed-up three months later (i.e. six months after treatment began).

**iv) PFMT versus drug therapy:** Random allocation was concealed in only one of the six trials [139]. Outcome assessors were blind in the Burgio (1998) and Ghoniem (2005). Three trials randomised 25 women or fewer per group [141, 142, 190]. Ghoniem (2005) randomised approximately 50 per group. The two largest trials randomised about 80 [191] or 85 women per group [150]. Dropouts were not reported [142], none [141], 14% [150], 16% [190], 25% [191] and 36% [139]. All women were assessed post treatment, and Henalla (1989) also followed-up nine months later by questionnaire.

**v) PFMT versus surgery:** It was not clear if random allocation was adequately concealed, or if the outcome assessors were blinded [192]. Klarskov (1986) randomised approximately 25 women to each comparison group. It appears there were no dropouts at four months (post treatment assessment). There was further long-term follow-up at one year, then four to eight years.

2. Results

**i) PFMT versus VC:** Results of the individual studies were inconsistent. For cure, the trials favoured PFMT (RR 0.39, 95% CI 0.16 to 0.94, Bø 1999), neither PFMT nor VC (RR 1.00, 95% CI 0.56 to 1.81, Wilson 1998; RR 1.73, 95% CI 0.53 to 5.67, Williams 2006), or VC (RR 9.47, 95% CI 0.55 to 164.35, Arvonen 2001). Pooled data from the four trials showed no statistically significant difference in cure (RR 0.98, 95% CI 0.63 to 1.52); the pooled data showed statistically significant heterogeneity. For cure/ improvement, pooled data showed no statistically significant difference (RR 0.99, 95% CI 0.84 to 1.16, in five trials). PFMT was better than cones in terms of daily leakage episodes (WMD -0.61, 95% CI -1.05 to -0.16, three trials). Williams (2006) reported on the cost of intervention; PFMT was more expensive than VC, £338 versus £305 per person because of the amount of time spent with the therapist. With regard to adverse events, Arvonen (2001) and Williams (2006) stated that no women using VC reported any, while Bø (1999) and Cammu (1998) found that VC were associated with adverse events such as inability to use cones, pain, vaginitis, bleeding, and women finding cones unpleasant to use.

**ii) PFMT versus ESTim:** Pooled data from three trials in SUI women found self-reported cure was more likely with PFMT (RR 2.67, 95% CI 1.53 to 14.26) [145, 184, 187], although only Bø (1999) found a statistically significant difference when data from the trials was considered individually. It was not clear if the cure data reported by Hofbauer (1990) were derived from a symptom scale or a voiding diary; these data were therefore excluded. Pooled data from three trials in SUI women also found self-reported cure/improvement was more likely in PFMT women (RR 1.72, 95% CI 1.05 to 2.81) [145, 184, 185]; again only Bø (1999) found a statistically significant difference when trial data were considered individually. Only Bø (1999) measured leakage episodes and quality of life (Social Activity Index). There was no statistically significant difference between the groups for either outcome. At nine months post treatment, Henalla (1989) found that three out of 17 PFMT women and one out of eight in the ESTim group reported recurrent symptoms. Three trials reported side effects related to ESTim, including vaginal irritation and/or bleeding [145, 184, 187]. Spruijt (2003) recruited women with SUI, UUI or MUI,
and did not find a statistically significant difference between the groups for self-reported cure/improvement (RR 0.99, 95% CI 0.45 to 2.16). The trialists reported that EStim produced “physical and emotional stress” in the elderly women in their sample. Wang (2004) recruited women with UI, and did not find any statistically significant difference between the groups for self-reported cure (RR 0.74, 95% CI 0.38 to 1.42) or cure/improvement (RR 0.84, 95% CI 0.48 to 1.46). PFMT women had statistically significantly fewer leakage episodes per day (MD –1.22, 95% CI –2.37 to –0.07). On the KHQ there were no statistically significant differences in general health perception, incontinence impact, role limitation, physical limitation, social limitation, and personal relationship, but the EStim group had statistically significantly better scores for emotions, sleep/energy and severity measures. Some women using EStim reported discomfort during treatment.

**iii) PFMT versus BT:** Unfortunately, Yoon (2003) did not report any data for the outcomes of interest. Wyman (1998) recruited women with SUI, UUI or MUI. While more women in the PFMT group reported symptomatic improvement or fewer leakage episodes the difference did not reach statistical significance post-treatment (RR for symptomatic improvement 1.73, 95% CI 0.83 to 3.60; MD for leakage episodes –0.14, 95% CI –0.83 to 0.55) or three months later (RR 1.96, 95% CI 0.97 to 3.94; MD –0.09, 95% CI –0.73 to 0.55). Nor were there statistically significant differences in Incontinence Impact Questionnaire (IIQ) or Urogenital Distress Inventory (UDI) between the groups at either time point. Sherburn’s (2007) trial recruited women with SUI only. However, Sherburn (2007) found in SUI women, a significant difference between the two groups in the ICI-Q SF (p=0.003), leakage episodes (p=0.03) and the VAS (p=0.009) in favour of the PFMT group, although the generic health related QOL did not differ between the two groups. No adverse event data were reported in either trial.

**iv) PFMT versus drug:** Neither of the two trials comparing vaginal oestrogens versus PFMT in urodynamic SUI women reported data for the outcomes of interest [141, 142]. Of those that responded to a follow-up questionnaire at nine months, three out of 17 PFMT women and three women using oestrogens reported recurrent symptoms. Adverse events were not reported in either trial.

Two trials compared an adrenergic agonist and PFMT in women with SUI or MUI. Ishiko (2000) did not find any statistically significant difference in the proportion of women reporting no leakage episodes (cure) after treatment (RR 0.68, 95% CI 0.41 to 1.15), and Wells (1991) did not find any statistically significant difference for self-reported cure/improvement (RR 0.92, 0.77 to 1.10). Wells (1991) reported data for leakage episodes per day in SUI women only; PFMT women had statistically significantly more leaks per day than women in the drug group (MD 0.08, 95% CI 0.02 to 0.14). Ishiko (2000) reported that the drug side effects were sufficient for some women to withdraw; others discontinued the drug, but remained in the trial. Wells (1991) did not report data on drug side effects.

In the comparison of PFMT and oxybutynin in women with DO (DO), or DO with urodynamic SUI, Burgio (1998) reported no statistically significant difference for the number of women who were dry (cured) (RR 1.31, 95% CI 0.73 to 2.34), but PFMT women were more likely to report they were much better than women receiving the drug treatment (RR 1.46, 95% CI 1.08 to 1.97). PFMT women also had fewer leakage episodes per day (MD –0.41, 95% CI –0.80 to -0.02). Some women taking oxybutynin reported side effects (dry mouth and inability to void in particular).

Ghoniem (2005) reported that duloxetine had a significantly greater impact in decreasing Incontinence episodes than PFMT (57% versus 35% median decrease in UI episode frequency between drug and PFMT respectively, p=0.004), but there were no significant differences between the treatments with respect to Incontinence Quality of Life (i-QoL).

**v) PFMT versus surgery:** At four months PFMT women with urodynamic SUI were less likely to report cure than women who had surgery (RR 0.20, 95% CI 0.07 to 0.61), although there was no statistically significant difference in the proportions reporting cure/improvement (RR 0.80, 95% CI 0.60 to 1.07). At 12 months, 10 out of the 24 women from the PFMT group were satisfied with the initial therapy, versus 19 out of the 26 women randomised to surgery. Long-term data (four to eight years) were not presented by group allocation. All reported adverse events were associated with surgery; women reported new UUI, retropubic or pelvic pain, or dyspareunia [192].

**Summary**

Eight trials compared PFMT with VC in SUI women. No consistent pattern emerged in the data; data on self-reported cure were inconsistent (four trials), there was no difference in pooled data from four trials for self-reported cure/improvement, but there were fewer leakage episodes per day with PFMT in pooled data from three trials (Level of Evidence: 1). Treatment with VC may be inappropriate in some cases due to side effects such as bleeding, and some women appear to find them unpleasant to use.

Eight trials compared PFMT with EStim in SUI women. Pooled data demonstrated that self-reported cure and cure/improvement were more likely in PFMT than in EStim groups (Level of Evidence: 1). It is worth noting that only one trial individually demonstrated a statistically significant difference in these outcomes and there was more health professional contact in the PFMT arm. There were no statistically significant differences between PFMT and EStim groups for
leakage episodes or quality of life, based on a single trial (Level of Evidence: 2). In the one trial that recruited women with SUI, UUI or MUI self-reported cure/improvement rates were not statistically significantly different (Level of Evidence: 2). Self-reported cure and cure/improvement rates were not statistically significantly different in a trial in women with UUI, although PFMT women had fewer leakage episodes per day, and women in the EStim group had better quality of life in three of the nine domains measured (Level of Evidence: 2). Some women reported adverse events attributable to ES.

Three trials compared PFMT and BT, but only two reported data of interest. In women with SUI symptomatic improvement, leakage episodes and quality of life were statistically significantly better in the PFMT group (Level of Evidence: 2). In contrast the study that recruited women with SUI, UUI and MUI did not find statistically significant differences between the groups for these outcomes (Level of Evidence: 2).

In the absence of useful data there is insufficient evidence to determine if PFMT is better than vaginal oestrogens. Neither trial that compared an adrenergic agonist with PFMT in women with SUI or MUI found a difference in self-reported cure/improvement, although in one study women who took the drug had fewer leakage episodes per day (Level of Evidence: 2). Adrenergic agonist side effects were sufficient to discontinue treatment in some women. One trial of PFMT versus oxybutynin in women with DO or DO with urodynamic SUI found PFMT women were more likely to report improvement and had fewer leakage episodes per day after treatment (Level of Evidence: 2). Some women taking oxybutynin reported drug-related side effects. One trial compared a serotonin-norepinephrine reuptake inhibitor (duloxetine) with PFMT and while women who took the drug had fewer leakage episodes, there was no difference in terms of quality of life between the two groups (Level of Evidence: 2). Serotonin-norepinephrine reuptake inhibitor drug side effects were sufficient to discontinue treatment in some women.

Based on one trial it seemed self-reported cure was more likely after surgery than PFMT for women with urodynamic SUI; although there was no statistically significant difference in the proportion of women reporting cure/improvement (Level of Evidence: 2). There was insufficient detail about the PFMT programme to make a judgment about how effective it might have been.

**Recommendations**

For women with SUI:

- PFMT is better than EStim as first line conservative therapy, particularly if PFMT is intensively supervised (Grade of Recommendation: B).
- PFMT is better than BT as first line conservative therapy (Grade of Recommendation: B).
- PFMT and duloxetine are both effective in first line therapy, although PFMT is better because of the side effects experienced with the drug (Grade of Recommendation: C).
- PFMT and surgery are both effective therapies, although PFMT is better as first line therapy because it is less invasive (Grade of Recommendation: C).

For women with SUI or MUI:

- PFMT is better than VC as first line conservative therapy (Grade of Recommendation: B).
- PFMT is better than clenbuterol or phenylpropanolamine hydrochloride as first line therapy because of the side effects experienced with the medications (Grade of Recommendation: B).

For women with UUI or MUI:

- PFMT and BT are both effective first line conservative therapy (Grade of Recommendation: B).
- PFMT is better than oxybutynin as first line therapy (Grade of Recommendation: B).

Larger, good quality trials are needed to address each of the above comparisons if these are of interest to women. In planning comparisons researchers should consider carefully the potential impact of different levels of supervisory intensity between groups, particularly in comparisons of conservative therapies. A comparison of surgery and PFMT might be least useful, because PFMT is usually first-line therapy with surgery reserved for those in whom PFMT was unsuccessful or is not the treatment of choice.

**d) Does the addition of PFMT to other treatments add benefit?**

To be included, trials needed to investigate the effects of PFMT combined with therapy A versus therapy A alone, to address the additive benefit of PFMT over therapy A. Nine RCTs were found, and of these three were excluded. Jeyaseelan et al (2002), a conference abstract, did not report any useable data [178]. Millard (2004) included men and women and the data were not reported separately by sex [193]. Dowell (1997) used a combination BT/PFMT programme [194].

**j) PFMT/VC versus VC:** Two trials, in women with urodynamic SUI [195] or SUI [129], compared combined PFMT/VC versus VC. In both arms of each study the recommended VC regime was twice daily for 15 minutes, with cone weight progressing from 20g to 70g [195] or 100g [129]. Both PFMT programmes asked women to do 100 PFM contractions per day; Wise (1993) recommended 10 contractions 10 times a day, and Wilson (1998) recommended a combination of fast and slow contractions. Treatment duration was 12 weeks in both arms of both studies.
(ii) PFMT/EStim versus EStim: In women with urodynamic SUI, Hofbauer (1990) compared EStim (10 minutes, three times weekly, sufficient intensity to provoke a visible contraction to which the patient added their own PFM contraction, extravaginal and lumbar electrodes) to PFMT/ES (daily PFMT home programme (not specified) and a twice weekly exercise class plus the same ES programme). Treatment duration was six weeks in both arms.

(iii) PFMT/BT versus BT: In women with urodynamic SUI, or urodynamic SUI with DO, Wyman (1998) compared BT (progressive voiding schedule, advice on urge inhibition techniques such as affirmations, distraction and relaxation) to PFMT/BT (twice daily PFMT, maximum of 10 fast contraction with three second holds and 40 sustained contractions with 10 second holds in addition to bladder training as above). The combined PFMT/BT group began with BT and added PFMT in the 3rd week of the intervention. Women in both groups received the same preliminary education programme and treatment duration was 12 weeks in both arms.

(iv) PFMT/drug versus drug: Two trials compared PFMT/drug to drug alone in women with SUI [139, 190]. Ishiko (2000) compared drug (oral beta(2)-adrenergic agonist (clenbuterol) 20mg bid) to PFMT/drug (clenbuterol as above plus daily 10 minutes of PFMT contraction programme, no further detail of training was given), Ghoniem (2005) compared drug (duloxetine, 4mg twice daily plus sham PFMT) to PFMT/drug (duloxetine as above plus PFMT four times a week comprising three sets of 10 long contractions held six to eight seconds and two sets of 10 rapid contractions held one to two seconds). Treatment duration was 12 weeks in both arms in both studies [139, 190].

1. Quality of Data

i) PFM/VC versus VC: Wilson (1998) reported adequate allocation concealment and some outcome assessment was blind. Neither of these was clearly reported in the study by Wise (1993). There were approximately 39 women in each comparison group in Wilson (1998) and approximately 20 women in each comparison group in Wise (1993). In Wilson (1998) 63% of the women in the PFM/VC group dropped out compared to 41% in the VC group while in Wise (1993) 30% of the PFM/VC group dropped out compared to 9% in the VC group only.

ii) PFMT/EStim versus EStim: It was not clear if random allocation concealment was adequate or whether assessors were blind [143]. There were only 11 women in each comparison group. There did not appear to be any dropouts.

iii) PFMT/BT versus BT: It was not clear if random allocation concealment was adequate and outcome assessors were not blind [188]. There were 68 women in the BT group and 67 in combination therapy. There were fewer than 10% dropouts after 12 weeks of treatment. Further follow-up was reported at six months and approximately three years after study entry.

iv) PFMT/drug versus drug: Although adequate allocation concealment and blinded assessors where used in Ghoniem (2005) it was not clear in Ishiko’s (2000) trial. In Ishiko’s (2000) trial, there were 18 women in the drug group, and 23 in the combination therapy group. Five (27%) and four (17%) women dropped out of these groups respectively, principally because of drug-related side effects. Ghoniem (2005) randomised approximately 50 SUI women to each group; some 30% of whom dropped out of both treatment groups.

2. Results

i) PFM/VC versus VC: In this comparison, neither of the two trials identified any statistically significant differences between the groups (for patient reported cure, improvement as measured by a Visual Analogue Scale or pad test) and all of the confidence intervals were wide [129, 195].

ii) PFMT/EStim versus EStim: Although Hofbauer (1990) reported cure/improvement, it was not clear whether this was based on data from a symptom scale or a urinary diary. There were no data reported for the other outcomes of interest.

iii) PFMT/BT versus BT: Wyman (1998) did not find a statistically significant difference between the combination versus single therapy in the number of women reporting they were much better, however more in the combination group reported they were much better, six months after treatment began (RR 0.61, 95% CI 0.39 to 0.94). There was no statistically significant difference in the number of leakage episodes per day between the groups after treatment or at six months. With regard to quality of life the combination therapy group had statistically significantly better scores on UDI (MD 31.10, 95% CI 13.26 to 48.94) and IIQ (MD 25.50, 95% CI 1.05 to 49.95) after treatment, but there was no statistically significant difference in either measure six months after treatment had begun. Approximately three years later, a similar number in each group had sought further treatment for UI (19 of 48 BT, 18 of 48 PFMT/BT). Of the women who had not sought further treatment, fewer were free of leakage episodes in the BT group (four of 22 in BT group versus eight of 16 in the combination group). Adverse events are not mentioned.

iv) PFMT/drug versus drug: Ishiko (2000) did not report data for any of the primary outcomes of interest. They did state that 10 of the 13 women in the drug group, and 17 of the 19 in the combination therapy group had no leakage episodes per week post treatment, and some women reported drug-related side effects sufficient enough to withdraw from
treatment. Ghoniem (2005) reported that the combined treatment was not significantly different from the drug-only-treatment in terms of frequency of incontinence episodes, quality of life (IQOL) and Patient Global Impression of Improvement Scale.

SUMMARY

There were few trials addressing the effect of adding PFMT to another therapy, and only three of the eight studies reported useful data. The findings of Wilson (1988) and Ghoniem (2005) did not suggest any benefit of adding PFMT to VC or duloxetine respectively in women with SUI (Level of Evidence: 2). The study of Wyman (1998) suggested there is a benefit to adding PFMT to BT for women with USI or USI with DO in the short term (three months), but it is not clear if this benefit persists at six months or more (Level of Evidence: 2). There is not sufficient evidence to be sure if there is any benefit in adding PFMT to EStim.

RECOMMENDATIONS

For women with SUI or MUI a combination of PFMT/BT may be better than PFMT alone in the short-term (Grade of Recommendation: C). If a woman is taking duloxetine or using VC, it may not help to add PFMT (Grade of Recommendation: C). However, these recommendations are based on single trials of variable quality and larger, good quality trials are needed to address each of the above comparisons if these are of interest to women.

4. OTHER LUTS

Only two of the many trials included above reported data for other LUTS, e.g. frequency, nocturia, bladder pain.

Lin (2004) looked at the effect of a PFMT programme on frequency, nocturia and urgency in women with MUI [172]. Based on self report of symptom bother both frequency and nocturia improved significantly more in the PFMT group (OR for frequency 0.57, 95% CI 0.35 to 0.95; OR for nocturia 0.52, 95% CI 0.30 to 0.93), while urgency persisted (OR: 0.73, 95% CI 0.456 to 1.17).

A secondary analysis of Burgio (1998) looked at the effect of PFMT versus drug therapy on nocturia in older women with UUI or MUI [150]. The PFMT group reduced nocturia by a median of 0.5 episodes per night; this was significantly more effective than drug treatment (median reduction 0.03 episodes per night; p = 0.02).

5. FACTORS AFFECTING OUTCOME

Apart from differences in effect attributed to PFMT or comparison interventions, there might be other factors affecting treatment outcome. Of particular interest is the effect of older age; this and other factors are considered here.

a) Age

Firstly we looked for trials included above that specifically recruited older woman; there were six. Women were aged 55 or more [135, 149, 150, 191], or 65 or more [186, 189]. The average age of women in these trials was between 60 and 70 years [135, 149, 150, 191], or over 70 years [186, 189], compared with a mean age of 40 to 55 in most other included studies. It was not possible to compare the data from older women with data from younger women for the following comparisons: PFMT versus EStim [186], PFMT versus drug [150, 191], and PFMT versus BT [189].

For three comparisons (PFMT versus no treatment, [149] PFMT versus placebo/sham/control, [135, 150] BF assisted PFMT versus PFMT alone, [149] there were no clear differences in the size or direction of effect when the data from the trials in older women were compared with data from other trials. The recommendations arising from these comparisons appear to apply to older women. Namely, that PFMT should be offered, as first-line therapy, to all women with SUI, UUI or MUI, and that there does not appear to be added benefit of BF assisted PFMT over PFMT alone.

Secondly, the methods of included trials were checked for use of regression or other methods to investigate association between baseline characteristics (specifically age) and outcome. The literature search also located some papers that reported secondary analysis of data from the included trials. Papers that reported an association between age and outcome, but did not describe the methods of testing association are not discussed here.

Two reports detailed the testing of independent associations between patient characteristics (including age) and outcome [159, 196]. Burgio (2003)[196] used data from PFMT groups in three RCTs [135, 136, 150]. The individual trials restricted entry to women 55 years and older [135, 150] or 40 years and over [136]. In multivariate analysis, age was not a significant predictor of reduction in leakage episodes for PFMT women with SUI, UUI or MUI. Hay-Smith (2003) investigated the associations between leakage on paper towel test and patient characteristics using data from a trial that compared two approaches to PFMT for SUI women. Older age was associated with more leakage in univariate models, but was not significant in multivariate analysis.

One further trial [188] used correlation methods, and one study [197] categorised women as successes or failures, to investigate the association between age and outcome. In a secondary analysis of data from the trial by Wyman (1998) there was no statistically
significant correlation between age and reduction in leakage episodes or change in PFM activity after PFMT or BT in women with SUI, UUI or MUI [198]. Be characterised participants in the intensive PFMT group from the Bø (1990) trial as treatment responders or non-responders [197]. Treatment responders were statistically significantly older than borderline responders; there were no non-responders.

Considering the number of included trials, there were few that restricted entry to older women and/or investigated the association between age and treatment outcome. Only two studies have used the most appropriate methods to test independent associations. More research is needed to investigate the association between age and treatment outcome. Neither study using multivariate models found an association between age and outcome, nor was there a reported correlation in another. The two studies that categorised women as treatment successes or failures had conflicting results.

**Summary**

There is no good evidence to date to suggest that ‘healthy’ older women with UI do not benefit from PFMT as much as younger women.

**b) Other**

Aside from age, other factors have the potential to mediate treatment outcome, e.g. baseline UI severity and duration of symptoms. Trial reports, and subsequent publications of the included trials, were checked for methods investigating the association between baseline characteristics and treatment outcome. Some of the included studies reported predictors of outcome that appeared to be based on researcher observation, but did not describe the methods for checking the association; these data are not discussed here. Seven reports of interest were found [149, 159, 191, 196-199]. A wide range of patient characteristics were considered in these papers; it is not clear whether it is more important to know which baseline characteristics might be predictors of outcome, or which ones might not. To eliminate long lists of non-significant associations, a pragmatic choice was made to report only significant associations although this creates a false impression of some consistent associations. None of the variables discussed here has demonstrated a consistent association with outcome, and all are worthy of further investigation.

Two reports described the testing of independent associations between patient characteristics and outcome [159, 196]. Burgio (2003) used data from PFMT groups in three RCTs [135, 136, 150]. In multivariate analysis of data from PFMT women with UUI or urge predominant MUI, a 75% reduction in leakage episodes was more likely if women did not use protection (e.g. pads) prior to treatment. Continence (100% reduction in leakage episodes) was more likely if women had fewer Incontinence episodes at baseline and had a lower educational level, but less likely if they had prior UI surgery. For PFMT women with SUI or stress predominant MUI a 75% reduction in leakage episodes was less likely if women had previously been evaluated for UI or had more than 10 leakage episodes per week pre-treatment. Hay-Smith (2003) investigated the associations between patient characteristics and two outcomes (leakage on paper towel test, self-reported improvement) using data from a trial that compared two approaches to PFMT for SUI women. In multivariate models increasing parity was associated with less improvement in leakage symptoms and more risk of leakage on a paper towel test. Shorter symptom duration and higher body mass index were both associated with more improvement in symptoms. Leakage once or more per day was associated with greater risk of leakage on a paper towel test; the reverse was true for women with a history of constipation.

Theofrastous (2002) used correlation methods to investigate the association between patient characteristics and outcome in a secondary analysis of data from the trial by Wyman (1998). There was no statistically significant correlation between any of the baseline characteristics listed and the two outcomes (reduction in leakage episodes or change in PFM activity). One study categorised women as successes or failures, to investigate the association between patient characteristics and outcome. Bø (1992) characterised participants in the intensive PFMT group from the Bø (1990) trial as treatment responders or non-responders. Treatment responders had statistically significantly longer symptom duration, higher body mass index, stronger PFM, and were more motivated (clinician judgement) than borderline responders; there were no non-responders.

Few included studies investigated the association between patient characteristics and treatment outcome. Even fewer used appropriate methods. More research is needed to test for independent associations between patient characteristics and outcome. No consistent pattern emerged from the available data. Given the few data available, and the methodological limitations of some papers, any patient characteristic described above that was associated with outcome should be considered as a possible rather than established prognostic factor.

**Summary**

It is not clear if there are any reliable predictors of PFMT outcome. Too few trials have appropriately investigated the association between patient characteristics and outcome to be sure.
Weighted vaginal cones (VC) were developed by Plevnik as a method for testing PFM function and to provide overload for PFM strengthening exercises [183, 200]. The cones are inserted into the vagina, above the PFM. Theoretically, when a cone is inserted into the vagina, the sensation of ‘losing the cone’ provides strong sensory feedback prompting the PFM to contract in order not to let the cone slip. Starting with a weight held inside the vagina for at least one minute in the standing position, women train by building up to the ability to keep the cone in place for at least 20 minutes. When the woman is able to walk around for 20 minutes without losing the weight, she then moves on to progressively heavier weights, advancing towards overload of the muscles over the course of the exercise programme [183, 200].

Since their introduction, a variety of cones have been developed encompassing different sizes, shapes and weights (Figure 3). However, the effectiveness of the VC training method has been questioned over the years. First, the PFM contraction is not the only reason why the cone stays in place. As the orientation of the vagina is not vertical, it is possible for some women to retain the cone without contracting the pelvic floor; the transverse lie of the cones has been shown by radiology [201]. Moreover, depending on the axis of her vagina, a woman will need to produce different force intensities to retain the cone. Therefore, using the cone as a measurement of PFM function does not appear to be valid. Additionally, retaining the cone in the vagina for 15 minutes requires sustained low load contractions, which is not congruent with the principles of strength straining used in most pelvic floor rehabilitation [84]. Conversely, VC training may actually favour endurance, which could be important in retraining the pelvic floor. Finally, for some women, it may be impossible to insert the cone because of narrowed vaginal opening or to retain it because of either an enlarged vaginal opening or insufficient PFM contraction to hold even the lightest cone.

This section will examine the evidence for the use of VC for the prevention and treatment of UI in women. Questions addressed are:

- Are VC better than no treatment, placebo or control for the prevention of UI?
- Are VC better than no treatment, placebo or control for the treatment of UI?
- Are VC as effective as any other treatment for the treatment of UI?
- Are VC combined with PFMT better than PFMT alone for the treatment of UI?

To address these questions, the literature was searched for reports of relevant systematic reviews, RCTs and quasi-RCTs. Therefore, only Level 1 evidence is considered in this section. Recommendations are based on the findings of two systematic RCTs reviews undertaken by Hay-Smith (2002) on UI prevention and by Herbison (2004) who reviewed management of UI with cones [112, 202].

### 1. PREVENTION

No trials investigating the primary/secondary prevention effects of training with VC for women with UI were found. The literature search revealed two reviews on the prevention of UI [113, 203]. Only Hay-Smith (2002) considered VC prevention trials, but none of the trials measured the effect on UI; all the measures were of PFM activity. Because no continence related outcomes were measured, these trials were not reviewed here. The current Cochrane review of VC does not consider prevention [202], and our own searching has not revealed any new RCTs on VC for prevention.

### 2. TREATMENT

The literature search revealed one systematic review that specifically addressed the effects of VC in the treatment of UI in women [202]. The review, together with one RCT published after the review, is the basis of this subsection [155].

#### a) Are VC better than no treatment, placebo or control treatments?

Three RCTs compared VC with control treatments for women with UI [129, 145, 155]. Wilson (1998) compared VC with standard postnatal care in women with symptoms of UI three months postpartum (controls were requested to continue with their normal postnatal PFMT programme).

Bø (1999) compared VC with a control treatment (use of Continence Guard, Coloplast AG) in women with urodynamically proven SUI.
b) Are VC as effective as any other treatment?

VC have been compared with PFMT, and with EStim, but not with other therapies such as drugs, BT or with surgery.

i) VC versus PFMT: Eight trials compared VC with PFMT [129, 145, 155, 164, 177, 181-183]. This comparison has been addressed previously and for details of the trials (quality and results) readers are referred to section B.2.3d.

ii) VC versus EStim: Four trials compared VC with EStim [145, 195, 204, 205]. Important differences were noted in all the VC and EStim interventions. Delneri (2000) compared VC (25 to 35 minutes daily progressing through cone weights of 20 to 70g) to EStim (30 minutes daily with a low-frequency bipolar current of 50 Hz, 0.2ms pulse width at an intensity of between 0-120 mA). Treatment duration was six months in both arms. Bø (1999) compared VC (20 minutes daily progressing through three cone weights of 20, 40 and 70g) to EStim (30 minutes daily with a low-frequency bipolar current of 50 Hz, 0.2ms pulse width at an intensity of between 0-120 mA). Treatment duration was four weeks in both arms. Bø (1999) compared VC (20 minutes daily progressing through cone weights of 20 to 70g) to EStim (30 minutes daily with a low-frequency bipolar current of 50 Hz, 0.2ms pulse width at an intensity of between 0-120 mA). Treatment duration was four weeks in both arms. Wise (1993) compared VC (15 minutes twice daily progressing through cone weights of 20 to 100 grams) to EStim (15 minutes, three times per week with interferential current of 0-100 Hz, at maximum tolerated intensity); treatment duration was four weeks in both arms. Wise (1993) compared VC (15 minutes twice daily progressing through cone weights of 20 to 70g) to EStim (20 minutes daily of continuous stimulation of 20 MHz frequency and 0.75ms pulse width at the maximum tolerated intensity of 0-90 mA). Treatment duration was 12 weeks in both treatment arms.

1. Quality of data

All trials reported adequate randomisation concealment and blinded outcome assessors. Two randomised about 30 women to VC; however, while Be (1999) randomised a similar number to the control group, Wilson (1998) had around 100 women in the control group (factorial design). Williams randomised about 80 women in each group.

Dropout rates were 3% [155], 12% [145] and 40% [129]. There were more dropouts from VC (42%) than the control group (22%) in the latter.

2. Results

Pooled data from all three trials for self-reported cure showed suggested women in the VC group were more likely to report they were cured than controls (RR 1.98, 95% CI 1.21 to 3.23).

Pooled data from two trials for self-reported improvement or cure showed statistically significant heterogeneity. Individually, one trial favoured VC (RR 18.89, 95% CI 2.68 to 132.58 [145]) and the other neither control nor VC (RR 0.95, 95% CI 0.76 to 1.19 [155]). Be (1999) also reported that VC were better than the control for the Leakage Index but there were no statistically differences in the 24 hour pad test or the Social Activity Index.

Summary

There is evidence from three good RCTs suggesting that VC is better than control treatments (for subjective reporting of cure or cure/improvement) in the treatment of SUI (Level of Evidence: 1). Treatment with VC may be inappropriate in some cases due to side effects such as bleeding, and some women appear to find them unpleasant to use.

Recommendations

For women with SUI, VC can be offered as first line conservative therapy to those who can and are prepared to use them (Grade of Recommendation: B); VC may be inappropriate in some cases due to side effects and discomfort.
**SUMMARY**

In summary, eight trials compared PFMT with VC in SUI women. No consistent pattern emerged in the data; data on self-reported cure were inconsistent (four trials), there was no difference in pooled data from four trials for self-reported cure/improvement, but there were fewer leakage episodes per day with PFMT in pooled data from three trials (Level of Evidence: 1).

Pooled data demonstrated no statistically significant differences between VC and EStim groups for self-reported cure, cure/improvement or leakage episodes (Level of Evidence: 1). Both VC and EStim groups reported adverse events. Two trials had to exclude some women prior to randomisation because they could not use VC (e.g. wedging of the cone).

**RECOMMENDATIONS**

PFMT is better than VC as a first choice for conservative therapy, because some women cannot or do not like to use cones (Grade of Recommendation: B). VC and EStim seem equally effective in the treatment of SUI and MUI, but the usefulness of VC and EStim in practice might be limited because of side effects and discomfort (Grade of Recommendation: B).

c) Are VC combined with PFMT better than PFMT alone?

Two trials compared a combined PFMT/VC to PFMT alone [129, 206]. Pieber (1995) compared PFMT (100 PFM contractions daily supplemented by an initial visit with a physiotherapist and additional visits at intervals of two to four weeks) versus PFMT/VC (the same PFMT programme combined with 15 minutes of VC daily progressing through cone weights of 20 to 70g). Treatment duration was 12 weeks in both treatment arms. Wilson (1998) compared PFMT (100 fast and slow PFM contractions daily supplemented with one training session and three follow up visits) versus PFMT/VC (the same PFMT programme combined with 15 minutes of VC twice daily progressing through three cone weights of 20 to 100g). Treatment duration was 12 months in both treatment arms. None of the outcomes used in the two trials overlapped.

**1. QUALITY OF DATA**

Wilson (1998) reported allocation concealment and some outcomes had blinded assessors, but neither was clearly reported by Pieber (1995).

**2. RESULTS**

No statistically significant difference detected for cure (RR 1.21, 95% CI 0.63 to 2.32) [129], cure/improvement after six weeks (RR 1.41, 95% CI 0.81 to 2.45) [206], cure/improvement after 12 weeks (RR 0.92, 95% CI 0.51 to 1.64) [206], but confidence intervals were wide. Dropout rates were higher in the combined PFMT/VC group in both trials.

**SUMMARY**

The limited evidence available suggested no benefit from adding VC to PFMT for SUI women (Level of Evidence: 2).

**RECOMMENDATIONS**

If the combination of VC with PFMT is an intervention of interest for women, then more research is needed to confirm or refute the effect of this combination.

**3. OTHER LUTS**

None of the trials included in this section on VC reported other LUTS data.

**4. FACTORS AFFECTING OUTCOME**

None of the included trials addressed the effect of age or any other factors on outcome of VC training. However, it is worth noting that in the 16 trials included in this section on average 23% of the women being treated with VC (range 0 to 63%) withdrew or dropped out. Although few trials examined the reasons for dropping out, those who did reported low compliance, motivation problems, unpleasantness, aesthetic dislike, discomfort, bleeding and vaginal prolapse. However none of these were predominant.

**IV. ELECTRICAL STIMULATION (EStim)**

The literature concerning EStim in the management of UI is very difficult to interpret, due to the lack of a well-substantiated biological rationale underpinning the use of EStim. However, the theoretical basis of stimulation interventions is emerging with increasing understanding of the neuroanatomy and physiology of the central and peripheral nervous systems. It is also becoming clear that the mechanisms of action may vary depending on the cause(s) of UI and the structure(s) being targeted by EStim, e.g. PFM or detrusor muscle, peripheral or central nervous system. In general, the aim of EStim for women with SUI appears to be to improve the function of the PFM, while for women with UUI the objective seems to be to inhibit DO (DO). Overall, studies poorly report the biological rationale underpinning the application of EStim being tested [207, 208].

EStim is provided by clinic based mains powered machines or portable battery powered stimulators.
EStim also offers a seemingly infinite combination of current types, waveforms, frequencies, intensities, electrode types and placements (Figure 5). Without a clear biological rationale it is difficult to make reasoned choices of EStim parameters. Additional confusion is created by the relatively rapid developments in the area of EStim and a wide variety of stimulation devices and protocols have been used even for the same condition. For example, in the last 25 years or so women with SUI have been treated using anything from a single clinic based episode of maximal EStim under general anaesthetic for 20 minutes with vaginal and buttock electrodes [209], to 10 sessions of interfential current at 10 to 40 Hz with perineal body and symphysis pubis electrodes [180], to eight weeks of home-based stimulation using a “new pattern of background low frequency and intermediate frequency with an initial doublet”, for an hour a day [210, 211], to six months of low intensity stimulation at 10 Hz using a vaginal electrode [212].

Finally the nomenclature used to describe EStim has been inconsistent. Stimulation has sometimes been described on the basis of the type of current being used (e.g. faradic, interferential), but is also described on the basis of the structures being targeted (e.g. neuromuscular), the current intensity (e.g. low-intensity, or maximal stimulation), and the proposed mechanism of action (e.g. neuromodulation). In the absence of agreement of how best to classify EStim the authors of this chapter have made no attempt to do so. The authors were also reluctant to use any existing system to group the EStim protocols as many were poorly described and could therefore be erroneously classified.

In this review only non-surgical or non-invasive EStim (i.e. stimulation without implanted electrodes) is considered. The questions to be addressed are:

- What evidence is there that EStim can prevent UI?
- What is the most appropriate EStim protocol for treatment of UI?
- Is EStim better than no treatment, placebo or control treatments for UI?
- Is EStim better than other treatments?
- Does the addition of EStim to other treatments add any benefit?
- What is the effect of EStim on other LUTS?
- What factors might affect the outcome of EStim?

This section is underpinned by a Cochrane review of non-invasive EStim (submitted, Berghmans et al, personal communication) and four published systematic reviews [93, 112, 213, 214]. The review reported here is based on the trials included in prior systematic reviews with addition of trials completed after publication of the reviews and/or located through additional searching (see appendix). To be included in this section a study needed to (a) be a RCT, (b) include women with UI, and (c) address one of the questions listed above. Published abstracts were included but reports of trials in progress were excluded.

1. PREVENTION

It seems EStim has not been investigated for either the primary or secondary prevention of UI or LUTS; no published trials were found.

2. TREATMENT

a) What is the most appropriate EStim protocol for treatment of UI?

On the basis of trial reports to date it appeared that there was considerable variation in EStim protocols with no consistent pattern emerging. EStim protocols are often poorly reported, lacking detail of stimulation parameters, devices and methods of delivery. Therefore, one plausible explanation for differences in the findings of trials included in this section may be differences in the effectiveness of the wide range of protocols that have been tested. Equally it may be that some populations or subgroups of women benefit from EStim more than others. For example, anecdotal
evidence suggests that EStim is used with particular effect for women who are unable to perform a voluntary PFM contraction on initial assessment. However, this observation has not been investigated to date. Interestingly, there are also clinical questions about EStim that have not yet been investigated in trials, such as whether ‘active’ EStim (i.e. the patient voluntarily contracts the PFM during stimulation) is better than ‘passive’ EStim.

As the biological rational and purpose of EStim might be different depending on diagnosis, the EStim protocols from the trials included in this section are presented below for women with SUI (Table 1), women with urgency, UUI or DO (Table 2), and trials that recruited women with SUI or UUI or MUI (Table 3). There was a single trial in women with MUI only [215].

Amaro (2006) used a vaginal electrode to deliver an alternating current at 4Hz, with a bipolar square wave, 0.1msec pulse duration, a 1:2 duty cycle (2 seconds on and 4 off), at maximum tolerable intensity, for 30 minutes, three times a week for seven weeks.

It is clear there is no consistency in the EStim protocols used for women with SUI, or UUI, or MUI, or DO. It was not possible to identify an optimal set of EStim parameters. Some approaches to treatment are now rare, such as the use of faradic current or external electrodes. There seems to be a trend to use maximal tolerable current intensity, and in women with SUI some trials used a combination of EStim with a voluntary PFM contraction.

Rather than repeating the detail of stimulation parameters throughout this section, readers are referred back to these tables.

- **Comparison of EStim protocols**

Three studies compared one approach to EStim versus another, one in women with SUI [212], two in women with DO and sensory urge [218, 222].

### 1. Quality of data

Random allocation concealment was adequate in one [212] of the three trials. Blinding of assessors and patients was reported in one trial [222], but not in the

---

**Table 1. EStim protocols for trials that recruited women with SUI**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Variations</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>interferential</td>
<td>141, 180, 185, 205</td>
</tr>
<tr>
<td></td>
<td>faradic (i.e. low frequency interrupted direct)</td>
<td>[179, 216]</td>
</tr>
<tr>
<td></td>
<td>alternating</td>
<td>[136, 143-145, 174, 184, 195, 209, 210, 212, 217-223]</td>
</tr>
<tr>
<td>Pulse shape</td>
<td>Alternating bipolar square wave [217], alternating square [223]</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>single frequency, Hz</td>
<td>20 [195, 217]; 50 [145, 184, 219, 223];</td>
</tr>
<tr>
<td></td>
<td>two frequencies, Hz</td>
<td>10 and 35 [212, 220]; low and intermediate [210]; 12.5 and 50 [221];</td>
</tr>
<tr>
<td></td>
<td>frequency range, Hz</td>
<td>10 to 50 [209]; 0 to 100 [141, 205]; 10 to 40, and 1Hz and 40Hz [180]</td>
</tr>
<tr>
<td>Pulse duration</td>
<td>duration, msec</td>
<td>0.08 [220]; 100 [217]</td>
</tr>
<tr>
<td>Duty cycle</td>
<td>single, ratio</td>
<td>1:1 [136, 212, 220]; 1:2 [217, 219];</td>
</tr>
<tr>
<td></td>
<td>alternating, ratio</td>
<td>1:3 [222]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:1 and 1:2 [221]</td>
</tr>
<tr>
<td>Current intensity</td>
<td>maximum tolerable intensity</td>
<td>[136, 145, 180, 195, 205, 217, 221, 223],</td>
</tr>
<tr>
<td></td>
<td>noticeable muscle contraction</td>
<td>[209]</td>
</tr>
<tr>
<td></td>
<td>EStim + voluntary PFM contraction</td>
<td>212] (only in maximal stimulation group), [136, 143]</td>
</tr>
<tr>
<td>Electrodes</td>
<td>single vaginal electrode</td>
<td>[136, 184, 195, 212, 216, 217, 219, 221, 222]</td>
</tr>
<tr>
<td></td>
<td>vaginal &amp; buttock electrodes</td>
<td>[144]</td>
</tr>
<tr>
<td></td>
<td>external electrodes only</td>
<td>[174, 180, 220]</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>daily at home</td>
<td>4 weeks [223]; six weeks [220]; eight weeks [210]; 6 months [145, 184, 212]</td>
</tr>
<tr>
<td></td>
<td>every other day at home</td>
<td>8 weeks [136]</td>
</tr>
<tr>
<td></td>
<td>twice-daily at home</td>
<td>8 weeks [217]; 12 weeks [219, 221]</td>
</tr>
<tr>
<td></td>
<td>clinic-based treatments, number of sessions</td>
<td>10 [141, 180]; 12 [205]; 16 [212]; 18 [209]</td>
</tr>
</tbody>
</table>
### Table 2. EStim protocols from trials that recruited women with urgency or UUI or DO

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Variations</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>alternating (not further specified)</td>
<td>[146, 218, 222, 224-227]</td>
</tr>
<tr>
<td></td>
<td>alternating</td>
<td>Biphasic [228]; bipolar [217]; biphasis pulsed [187]</td>
</tr>
<tr>
<td>Pulse shape</td>
<td>rectangular</td>
<td>[228]</td>
</tr>
<tr>
<td></td>
<td>square</td>
<td>[217, 224, 225]</td>
</tr>
<tr>
<td></td>
<td>asymmetric</td>
<td>[187]</td>
</tr>
<tr>
<td>Frequency</td>
<td>single frequency, Hz</td>
<td>10 [222, 224, 225]; 20 [217, 226]; 150 [222]</td>
</tr>
<tr>
<td></td>
<td>two frequencies, Hz</td>
<td>12.5 and 50 [187]</td>
</tr>
<tr>
<td></td>
<td>frequency stochastic range, Hz</td>
<td>4 to 10 [228]</td>
</tr>
<tr>
<td>Pulse duration</td>
<td>pulse duration, msec</td>
<td>0.001 [217]; 0.2 [222, 226, 228]; 0.3 [187]; 1.0 [224, 225]</td>
</tr>
<tr>
<td>Duty cycle</td>
<td>single, ratio</td>
<td>1:2 [187, 217]</td>
</tr>
<tr>
<td>Current intensity</td>
<td>progressive, mA</td>
<td>5 to 25 [187]</td>
</tr>
<tr>
<td></td>
<td>maximum tolerable intensity</td>
<td>[217, 222, 224, 225, 228]</td>
</tr>
<tr>
<td></td>
<td>to pain threshold</td>
<td>[227]</td>
</tr>
<tr>
<td></td>
<td>tickling sensation</td>
<td>[226]</td>
</tr>
<tr>
<td>Electrodes</td>
<td>single vaginal electrode</td>
<td>[187, 217, 224, 225, 228]</td>
</tr>
<tr>
<td></td>
<td>vaginal &amp; anal electrodes</td>
<td>[218, 227]</td>
</tr>
<tr>
<td></td>
<td>transcutaneous self-adhesive electrodes</td>
<td>[226]</td>
</tr>
<tr>
<td></td>
<td>external electrodes</td>
<td>[222]</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>daily at home</td>
<td>6 hours a day for 6 weeks [226]; 4 months [187]</td>
</tr>
<tr>
<td></td>
<td>twice daily at home</td>
<td>4 weeks [224]; 8 weeks [217]; 9 weeks [146, 228]; 12 weeks [227]</td>
</tr>
<tr>
<td></td>
<td>single episode</td>
<td>[222]</td>
</tr>
</tbody>
</table>

### Table 3. EStim protocols from trials that recruited women with SUI or UUI or MUI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variations</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>alternating biphasic</td>
<td>[186, 229]</td>
</tr>
<tr>
<td>Pulse shape</td>
<td>asymmetric</td>
<td>[229]</td>
</tr>
<tr>
<td>Frequency, Hz</td>
<td>predominant SUI</td>
<td>50 [186, 229]</td>
</tr>
<tr>
<td></td>
<td>predominant UUI</td>
<td>20 [229]</td>
</tr>
<tr>
<td>Pulse duration</td>
<td>pulse duration, msec</td>
<td>0.3 [229]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 [186]</td>
</tr>
<tr>
<td>Duty cycle</td>
<td>ratio</td>
<td>1:2 [186]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:1 [229]</td>
</tr>
<tr>
<td>Current intensity</td>
<td>maximum tolerable intensity</td>
<td>[186, 229]</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>single vaginal electrode</td>
<td>[186, 229]</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>3 times a week for 8 weeks</td>
<td>[186]</td>
</tr>
<tr>
<td></td>
<td>20 minutes twice daily at</td>
<td>[186]</td>
</tr>
<tr>
<td></td>
<td>home for 12 weeks [229]</td>
<td></td>
</tr>
</tbody>
</table>
other two. Fewer than 25 women were allocated to each comparison group in all three trials; in Bower (1997) sample size was based on a power calculation. Bower (1997) had no dropouts or losses to follow up, with 12% [218] and 19% [212] lost to post-treatment follow-up in the other two studies. Two trials had longer term follow up, one [218] to six months [212] after treatment ended; in the latter 28% had dropped out by six months.

2. RESULTS
   
i) Women with SUI: In a small trial comparing maximal clinic based (n=20) versus low intensity home based (n=19) EStim in women with SUI, Knight (1998) found a significant difference in patient perceived recovery (OR 4.44, 95% CI 1.08 to 18.36) and pad test (WMD -12.40, 95% CI -16.64 to -8.16). After treatment more women in the low intensity home based EStim group reported cure or great improvement (80% home versus 47.3% clinic for cure, p=0.034; 85% versus 44.8% for improvement, p=0.009), although intention to treat analysis reduced the apparent success of treatment (66.7% versus 36%).

   Long term follow up (12 months) suggested that women in both groups continued to improve subjectively, and this was most noticeable in the group of women who had received low intensity stimulation.

   ii) Women with DO or urgency: Bower (1997) compared 10 Hz (sacral electrodes) versus 150 Hz (symphysis pubis electrodes) in women with DO (n=49) or sensory urgency (n=31). The same proportion (44%) of women in each stimulation group demonstrated a ‘stable’ bladder post stimulation and only the 150 Hz group showed a statistically significant improvement in the threshold volume (p=0.037).

   Lobel (1998) did not find any statistically significant differences in leakage episodes and quality of life between the groups. Although more than half the women in the study were improved symptomatically, only 25% were sufficiently satisfied with outcome that they did not wish for further treatment.

   SUMMARY

There were three small trials comparing different EStim protocols; the clinical heterogeneity meant it was not appropriate to pool the data from the studies. Based on a single trial low intensity home based stimulation may be more effective than maximal clinical based stimulation (Level of Evidence: 2). The other two studies did not find clinically important differences between stimulation groups; the studies were small and may have been underpowered. Further comparisons of EStim protocols are needed.

RECOMMENDATIONS

For women with SUI low intensity home based EStim daily for six months might be better than 16 sessions of maximal clinic based EStim (Grade of Recommendation: C). There is a need for studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups, so these can then be tested and compared in clinical trials.

b) Is EStim better than no treatment, sham or control treatments for treatment of UI?

• EStim versus no treatment, or control treatment

Three trials were included [141, 145, 228]. Data were also gathered from two conference abstracts [214, 230] of the full publication by Berghmans (2002).

1. QUALITY OF DATA

Random allocation concealment was adequate, and outcome assessment was blind, in two of the trials [145, 228]. Henalla (1989) stated that outcome assessors were not blind. In two studies the size of the study population was based on a power calculation [145, 228]. Group sizes were less than 25 women per group in Berghmans (2002), and from 25 to 49 in the other two studies [141, 145]. The proportion of dropouts was less than 10% in one trial [141], and about 12% in the other two [145, 228]. Henalla (1989) followed women up beyond the post treatment evaluation for six months.

2. RESULTS

i) Women with SUI: Henalla (1989) compared interferential stimulation with no treatment. In addition to the EStim and no treatment arms there were two other arms in the study. Eight of the 25 women receiving EStim were had a negative pad test or more than 50% reduction in pad test at three months, versus none of the 25 controls. Be (1999) compared 50Hz daily EStim for six months versus the offer of the Continence Guard (Coloplast AS); the Continence Guard was used by 14 out of 30 women. There was no statistically significant difference between the groups for women reporting symptoms were “unproblematic” after treatment; 28/30 controls and 19/25 in the EStim group wanted further treatment. Two of 30 controls were cured (< 2g leakage) on pad test with standardised bladder volume compared to 7/25 in the EStim group, and the EStim group had less pad weight gain than controls (MD -6.60g, 95% CI -8.60 to -4.60). Leakage Index score was better in the EStim group (MD -1.60, 95% CI -1.79 to -1.41), but did not retain significance with intention to treat analysis. In Henalla (1989) no side effects were reported, but Be (1999) reported that two out of 25 women in the EStim group had smarting and/or discomfort.


**ii) Women with DO:** In a four arm RCT in 68 women with DO, Berghmans (2002) investigated the effect of no treatment (n=14) versus nine weeks of 4 to 10Hz twice daily EStim at home (n=17). There was more improvement in Detrusor Overactivity Index score (DAI, lower score better) in the EStim group compared to controls (p=0.032), and less self reported symptom impact on the Dutch Incontinence Impact Questionnaire (DI-QOL). There were no reports of side effects or adverse events.

**SUMMARY**

Single trials suggest that EStim might be better than no treatment in women with SUI, and women with DO (Level of Evidence: 2). These findings need to be confirmed in further trials.

**RECOMMENDATIONS**

For women with DO nine weeks of 4 to 10Hz twice daily EStim at home, and for women with SUI six months of 50Hz daily EStim at home, might be better than no treatment (Grade of Recommendation: C). However, these are single small studies, and the recommendation should be viewed with caution until the findings are supported or refuted in further trials; it would be particularly useful if further trials used a validated and reliable quality life measure as a primary outcome.

- **EStim versus sham EStim**

  Fourteen trials were included. The sham stimulation comprised a device that:
  - delivered a limited output that the trialists considered would have no treatment effect [187, 210, 220, 221].
  - appeared to be working but there was no electrical output [180, 209, 217, 219, 222, 224, 227-229].

  In the remaining trial placebo stimulation was not described at all [231].

  Eight of the 14 trials specifically reported that some attempt was made to remove the participants’ expectations of the physical sensations that might accompany stimulation in an effort to mask participants to their allocation to active or sham stimulation [180, 217, 219, 221, 222, 224, 228, 229]. In one trial the stimulation was delivered under general anaesthesia [209].

**1. QUALITY OF DATA**

Random allocation concealment was adequate in seven of the 14 trials [209, 210, 217, 219, 221, 228, 229]. Blinding of assessors was clearly stated in eight trials [209, 219-224, 231]. One trial stated that outcome assessors were not blinded [180].

In six studies the size of the study population was based on a power calculation [210, 215, 219, 221, 222, 229]. Two trials randomised more than 50 women to each comparison group [209, 217]. In three trials the group sizes ranged from 25 to 49 [219, 221, 224], and the remaining nine trials allocated less than 25 women to each comparison group.

Three trials had no dropouts or losses to follow up [180, 187, 222]. The proportion of dropouts was less than 10% in two trials [220, 223] and in the remainder it varied from 11% [210] to 12% [209, 224] to 21% [226, 227].

Eight trials followed women up beyond the post treatment evaluation [180, 187, 209, 215, 220, 223, 224, 229]. The length of follow-up varied from six weeks [209] to six months [187, 220, 229]. Yamanishi [223, 224] only followed up those participants who had improved with treatment, monthly for several months.

Readers should note that the trial by Yamanishi (1997) included men and women with UI. It is possible that the effects of stimulation might be different between sexes (due to difference in electrode placement for example) so this study has not contributed to the analysis where the trialists did not differentiate the effects of treatment in women versus men.

**2. RESULTS**

- **i) Women with SUI:** Eight trials compared EStim with sham stimulation in women with urodynamic SUI [143, 180, 210, 219-221], or men and women with urodynamic SUI [223], or reported a subgroup analysis of women with SUI [217]. Blowman (1991) compared EStim plus PFMT versus sham EStim plus PFMT and for the purposes of analysis this trial was considered to be a comparison of EStim with placebo EStim, as there is currently no evidence that PFMT enhances the effect of EStim. Two trials contributed no data to the analysis. Hofbauer (1990) provided minimal detail of participants, methods and stimulation parameters, and it was not clear how ‘cure’ was defined (self report or urinary diary). Yamanishi (1997) did not report any subgroup data for women.

  Two trials were reasonably similar with regard to EStim. Both Sand (1995) and Luber (1997) used twice daily alternating current at home for 12 weeks at 50Hz [219] or 12.5 and 50Hz [219]. Sand (1995) found that the EStim group had significantly greater changes in patient perceived recovery (OR 2.76, 95% CI 0.66 to 11.44), but Luber (1997) did not find any statistically significant difference between EStim and sham (OR 0.81, 95% CI 0.21 to 3.10). The same two trials also had contradictory findings for leakage episodes; Sand (1995) reported a statistically significant difference in the number of leakage episodes in 24 hours (MD 0.90, 95% CI 0.83 to 0.97) whereas Luber (1997) did not (MD 0.10, 95% CI -0.87 to 1.07). A third study, that also used twice daily home stimulation but at 20 Hz (rather than 50) and for eight weeks (rather than 12),
had similar findings to that of Sand (1995) with a significant difference in patient perceived recovery (OR 2.63, 95% CI 1.11 to 6.20) and fewer leakage episodes (MD 2.80, 95% CI 1.06 to 4.54) in favour of EStim; this was a subgroup analysis of 60 women with SUI in a larger trial [217]. Finally, Luber (1997) did not find any statistically significant difference between active and sham groups for health status (SF-36).

Two trials used daily home alternating current for six weeks [210], at 10 and 35Hz [220] or a “low” frequency (to target the slow twitch fibres) and “intermediate” frequency (to target the fast twitch fibres). Neither study found a statistically significant difference in leakage episodes between active and sham groups, nor did Jeyaseelan (2000) find statistically significant difference in pad test findings or UDI scores.

Laycock (1993) used clinic based, short-term (10 treatments) maximal stimulation with an interferential current, and did not find a significant difference in leakage episodes between the groups post treatment.

With regard to side effects, three studies collected this data but no adverse events or side effects were reported [219-221].

### ii) Women with DO or UUI:
The three trials were sufficiently heterogeneous with respect to EStim and sample populations their results are described separately. A fourth study reported a subgroup analysis of women with DO from a larger trial [217].

Abel (1996) randomised 28 postmenopausal UUI women to maximal anal or vaginal alternating current for 20 minutes once a week for 12 weeks, or sham. In both groups there was a significant improvement in subjective parameters (VAS) but not in objective measurements (24 hour pad test and incontinence episodes per day).

Bower (1997) in a three arm study used a single stimulation episode of alternating current (either 10 Hz, sacral electrodes or 150 Hz, symphysis pubis electrodes) given after the voiding phase of cystometry and before repeat bladder filling.

The results were reported separately for women with DO and those with urgency. In DO both stimulation groups showed statistically significant improvements in urodynamic measures when compared with sham although the clinical relevance of this in terms of benefit felt by patients remains unclear. In women with urgency between group comparisons were not reported.

Yamanishi (2000a) investigated maximum intensity alternating current delivered daily for four weeks in men and women with DO. For the one outcome reported separately for women, more women in the EStim group reported cure/improvement than women in the sham group (p=0.0091).

In a subgroup analysis of 61 women with DO (DO alone, or DO with urodynamic SUI), Brubaker (1997) found that after bipolar alternating current 16 of 33 women with pre-treatment DO had post treatment DO. In contrast 24 of 28 women in the sham group had persistent DO, although there were no statistically significant differences between the EStim and sham groups with respect to post treatment urodynamic diagnosis of DO (p=0.22).

### iii) Women with SUI or UUI or MUI:
Amaro (2006) compared intravaginal EStim with sham in 40 women. Leakage was evaluated using a 60 minute pad test, and was statistically significantly reduced in both groups (mean 6.9g SD 3.5 and mean 1.1g SD 0.5 before and after EStim respectively; mean 3.1g SD 3.6 and mean 1.1g SD 0.5 before and after sham respectively).

Although the authors stated that there was no significant difference between groups, our re-analysis revealed a small difference, favouring EStim (MD 3.89, 95% CI 2.58 to 5.20). There were fewer micturitions in 24 hours in the EStim group than sham group post treatment (MD 3.00, 95% CI 1.74 to 4.26). Eighty percent of the EStim group and 65% of the sham group were satisfied with their final result.

### iv) Women with SUI or UUI or MUI:
EStim and sham stimulation were compared in two trials that included women with symptoms of SUI (n=42), UUI (n=26) or MUI (n=39) [209] or urodynamic diagnoses of SUI (n=60), UUI or DO (n=28) or MUI (n=33) [217].

Shepherd (1984) suggested a slightly higher likelihood of patient perceived cure in the EStim group than in the sham group (MD 1.38, 95% CI 0.59 to 3.20), although neither trial found any significant differences between the stimulation and sham groups for a range of outcomes including frequency, number of leakage episodes, quality of life.

### SUMMARY

Due to the clinical heterogeneity of the studies, in terms of EStim protocols and diagnoses, it is difficult to interpret the findings of trials comparing EStim with sham. For women with urodynamic SUI the findings of two trials using similar stimulation protocols were contradictory (Level of Evidence: 2). There was insufficient evidence (small trials, different EStim protocols) to determine if EStim was more effective than sham in other groups of women.

### c) Is EStim better than other treatments for UI?

EStim has been compared with magnetic stimulation (MStim), PFMT, VC, and drugs. The comparisons of EStim versus PFMT, and EStim versus VC, have been addressed previously (see B.2.3d and B.3.2b respectively). Two of the trials comparing EStim with another treatment included men and women [225,
226], and these studies have not contributed to the analysis where they did not differentiate the effects of treatment in women versus men.

• ESTim versus MStim

In the single, small trial intravaginal ESTim was compared with MSTim; stimulation was applied continuously at 10 Hz in both groups [225]. Neither of the interventions was well described.

1. QUALITY OF DATA

Random allocation concealment was adequate. It was not clear if outcome assessors were blind or if there were any dropouts or losses to follow up.

2. RESULTS

Bladder capacity at first desire to void and maximum cystometric capacity increased significantly in both groups, and maximum cystometric capacity was statistically significantly greater in the MSTim group (114.2ml SD 124.1 versus 32.3ml SD 56.6).

SUMMARY

With only one single small trial comparing ESTim with magnetic stimulation there is insufficient evidence to determine if ESTim is better than magnetic stimulation in women with DO.

• ESTim versus medication

Henalla (1989), in a four arm trial, compared ESTim (interferential) versus vaginal oestrogen (Premarin) in 104 women with urodynamic SUI [141]. Smith (1996) compared ESTim with propantheline bromide in 38 women with OAB [187].

Soomro (2001) compared transcutaneous electrical nerve stimulation (TENS) with oxybutynin in both men and women with DO in a crossover design [226]. Results were not separately presented by gender, which meant it was not possible to draw any conclusions from this study about the effect of TENS in women with DO.

1. QUALITY OF DATA

Outcome assessment was not blind in either trial, and random allocation concealment was unclear in one study [141] and inadequate in the other [187]. There were few dropouts in either study, and Henalla (1989) followed women up at nine months.

2. RESULTS

i) Women with SUI: Eight of 25 women in the ESTim group reported they were cured or improved versus 3/24 in the oestrogen group [141]. Nine month follow-up found that one of the eight women in the ESTim group who had reported cure/improvement post treatment had recurrent symptoms, as did all three women in the oestrogen group once oestrogen therapy ceased. Differences in leakage on pad test, and maximum urethral closure pressure did not reach statistical significance. There was no report of side effects or adverse events.

ii) Women with DO: There was a statistically significant difference in patient perceived recovery in favour of the ESTim group (OR 0.38, 95% CI 0.10 to 1.49), but no difference in leakage episodes [187].

SUMMARY

With only single trials, with small numbers per comparison group, there is insufficient evidence to determine if ESTim is better than vaginal oestrogens in women with SUI, or propantheline bromide in women with DO.

d) Does the addition of ESTim to other treatments add benefit for the treatment of UI?

• ESTim with BF assisted PFMT versus BF assisted PFMT alone

One study was found, investigating ESTim with BF assisted PFMT versus BF assisted PFMT alone in women with SUI, or MUI [136].

1. QUALITY OF DATA

Random allocation concealment was adequate; blinding of assessors was not reported. Goode (2003) reported a power calculation and randomised more that 50 patients to each group. The dropout rate was 22.5%.

2. RESULTS

Intention-to-treat analysis showed similar perception of improvement between the comparison groups (OR 0.98, 95% CI 0.06 to 16.08), and there was no difference between the groups for leakage episodes. The authors reported no adverse events, but there were side effects in four women; problems were vaginal irritation, slippage of the ESTim probe resulting in a pinching sensation, and reaction to the conduction gel which resolved after changing brands.

SUMMARY

A single trial found that the addition of ESTim to a BF assisted PFMT was no more effective than BF assisted PFMT in women with SUI, or MUI (in which stress leakage was the predominant symptom) (Level of Evidence: 2). A few women experienced side effects with ESTim.

RECOMMENDATIONS

The addition of ESTim to a BF assisted PFMT programme does not appear to add benefit (Grade of Recommendation: C); this hypothesis needs to be investigated further with high quality trials if it is a clinical/research question of interest to women.
• EStim with PFMT versus PFMT alone

Four trials compared EStim combined with PFMT versus PFMT alone in women with SUI [143, 179, 212, 216]. Tapp (1987, 1989) used faradic stimulation in combination with PFMT in two small trials reported in conference abstracts, and another small trial gave minimal detail of participants, methods and stimulation parameters [143]. Knight (1998) combined clinic based maximal intensity alternating current with PFMT. In a four arm RCT with 68 women with proven DO Berghmans (2002) investigated the effect of PFMT alone, alternating biphasic EStim alone, and EStim in combination with PFMT in comparison with no treatment [212, 228].

1. Quality of Data

Of the five trials random allocation concealment was adequate in two [212, 228], a blind outcome assessment clearly stated in just one [228]. The trials were generally small, with only Berghmans (2002) reporting a power calculation. Group size was less than 25 in four [143, 212, 216, 228] of the trials, and between 25 to 49 in the fifth [179]. Two trials had no dropouts or losses to follow up [143, 216], and two followed women up six months post treatment [143, 212].

2. Results

i) Women with SUI: Three of the four trials were small and poorly reported; none of them reported statistically significant differences between the groups receiving combined ES/PFMT and PFMT alone [143, 179, 216]. The fourth trial was also small although better reported [212]. In this study 10 of 21 women in the PFMT group and 16/24 in combination therapy group reported cure or great improvement; a difference in favour of combination therapy (OR 0.23, 95% CI 0.05 to 0.93), but there were no statistically significant differences in improvement in pad test or vaginal squeeze pressure. Neither Hofbauer (1990) nor Knight (1998) recorded any adverse events from stimulation.

ii) Women with DO: No data were provided on the comparison of combined PFMT/EStim versus PFMT. No women had any side effects or adverse events.

Summary

For comparisons of EStim with PFMT versus PFMT alone the reporting was very poor in three of the four trials in women with SUI, and only a single trial that did not report any data for the comparison of interest was found for women with DO. There is insufficient evidence to draw any conclusion about the effect of adding EStim to PFMT.

3. OTHER LUTS

No studies were identified that analysed the effect of EStim on lower urinary tract symptoms alone, i.e., frequency of voiding, urgency and/or nocturia.

4. FACTORS AFFECTING OUTCOME

a) Age

This section considers the effect of EStim in older age, from studies recruiting independent, community dwelling elderly; the frail elderly are considered in the chapter on the elderly.

Only one of the trials in this section on EStim specifically recruited older women [186]. Spruijt (2003) compared the effectiveness of eight weeks of vaginal EStim in women aged more than 65 years with symptoms of SUI, UUI or MUI with a daily pelvic floor muscle training (PFMT). This comparison of EStim and PFMT was considered in the section on PFMT (see B.2.3d). No statistically significant differences between the groups were found for leakage or self reported improvement, but this study was small (n=37) and a post hoc power analysis suggested that the study was underpowered. In view of the likelihood of type II error, the finding of no difference should be treated with caution. In the study report, Spruijt (2003) observed that EStim does not appear to have any serious side-effects in the elderly (apart from interfering with pacemaker activity), but can give an unpleasant vaginal, anal and perineal sensation which can easily lead to a lesser degree of cooperativeness, informed consent and motivation, especially in the elderly. Nevertheless, in general, EStim seems to be a well tolerated and acceptable treatment modality in the older person [186].

One other study included in this section completed a secondary analysis on the basis of age. In a double-blind RCT, Yamanishi (1997) studied EStim compared to a sham device in 68 patients with UUI [223]. EStim was delivered by surface, anal, or vaginal electrodes 15 minutes twice daily for four weeks, using 10Hz and a maximum output current of 60mA. Mean age was 70 years (SD 11) and the secondary analysis considered the effect of treatment in ‘older’ and ‘younger’ patients. There was no difference in treatment outcomes based on age (older or younger than 60 years).

In a moderate sized prospective study of 3198 women treated with home-managed EStim in Norway during 1992-1994, there was no association between self-reported improvement and age, although the physicians thought success rates were higher in younger patients [232].
SUMMARY

On the limited evidence available it seems older women may respond to EStim as well as younger women. On this basis there is no reason to exclude older women from studies of EStim, or not to offer EStim as part of a conservative management programme, except where recognised contraindications such as a cardiac pacemaker are present. More trials need to consider investigating the association between age and treatment outcome.

b) Other

Aside from age, other factors have the potential to mediate treatment outcome, e.g. diagnosis and underlying cause of UI. A range of other factors are considered below.

1. Diagnosis and underlying cause of UI

It is not clear whether one diagnostic group may benefit more than another from EStim. It has been hypothesised that, in women with SUI who cannot voluntarily contract the PFM to begin a PFMT programme, EStim might help initiate or substitute for a voluntary contraction. However, most studies focusing on the efficacy of EStim do use EStim to initiate or substitute for a voluntary PFM contraction [233]. To date, there has been no trial addressing this hypothesis.

2. Patient selection

EStim is reported to be unsuccessful in patients with major descent of the vagina and prolapse of the uterus [219]. Also denervated PFM muscles might not respond to EStim [234]. This means that in patients with no or reduced integrity of the relevant nerve pathways EStim provides no or little chance of cure/improvement [207]. It has also been reported that EStim will fail if EStim does not increase urethral pressure profile [235], although age, oestrogenisation, and urethral mobility are also affect urethral pressure profile and may influence therapeutic outcome [235]. It is unfortunate that it is difficult to assess patients easily in the clinical setting with regard to integrity of the sacral arc, and other factors, to determine the suitability of EStim as a treatment modality.

3. Treatment adherence

As with all conservative therapy modalities one of the key factors to success or failure of EStim is treatment adherence. Three trials made some comment about adherence or reported adherence data. Barosso (2004) stated that adherence to EStim was satisfactory, and attributed this to the ability of the doctor to motivate patients to continue with EStim if the considered stopping prematurely. Bø (1999) found that adherence to EStim (75%) was less than that for PFMT (93%), and the reasons for non-adherence to EStim were a lack of motivation (four women) and smarting or discomfort (two women). Sand (1991) reported that 80% adherence was achieved by 61% of the active EStim group and 89% of the sham group.

One of the main factors that may influence adherence is side effects of the treatment. Some of the studies included in this section noted some women had side effects attributable to EStim, others stated no side effects were reported by women, and some trials did not mention side effects at all. None of the side effects reported were serious, and all could be resolved with cessation of treatment or some other treatment adaptation (such as change of conduction gel). In a prospective study of about 1300 women in Norway, Indrekvam (2001) found that the most common side effects of EStim included pain (20%), soreness/local irritation (26%), and psychological distress (7%) were the most common side effects but none of the side effects reported was serious [232]. It seemed users of maximal stimulation experienced more pain than users of long-term stimulators (25% versus 15%).

SUMMARY

It is possible that diagnosis, other factors such as neural pathway integrity, and treatment adherence, will affect treatment outcome. None of these have been adequately investigated to date.

V. MAGNETIC STIMULATION (MSTIM)

MStim has been developed for stimulating both central and peripheral nervous systems noninvasively [236]. MStim for the treatment of UI was reported for the first time in 1999 by Galloway (1999) [237]. In contrast to EStim, extracorporeal magnetic innervation (more commonly called magnetic stimulation) stimulates the PFM and sacral nerve roots without insertion of an anal or vaginal probe [238, 239]. For treatment, the patient is positioned in a chair. Within the seat is a magnetic field generator (therapy head) that is powered and controlled by an external power unit (Figure 6). A concentrated steep gradient magnetic field is directed vertically through the seat of the chair. When seated, the patient’s perineum is centred in the middle of the seat, which places the PFM and sphincters directly on the primary axis of the pulsing magnetic field (Figure 7). Because of this all tissues of the perineum can be penetrated by the magnetic field. Galloway (1999) says that no electricity, but only magnetic flux enters the patient’s body from the device. Goldberg (2000) has suggested that, in contrast to electrical current, the conduction of magnetic energy is unaffected by tissue impedance, creating a theoretical advantage in its clinical application compared to EStim as structures such as sacral roots or pudendal nerves can be magnetically stimulated without patient discomfort or
Conventional magnetic stimulators deliver, at frequencies of 10 to 50 Hz, repetitive pulses of current lasting less than 100 µsec [238] and 275 µs [237] in duration. Size and strength of the magnetic field is determined by adjustments of this amplitude by the therapist [237].

Possible advantages of MStim are that it is performed through full clothing, needs no probes, skin preparation, or physical or electrical contact with the skin surface. On the other hand, the need for repeated clinic based treatment sessions is a potential disadvantage. In contrast to EStim, MStim lacks portability, although in 2003 But reported the development of a small electromagnetic device (Pulsegen) for home use [240]. Further, because both the depth and width of magnetic field penetration is proportional to coil diameter, the present technology is still best suited for stimulation of a field, rather than a narrowly focused target as the sacral roots or the pudendal nerve [238].

MStim of the sacral nerve roots and pelvic floor is said to be effective for both UUI and SUI [238], although the mechanism of action is not fully understood [241]. Some authors have suggested that in SUI stimulation of the PFM causes external sphincter contraction [242], acts as a passive Kegel exercise [243], and increases maximal urethral closure pressure [240]. In UUI, MStim might suppress DO through activation of pudendal nerve afferents blocking parasympathetic detrusor motor fibres at the spinal reflex arc, activation of inhibitory hypogastric sympathetic neurons, or a combination of both mechanisms [244]. Stimulation of sympathetic fibres maintaining smooth muscle tone within the intrinsic urethral sphincter and modulation of pudendal nerve afferent branches stimulating an inhibitory spinal reflex at the S3 nerve root, are also suggested to play a role in this mechanism of action [244].

This section will examine the evidence for the use of MStim for the prevention and treatment of UI in women. Questions addressed are:

- Can MStim prevent UI?
- Is MStim better than no treatment, placebo or control treatments for UI?
- Is one type of MStim better than another?
- Is MStim better than other treatments?
- What factors might affect the outcome of magnetic stimulation?

A literature search for reports of relevant systematic reviews and reports of RCTs and quasi-RCTs, e.g. alternate assignment (see appendix) was performed. No other types of study design were considered.

1. PREVENTION

No trials investigating the primary or secondary prevention effects of MStim for women with UI were found.

2. TREATMENT

The literature search revealed three reviews, two in English and one in the German language, that addressed the indications for and the use of MStim and provided an historical overview of the therapeutic application possibilities of this treatment modality for UI [202, 241, 245].

These reviews were used to provide some background information regarding MStim, but did not otherwise contribute to the review.

Seven trials were found [225, 240, 246-250]. One report was an abstract; the trial has not yet been fully published [249]. Since the 3rd ICI two new trials have been published [246, 247].
a) Is MStim better than no treatment, placebo, or control treatment?

Six RCTs comparing MStim with sham for women with UI were found [240, 246-250].

But (2003) compared MStim from a home device (Pulsegen) with sham (identical but inactive device) in women with SUI, UUI and MUI [240], and subsequently in a sample with MUI [246]. In active and sham groups in both trials women were asked to wear the Pulsegen device day and night for two months; in the active group the device produced a pulsating magnetic field of B=10 μT intensity and a pulse frequency of 10Hz [240] or 18.5Hz [246].

Fujishiro (2000) compared a single session of MStim with sham in women with SUI [248], and subsequently women with urinary frequency and UUI [248]. In both trials the active group received 15Hz repetitive MStim of the sacral roots with 50% intensity output for five seconds per minute for 30 minutes. MStim was performed with the patient prone using a rapid rate stimulator with a Rapid circular coil. The coil was fixed over the sacrum to cover the bilateral third sacral foramina. The sham group received exactly the same treatment except the sham stimulating coil did not induce any electromagnetic field.

Gilling (2001) recruited SUI women, and compared MStim of the pelvic floor to sham, using a chair with an inbuilt magnetic coil (Neocontrol device) for 20 minutes [249]. A total of 16 treatments (three per week) were performed over six weeks. Both groups were also asked to do home PFMT.

Morris (2007) compared active MStim (Neocontrol device) with sham (an identical looking/sounding device containing a deflector plate to degrade the magnetic field). Treatment comprised 20 treatment sessions over six weeks, with at least 36 to 72 hours between sessions. Each session comprised two 10 minute periods of stimulation, at individual maximum tolerance, separated by two minutes rest. Frequency was 10Hz. The sham stimulation, with deflector in place, was run at a fixed intensity of 25% in order to provide the same noise as with the active device and to stay below the level required for patient perception.

1. Quality of data

Random allocation concealment was adequate in three of the trials [240]. Patients were blind in five of the trials [240, 248, 250], and blind outcome assessors were used by But (2003, 2005) and Morris (2007).

Only Morris (2007) based the size of the study population on an a priori power calculation, but due to a high dropout rate the analysis included only 29 of the 40 women needed. Fujishiro (2000) included 62 women (31 in each group) whilst Gilling (2001) randomised 70 women (35 in each group). In the studies by But, group sizes were 30 [240] and 23 [246] in the active and 22 [240] and 16 [246] in the sham group.

The proportion of dropouts was less than 10% in two trials [240], 34% in Morris (2007), and in the remainder this was not reported adequately. Two trials followed women up beyond the post treatment evaluation; Morris (2007) followed women up for six weeks, and Gilling (2001) reported six and 12 month follow up in their conference abstract but did not report these data in the full publication.

2. Results

i) Women with SUI: Fujishiro (2000) compared one session of sacral root MStim with sham in 62 women with SUI [248]. Active treatment was statistically significantly better than sham for leakage episodes (p=0.0023), leakage on pad test (p=0.037), and quality of life (p=0.0126). Based on these three measures 3% and 32% of the sham group were considered cured and improved respectively, versus 13% and 74% in the active MStim group, with more cured or improved in the active group (p=0.0009).

Gilling (2001) compared MStim with sham in 70 women with SUI and found no statistically significant difference between the active and sham groups at eight weeks for any outcome, nor between baseline and eight weeks in either group. A posthoc subgroup analysis suggested the women with poor PFM tone at baseline did better with active treatment than sham. The authors reported that follow-up was ongoing, but no data have been published.

ii) Women with UUI: Fujishiro (2002) compared a single session of sacral root MStim with sham in 48 women with urinary frequency and UUI. Active treatment was statistically significantly better than sham for voided volume/day (p=0.04), number of leakage episodes in three days (p=0.04), and quality of life score (p=0.01). No adverse effects were noted.

Morris (2007) found no between group differences for mean number of daytime voids, maximum interval, volume of leakage on pad test, number of leakage episodes, or quality of life. The only statistically significant difference was in the mean number of urge episodes per day (p=0.003); this difference favoured the MStim group.

iii) Women with MUI: But (2005) compared home-based MStim with sham in 39 women with MUI. Within group comparison suggested greater improvement in daytime frequency, nocturia, and pad use in favour of active MStim. Between group comparison showed statistically significant differences in favour of active MStim for time to first sensation of bladder filling (p=0.003), maximum cystometric capacity (p=0.0004), and self reported treatment success (p=0.021). There were no adverse effects in either group.
iv) Women with SUI, UUI, or MUI: But (2003) included 52 women of whom 21 had MUI, 22 UUI, and nine SUI, and compared MStim with sham. There were statistically significant differences in favour of MStim for pad use ($p=0.0017$), pad weight ($p=0.038$), power and duration of PFM contractions ($p=0.0071$ and $p=0.038$ respectively), self reported improvement in symptoms ($p=0.00012$).

**SUMMARY**

There was little duplication of MStim interventions, or sample populations, in the six small trials so it was not thought appropriate to combine study findings. For women with SUI one session of sacral root MStim might be better than sham (Level of Evidence: 2), but 16 sessions using a chair based MStim might not be better than sham (Level of Evidence: 2). Similarly in women with UUI, one session of sacral root MStim might be better than sham (Level of Evidence: 2), but chair based MStim might not be better than sham (Level of Evidence: 2). Home-based MStim might be better than sham in women with MUI (Level of Evidence: 2), and women with SUI, UUI or MUI (Level of Evidence: 2). No adverse events were reported.

**RECOMMENDATIONS**

Of the MStim protocols investigated to date, it seems that both sacral root MStim and home-based MStim, are worthy of further investigation in women with UI.

b) Is one approach to MStim better than another?

No studies were found addressing this question.

c) Is MStim better than other treatments?

A single trial was found that addressed this comparison; intravaginal EStim was compared with MStim in 17 women and 15 men with DO; stimulation was applied continuously at 10 Hz in both groups [225]. This trial was described and discussed in section B.4.2c. With only one small trial or poor methodological quality, in men and women with UI, it is not clear whether there is any difference in effect of MStim compared to EStim.

3. OTHER LUTS

No studies were found that reported the effects of MStim of other LUTS.

4. FACTORS AFFECTING OUTCOME

None of the included trials addressed the effect of age, or any other factor, on outcome of MStim. Sand (1999), in a prospective multi-centre study investigated factors predicting success of MStim [251]. Treatment success was associated with no prior hysterectomy, no prior anti-incontinence operations, UI symptoms for less than 10 years, and no use of medications known to cause UI. Brodak (1993) has suggested that detrusor response to stimulation might be better in 'thin' patients (presumably due to a shorter distance between the stimulating coil and the sacral nerve roots) and at low bladder volumes [252]. Overall, little is known about the factors affecting outcome of MStim.

VI. SCHEDULED VOIDING REGIMENS

This section examines the evidence on use of scheduled voiding regimens in cognitively intact, non-institutionalised women with UUI, SUI, and MUI and provides recommendations for their use in clinical practice. A summary of the search strategy and inclusion/exclusion criteria for selecting studies for review is provided (See appendix). See the chapter on the Frail Elderly for a detailed discussion of scheduled voiding regimens that are used in the management of UI in cognitively impaired, institutionalised, or homebound older adults, and the chapter on Neurogenic Incontinence for those voiding regimens appropriate for individuals with UI secondary to central nervous system or spinal cord disease.

- **Scheduled Voiding Regimens**

Bladder training is a term that has been broadly and sometimes inaccurately applied to any type of a scheduled toileting intervention. This has created conceptual confusion in interpreting research reports where few details are provided other than the statement that bladder training was used. The types of scheduled voiding regimens can be categorised as: bladder training, timed voiding, habit training, and prompted voiding [253]. Although these regimens share a common feature of a toileting schedule, they differ on the basis of adjustments to the voiding schedule; the active or passive involvement of the patient; the nature of patient education including the teaching of strategies to control urgency and prevent stress leakage, the use of reinforcement techniques, and the nature of the interactions between clinicians and patients. In practice, however, scheduled voiding regimens may share aspects of one or more of these features.

- **Bladder training**

Bladder training (also referred to as bladder drill, bladder discipline, bladder re-education, and bladder retraining) involves a programme of patient education along with a scheduled voiding regimen with gradually progressive voiding intervals. Specific goals of bladder training are to correct faulty habit patterns of frequent urination (if present), improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes, and restore
patient confidence in controlling bladder function. The underlying mechanism of how bladder training achieves its effect is poorly understood. Several hypotheses have been proposed including improved cortical inhibition over detrusor contractions; improved cortical facilitation over urethral closure during bladder filling; improved central modulation of afferent sensory impulses; altered behaviour resulting from better individual awareness of the lower urinary tract function and circumstances that cause UI, and increasing the “reserve capacity” of the lower urinary tract system [188, 254, 255].

• Timed voiding
Timed voiding is a fixed voiding schedule that remains unchanged over the course of treatment [253]. The goal of timed voiding is to prevent UI by providing regular opportunities for bladder emptying prior to exceeding bladder capacity. Timed voiding has been recommended for patients who cannot participate in independent toileting [256]. It has been primarily used in institutional settings as a passive toileting assistance programme where a caregiver takes the patient to void every two to four hours including at night, and for patients with neurogenic bladders associated with spinal cord injuries (see Neurogenic chapter) [257]. However, it has applicability for use in outpatient settings with incontinent women who have infrequent or irregular voiding patterns [258] (and men who are independent in their voiding function [259]).

• Habit training
Habit training is a toileting schedule that is matched to the patient’s voiding pattern. Using the patient’s voiding chart, a toileting schedule is assigned to fit a time interval that is shorter than the patient’s normal voiding pattern and precedes the time period when incontinent episodes are expected. Thus, the voiding interval may be lengthened or shortened throughout the day depending on the patient’s voiding pattern with the goal to pre-empt UI. Habit training is usually implemented by caregivers, but patients may also be encouraged to suppress the urge to void until the assigned time. Habit training has been used primarily in institutional settings with cognitively and/or physically impaired adults, but it has also been tested in homebound older adults [260]. It is potentially useful for adults without cognitive or physical impairment, who have a consistent pattern of UI [258].

A Cochrane review on habit training was published in 2004 [261]. Prior to this, the last literature review was published in 1986 [253]. The Cochrane review identified three trials that described the effects of habit training combined with other treatment components compared to usual care on the frequency and severity of UI [260, 262, 263]. Participants were primarily care-dependent women with cognitive and/or mobility impairment, and thus, did not meet the criteria for this chapter. No studies were located that investigated habit retraining in independent-living women.

• Prompted voiding
Prompted voiding refers to a caregiver education programme in combination with a scheduled voiding regimen, typically every two hours. It is used to teach people with or without cognitive impairment to initiate their own toileting through requests for help and positive reinforcement from caregivers when they do so [264]. Although it has been used primarily in institutionalized settings with cognitively and physically impaired older adults, prompted voiding has applicability for use with homebound older adults (see the chapter on the Frail Elderly for a full review).

This section will examine the evidence for the use of timed voiding and bladder training for the prevention and treatment of UI in non-institutionalised women of all ages without cognitive or mobility impairments. However, the majority of evidence available pertains to bladder training thus the effects of bladder training are the focus of this section.

Questions addressed are:
• Can scheduled voiding regimes prevent UI?
• What is the most appropriate bladder training protocol?
• Is bladder training better than no treatment, placebo or control treatments?
• Is bladder training better than other treatments?
• Can any other treatment be added to bladder training to add benefit?
• Does the addition of bladder training to other treatments add any benefit?
• What is the effect of bladder training on other LUTS?
• What factors might affect the outcome of bladder training?

This section is based on previously published systematic reviews, including Cochrane reviews, and additional searches of the literature. Studies that were excluded from prior systematic reviews, due to the inclusion criteria for the review or restriction to RCTs or quasi-RCTs, were also considered. Conference abstracts were considered where adequate information was available.

1. PREVENTION

No trials were identified that examined scheduled voiding regimens as a sole intervention in the prevention of UI.

2. TREATMENT

Four systematic reviews on bladder training were
located that provided descriptive synthesis with evidence grading [214, 256, 265, 266]. The Cochrane Collaboration published a review in 1998 that has been updated in 1999, 2004, and 2007 [265].

**a) What is the most appropriate bladder training (BT) protocol**

No trials were identified that compared two or more methods of bladder training (BT). In the absence of trials comparing two or more approaches, a content analysis of the protocols used in trials investigating the effects of BT was performed. Fifteen trials on BT involving a total of 1,774 women were identified. Six of the trials provided no or minimal details regarding the specific BT protocol used [151, 267-271]. In trials that did provide some description, BT protocols were implemented in several ways.

All protocols involved some type of patient education, namely:

- Brief verbal instruction [268, 269]
- Brief written instructions [272]
- Verbal, written, and audiovisual instruction [188, 255]
- Participants were introduced to an individual who successfully completed BT [270]
- If specified, the education was provided by nurses [151, 188, 255, 267, 273, 274], or general practitioners [275].

Scheduling of voids varied in the following ways:

- Assignment of the initial voiding interval varied from 30 minutes to two hours, with one hour being the most common interval based upon the participant’s voiding pattern or 30 minutes beyond the participant’s average voiding interval [276].
- Adjustments to the voiding interval varied from 15 to 30 minutes, with 30 minutes the most common interval. Increases were made daily for inpatient regimens [271], after 48 hours of dryness [277], every four to five days [276], or weekly if schedule was well-tolerated [188, 255].
- Goals for optimal voiding interval varied from three to four hours.
- Voiding was ‘mandatory’ with restriction of voiding in between assigned toileting times even if UI occurred [271], a scheduled voiding regimen that allowed interruptions in the schedule if urgency became unbearable [188, 255, 273], or self-scheduling of voiding with a target goal to reach [272].
- Voids were not scheduled (allowed) during sleeping hours [271]; none of the other protocols identified how voids were handled during sleeping hours.

In some protocols the scheduled voiding regimen was supplemented by specific strategies to control urgency and/or stress leakage, including distraction and relaxation [188, 255, 272, 273], and pelvic floor muscle contraction [188, 267]. In other studies there was encouragement to suppress urge but it was not clear what strategies were used [55, 269, 275]. Feedback techniques included self-monitoring [188, 255, 268, 270, 273], goal setting with feedback of progress [274], and positive reinforcement [188, 255, 276].

Several protocols included use of adjunctive treatments:

- Fluid and caffeine adjustments [55, 273]
- Fluids allowed up to a certain level (1,500 ml) [277]
- No fluid modifications [188, 255, 272, 275]
- Advice on constipation prevention [273]

Finally, both in and outpatient BT programmes have been used. Early inpatient BT programmes involved five to 13 days of hospitalisation to ensure strict protocol adherence [271]. Outpatient programmes are more commonly described and the amount of health professional contacted had ranged from weekly visits for six weeks with fortnightly telephone calls for six additional weeks [188], to weekly visits [151, 255], fortnightly visits [276], and monthly visits [277].

Overall, there is a lack of consistency in BT protocols. Based on the BT protocols described in the literature to date is seems that a reasonable outpatient BT protocol would include:

- an initial voiding interval typically beginning at one hour during waking hours, which is increased by 15 to 30 minutes per week depending on tolerance of the schedule (such as fewer incontinent episodes than the previous week, minimal interruptions to the schedule, and the woman’s feeling of control over urgency and confidence to expand the voiding interval), until a two to three hour voiding interval is achieved. A shorter initial voiding interval, e.g. 30 minutes or less, may be necessary for women whose baseline micturition patterns reveal an average daytime voiding interval of less than one hour.
- education about normal bladder control and methods to control urgency such as distraction and relaxation techniques and PFM contraction.
- self-monitoring of voiding behaviour using diaries or logs in order to determine adherence to the schedule, enhance self-awareness, evaluate progress, and determine whether the voiding interval should be changed (Figure 8).

a supervising clinician to monitor progress, suggest adjustments to the voiding interval, and provide positive reinforcement to women undergoing BT at least weekly during the training period.
If there is no improvement after three weeks of BT, re-evaluation is warranted and other treatment options would be considered. Inpatient BT programmes may follow a more rigid scheduling regimen with progression of the voiding interval on a daily basis.

**SUMMARY**

There is no trials evidence to suggest the most effective method or specific parameters of BT. For those undertaking BT it is likely that more health professional contact will be better than less, based on the developing evidence for PFMT, which like BT requires behavioural change. The literature suggests several variables that could be investigated in future trials including the instructional approach, supervisory intensity, strategies for controlling urgency, scheduling parameters, frequency of schedule adjustments, length of treatment, and use of adjunctive treatments.

**RECOMMENDATIONS**

It is not clear what the most effective BT parameters are. Clinicians and researchers are advised to refer to the operant conditioning and educational literature to provide a rationale for their choice of BT parameters or approach (Grade of Recommendation: D). Clinicians should provide the most intensive BT supervision that is possible within service constraints (Grade of Recommendation: D). More research is needed to investigate which BT parameters, supervisory intensity, and adjunctive treatments are most effective. Future trials should include outcomes that matter to patients including the length and frequency of supervisory contact.

**b) Is BT better than no treatment, placebo or control treatments?**

BT as the sole therapy has been used in the treatment of DO, urodynamic SUI, MUI, UUI, UUI with a stable bladder, and OAB syndrome (also called urgency-frequency syndrome). Individual RCTs that met inclusion criteria and the Cochrane review [265] were used to address the question of whether BT is better than no treatment, placebo, or control treatments for UI.

Five RCTs reporting on 515 women were identified that compared the effect of BT to no treatment or control [151, 255, 270, 273, 275]. In one trial, it was not possible to identify the effect of BT alone, because results of participants in the treatment group who received BT (those with UUI or MUI) were combined with those who also received PFMT (SUI participants) [275]. However, in the Cochrane review, additional data were provided by the lead author to describe the women with DO who were randomised to BT versus control. In another trial with three consecutive treatments (self-monitoring, BT, and PFMT; with the decision for which treatments were implemented being based on participants' goals), it was difficult to discern the effect of BT alone as compared to a control group, because some participants had already undergone lifestyle modifications (caffeine and fluid modifications and constipation advice) and diary keeping in a prior self-monitoring condition [273]. Thus, this trial is not discussed further in this section.

In the four trials with analysable data, Jarvis (1980) investigated the effect of an in-patient BT programme in 60 women aged 27 to 79 years with a diagnosis of DO or coexisting SUI, whereas three trials [151, 255, 275] examined the effect of an outpatient programme. Fantl (1991) studied the effect of a six week outpatient programme in 123 women aged 55 to 90 years with urodynamic SUI, DO, or both who reported at least one incontinent episode on a weekly voiding diary. Yoon (2003) examined the effect of an eight week outpatient programme in 50 women aged 35 to 55

---

Figure 8: Self-monitoring of voiding behaviour (Courtesy of Dr Jean Wyman, University of Minnesota, USA)
years with UI (type not identified) who had pad test weights at least 1g or more and 14 or more voids during a two day diary. Lagro-Jansen (1992) studied the effect of an outpatient programme in 18 women aged 20 to 65 years who reported UI twice or more per month and had uro-dynamically confirmed DO.

1. Quality of data

In one trial random allocation concealment was inadequate [275]; in the remainder it was not clear if concealed. One trial used stratification based on urodynamic diagnosis of urodynamic SUI and/or DO [255]. Blinding of outcome assessors was described in only one trial [151].

Sample sizes in the four analysable trials were 50 [151], 60 [270], 123 [255], and 18 [275]. Fantl (1991) reported a power calculation although details were not described. Losses to follow up were none in one trial, although it was not clear if this was due to having no dropouts or due to lack of reporting [270]. In the other two analysable RCTs, loss to follow up was 6% [255] and 14% [151]. Dropout rates at the immediate follow-up time point seemed similar between the BT and the control groups; they ranged from 8% versus. 5%, respectively [255] to 10% versus 14%, respectively [151]. No trials reported whether analyses were based on intent-to-treat principles. Follow-up periods ranged from six weeks [255] to eight [151] and 12 weeks [270, 275], with an additional evaluation six months [270] and nine months [255] after initiation of treatment. Two trials noted whether there were adverse events with BT [255, 270]. No trial reported on adherence.

All of these RCTs, with the exception of the one by Jarvis (1980), were considered in the Cochrane review [265]. The Cochrane reviewers based their conclusions on data available from 172 women in the other three trials.

2. Results

Three of the four RCTs reported statistically significant improvements in the BT group as compared to an untreated control group with respect to incontinent episodes [255, 270, 275]; the fourth did not report data on incontinent episodes [151].

Jarvis (1980) reported that 90% of the participants in the treatment group were continent and 83% were symptom free at six months (method for determination of continence and symptom status was not specified but probably self-report) as compared to 23% of the control group who were both continent and symptom free. All women who were symptom free after treatment reverted to a normal cystometrogram.

Fantl (1991) reported that 12% of participants in the treatment group were continent and 75% had reduced their incontinent episodes by at least 50% or more at six weeks, as measured by a seven day voiding diary, as compared to 3% of controls with no incontinent episodes and 24% with at least 50% reduction in their incontinent episodes. These results were maintained at six months. Women with DO and those with urodynamic SUI with and without DO had similar improvement rates. Participants in the treatment group also significantly decreased the grams of fluid lost on a retrograde pad filling test by 54% with results maintained six months later; this was more pronounced in those who had DO with or without urodynamic stress UI. While some women did revert back to normal bladder function following BT, no relationship was found between changes in urodynamic variables and the number of incontinent episodes [278].

Lagro-Jansen (1992) reported that eight or nine patients in BT perceived improvement of UI compared to none of nine in the control group. Yoon (2003) reported that there was no difference between the BT and control groups in the amount of leaked urine at an immediate follow-up; however, it was not clear if this referred to pad test weights solely or a UI severity score. Conclusions from this trial are uninterpretable because of insufficient power.

The Cochrane review [265] noted that the few data available tend to favour BT; however, the scarcity of data implies that they should be interpreted cautiously.

Summary

From the few trials available, there is scant Level 1 evidence that BT may be an effective treatment for women with UUI, SUI, and MUI (Level of Evidence: 1)

Recommendations

BT is an appropriate first line conservative therapy for UI in women (Grade of Recommendation: A). Additional high quality studies are needed that examine the effect of BT versus no treatment in treatment of women with UUI, SUI, and MUI.

c) Is BT better than other treatments?

To be included in this section, trials needed to compare BT alone versus another active therapy. For the comparison of BT versus PFMT see B.2.3d. The only other comparison for which trials were found was BT versus drug therapy. Individual trial reports that met inclusion criteria and the Cochrane review [265] were used as the basis of the review of BT versus drug therapy.

Three RCTs were located that compared BT to drug therapy in 322 women [267, 271, 276]. The study by Park and colleagues [267] compared a 12-week BT programme to 2mg tolterodine twice daily in women (ages unknown) with OAB (unclear if UI was present); because there were no findings reported on UI, this trial is discussed in the section on Other LUTS (B.6.3).
The two trials included in this section used a combination of flavoxate hydrochloride and imipramine [271], or used immediate-release oxybutynin chloride [276].

1. Quality of Data

One trial reported adequate random allocation concealment [276]. Sample sizes were 50 [271] and 79 [276]. Neither trial reported a power calculation;

Follow up periods varied from four weeks [271] to six [276] and 12 weeks [271], and six months [276]. Both RCTs evaluated drug tolerability and adverse events. Dropouts were none in one trial; however, it is not clear whether this was a reporting issue [271]. In the other trial loss to follow up was 7% [276]. Neither trial identified whether intent-to-treat principles were followed. The Cochrane review [265] based their conclusions on the same trials.

2. Results

One RCT suggested that BT may be superior to drug therapy in women with DO [271]. Jarvis (1981) compared inpatient BT to outpatient treatment of 200mg of flavoxate hydrochloride (three times a day) and 25mg of imipramine (three times per day) in 50 women aged 17 to 78 years with DO, and concluded that BT was more effective. In the BT group, significantly more patients (84%) became continent and symptom free (76%) assessed by self-report, as compared to the drug group where 56% became continent and 48% were symptom free at four weeks. Patients who were symptom free at four weeks were able to maintain their outcomes at 12 weeks. In the analysis by the Cochrane review group, more participants in the BT group perceived that they were cured at the end of the treatment phase and approximately two month after treatment ended (RR 1.13; CI 0.94 to1.35). Adverse events included dry mouth, dizziness, headache, nausea, vomiting, and drowsiness in participants who received drug therapy; there were none in those who received BT.

Columbo (1995) reported that a six week course of 5mg oxybutynin chloride (immediate release) (three times per day) had a similar clinical cure rate (i.e. self-reported total disappearance of UI) in patients who received BT. This is consistent with the findings of the Cochrane review [265], which concluded that BT was more effective. In the BT group, 63% of patients were self-reported total disappearance of UI at 12 weeks. In the drug group, 59% of patients were self-reported total disappearance of UI at 12 weeks. Patients who were symptom free at four weeks were able to maintain their outcomes at 12 weeks. In the analysis by the Cochrane review group, more participants in the BT group perceived that they were cured at the end of the treatment phase and approximately two month after treatment ended (RR 1.13; CI 0.94 to1.35). Adverse events included dry mouth, dizziness, headache, nausea, vomiting, and drowsiness in participants who received drug therapy; there were none in those who received BT.

Columbo (1995) reported that a six week course of 5mg oxybutynin chloride (immediate release) (three times per day) had a similar clinical cure rate (i.e. self-reported total disappearance of UI) in patients who received BT. This is consistent with the findings of the Cochrane review [265], which concluded that BT was more effective. In the BT group, 63% of patients were self-reported total disappearance of UI at 12 weeks. In the drug group, 59% of patients were self-reported total disappearance of UI at 12 weeks. Patients who were symptom free at four weeks were able to maintain their outcomes at 12 weeks. In the analysis by the Cochrane review group, more participants in the BT group perceived that they were cured at the end of the treatment phase and approximately two month after treatment ended (RR 1.13; CI 0.94 to1.35). Adverse events included dry mouth, dizziness, headache, nausea, vomiting, and drowsiness in participants who received drug therapy; there were none in those who received BT.

3. Summary

It is not clear whether BT is more effective than drug therapy for women with DO or UUI (Level of Evidence: 1). This is consistent with the findings of the Cochrane review [265], which concluded that there was not enough evidence to determine whether first line therapy should be BT or anticholinergic drugs.

4. Recommendations

In a choice between BT and anticholinergic drug therapy for women with DO or UUI, either may be effective (Grade of Recommendation: B). BT may be preferred by some clinicians and women because it does not produce the side effects and adverse events associated with drug therapy (Grade of Recommendation: D).

d) Can any other treatment be added to BT to add benefit?

To be included, trials needed to investigate the effects of BT versus BT plus therapy A to address the additive benefit of therapy A to BT. Trials addressing the additional benefit of three other treatments were found: caffeine reduction, PFMT, and drug therapy. The trial addressing the added benefit of caffeine reduction [55] is considered in the section on Lifestyle Interventions (B.1.2d), and the trial addressing the added benefit of PFMT [188] is considered in the section on PFMT (B.2.3e). The trials addressing the added benefit of drug therapy are considered below.

One RCT was found that compared BT alone versus BT with tolterodine (2mg, twice daily) in 99 women with OAB [267]. However, incontinence status of the participants was unknown, and details regarding the study methodology were limited (abstract only). Therefore this trial was not considered further in this section.

A further three RCTs compared BT with placebo drug versus BT with drug therapy in patients with DO. One of these used terodoline (a drug that was withdrawn from the market) [269]. Therefore, this trial was not considered further in this section. In the other two trials the drugs used were imipramine [277] and immediate release oxybutynin [268].

Castleden (1986) studied 34 patients with DO (28
women aged 30 to 91 years and six men). Szonyi (1995) recruited 60 patients aged 70 years and over (56 women, four men). While it is possible that the placebo drug could augment BT, and both these trials included a small number of men in addition to women (and data for women were not reported separately), a pragmatic decision was made to review these two trials in this section.

1. QUALITY OF DATA

Neither Castleden (1986) nor Szonyi (1995) reported adequate random allocation concealment, or blinding. In Szonyi (1995) study size was based on a power calculation. Post-treatment follow up periods were variable. One trial evaluated participants at six weeks [268]; 16 were lost to follow up. The other trial did not have a clear endpoint but followed participants for one to 11 months; one participant was lost to follow-up [277].

2. RESULTS

It was not possible to discern the treatment effects in women only in these two trials, and the findings were inconsistent. Castleden (1986) found that more patients became dry on BT plus imipramine 25mg or more per day (14 of 19) compared to those in the BT plus placebo group (six of 14), but the authors reported that there was no statistically significant difference in outcome between the two groups. One patient in the imipramine group became confused and another complained that the drug made him feel ill. Several patients taking imipramine reported dry mouth and constipation (data not reported), but none on placebo.

Szonyi (1995) found no difference between BT plus 2.5mg of immediate release oxybutynin (twice daily) compared to BT and placebo for reducing incontinent episodes. Szonyi (1995) concluded, however, that the combined therapy group was superior to the BT and placebo group, because it had greater subjective benefit (86% versus 55%), and adverse events were similar in the two groups at 50%.

SUMMARY

In two small trials comparing BT plus placebo drug versus BT plus drug in DO, there was a suggestion that the effect of BT might be enhanced by active drug (Level of Evidence: 2). However both trials were small, placebo controlled, conducted in gender mixed sample populations, and the outcomes were not common to both trials. Thus, there is insufficient evidence to derive a conclusion related to the effectiveness of augmenting BT with drug therapy.

e) Does the addition of BT to any other treatment add benefit?

To be included, trials needed to investigate the effects of Therapy A versus Therapy A plus BT to assess the added benefit of BT over Therapy A alone. Trials were located that investigated the effects of PFMT alone versus PFMT plus BT, and drug therapy alone versus BT plus drug therapy.

Wyman (1998) compared the efficacy of BT, PFMT, and combination therapy in 204 community dwelling women aged 45 years and older with SUI and/or DO [188].

Two RCTs were identified that compared BT plus tolterodine (2mg twice daily) [267, 272] to drug therapy alone. In a three arm trial, Park (2002) included 99 women with OAB but it was unclear if UI was present. Therefore this trial was not considered further.

1. QUALITY OF DATA

i) BT plus PFMT versus PFMT alone: In a three arm RCT (n=204) Wyman (1998) randomised 136 women to PFMT (n=69) or PFMT with BT (n=67). Outcomes were assessed after the 12 week intervention and three months later. It was not clear if random allocation was adequate or outcome assessors were blind. Study size was based on a power calculation. Losses to follow-up were six at 12 weeks, and 16 three months later.

ii) BT plus drug therapy versus drug therapy alone: Mattiasson (2003) evaluated “simplified” BT (consisting of a one page instruction sheet) in a single blind study of 501 participants (378 women and 123 men) aged 18 years and over with OAB with or without UUI. Allocation concealment, blinding of assessors, and a priori power calculation were not described. Post-treatment follow up was 12 weeks, and then 24 weeks. Seven participants were lost to follow-up; five in drug therapy and two in combination therapy. Analyses were based on intent-to-treat principles. However, because of reporting issues, it was not possible to discern the effect of treatment in women alone.

2. RESULTS

i) BT plus PFMT versus PFMT alone: Post-treatment the combination therapy group had significantly fewer incontinence episodes compared to PFMT alone. More women in the combination therapy group than PFMT group reported cure (31% versus 13% respectively), or 50% improvement or more (70% versus 50%).

The combination therapy group also reported greater perception of improvement and more satisfaction with treatment than PFMT alone. However, three months later between group differences were not statistically significantly different for cure (27% versus 20%), improvement (59% versus 56%), perception of improvement, or satisfaction with treatment.
**ii) BT plus drug therapy versus drug therapy alone:**
Mattiasson (2003) reported no difference between participants who received brief written BT instructions plus tolterodine versus tolterodine alone with respect to reducing incontinent episodes (median reduction 87% versus 81%, respectively). Data were combined for men and women and most data were not presented separately for those who had UI versus those who did not.

**SUMMARY**
A single trial found that combining BT with PFMT improves short-term outcomes compared to PFMT alone, but the added benefit did not persist three months later. There is no evidence for an added benefit of combining brief written BT instructions with tolterodine (2mg twice daily) compared to tolterodine alone for urge incontinence (Level of Evidence: 2), although this trial included men and women and it is not known if one gender did better than the other with respect to outcome.

**Recommendations**
For women taking an antimuscarinic drug there may be no clinical benefit in adding brief written instruction in BT (Grade of Recommendation: B). More research is needed using an appropriately supervised BT programme (see B.6.2a) combined with anticholinergic or antimuscarinic drug therapies versus drug alone.

**f) Timed voiding**
There are anecdotal reports that timed voiding involving a two or three hour schedule may be beneficial in clinical practice. A Cochrane review on timed voiding for management of UI in adults was published in 2007 [257]. A previous literature review was published in 1986 [253].

Ostaszkiewicz (2007) considered randomised and quasi-randomised trials only and identified two trials that compared timed voiding combined with additional interventions (including medications) to usual care. Both trials were conducted in nursing facilities and most participants were elderly women with cognitive impairment, therefore neither study recruited participants that met the criteria of interest for this chapter.

Two non-randomised studies that were not included in the Cochrane review reported findings related to the effects of timed voiding in women with UUI, stable bladders with UUI, and MUI [279, 280]. Klariskov (1986) reported a consecutive series of 20 women aged 27 to 75 years with a double-blind crossover to compare timed voiding plus anticholinergic drug therapy (terodoline) to timed voiding plus placebo. As terodoline has been withdrawn from the market, this study is not considered further.

**1. QUALITY OF DATA**
Godec (1984) reported a case series report involved 20 women aged 24 to 94 years in women with a mild degree of UI, irregular voiding patterns, and normal urodynamic parameters (UI type not clearly reported) [279]. The voiding schedule consisted of a two hour voiding interval. Follow-up periods ranged from six weeks to eight months after treatment [279].

**2. RESULTS**
Godec (1984), reported a 79% success rate (not objectively quantified). Fifteen patients became totally continent, one had less leakage, three (with neurogenic diseases) remained unchanged, and one patient was lost to follow-up.

**SUMMARY**
There are no RCTs, or high quality observational studies, providing evidence on the effects of timed voiding for UI in women. Based upon the data from one small uncontrolled study, it seems a two hour timed voiding schedule may be beneficial in treating women with mild UI, infrequent voiding patterns, and stable bladder function (Level of Evidence: 3).

**Recommendations**
Timed voiding with a two hour voiding interval may be beneficial as a sole intervention for women with mild UI infrequent voiding patterns (Grade of Recommendation: C). It may also be helpful as an adjunct to other treatment.

**3. OTHER LUTS**
One trial was excluded from sections above, because it recruited participants with OAB and the continence status of participants was not clear [267]. Park (2002) compared BT versus tolterodine (2mg, twice daily) versus the combination of BT and tolterodine in 99 women with OAB [267]; this study was reported as a conference abstract. Park (2002) found that the tolterodine/BT group had greater reductions in diurnal micturition (32.6%), nocturnal micturition (63.2%), urgency scores (63.2%), and bladder symptom improvement rates (69.3%) than those in BT alone (27.1%, 55.8%, 48.4%, 50%, respectively) or tolterodine alone (30.3%, 61.9%, 62.5%, 58.3%, respectively). However, only the bladder symptom improvement scores were statistically significantly better in the combination therapy group. Thus, it is not clear if BT alone, tolterodine alone, or the combination, is better for LUTS other than UI in women with OAB symptoms.

The most common LUTS, aside from UI, are urgency, daytime (or diurnal) frequency and nocturia. Some trials that contributed to the sections above reported data specifically for these symptoms.
a) Urgency: Jarvis (1981) compared BT and drug therapy (flavoxate and imipramine), and 16% versus 44% of participants reported they continued to experience urgency post-treatment. Mattiasson (2003) compared BT with tolterodine versus tolterodine alone and patient rating of urgency was somewhat less in the combination therapy group.

b) Daytime (diurnal) frequency: Data on frequency are more commonly collected that data on urgency. Three trials reported diurnal frequency in comparisons of BT with no treatment. Jarvis (1980) reported a small controlled trial of inpatient bladder drill for DO [270]. After BT 17% in the treatment group and 77% in the control group continued to have symptoms of diurnal frequency. Fantl (1991), in subgroup analyses, found a significant reduction in diurnal frequency in participants with urodynamic SUI who had a baseline diurnal micturition frequency of at least 61 per week, and also in participants with DO with or without urodynamic SUI who had at least 57 diurnal micturitions per week [255]. Finally, Yoon (2003) reported that the BT group significantly reduced diurnal micturitions, whereas the control group deteriorated slightly [151].

Two trials compared BT with drug therapy. Jarvis (1981) reported that 24% of the BT group continued to experience frequency as compared to 48% of the drug group (flavoxate and imipramine) [271]. Columbo (1995) found that diurnal frequency was resolved in 18 (56%) of 32 patients taking oxybutynin versus 20 (69%) of 29 BT patients [276].

Another trial compared BT plus placebo versus BT plus drug [268]. Szonyi (1995) found that there was a greater reduction in diurnal micturition frequencies in participants taking oxybutynin alongside BT compared to those on placebo and BT. Similarly, in a trial of BT plus drug versus drug alone Mattiasson (2003) found that “simplified” BT significantly augmented the effect of tolterodine compared to drug alone for voiding frequency (33% versus 25% improvement, respectively; p<0.001).

c) Nocturia: Three trials reported data on nocturia in comparisons of BT with no treatment. Jarvis (1980) reported a small controlled trial of inpatient bladder drill for DO. After bladder training, there were 11% in the treatment group and 80% in the control group who continued to have symptoms of nocturnal frequency [270]. Fantl (1991) also found significant reductions in nocturnal frequency [255].

In subgroup analyses, nocturnal micturitions were only significantly decreased in women with urodynamic SUI alone, who experienced at least five episodes of nocturia per week, and not in those who had DO. Yoon (2003) reported that the BT group significantly reduced nocturnal micturitions, whereas the control group deteriorated slightly [151].

Two trials compared BT with drug therapy. Jarvis (1981) reported that the 19% of the BT group continued to experience nocturia compared to 68% of the drug group (flavoxate and imipramine) [271]. Columbo (1995) found that nocturia disappeared in three (27%) of 11 patients taking oxybutynin and 11 (61%) of 18 BT patients [276]. Another trial compared BT plus placebo versus BT plus drug [268]. Szonyi (1995) found no difference in nocturnal micturition frequencies.

Summary

Scheduled voiding regimens have been implemented in many forms and with a variety of intensities, ranging from strict in-patient regimens to simple instruction sheets. Most research has examined BT, and most of these trials have recruited women with symptoms of UUI or OAB. It is therefore disappointing that there is so little data about LUTS other than UI. The indications so far are that BT is effective for reducing UI, as well as frequency of micturition. The scant research comparing BT to drug therapy is inconsistent with some evidence for the superiority of each. It is not yet clear whether drug therapy can enhance BT, or whether BT can enhance UI outcomes from drug therapy, although it appears that reductions in frequency of micturition may be greater with the addition of BT.

4. FACTORS AFFECTING OUTCOME

a) Age

All trials with the exception of two RCTs [151, 275] included older women in their study populations. Three trials specifically recruited elderly women aged 65 to 70 years and over [268, 269, 277]; and two trials recruited women aged 55 years and over [255, 273]. In conducting analyses of factors predicting outcomes of BT alone, two trials reported that age was not a factor in treatment outcome [188]. Similarly, age was also not a predictor of outcome in a trial incorporating an intervention in which three consecutive interventions could be implemented depending on participant goals (self-monitoring, BT, PFMT) [273].

b) Other

Few BT trials examined other predictors of treatment response. Several trials discussed the effect of diagnosis on treatment outcome. Two trials reported that urodynamic diagnosis did not have an effect on treatment outcome as measured by incontinent episodes and the Incontinence Impact Questionnaire [188, 255]. These RCTs included women with urodynamic SUI, DO, or both diagnoses. BT also led to more clinical cures in one small drug trial. BT in women with sensory urgency (81%) and low compliance bladders (75%) produced better outcomes than in those on oxybutynin immediate release (60%, 67%, respectively); however, oxybutynin led to greater cure rates in patients with DO (93% versus 62%).
VII. COMPLEMENTARY AND ALTERNATIVE MEDICINES

There is emerging evidence that complementary and alternative medicines (CAMs) may influence both physiologic function and health outcomes. CAMs include those therapies that are not part of the traditional biomedical model, such as meditation, imagery, hypnosis, acupuncture and naturopathic and herbal remedies. While some consider BF part of complementary therapy, we have included BF in this chapter as an adjunct to physical therapies.

A search of AMED (Allied and Complementary Medicine) using the key words randomized controlled trials, and urine or urinary, retrieved 18 records. None of these reported a randomised controlled trial investigating the effect of CAMs that had not already been considered in this chapter.

No trials were found in a similar search when the report for the 3rd Consultation was prepared. A decision was made not to update this section of the report based on further uncontrolled studies.

Given the high placebo response rate in many studies of conservative therapies for UI it is crucial that further studies of CAMs include a control group. When placebo treatment is not possible due to the nature of the intervention, a standard treatment control group should be used.

Interested readers are referred to the report from the 3rd Consultation for the previous summary of the few uncontrolled studies of CAMs found prior to 2005.

VIII. SUMMARY

Some aspects of the conservative management of UI in women have received the bulk of research attention to date, such as the effect of PFMT. There are other areas, such as the effect of lifestyle interventions, which have received little. Although a reasonable number of trials were found investigating the effects of conservative management of UI in women, the standards of trial conduct and reporting vary considerably and the size of the trials is often small. All these factors contribute to the lack of data that can meaningfully be compared.

1. RECOMMENDATIONS FOR PRACTICE

While there are some recommendations underpinned by good and consistent evidence of effect, there are also many recommendations that are essentially hypotheses that need further testing because there is insufficient Level 1 or 2 evidence to be sure about the effect of an intervention.

a) Lifestyle interventions

- For morbidly and moderately obese women weight loss is a useful treatment to reduce UI prevalence (Grade of Recommendation: A) (Changed).
- A reduction in caffeine intake may help those with incontinence symptoms (Grade of Recommendation: B) (Changed).
- Given the fact that decreasing fluids may lead to urinary tract infections, constipation, or dehydration, this intervention should be reserved for patients with abnormally high fluid intakes (Grade of Recommendation: C) (Unchanged).
- Crossing the legs and bending forward might be useful in reducing leakage during coughing or other provocation (Grade of Recommendation: C) (Unchanged).

b) Pelvic floor muscle training (PFMT): Principal recommendations

The principal recommendations of the committee are that:

- PFMT is offered as first line conservative therapy to women with stress, urge, or mixed urinary incontinence (Grade of Recommendation: A) (Unchanged).
- Clinicians should provide the most intensive PFMT programme possible (in terms of exercise dose and health professional supervision) within service constraints because health professional taught and supervised programmes are better than self-directed programmes, and more health professional contact is better than less (Grade of Recommendation: A) (Changed).
- There does not appear to any benefit of adding clinic BF (Grade of Recommendation: A), or home based BF (Grade of Recommendation: B) to the PFMT programme (Changed).

b) Pelvic floor muscle training (PFMT): Other recommendations

The recommendations that follow may help with decision making in specific groups. Most of these are essentially hypotheses that need further testing.

Pregnant women expecting their first baby:

- Should be offered an intensive strengthening antepartum PFMT, with regular health professional contact to supervise training, to prevent postpartum urinary incontinence (Grades of Recommendation: A (for women continent at 18 weeks) and B (for population approaches, that is intervention offered whether women are continent or not at 20 weeks gestation)) (Changed).
Postnatal women, immediately after delivery:
- Who had a vaginal delivery of a large baby (4000g or more) or a forceps delivery will benefit from an individually taught PFMT programme that incorporates adherence strategies (Grade of Recommendation: C) (Unchanged).

For postnatal women with persistent symptoms of UI three months after delivery:
- PFMT is offered as first line conservative therapy (Grade of Recommendation: A) (Changed).
- The ‘best’ PFMT programmes are ‘intensive’ with regard to supervision and exercise content (Grade of Recommendation: B) (Changed).

For women with SUI:
- PFMT is better than EStim as first line conservative therapy, particularly if PFMT is intensively supervised (Grade of Recommendation: B) (Unchanged).
- PFMT is better than BT as first line conservative therapy (Grade of Recommendation: B) (Changed).
- PFMT and duloxetine are both effective therapies, although clinicians and women may choose to try PFMT first because of the side effects experienced with the drug (Grade of Recommendation: C) (New).
- PFMT and surgery are both effective therapies, although many clinicians and women may prefer PFMT as a first choice therapy because it is less invasive (Grade of Recommendation: C) (Changed).

For women with SUI or MUI:
- PFMT and VC are both effective therapies, although it seems PFMT is better as a first choice because of better leakage outcomes and because some women cannot or do not like to use cones (Grade of Recommendation: B) (Changed).
- PFMT is better than clenbuterol or phenylpropanolamine hydrochloride as first line therapy because of the side effects experienced with the medications (Grade of Recommendation: B) (Unchanged).
- A combination of PFMT/BT may be better than PFMT alone in the short-term (Grade of Recommendation: C).

For women with UUI or MUI:
- PFMT and BT are both effective first line conservative therapy (Grade of Recommendation: B) (Unchanged).
- PFMT is better than oxybutynin as first line therapy (Grade of Recommendation: B) (Unchanged).

**d) Vaginal cones (VC)**

For women with SUI or MUI:
- VC can be offered as first line conservative therapy to those who can and are prepared to use them (Grade of Recommendation: B); VC may be inappropriate in some cases due to side effects and discomfort.
- VC and EStim seem equally effective in the treatment of SUI and MUI, but the usefulness of VC and EStim in practice might be limited because of side effects and discomfort (Grade of Recommendation: B).

**e) Electrical stimulation (EStim)**

While the usefulness of EStim in practice might be limited because some women cannot use it (due to contraindications), have difficulty using it, or dislike it:
- For women with SUI, (a) six months of 50Hz daily EStim at home might be better than no treatment (Grade of Recommendation: C) (New), and (b) low intensity home based EStim daily for six months might be better than 16 sessions of maximal clinic based EStim (Grade of Recommendation: C) (New).
- For women with DO nine weeks of 4 to 10Hz twice daily EStim at home might be better than no treatment (Grade of Recommendation: C) (New).
- The addition of EStim to a BF assisted PFMT programme does not appear to add benefit (Grade of Recommendation: C) (New).

**f) Magnetic stimulation (MStim)**

- Any clinical use of MStim should only be in the context of a randomised clinical trial as the benefit of this intervention has not been established (Grade of Recommendation: D) (New).

**g) Bladder training (BT)**

With regard to Grade A recommendations for BT:
- BT is an appropriate a first line treatment for UI in women (Unchanged).

Grade B recommendations are:
- Either BT or antimuscarinic drug may be effective (Unchanged), although BT may be preferred by some because it does not produce the side effects and adverse events associated with drug therapy.
- There may be no benefit in adding brief written instruction in BT to drug therapy (New).
- For women with symptoms of SUI or MUI a combination of PFMT/BT may be better than PFMT alone in the short-term (Unchanged).

There are two Grade D recommendations, drawn
from expert opinion and narrative review of the existing literature, being:

• Clinicians and researchers should refer to the operant conditioning and educational literature to provide a rationale for their choice of training parameters or approach (New).
• Clinicians should provide the most intensive BT supervision that is possible within service constraints (New).

h) Timed voiding

• Timed voiding with a two hour voiding interval may be beneficial as a sole intervention for women with mild UI infrequent voiding patterns (Grade of Recommendation: C) (Unchanged).

2. FUTURE RESEARCH DIRECTIONS

There continues to be much scope for research on the effects of conservative therapies for UI and LUTS in women. Research that is urgently needed, in the opinion of the committee members, is highlighted with the use of italics. There are a few recommendations that apply to all further studies in women, namely:

• All future trials must be designed, implemented and reported in ways that maximise their usefulness in practice; this includes evaluation of cost-effectiveness and planned secondary analysis of trial data to investigate factors affecting outcome. Readers are referred to the revised CONSORT statement for guidance.
• Studies need to be larger, with longer follow up.
• Future trials should use a validated and reliable quality life measure as the primary outcome.

a) Lifestyle interventions

• The dual issues of weight loss and prevention of weight gain (and the role of exercise in these) should receive high research priority in UI research given the prevalence of both UI and obesity in women.
• Given the large proportion of women employed in occupations that require heavy lifting the association of such exertions and UI should be investigate further. Specifically research must establish whether heavy exertion is an etiologic factor in the pathogenesis of UI and whether changing exertions can alleviate established UI.
• Further prospective studies are needed to determine whether smoking cessation prevents the onset, or promotes the resolution, of UI.
• Larger RCTs to assess the effect of dietary factors, in particular caffeine reduction, are feasible and important.
• Further research is needed to delineate the role of straining in the pathogenesis of UI.
• High quality studies evaluating the effect of all other lifestyle interventions on UI are warranted.
• Future work should separately evaluate the impact of lifestyle interventions on nocturia, diurnal frequency, urgency and UI to delineate whether certain interventions preferentially affect different areas of OAB.

b) Pelvic floor muscle training (PFMT)

In antenatal and postnatal women, trials are needed to investigate:

• The effect of antepartum PFMT on preventing postpartum UI in multiparous women.
• The effect of a postpartum PFMT programme (suitable exercise dose and supervision) in the long term (five plus years).
• The effect of periodic refresher sessions after an initial supervised postpartum PFMT programme, in the long term (five plus years).

In all women, trials are needed to investigate:

• The effects of PFMT in the long term (five plus years)
• The effects of different types of PFM exercise (strengthening, endurance, co-ordination, functional training) and supervisory styles (e.g. individual versus group).
• Whether any indirect method of PFMT (Paula method, transversus abdominus training, hip abductor or adductor exercise) might be as effective as direct PFMT, or add benefit to a direct PFMT programme.
• Whether BF may benefit certain women, such as those with a weak PFM or with difficulty contracting the PFM in isolation.
• Whether the addition of any of the following adds benefit to PFMT: intravaginal resistance, cues to exercise, or bladder training.
• Whether the addition of PFMT to either vaginal cones or duloxetine adds benefit.

c) Vaginal cones (VC)

• If the combination of VC with PFMT is an intervention of interest for women then this combination of therapies could be explored further. VC could be used as an overload progression to active PFM strengthening exercises.

Thus, a VC programme could be offered to women with a demonstrated minimum PFM strength level and could be aimed at either additional strength training by pulling on the cone for three series of eight to 12 contractions daily [181], or endurance training, using a low-load over a sustained period of time.
d) Electrical stimulation (EStim) and magnetic stimulation (MStim)

- There is a need for studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups, so these can then be tested and compared in clinical trials.
- Comparisons of EStim with other treatments that seem to be effective such as PFMT, vaginal cones, and bladder training are more important than comparison of EStim with sham.
- There is also scope for trials of EStim as an adjunct to treatments that seem to be effective such as PFMT, vaginal cones, and bladder training.
- Of the MStim protocols investigated to date, it seems that both sacral root MStim and home-based MStim, are worthy of further investigation.

e) Scheduled voiding regimes, especially bladder training (BT)

- There are several BT variables that could be investigated in future trials including the instructional approach, supervisory intensity, strategies for controlling urgency, scheduling parameters, frequency of schedule adjustments, length of treatment, and use of adjunctive treatments.
- Although additional studies are needed that examine the effect of BT versus no treatment, more important clinically are trials of BT versus another active treatment such as PFMT or drug.
- The potential benefits of combining BT and anticholinergic/antimuscarinic drug need further investigation, including comparisons of BT plus drug versus drug alone, and BT plus drug versus BT alone.
- Research is needed on habit training in women with a consistent pattern of UI who are ambulatory and cognitively intact.

**B. URINARY INCONTINENCE IN MEN**

UI in men remains under-reported and under-studied in comparison to studies including women. The report from the 3rd ICI indicated that the prevalence of UI and LUTS in men ranged from eight to 23% depending on the method of data collection, population accessed, and location [281]. Despite the prevalence of UI and LUTS in older men, the only aspect which continues to receive systematic consideration with respect to conservative management is post-prostatectomy urinary symptoms. Thus, the focus of this section is the prevention and treatment of UI after prostatectomy for benign or malignant disease. All prostatectomy types and approaches were considered for inclusion including radical prostatectomy (open radical retropubic or perineal, laparoscopic, and robotic) or endoscopic procedures (such as transurethral prostatic resection, high intensity microwave therapy).

- **Aetiology of UI after prostatectomy**
  For purposes of the current review, the reader is directed to the report from the 3rd ICI [281] in which the aetiology of UI after prostatectomy is covered in detail (see report from Committee 13: Surgery for urinary incontinence in men). In brief, risk factors which have been repeatedly identified for UI after radical prostatectomy and transurethral resection of prostate (TURP) are abnormalities of detrusor contractility [282] and age [283]. Other related factors include neurovascular injury during surgery, previous TURP [284], preoperative radiotherapy, trauma, spinal cord lesion, new obstruction such as prostatic regrowth, bladder neck contracture, urethral stricture, Parkinson’s disease [285, 286], dementia, and medications [281].

- **Treatment**
  The primary conservative treatment for UI after prostatectomy remains physical therapies with or without some form of BF. PFMT, along with anal EStim, BF or transcutaneous electrical nerve stimulation (TENS), MStim, and even pharmaceuticals have all been utilised and reported as modestly successful in some trials and not in others.

A literature search of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed (see appendix). No other types of study design were considered. The report of the 3rd ICI [281] identified 14 relevant RCTs on conservative management of UI post radical prostatectomy (n= 12) or TURP (n=2) [287-300]. Seven new published trials and two abstracts [301, 302] were found, all in men undergoing radical prostatectomy [301-309]. One was excluded as it was not published in English and no translation was available [306]; another trial [288] was not an RCT but assigned the first 25 to control and the next 25 to treatment. This trial had been included in the previous ICI report but has been excluded from the current review because of the potential for bias in a non-randomised trial. Thus, one trial was removed and eight trials added to the current evidence base for a total of 20 trials on some aspect of continence treatment after radical prostatectomy and two on treatment after TURP.

**I. LIFESTYLE INTERVENTIONS**

Typically, as part of standard practice in the treatment of people with UI, lifestyle recommendations are made to stop smoking, maintain a healthy body weight,
avoid or reduce caffeine containing drinks, avoid constipation, and to drink approximately eight glasses of liquid a day. Whether these factors have a direct impact on continence is suggested but not known. To date, no trials have addressed the topic of lifestyle interventions for men with UI. Nevertheless, in practice, it seems reasonable to offer advice on healthy lifestyle choices that may reduce or delay the onset of continence problems.

II. PELVIC FLOOR MUSCLE TRAINING (PFMT)

The quality of trials included in this update of PFMT has improved from earlier ICI reports although heterogeneity and varying outcome measures continue to affect the ability to compare trial findings.

1. PREVENTION

Trials in this section addressed the effect of PFMT initiated preoperatively or postoperatively but before continence/incontinence was established. Four new trials were found [301, 303, 305, 309] making a total of nine trials in this category [287, 294, 295, 297, 300, 301, 303, 305, 309].

Two trials utilised preoperative BF assisted instruction in PFMT followed by postoperative self-PFMT at home, and compared this with postoperative verbal instruction [287], or usual postoperative exercise advice [303]. In Bales (2000) (n=100; 93 completing) initial instruction on PFMT was provided using surface BF two to four weeks prior to radical retropubic prostatectomy. The control group received only postoperative verbal instruction; both groups had written information and were encouraged to practice PFMT four times daily once the catheter was removed two weeks after surgery. In Burgio (2006) (n=125; 102 completed), participants had one BF session (rectal probe with three small balloons) two to four weeks preoperatively, plus daily pre and postoperative home exercises. The control group had no therapist contact and practiced postoperative exercises as per standard care (starting and stopping stream). Primary outcome was continence, defined as use of zero or one pad per day [287] or no leaks recorded on bladder diary [303]. In Lilli (2006) (reported only in abstract), 90 participants (all completed) were assigned to PFMT plus BF (method/type not described) or PFMT alone. Both groups were encouraged to do home exercises. Primary outcome was pad use, assessed at one, three, and six months post surgery.

One trial compared active pre- and post-operative PFMT programme to no PFMT instruction [297] and another pre- and post-operative instruction versus post-operative instruction [295]. Participants in Parekh (2003) (n=38; 36 completing) had two pre-operative and four post-operative sessions of anal probe BF plus post-operative home PFMT using an exercise ball, or no intervention (similar to Burgio (2006) above). Continence was assessed by patient reported number of pads and continence questionnaires at six, 12, 16, 20, 28 and 52 weeks post surgery. Sveppel (2001) randomised 16 men (no dropouts) to two pre-operative and five post-operative sessions of anal probe BF or five post-operative sessions. Both groups were asked to do self directed home PFMT. Continence and quality of life were assessed by AUA symptom score and quality of life questionnaire, pad count, 45 minute standardised pad test, and a leakage questionnaire at six weeks and one year post surgery.

In the study by Mathewson-Chapman (1997) all 51 (50 completing) participants had one session of preoperative instruction using BF and verbal coaching and were then randomised to intervention or control groups. The intervention group (n=26) practised PFMT daily with a home BF unit (anal probe) from weeks three to 12 after surgery, whereas the control group (n=24) only followed written instructions. Both groups completed questionnaires, pad counts, and 24 hour pad tests at two, five and 12 weeks post-operatively.

Finally, three trials commenced post-operative PFMT immediately after catheter removal [300, 305, 309]. Filocamo (2005) randomised 300 men to a PFMT programme or no formal instruction. Outcomes were ICS Male Questionnaire (ICS MaleQ), pad count, and pad test (one and 24 hours). Overgård (in press 2008) assigned 85 men (80 completing) preoperatively to one of two groups: 42 received weekly 45 minute PFMT guided by a physiotherapist and 43 received one PFMT training session then practiced home exercises. Outcomes were proportion of continent men, defined as self-report of no pads, 24 hour pad test, subject report and PFM strength obtained at six, 12, 24 and 52 weeks post surgery. Immediately after catheter removal, Wille (2003) assigned 139 subjects (128 completing) to one of three active groups: PFMT (method unclear), encouragement to do home exercises, and a three week rehabilitation programme (not described); twice daily PFMT with ESTim taught with surface anal electrodes, or PFMT with ESTim and BF using anal probe. All subjects received three therapist guided sessions immediately after surgery and at three and six weeks plus performed PFMT at home; the two intervention groups also utilised an ESTim or BF device twice daily at home (see also C.3). Outcomes were pad count with continence defined as use of zero to one pad per day or 20 minute pad test (continence was less than 1g urine loss) collected at three and 12 months post surgery.

1. QUALITY OF DATA

Of the nine trials in this section, only Burgio (2006) reported adequate random allocation concealment. With regard to blinding of outcome assessment, Bales (2000) attempted to control for bias in outcome...
assistance by having a nurse not directly involved in the study interview the subjects. It is not clear whether he/she was blinded to allocation group. Overgärd (in press 2008) had surgeons blinded to group allocation. Wille (2003) had data analysed by a professional statistician. Burgio (2006) had outcomes assessors blinded to group assignment. Dropouts were described by Burgio (2006), Filocamo (2005), Overgärd (2008), and number of dropouts was provided by Wille (2003) but reasons were not described. Sueppel (2001) indicated incomplete data but did not describe dropouts. Burgio (2006), Filocamo (2005) and Wille (2003) described ITT analysis.

2. RESULTS

i) Preoperative PFMT instruction with postoperative home PFMT versus control [287, 301, 303]: Burgio (2006) reported a statistically significant difference in favour of PFMT in time to regain continence (p=0.03) and proportion of men with severe or continual leakage measured by voiding diary at six months, 32/54 PFMT (59%) versus 40/51 controls (78%) (p=0.04); additional data provided by the authors on the 24 hour pad test did not indicate a difference between groups. Bales (2000) found no significant group difference on participant report of number of pads used or time to return to continence. Lilli (2006) did not find a difference between participants who received BF in addition to PFMT at any of the time points; at six months, 32/45 (71%) and 30/45(67%) respectively were reported as dry and no use of pads. In the Lilli trial both groups received intervention and it is not clear how intensive the pre-operative PFMT instruction was.

ii) Pre-operative PFMT instruction followed by supervised post-operative PFMT versus postoperative PFMT [294, 295, 297]: Parekh (2003) found more men continent in the pre and post treatment group at 12 weeks but there was no statistically significant difference at any other time point to 12 months. Sueppel (2001) reported that at one year the pre and post treatment group had less leakage on a standardised 45 minute pad test compared to the postoperative group (mean 2.8g (range 0.0-13.0g) versus 33.3g (range 0 to 194g)); statistical significance was not reported. Mathewson-Chapman (1997) found no statistically significant differences between groups at any of the time points.

iii) Post-operative PFMT immediately after catheter removal (no pre-operative instruction) [300, 305, 309]: The Filocamo (2005) trial favoured treatment at three months with 39/50 (78%) versus 105/150 (70%) reporting one or fewer pads a day. At six months 115 in the treatment group and 48 in the control reported themselves as ‘completely dry’ and at 12 months 134 and 101 were dry respectively. Differences between treatment and control were 96% versus 65% (p=0.00001) at six months and at one year 99% and 88% (not significant). There were no significant differences between groups on 24 hour pad test (Filocamo, personal communication). Overgärd (in press 2008) reported no difference between groups for proportion dry (no pads) or 24 hour pad test at three months; however, at 12 months, the proportion of continent men was statistically significantly greater in the treatment group (33/36; 96%) versus the control (28/39; 72%) (p=0.028). PFM strength and 24 hour pad test results did not differ between groups at any of the time points. Of note is that 20 participants in the treatment group did not receive face to face instruction due to distance from facility but rather followed detailed instructions provided on a DVD. Wille (2003) did not find a difference between groups at three and 12 months but all three groups received some sort of intervention.

SUMMARY

Nine trials were found addressing prevention of UI in a total of 803 men and used a variety of pre-operative or post-operative PFMT based interventions, or a combination of both. Any differences between experimental and control groups were modest and short term; differences did not appear to be sustained up to 12 months post surgery. A particular challenge in evaluating the trials is that participant reported outcomes in three of the recent studies [303, 305, 309] all indicate some level of improvement in the treatment groups; however, there are no clear differences in pad test results in any of the nine trials. Because all the studies reviewed were generally small, varied in design, and measures differed, it is difficult to interpret them as a whole. Whilst the evidence that therapist delivered PFMT with or without BF before or after surgery improves continence recovery after radical prostatectomy remains inconsistent; a growing number of recent trials suggest that men who undergo some sort of conservative management including PFMT will achieve continence in a shorter time frame than non-treated men but this difference is not significant at 12 months post surgery (Level of Evidence: 2).

Further discussion is needed on the outcomes of most importance. It is possible that the emphasis on quantitative outcomes is not meaningful to participants; men appear to find therapy personally helpful and value the direction provided by a therapist.

RECOMMENDATIONS

Some preoperative or immediate post-operative instruction in PFMT for men undergoing radical prostatectomy may be helpful (Grade of Recommendation: B); whether this is in the form of ‘hands on’ therapy of verbal instruction and support
remains unclear. Studies comparing the effectiveness of pre- versus post-operative PFMT, and the number of sessions required, are needed so that practitioners may advise men about pre-operative preparation and budget conscious health boards can make informed decisions on programme funding. In designing such studies, the natural history of UI after radical prostatectomy must be taken into account because the spontaneous recovery rate means that sample sizes must be large to detect any differences between protocols.

2. TREATMENT

a) PFMT with digital rectal feedback after radical prostatectomy

Two additional trials were identified [304, 307] resulting in a total of four [292, 293, 304, 307] in which PFMT was taught using digital rectal feedback (DRE) in at least one arm.

Dubbleman (2004) randomised 70 (63 completed) men to physiotherapy (not described) or written material on PFMT. Subjects received nine or fewer therapist-guided PFMT sessions using DRE starting at one week postoperatively. Joseph (2000) randomised a mixed group of 10 men (four radical retropubic prostatectomy and six radical perineal prostatectomy) to weekly verbal teaching plus DRE or BF assisted PFMT over a four week period. Manassero (2007) randomised 107 (94 completed) men to urologist taught PFMT using DRE (unclear how often) plus daily home exercises for up to a year; the control group did not receive any instruction. Participants were assessed at one, three, six and 12 months with a home pad test, VAS and DRE. In Moore (1999) 63 men (58 completed) were randomised to one of three groups: control (written materials only and no therapist contact), PFMT using DRE and abdominal palpation, or PFMT augmented with EStim via anal probe. Both treatment groups met with the therapist twice a week for up to 12 weeks.

1. QUALITY OF DATA

Only one trial [293] reported adequate random allocation concealment. Data were collected by blinded assessors in one trial [307]. In another, data were collected and outcomes assessed by the primary investigator who had a direct involvement in the trial, although treatment was provided by a therapist blinded to the control group outcomes [293]. Three studies described reasons for dropout [293, 304, 307], but none indicated how withdrawals/dropouts were dealt with in the analysis.

There was considerable variation in the type and intensity of interventions, follow-up ranged from six and a half months to 12 months, and primary outcomes varied from pad test, pad count or subject report.

2. RESULTS

Between them, the four trials had a total of 225 participants with complete data. Three of the four studies did not find statistically significant differences between the groups. Dubbelman (2004) found no significant differences at 26 weeks post catheter removal between physiotherapy and written PFMT information groups in one and 24 hour pad tests. Similarly, in the small study by Joseph (2000) no differences were found in outcomes measured by 24 hour pad test, voiding diary or quality of life (IIQ-7) between PFMT and PFMT with BF groups. Moore (1999) found no differences in pad test between PFMT and PFMT with EStim groups but confidence intervals were wide and subjects began treatment anywhere between eight weeks and 12 months post surgery.

Manassero (2007) reported a statistically significant difference (p=0.01) in proportion of continent subjects (<2g on 24 hour pad test) in the PFMT group at three, six and 12 months (54%, 33%, 17% compared to 78%, 60%, and 53% for the controls), with 9/54 versus 21/40 incontinent at 12 months.

SUMMARY

In the most recent and largest trial [307], which compared PFMT taught by DRE or no instruction there was a statistically significant difference in the proportion of continent men (based on 24 hour pad test) in the treatment group at three, six and 12 months. In the three other smaller and earlier trials, in which the control groups had written or verbal instruction on PFMT, there were no statistically significant differences between groups on pad test. (Level of Evidence: 2). Clinical heterogeneity meant that it was difficult to consider the findings from the studies as a whole.

RECOMMENDATIONS

Some instruction in PFMT may be helpful; it is not clear whether PFMT taught by DRE offers any benefit over and above verbal or written instruction (Grade of Recommendation: B). Further well designed studies are needed to test this hypothesis.

b) PFMT with BF after radical prostatectomy

Two new trials were available [308][302] abstract only), to make a total of six evaluating PFMT with BF compared to a non active or alternate treatment commencing after radical prostatectomy [290, 291, 296, 299, 302, 308].

Three of these trials compared PFMT with BF versus no treatment, placebo treatment, or usual care. Franke (2000) randomised participants (n=30; 15 completing) to PFMT with BF versus no treatment. PFMT was delivered via BF from perineal patch electromyography
in weeks six, seven, nine, 11 and 16 postoperatively, supplemented with home exercises. The control group received no written or verbal instruction about PFMT. Outcomes were number of incontinent episodes and 48 hour pad test averaged over 24 hours. Van Kampen (2000) randomised 102 men (98 completing) to PFMT with BF or placebo EStim. Treatment group subjects received detailed instruction on PFMT, received active treatment once a week and practiced home exercises three times a day; the control did not receive any instruction and had weekly placebo EStim. Both groups did home 24 hour pad tests daily until continent and practiced home exercises. Continence was measured by 48 hour pad test.

Three trials compared PFMT with BF versus verbal instruction and home PFMT [290, 296, 308]. Floratos (2002) randomised 42 men (all completed) to PFMT with EMG BF, 15 sessions three times a week for five weeks or one session of DRE guidance and verbal instruction starting approximately one week after catheter removal. Both groups practiced daily PFMT at home. Primary outcome was one hour pad test at one, two, three and six months. Moore (in press 2008) compared verbal instruction and written materials on home exercises versus weekly therapist provided PFMT with BF via anal probe plus daily home exercises (n=205; 166 completing). Primary outcomes were 24 hour pad test at four, eight, 12, 16, 28, and 52 weeks post surgery. Opsomer (1994) randomised 43 (39 completing) men to two sessions a week of PFMT with BF plus EStim (method not described) or to one session of verbal instruction on PFMT plus home exercises. Continence was measured by 48 hour pad test.

1. Quality of data

Two trials appeared to have adequate random allocation and concealment [299, 308], although in the latter treatment was provided by the primary investigator who was aware of group assignment. In Moore (in press 2008), therapists were blinded to the results of the control group; pads were weighed by a person unaware of group assignment; data was entered by a data manager. Van Kampen (2000) had pad weights done directly by the patient at home. Dropouts were accounted for and described fully by Moore (in press 2008) and Van Kampen (2000), partially by Opsomer (1994). There was a high dropout rate in Franke (2000) and these data were not accounted for in the analysis. There were no reported dropouts in the Floratos (2002) or Ribeiro (2008) trials. Floratos (2002), Moore (in press 2008), Van Kampen (2000) all described ITT analysis.

Continence evaluation was different for each study as well as timing of recruitment and intervention, content of intervention and control treatments. Outcomes varied widely: percentage of participants pad free [291], one hour pad test [290], 24 hour pad test (<2g=continent, Ribeiro 2008; Van Kampen 2000; <8g=continent, Moore (in press 2008) and a pad test not described [296]. Follow up ranged from 12 weeks to one year.

2. Results

Three trials compared PFMT and BF to a control condition. At 12 weeks, Ribeiro (2008) reported statistically significant difference in 24 hour pad tests (51g, SD 119 versus 197g, SD 269, p=0.026), but there was no statistically significant difference at six months post surgery.

In the Van Kampen (2000) trial at eight weeks, there was a statistically significant difference in mean urine loss (30g treatment; 82g control) but by 12 weeks this difference was no longer statistically significant. Van Kampen (2000) also found a statistically significant difference in proportion of treatment group participants reporting continence at three months compared to control (43/50 (88%) versus 29/52 (56%)), but no differences beyond three months. Franke (2000) reported no difference between groups on 24 hour pad test or pad-free rates but sample was small and dropout rate nearly 50%.

None of the three trials that utilised PFMT and BF versus verbal or written instruction on home PFMT showed statistically significant differences between the groups. Outcomes were measured using one hour pad test or number of pads [290], 24 hour pad test, International Prostate Symptom Score (IPSS), or subjective report of continence at eight, 12, 16, 18, or 52 weeks [308], and pad test at 12 weeks [296].

Summary

Health professional instruction in PFMT with BF when compared with control conditions seemed to reduce the amount of leakage in the early weeks of recovery (up to three months). However, comparisons of PFMT with clinic BF versus PFMT at home did not find similar differences. Based on the current evidence the addition of EStim or BF does not appear to improve continence outcomes over and above PFMT. (Level of Evidence: 2). However, BF may be less difficult for the therapist than DRE.

It seems those who do PFMT compared to no active treatment, might have less leakage in the first three months postoperatively. To the patient, this early improvement may be important in activity, wellbeing, and socialising. Such concepts require further investigation.
RECOMMENDATIONS

The use of BF in clinic, over and above home PFMT, is currently a therapist/patient decision based on economics and preference. (Grade of Recommendation: B).

c) PFMT after TURP

Little study has been dedicated to UI after TURP. In fact, the issue has been largely ignored, perhaps because the incidence of UI after TURP is reported to be very low. Two trials were potentially eligible for inclusion [292, 298], but the latter trial was grouped with studies of PFMT after radical prostatectomy because the 11 participants comprised one following TURP and 10 following radical prostatectomy. No new trials were found on PFMT after TURP. There is one on-going large trial with results anticipated in 2010 [310].

Porru (2001) randomised 58 men booked for TURP. At the baseline preoperative visit, PFM strength, tone and grading were established with a DRE. There were weekly follow up sessions for four weeks post TURP. It was unclear what information, if any, the control group received.

1. QUALITY OF DATA

It was not clear if random allocation was concealed or outcome assessment blinded, and the proportion of dropouts was not stated.

2. RESULTS

While there were statistically significant differences in UI and post micturition dribble as measured by voiding diary and IPSS, there was no statistically significant difference at four weeks.

SUMMARY

In the absence of sufficient data from rigorous and well-reported trials it is not known if PFMT reduces UI following TURP. More systematic investigation of the the natural history of UI after TURP is probably needed, to establish the potential cost/benefit of intervention, before further trials are initiated.

3. OTHER LUTS

Post micturition dribble (PMD) is an annoying problem experienced by many men of all ages likely due to a failure of the bulbocavernous muscle to evacuate the bulbular portion of the urethra, causing pooling of urine in the bulbular urethra which then dribbles with movement.

The 3rd ICI identified two RCTs on conservative management of PMD [289, 311] and no further trials were found for the current update. No trials were found on prevention of PMD and it is unlikely that such studies would be undertaken because of the longitudinal nature of such an exploration.

a) PFMT for post micturition dribble (PMD)

Two RCTs totalling 85 participants who had not undergone prostatectomy have been reported in which PFMT and/or urethral milking were compared to verbal instruction and lifestyle changes [289, 311]. Paterson (1997) assessed men assigned to one of three groups: daily PFMT, urethral milking, or lifestyle changes (consisting of relaxation therapy and oedema management) using four hour pad test at five, nine, and 13 weeks. In a study on erectile dysfunction [289], over 65% (n=36) of participants also complained of PMD. Participants were randomised to PFMT using BF (five weekly treatments plus home exercises) or lifestyle advice addressing smoking, alcohol intake, general fitness, a healthy diet, weight reduction, and saddle pressure. Outcome was patient report using a standardised questionnaire administered by an interviewer unaware of group assignment.

1. QUALITY OF DATA

It was not clear if allocation was adequately concealed in either study. In both studies data collection was done by the researchers but data analysis was done by a separate party.

2. RESULTS

Paterson (1997) found both PFMT and urethral milking were equally effective and better than lifestyle changes. Dorey (2004) found that the PFMT group not only reported a significant improvement in erectile function measured by International Index of Erectile Function (p=0.001) but also a significant improvement in PMD measured by standardised questionnaire (67% improved in treatment group compared to 7% of controls; p<0.002).

SUMMARY

Based on two small studies, it seems that PFMT and urethral milking might both be effective in the control of the annoying symptom of PMD (Level of Evidence: 2).

RECOMMENDATIONS

Men can be offered instruction to do a strong PFM contraction immediately after voiding, or urethral massage to empty the urethra, to improve symptoms of PMD (Grade of Recommendation: C).

4. FACTORS AFFECTING OUTCOME

Based on the current evidence, it appears that time from surgery to implementation of exercises does affect outcome and that by three months after surgery less improvement is noted. Future trials could consider analysis to evaluate the effect of length of time from prostatectomy surgery, co-morbid conditions, prior pelvic surgery, and medications (including smoking and alcohol use) on treatment outcome.
Electrical stimulation (EStim) is reported to be effective in the treatment of both UUI and SUI in men [223, 235, 312].

For men with DO and UUI there is often no known cause (idiopathic DO), although in some men symptoms can be associated with neurogenic disorders and to bladder outlet obstruction such as benign prostatic hyperplasia. It is believed that EStim for UUI acts through reflex inhibition of pelvic efferents or activation of hypogastric efferents through stimulation of the afferent input in the sacral route [225, 312].

Male SUI is rare but radical prostatectomy and, rarely, TURP may cause sphincter injury leading to SUI [293, 313-315]. DO, poor compliance and decreased contractility may also be factors related to post-prostatectomy incontinence [293, 316]. For male SUI, EStim can be used to enhance contractility of the PFMs in the same way as female SUI [317, 318], and may be used as stand alone therapy, as a second-line treatment when other methods have failed, or in combination with PFMT [300, 319]. It has been postulated that continence is regained more rapidly [320] and the duration of the application of EStim is reduced when PFMT is augmented with EStim [320, 321]. EStim is also believed to be more effective in patients who are initially unable to identify and contract the correct PFMs [213]. Interestingly, it is generally agreed amongst those using EStim that it should be avoided for those with carcinoma of the bladder for fear that EStim may increase abnormal cell activity [322]. Although there are no data to confirm or refute this, many physiotherapists are unwilling to use EStim for patients with cancer and, therefore, post radical prostatectomy. Further research is needed to clarify this risk.

This section will examine evidence for the use of EStim for the prevention and treatment of UI in men. Questions addressed are:

- What is the most appropriate electrical stimulation protocol?
- Can electrical stimulation prevent UI?
- Is electrical stimulation better than no treatment, placebo or control treatments for UI?
- Is electrical stimulation better than other treatments?
- Does the addition of electrical stimulation to other treatments add any benefit?
- What is the effect of electrical stimulation on LUTS other than UI?
- What factors might affect the outcome of electrical stimulation?

A literature search for reports of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed (see appendix). No other types of study design were considered. Since the 3rd ICI only one new RCT [323] was identified and included in this chapter. A previous relevant Cochrane systematic review [324] was updated, and the new review [319] contributed to this section.

1. PREVENTION

There have been no studies on the effect of EStim for prevention of UUI or SUI (including post prostatectomy UI) in men.

2. TREATMENT

One systematic review was identified [319], along with nine RCTs [223-226, 239, 293, 296, 300, 323] of which one was new since the previous report [323]. An abstract of a trial by Ceresoli [325] reported data for men, but the separate effects of EStim could not be assessed and the study was excluded.

a) Is EStim better than no treatment, placebo or control treatments?

No studies were identified that compared EStim with no treatment or a control. Two placebo controlled trials were identified, and both included men and women. One included 29 men and 39 women with UUI [224], and the other 30 women and five men with SUI [223]. In the latter trial, four men had post-prostatectomy incontinence and one had sphincter deficiency due to sacral cord tumour.

1. QUALITY OF DATA

Both trials blinded patients and doctors to treatment allocation [223, 224]. For EStim in UUI, three patients (8%) in the active group and one (3%) in the sham group dropped out, and two patients in each group discontinued the treatment due to adverse events (5.4% and 6.5% respectively).

For EStim in SUI, two of 35 patients (6%) dropped out and none of the patients had adverse events.

2. RESULTS

i) Men with UUI: The authors reported statistically significant differences in cure (22% active and 4% sham) and improvement rates (81% active and 35% sham) between the groups; data were not differentiated for men and women [224].

ii) Men with SUI: None of the participants in the sham group were cured or improved. One man in the active EStim group was cured and a second was improved; five men participated in the study but it was not clear how many were allocated to sham and how many to active EStim.
EStim protocols for men are similar to those for women and like protocols in women vary widely. Intermittent, short-term stimulation (or maximal electrical stimulation) using a portable stimulation device at home [323] or in clinic [239, 293, 300] has most often been used. Rectal or surface electrodes are most common; surface electrodes are positioned over the perineal region [323]. For the treatment of SUI (and post-prostatectomy incontinence) EStim is most often used in combination with PFMT, but also as a monotherapy [239]. Usually a rectal electrode is used, and the stimulation artificially stimulates the pudendal nerve and its branches to cause direct reflex responses of the urethral and periurethral striated muscles [293, 323].

Frequencies of 14Hz have been used for UUI [323], while 20Hz [239], 27Hz [300] and 50Hz [293] have been used for SUI. Pulse form is mostly biphasic; pulse width varies and includes 300 microseconds [239], 250 milliseconds [323], one [293] and five seconds [300]. Duration of the stimulation varies as well, from 15 minutes [300] to 30 minutes [293], and from twice daily [300] [239] to twice weekly [293]. Duration of treatment has ranged from one month [239], to three months [300].

**Summary**

So far, no studies comparing EStim protocols have been identified. The most appropriate EStim protocol for different types of symptoms is unknown. EStim protocols for men have been developed from studies in women. The variability in the findings of the trials included in the remainder of this section may in part be due to differences in the effectiveness of the wide range of protocols that have been tested. There are many differences in clinical application that have not yet been investigated. Some populations or subgroups of men may benefit from EStim more than others, but this observation has not yet been investigated.

**b) Is one approach to EStim better than another?**

EStim protocols for men are similar to those for women and like protocols in women vary widely. Intermittent, short-term stimulation (or maximal electrical stimulation) using a portable stimulation device at home [323] or in clinic [239, 293, 300] has most often been used. Rectal or surface electrodes are most common; surface electrodes are positioned over the perineal region [323].

For the treatment of SUI (and post-prostatectomy incontinence) EStim is most often used in combination with PFMT, but also as a monotherapy [239]. Usually a rectal electrode is used, and the stimulation artificially stimulates the pudendal nerve and its branches to cause direct reflex responses of the urethral and periurethral striated muscles [293, 323]. Frequencies of 14Hz have been used for UUI [323], while 20Hz [239], 27Hz [300] and 50Hz [293] have been used for SUI. Pulse form is mostly biphasic; pulse width varies and includes 300 microseconds [239], 250 milliseconds [323], one [293] and five seconds [300]. Duration of the stimulation varies as well, from 15 minutes [300] to 30 minutes [293], and from twice daily [300] [239] to twice weekly [293]. Duration of treatment has ranged from one month [239], to three months [300].

**c) Is EStim better than other treatments?**

Three RCTs have compared EStim with other treatments. In a three arm trial Yokoyama (2004) compared EStim, magnetic stimulation (MStim) and verbal/written instruction in PFMT in men with post-prostatectomy incontinence [239]. Two trials compared EStim with MStim [225] or medication [226] in men and women with UUI.

**1. Quality of data**

Yamanishi (2000b) compared EStim with MStim for inhibition of DO in a urodynamic study of 32 patients (15 males, 17 females; aged 62.3 years, SD 16.6) [225]. Random allocation concealment was adequate; results were not reported by gender.

Yokoyama (2004) compared EStim, MStim and verbal/written instruction on PFMT in men with post-prostatectomy incontinence [239]. This study did not report method of randomisation, whether or not allocation was adequately concealed, or blinding of patients, healthcare providers or assessors. The number of treatments, duration and intensity seemed to be different between groups. Home EStim comprised 15 minutes of twice daily stimulation for one month, at maximum tolerable level of intensity. For MStim, treatment sessions were 20 minutes, twice a week for two months, with stimulating intensity gradually increased up to the tolerable level. PFMT consisted of PFM exercises in supine position with instructions how to contract the anal muscles selectively. Verbal and written instructions for home practice were given to the patients. Patients were followed up for six months.

Soomro (2001) compared EStim (Transcutaneous Electrical Nerve Stimulation, TENS) with medication (oxybutynin) for UUI in 43 patients (13 men, 30 women) with DO using a crossover design [226]. Results were not reported by gender. No information about randomisation procedure, random allocation concealment, blinding of observers, or drop-outs (if any) was given. Oxybutynin was started at a dose of 2.5mg orally twice daily and titrated to 5mg orally three times daily by day seven. Dual channel TENS with two self-adhesive pads connected to the stimulator and applied bilaterally over the perianal region (S2 to S3 dermatome) was used. Stimulation parameters were set at a frequency of 20Hz and a pulse width of 0.2msecs on a continuous mode. TENS duration was up to six hours daily.

**2. Results**

**i) Men with DO**: In the urodynamic study of EStim versus MStim, bladder capacity at first desire to void and maximum cystometric capacity increased significantly in both groups compared to baseline; the increase in maximum cystometric capacity was statistically significantly greater in the MStim (106%, SD 130) than the EStim group (16%, SD 34) (p=0.0135).

Soomro (2001) reported that EStim and medication improved subjective parameters but only oxybutynin showed statistically significant improvements in objective urodynamic parameters such as bladder...
volume at first desire to void and at first overactive detrusor contraction.

**ii) Men with post-prostatectomy incontinence:**

Amount of leakage in the 24 hours after catheter removal was 684g, 698g and 664g for the EStim, MStim and PFMT groups respectively. At one month, it was 72g, 83g and 175g (EStim versus PFMT, p<0.05), and at two months was 54g, 18g and 92g respectively (MStim versus PFMT p<0.05). Finally, six months later, the average 24 hour leakage weight was less than 10g in all groups. Quality of life measures decreased after surgery, but gradually improved over time in all groups. No complications were noted in any of the groups. The authors concluded that both MStim and EStim offered earlier continence compared with PFMT after radical prostatectomy.

**Summary**

There were few men in either of the two trials comparing EStim and MStim, the single trial comparing EStim with verbal/written instruction in PFMT, or single crossover trial comparing EStim with oxybutynin. In the absence of sufficient data it is not known if EStim is better than MStim or written/verbal instruction in PFMT or oxybutynin for UI in men.

**d) Does the addition of EStim to other treatments add benefit?**

Four RCTs have been identified investigating the addition of EStim to other treatments for men with post-prostatectomy incontinence [293, 296, 300, 323]. Opsomer (1994) compared intensive PFMT plus EStim (once a week) plus BF versus simple PFMT in 43 men. As it was not possible to differentiate the effects of additive EStim from adjunctive BF this study was not further considered. No trials were found in men with UI.

**1. Quality of data**

Moore (1999) compared standard treatment (verbal and written instructions about PFMT) versus intensive PFMT, versus intensive PFMT plus rectal EStim in 63 men with UI ≥ 8 weeks after radical prostatectomy. Randomisation was adequately concealed, there was a power calculation, and adherence to protocol was monitored using patient-recorded diaries. Five patients dropped out, three in PFMT/EStim and two in the PFMT group. In one patient dropout was related to the use of EStim (rectal pain). Intensive PFMT, which focussed on strength, endurance, speed and control, comprised physiotherapy for 30 minutes twice a week for 12 weeks. Initial contractions were of 5-10 seconds with a 10-20 seconds rest, with 12-20 repetitions. Endurance exercises focused on maintaining contractions at 65-75% of maximal strength. In the PFMT/EStim group EStim and PFMT were alternated per session. EStim was provided by a surface anal electrode, with intensity to induce visual lifting of the levator ani. Stimulation parameters were 50Hz, biphasic pulse shape with one second burst, a one second pulse width and one second pulse trains. All therapy was performed by one experienced physiotherapist.

Wille (2003) compared PFMT alone (n=47) versus PFMT plus EStim (n=46) versus PFMT plus EStim plus BF (n=46) in 139 men who underwent radical prostatectomy. Because in the group with both EStim and BF the results of each treatment modality could not be differentiated, we considered only the data from the PFMT alone versus PFMT plus EStim comparison. Randomisation, blinding of observers, and withdrawal or dropout rates were not described. Patients in the PFMT group received verbal and written instructions about postoperative PFMT from a physiotherapist, intensive postoperative physiotherapy for 20 to 30 minutes for three days, a post-discharge rehabilitation programme for three weeks (not described), and a three month home PFMT programme. In the PFMT/EStim group EStim was provided by a bioimpulser surface anal electrode for 15 minutes. EStim parameters were 27Hz, biphasic pulse shape with one second bursts, a five second pulse width and two second pulse trains. Intensity of current was controlled by each patient from 10-100%.

Hoffmann (2005) compared percutaneous EStim plus PFMT versus anal EStim plus PFMT versus PFMT alone in men with post-prostatectomy incontinence; this trial allocated 60 men per group, the intervention was for four weeks, and each patient was followed up for three months. It was not clear if random allocation was concealed or if observers were blinded. Dropouts were 22/60 in the anal EStim/PFMT group, 4/60 in the percutaneous EStim/PFMT group and 0/60 in the PFMT group. PFMT consisted of a “specialized program” of “continence training”, lifestyle changes, osteopathy and “Feldenkrais Lehre” three times/week in the clinic and three times/day at home, with a daily maintenance home programme after finishing the therapy.

**2. Results**

Hoffmann (2005) found that 9/60 men in the anal EStim/PFMT group reported recovery, versus 11/60 in the percutaneous EStim/PFMT group; data were not reported for the PFMT only group. Wille (2003) found more men in the PFMT/EStim group reported recovery compared to PFMT alone, but the difference was not statistically significantly different (OR 0.48, 95% CI 0.21 to 1.09).

Pad test results were not consistent. Using a 24 hour pad test Moore (1999) found a statistically significant difference in decrease of urine loss favouring PFMT over EStim/PFMT (MD -182.00, 95% CI -276.56 to -87.44). Wille (2003) found that 37% in the EStim/PFMT group were continent on pad test versus 29% in the
PFMT alone group immediately after catheter removal. At three months 77% in EStim/PFMT group were continent versus 65% in the PFMT group, with 82% and 77% continent respectively after 12 months. None of these differences at any of the three time points were statistically significant.

EStim was associated with adverse events. In Moore (1999) three out of 19 men in the EStim group dropped out because of bladder neck contractures. Hoffman (2005) reported that the main reason for dropouts was discomfort with EStim (18 of 60).

**SUMMARY**

Three RCTs investigated the addition of EStim to PFMT for men with post-prostatectomy incontinence. Data suggested no further benefit of EStim when added to PFMT over PFMT alone; the numbers in each trial were relatively small. (Level of Evidence: 2)

**RECOMMENDATIONS**

For men with post-prostatectomy incontinence there does not appear to be any benefit of adding EStim to a PFMT programme (Grade of Recommendation: B).

**3. OTHER LUTS**

No studies were identified which addressed this comparison in men.

**4. FACTORS AFFECTING OUTCOME**

*a) Age*

There are no comparisons of the effects of EStim for UI between younger and older men. While many EStim studies include participants over 50 years most studies don’t include those over about 80 years [326]. In the studies of EStim for post-prostatectomy incontinence in this chapter the mean age of men is about 66 years. Although post-prostatectomy studies have included older men it may be unwise to extrapolate the effects of EStim in older men with SUI to older men with UUI, because in the former UI is usually as a result of sphincter incompetence whereas in the latter the symptoms are those of an OAB. Further, it is not known whether the efficacy of EStim for UUI in elderly men is similar to that for women [293].

*b) Other*

Many other factors, such as types of electrodes, intensity, frequency and duration of stimulation, electrode positioning, the number of treatment sessions, diagnosis and underlying cause, patient selection, and treatment adherence are plausible factors affecting outcome. Little is known about the effect of any of these and there are no trials investigating these factors in male patients.

**IV. MAGNETIC STIMULATION (MSTIM)**

Background information about extra corporeal magnetic innervation, more commonly called magnetic stimulation (MStim), has been given in the section on MStim for women (see B5). MStim has also been used in men; it is unclear whether the mode of action and effects of MStim are similar in men and women. In men, MStim is used to treat UI after radical prostatectomy [239, 327] and for the inhibition of DO [225].

The questions to be addressed are the same as those for women (see B5). A literature search for reports of relevant systematic reviews and reports of RCTs and quasi-randomised trials was performed (see appendix). No other types of study design were considered. Since the 3rd ICI one further RCT has been published. Suzuki (2007) compared the effect of MStim versus sham MStim for UUI in 39 patients (23 females and 16 males). The study was not included in the review below because both groups also received PFMT, and data were not reported separately for men and women [328].

**1. PREVENTION**

No trials investigating the primary or secondary prevention effects of MStim for men with UI were found.

**2. TREATMENT**

Three RCTs were identified; two full manuscripts [225, 239] and one abstract of an ongoing study without data [327]. The trial by Yamanishi (2000b) included both men and women with UI; because the effects of MStim might be different between sexes (due to differences in the underlying aetiology of symptoms) this study has only contributed to the analysis where the researchers’ differentiated the effects of treatment in men and women.

*a) Is MStim better than no treatment, placebo or control treatment?*

No studies were found addressing this question.

*b) Is one approach to MStim better than another?*

No studies were found addressing this question.

*c) Is MStim better than other treatments?*

Two studies were identified [225, 239]. Both compared MStim with EStim; the latter also compared MStim and PFMT. Readers are referred to section C.3.2c for a description of these studies, findings, and summary.

**3. OTHER LUTS**

No studies were found.
4. FACTORS AFFECTING OUTCOME

None of the included trials addressed the effect of age, or any other factor, on outcome of MSTim. The relationship between age (or any other factor, such as treatment parameters, treatment adherence, or diagnosis) and the outcome of MSTim has yet to be determined.

V. SCHEDULED VOIDING REGIMENS

Scheduled voiding regimens include bladder training (BT), timed voiding (TV), habit training and prompted voiding. They are frequently combined to achieve maximum benefits. Although there is evidence to indicate that scheduled voiding regimens, especially BT and TV, are commonly used in the treatment of men with UI and other LUTS, there has been substantially less research that addresses their use in men compared to the literature on their use in women.

1. PREVENTION

No trials investigating the preventive effects of scheduled voiding regimens for men with UI were found.

2. TREATMENT

Since the 3rd ICI, there have been no new reports of BT that have included men in the study population. Five RCTs have included men; however, most included only a small number of men in the sample [55, 268, 269, 272, 277]. Two observational studies, but no RCTs, were found regarding TV. No studies were located that addressed habit training or prompted voiding in men.

a) Bladder training

A total of five RCTs involving 142 men met the criteria for inclusion in this review. All trials (previously described in section B6) had predominantly female participants; one RCT compared BT to BT plus caffeine reduction (seven men, 86 women) [55]; and three RCTs compared BT plus placebo drug versus anticholinergic drug therapy available prior to 1995 (six men, 28 women [277]; four men, 30 women [269]; two men, 58 women [268]). The largest RCT compared drug therapy alone (tolterodine) to drug therapy plus BT (123 men, 378 women) [272]. A sixth study was located that compared BT supplemented with drug therapy after three months, but it was excluded from review because the full length report was in Japanese and an English translation was not available [329].

As none of the trials reported outcome data separately for men, and with the proportion of male participants being so small (3%, [268]; 8%, [55]; 12%, [269]; 8%, [277]; 25%, [272]), there is insufficient evidence available to comment on the effectiveness of BT in men.

b) Timed voiding

There have been two clinical series that investigated timed voiding in men only [259, 330]. In the first, Sogbein (1982) applied TV in incontinent men in a geriatric hospital [330]. In the second study, 20 men (ages 55 to 89 years) with persistent post-prostatectomy incontinence were advised to void every two hours and keep a daily bladder record for two weeks as a run-in to being treated with BF-assisted behavioural training [259]. Outcomes were measured by a two week voiding diary kept at baseline and during two weeks of timed voiding by patients diagnosed with SUI, UUI, and/or continual leakage.

1. QUALITY OF DATA

Both studies used a clinical series design and patients in both subsequently received other treatment if they were not adequately improved. In the Sogbein study, nurses checked the patients’ clothing for wetness at each two-hour voiding interval and recorded the results. Data in the Burgio study were based on bladder diaries completed by the patients. Reasons for dropout [330] and non-adherence [259] were provided.

2. RESULTS

Sogbein (1982) reported an 85% improvement rate in UI men in a geriatric hospital. Burgio (1989), in men with persistent post-prostatectomy incontinence, found the two hour TV schedule was used with only 12 out of 20 men, because they were either already on a voiding schedule, unwilling to go on a voiding schedule, or results were not presented because the patient was noncompliant. In five men with SUI, TV resulted in a 29% decrease of incontinent episodes; in three men with UUI, two improved and one dramatically regressed producing a 33% increase in incontinent episodes. In four patients with continual leakage, there was no reduction in percentage of wet intervals.

SUMMARY

With limited Level 3 evidence (and no higher order evidence), there is insufficient evidence available to comment on the effectiveness of TV in men.

3. OTHER LUTS

No studies were identified in men.

4. FACTORS AFFECTING OUTCOME

a) Age

The five RCTs involving BT included older men, as well as women, in their study populations. Three trials specifically recruited elderly adults aged 65 to 70 years and over [268, 269, 277]. The largest trial of men recruited adults aged 18 and over with a median age of 62 years. There was no subgroup analysis related
to age and gender effects, so it is not possible to draw conclusions regarding the effect of BT in older men [272]. Voiding regimens are of particular interest for the elderly, but some are effective in younger patients with UI [253].

b) Other

No studies were identified on other factors affecting outcome of TV or prompted voiding in men.

Patients who appear to benefit most from scheduled voiding regimens are highly motivated individuals without cognitive deficits. Men and women with SUI and UUI have benefited, whereas patients with severe sphincter damage (e.g. after radical prostatectomy) generally do not [253].

VI. COMPLEMENTARY AND ALTERNATIVE MEDICINES

Similar to women, complementary therapies are used for the treatment of male UI. Therapies include relaxation, meditation, imagery, hypnosis and naturopathic and herbal remedies, but only trials of acupuncture therapy have been found in men with UI. Therefore, only acupuncture will be considered in the remainder of this section.

Acupuncture is a traditional Chinese modality and has been used for the treatment of urinary disturbances. Acupuncture has been reported to relieve OAB symptoms including UI due to spinal cord injury [331], and idiopathic DO or MUI [332-334].

1. PREVENTION

No studies were identified on the preventative role of complementary therapies in men.

2. TREATMENT

Acupuncture has been shown to improve urodynamic parameters such as bladder capacity in men with UUI [331, 332]. Acupuncture is a form of somatic sensory stimulation [334]. The mechanism by which acupuncture inhibits DO remains unclear, but suppression of the spinal and supraspinal reflexes that lead to bladder contractions is considered one of the most important mechanisms of acupuncture stimulation. In an experimental study with anesthetised rats, an acupuncture-like stimulation of the perineal skin and muscles inhibited detrusor contraction [335, 336]. A release of neuropathies (e.g. endorphins) by acupuncture may be another possible mechanism of increasing bladder storage [334].

Acupuncture may also change sphincter activity, which may be useful for men with SUI. Urethral EMG in rats showed excitation when acupuncture-like stimulation was applied to the skin and underlying structures in the rostral half of the body, the hind paw, the perineal area, testis or urethra, while less excitation was seen when the bulbocavernousus, sacrococcygeus or pubococcygeus muscles were stimulated [337]. Kubista [338] showed a significant increase in the urethral closing pressure. However, there has been no report on the effects of acupuncture for male SUI or post-prostatectomy incontinence.

a) What is the most effective acupuncture protocol?

Acupuncture has been carried out with disposable stainless steel needles (0.3mm in diameter, 60mm in length) inserted into the bilateral BL-33 (Zhongliao) points on the skin of the third posterior sacral foramina [331-333] or several other points (BL-31,32, 21, 23, SP-6, KI-3, LI-11, CV-1, 2, 4, 5) [339], and usually performed once or twice weekly [331-334, 340]. Acupuncture protocols vary and there is no apparent consensus between investigators. It is not known if any acupuncture protocol is more effective than another.

b) Acupuncture versus no treatment, sham acupuncture or any other treatment

Only one RCT has been identified including both men and women [341], but there is no study exclusively for men. In a randomised, placebo-controlled, single-blind study among 20 elderly patients (three males, 17 females) Ellis (1990) showed that the frequency of voiding at night was reduced after acupuncture [341].

In an uncontrolled study, Kitakoji (1995) treated 11 patients (nine males, two females) with OAB including three participants with benign prostatic hyperplasia [332]. Improvement of symptoms was noted in nine, overactive detrusor contractions disappeared in six and significant improvements in both maximum cystometric capacity and bladder compliance were obtained after the treatment. Acupuncture was benefited all three patients with benign prostatic hyperplasia.

In a second uncontrolled study, Honjo (2000) reported an improvement in UI due to neurogenic DO in 13 patients (11 males, two females) with chronic spinal cord injury [331]. Treatment was repeated once a week for four weeks. UI disappeared in two and decreased to 50% or less compared to baseline in six. Maximum cystometric capacity increased significantly from 76ml (SD 62) to 148ml (SD 82) one week after the fourth acupuncture treatment.

The evidence of the effectiveness of acupuncture for men with UI is limited by the lack of controlled studies. To date, the studies are small, objective measures of UI are not included and long-term follow-up is lacking. Preliminary data from predominantly uncontrolled studies suggest that RCTs of acupuncture of UI in men are warranted.

3. OTHER LUTS

In a RCT in patients with sensory urgency after TURP, Ricci (2004) reported significant improvements by
acupuncture reflexotherapy (EStim of somatic and auricular points) in terms of IPSS, QOL scores, decrease of daytime frequency and nocturia, but no improvements with the use of placebo or oxybutynin [340].

Honjo (2000) reported the effects of acupuncture on mono-symptomatic nocturnal enuresis [331]. Fifteen participants (10 males, five females) with mono-symptomatic nocturnal enuresis were treated, and nocturnal enuresis was improved in six just after the treatment and two months later seven were improved. In the six ‘responders’ nocturnal bladder capacity increased significantly from 201 to 334ml (p<0.05).

4. FACTORS AFFECTING OUTCOME

Aside from Ellis (1990), reported above, who specifically recruited elderly participants there is a lack of evidence about the effect of any prognostic factor for the outcome of complementary therapies in men.

VII. SUMMARY

Despite the prevalence of UI and LUTS in older men, the only group that has received much attention in research is men following radical prostatectomy. Overall, the effect of conservative treatment (lifestyle interventions, physical therapies, schedule voiding regimes, complementary therapies) has received much less research attention in men compared to women.

1. RECOMMENDATIONS FOR PRACTICE

There is generally insufficient Level 1 or 2 evidence on which to base recommendations for practice, and most recommendations are in effect hypotheses that need further testing in research.

a) Lifestyle interventions

- It seems reasonable for health professionals to offer men advice on healthy lifestyle choices that may reduce or delay the onset of continence problems (Grade of Recommendation: D) (New).

b) Pelvic floor muscle training (PFMT)

- Some preoperative or immediate post-operative instruction in PFMT for men undergoing radical prostatectomy may be helpful (Grade of Recommendation: B) (Unchanged).

- It is not clear whether PFMT taught by digital rectal examination (DRE) offers any benefit over and above verbal or written instruction in PFMT (Grade of Recommendation: B) (New).

- The use of BF to assist PFMT is currently a therapist/patient decision based on economics and preference (Grade of Recommendation: B) (New).

- Use of a strong pelvic floor muscle contraction immediately after voiding, or urethral massage to empty the urethra, can improve symptoms of post micturition dribble (Grade of Recommendation: C) (Unchanged).

c) Electrical stimulation (EStim)

- For men with post-prostatectomy incontinence there does not appear to be any benefit of adding EStim to a PFMT programme (Grade of Recommendation: B) (Unchanged).

2. FUTURE RESEARCH DIRECTIONS

There is much scope for research on the effects of conservative therapies for UI and LUTS in men. Research that is urgently needed, in the opinion of committee members, is highlighted with the use of *italics*. There are a few recommendations that apply to all future studies in men, namely:

- All future intervention studies must be designed to allow standardised and comprehensive reporting of results based on the ICS and CONSORT recommendations.

- The natural history of UI after radical prostatectomy must be taken into account in study design as the spontaneous recovery rate means that sample sizes must be large to detect any differences between protocols.

- More research is needed to find out what are the most important outcomes for men with UI, so such measures can be incorporated as the primary outcome measures in further trials.

- Data are needed to establish to the cost, and cost effectiveness, of conservative therapies in men with UI.

- Surgical approaches with laparoscopy or robotics offer promising improvements in visualisation for nerve-sparing procedures; further research should address continence and erectile function after these newer surgical procedures.

a) Lifestyle interventions

- To date, no trials have addressed the topic of lifestyle interventions for men with UI.

- *The effects of interventions such as weight and caffeine reduction, both of which show some evidence of benefit in women, are priorities for future research.*
b) Pelvic floor muscle training (PFMT)

- A comparison of preoperative versus postoperative PFMT verbal and written feedback to reduce prevalence and severity of UI following radical prostatectomy is needed.

- Methods of PFMT instruction and supervision require further investigation. Two areas of research interest are:
  - Whether PFMT taught by DRE offers any benefit over and above verbal or written instruction.
  - The effect of group exercise. Because of the peer support that men may receive from participating in a group [342] this might be useful after radical prostatectomy; both Moore [293] and Opsomer [296] reported that support in the post operative period may be important to healthy recovery.

- More systematic investigation of the natural history of UI after TURP is needed, to establish the potential cost/benefit of intervention, before further trials are initiated.

- The relationship between age, or any other factor, and the outcome of PFMT for UI in men has yet to be determined.

c) Electrical stimulation (EStim) and magnetic stimulation (MStim)

- It is not known if pre or postoperative EStim or MStim has a role in reducing the prevalence of UI after radical prostatectomy.

- RCTs in larger samples, with long-term follow up, are needed to investigate all aspects of the effectiveness of EStim and MStim as a treatment for UI in men, including:
  - Either type of stimulation versus no treatment, sham stimulation or other control conditions.
  - Comparisons of both EStim and MStim protocols.
  - EStim versus MStim.
  - Either type of stimulation versus medication.
  - Whether the addition of either type of stimulation to other treatments adds benefit, in particular the addition of stimulation to PFMT.

- The effect of age, and other factors, on outcome of stimulation. Elderly men may have more co-morbid conditions than young men, such as dementia, changes in the secretion of vasopressin, venous insufficiency, renal disease, heart failure, drug intake, restricted mobility and constipation. A more pragmatic approach to inclusion in EStim studies is needed.

d) Scheduled voiding regimens

In the absence of trials exclusively in men, or trials that report data separately for men and women, there is a pressing need for high quality RCTs with an appropriate sample size and long-term follow up to address the effects of BT, TV, habit training and prompted voiding in men suffering from UI.

C. PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) is common and is seen in 50% of parous women [343]. Women with prolapse can experience a variety of pelvic floor symptoms.

Treatments include surgery and conservative management. Choice of treatment depends on the severity of the prolapse and its symptoms, and the woman’s general health. Conservative treatment is generally considered for women with a mild degree of prolapse, those who wish to have more children, the frail or those unwilling to undergo surgery. Conservative treatment is defined here as lifestyle interventions, physical therapies, pessaries and complementary therapies.

The aims of conservative treatment in the management of POP include:

- to prevent the prolapse becoming worse;
- to help decrease the frequency or severity of symptoms caused by prolapse (vaginal, backache, urinary, bowel and sexual symptoms);
- to avert or delay the need for surgery;
- to provide a therapeutic/diagnostic aid (e.g. to establish, when it is not clear, whether a patient’s symptoms are caused by prolapse; to determine whether urodynamics are indicated prior to prolapse surgery; or to confirm suspected UI).

This section will examine the evidence for the use of conservative treatments in the management of POP utilising information from two recent Cochrane systematic reviews [344, 345], and literature identified via a search strategy summarised in the appendix.

I. LIFESTYLE INTERVENTIONS

Lifestyle interventions include weight loss, reducing exacerbating activities (e.g. lifting, coughing) and treating constipation. These interventions seek to avoid exacerbation of the prolapse by decreasing intra-abdominal pressure. The extent to which any of these lifestyle interventions are effective in managing prolapse is thought to be unknown [346]. Studies that investigated lifestyle interventions for the prevention or treatment of prolapse were searched for.
1. Quality of data

No body of literature about the effects of lifestyle changes for the prevention of POP was found. However, several studies were identified that addressed the association between factors such as occupation (involving heavy lifting/strenuous physical activity), bodyweight and constipation, and POP. These studies are reported here.

i) Association between POP and occupation: Two case control studies addressed the association between occupation and surgery for POP [22, 347]. Jørgensen (1994) compared the incidence of surgery for a non-specified degree of prolapse among 28,619 Danish nursing assistants, whose occupation exposed them to repetitive heavy lifting, with 1,652,533 female population controls of similar age. No adjustment for parity was made. Chiaffarino (1999) compared 100 control women with 108 women admitted to undergo surgery for second or third degree uterovaginal prolapse and/or third degree cystocele. Adjustments were made in this study for potential confounding effects, although occupation was collected as a social class indicator and yielded no information about physical effort.

Two further case control studies, conducted in the 1980s, addressed the association between occupations and POP assessed by physical examination [348, 349]. Spernol (1983) and Bao (1989) assessed 200 and 364 women respectively to see whether occupations involving hard physical labour were associated with the risk of development of POP. In Bao (1989) women were classified according to weight carried, however in Spernol (1983) past work history was subjectively assessed as light, medium or heavy work. These parameters were not further quantified nor were the study outcome measures validated. Bodner-Adler (2007), in a case series of 96 women diagnosed and treated for second or third degree uterine prolapse over a three month period at one hospital in Nepal, reported on associated risk factors including heavy lifting/work. [350].

ii) Association between POP and bodyweight: Spernol (1983) also investigated the association between bodyweight and risk of POP. Hendrix (2002), in a more recent cross-sectional study of 27,342 postmenopausal women used questionnaires and a pelvic examination to investigate factors (including occupation as assessed in four broad categories, and bodyweight) associated with POP [351]. Although the large study population allowed examination of numerous associations the study was not designed specifically to determine risk factors for POP. Similarly, despite the examination for prolapse being standardised, no validated grading system (e.g. POP-Q examination) was used to measure prolapse. Four other epidemiological studies, designed to analyse risk factors for prolapse, explored the influence of bodyweight on risk of prolapse [352-355].

iii) Association between POP and bowel function: Rortveit (2007) reported risk factors for symptomatic prolapse from the “Reproductive Risks for Incontinence Study at Kaiser”, a population study of 2,001 randomly selected, community-dwelling women in California, aged 40 to 69 years [356]. Data were collected by a mix of self-report, interview, physical examination and medical record review. Risk factors assessed included irritable bowel syndrome and constipation. Kahn (2005) and Arya (2005) looked specifically at bowel symptoms and constipation and their relationship to prolapse in a cross-sectional study (n=1,004) and a case-control study (cases n=60, controls n=30) respectively [357, 358]. One limitation of Kahn (2005) was the use of a non-validated bowel symptom questionnaire. Arya (2005) collected data on constipation (Patient Assessment of Constipation Symptom Questionnaire) and dietary fibre intake (National Cancer Institute Dietary History Questionnaire). Jelovsek (2005) studied bowel function and constipation in 302 women presenting consecutively to a urogynaecology clinic with either prolapse or lower urinary tract symptoms [359].

iv) Association between POP and anaemia: Scherf (2002) examined and surveyed 1,348 women in rural Gambia, and presented data on the associations between severity of prolapse, and socio-demographic and morbidity variables, including presence of anaemia [360].

2. Results

i) Association between POP and occupation: All but one [351] of the studies reported above found a positive association between occupations associated with lifting and the presence of prolapse. Danish nursing assistants were 1.6 times (95% CI 1.3 to 1.9) more likely to undergo surgery for POP than general population control women but as noted this analysis did not adjust for parity [22]; Italian housewives were 3.1 times (95% CI 1.6 to 8.8) more likely to undergo surgery for POP than professional/managerial women [347]; 68% of women with uterine prolapse reported a history of medium/heavy work compared to 40% of control women without prolapse (p=0.0001) [348], the increased risk remaining after controlling for childbirth; and female workers that generally lifted more than 20kg were more likely to have uterine prolapse than other workers [349]. Heavy work in the early post-partum period was cited by Bodner-Adler (2007) [350] as a risk factor for uterine prolapse in Nepalese women; 88% with prolapse reported doing such work.

ii) Association between POP and bodyweight: Spernol (1983) reported that 77% of women with POP were overweight compared with 45% of women with...
no prolapse (p<0.001). Hendrix (2002) reported that being overweight was associated with a significantly higher prevalence of uterine prolapse by 31% (OR 95% CI 1.15 to 1.48); rectocele by 38% (OR 95% CI 1.25 to 1.53) and cystocele by 39% (OR 95% CI 1.28 to 1.51).

Also, obesity was associated with a significant 40% (OR 95% CI 1.24 to 1.59), 75% (OR 95% CI 1.54 to 1.99) and 57% (OR 95% CI 1.41 to 1.74) increase in each of these conditions respectively. Overweight women were also reported to be at increased risk of prolapse in both the British Oxford Family Planning Association Study [352] and the cross-sectional study in menopausal clinics in Italy [355]. This finding however was not confirmed by Rinne (1999) or Samuelsson (1999) who concluded that increased bodyweight/ obesity did not predispose women to genital prolapse [353, 354].

iii) Association between POP and bowel function:
In a cross-sectional study, Rortveit (2007) reported that current constipation, experienced monthly or more frequently, was associated with an odds ratio for symptomatic prolapse of 2.5 (95% CI 1.7 to 3.7), after controlling for age, race, education and number and type of delivery. Kahn (2005) found, in women attending for routine gynaecological care, weak relationships between prolapse severity (POP-Q measurements) and bowel symptoms, however straining at stool was found to be associated with anterior vaginal wall (measured by POP-Q point Ba) and perineal descent (POP-Q points Gh + Pb). Arya (2005) found women with prolapse had an increased risk of constipation compared to controls (after allowing for age, prior pelvic surgery and total fibre intake), and this was partially due to their lower intake of dietary insoluble fibre. Jelovsek (2005) found that neither overall POP-Q stage of prolapse nor stage of posterior vaginal wall prolapse was associated with constipation. There was no difference in the prevalence of constipation between those with UI and those with stage III or IV prolapse in this study.

iv) Association between POP and anaemia: Scherf (2002) found that 46% of women had prolapse on vaginal examination (most commonly cystocele: 57%), and in those not pregnant at the time, moderate/severe anaemia (Hb<10) was associated with a two-fold increased odds of having prolapse.

Constipation is a modifiable risk factor which perhaps has potential to impact on development of prolapse symptoms. However, evidence regarding the association between constipation or straining at stool and prolapse was conflicting. Existing studies, particularly older ones, are hampered by their cross-sectional nature, inconsistent definitions of POP and use of un validated outcome measures, and failure to adjust for potentially important variables (such as parity and socioeconomic status).

Anaemia is a treatable condition, either through diet or medication, which may be worth considering further in research on prevention of prolapse.

2. TREATMENT
No studies have been identified to date that evaluate the effectiveness of lifestyle interventions in the treatment of women with POP.

II. PHYSICAL THERAPIES

The primary physical therapy for POP is PFMT, with or without other adjuncts. PFMT may include PFM assessment and education, PFM exercise instruction, and PFM bracing against increased intra-abdominal pressure, for example when coughing and sneezing (termed “The Knack” [361]).

Adjuncts (such as BF) or other physical therapies (such as neuromuscular EStim) may be used. These therapies aim to improve PFM strength, endurance, coordination and function.

The promotion of PFMT for prolapse varies between treatment centres with some providing only a patient information leaflet and others giving individual instruction from a physiotherapist [362]. Research shows that verbal teaching of pelvic floor exercises alone is insufficient [363]. It is suggested that 15% of women are incorrectly ‘bearing down’ when trying to carry out these exercises [363]. In women with prolapse, this could further add to the strain on the area and worsen the condition.

A Cochrane systematic review has indicated that PFMT should be offered as first-line conservative management for urinary stress, urge and mixed incontinence [134]. However, its role in managing prolapse is not established [364]. Some authors have extrapolated the results of trials relating to UI, implying for example that PFMT would be effective for prolapse. The importance of clarifying the place of PFMT in the prevention and management of prolapse has been highlighted [365, 366].

No prospective studies of lifestyle interventions to prevent prolapse were found. There is some evidence that occupations involving heavy lifting/hard physical labour or being overweight may play a role in the development of POP (Level of Evidence: 3).
1. PREVENTION

1. QUALITY OF DATA

No studies have been identified to date that evaluate the role of PFMT in prevention of POP. This lack of evidence was noted by Harvey (2003) in a systematic review of PFMT during and after pregnancy [113]. A longitudinal 12-year follow-up of women originally enrolled in an RCT of post-natal PFMT is currently underway (http://www.wellbeingofwomen.org.uk/index.asp?PageID=279), examining the prevalence of prolapse in this cohort who were randomised to a PFMT intervention or control group. No data are yet available. Borello-France (2007) examined 317 women without SUI, prior to prolapse surgery, to determine PFM function (Brink scale score) and prolapse stage (POP-Q) [367]. The association between PFM strength and severity of prolapse was reported.

2. RESULTS

Borello-France (2007) found the Brink Vertical Displacement subscore was significantly higher in women with less severe prolapse. That is, women with stage II prolapse were better able to elevate their pelvic floor than those with stage III or IV. The authors hypothesise that poor PFMs may be a contributory factor in the development of prolapse. Interventions to improve PFM function might thus prevent prolapse. However, conversely, the prolapse itself might contribute to PFM weakness.

SUMMARY

Currently, there is no evidence from intervention studies regarding the role of PFMT or other physical therapies in the prevention of POP; improved PFM strength could prevent prolapse (Level of Evidence: 3).

2. TREATMENT

An evidence-base is now emerging regarding the role of PFMT in the treatment of prolapse, both as a treatment in itself and as an adjunct. Data from five completed trials are now available, two of which had been ongoing at the time of the 3rd ICI. In addition, three sizeable trials are currently ongoing. Feasibility work for a further trial is in progress.

Five completed RCTs were found that evaluated the effects of PFMT in women with prolapse [368-372]. Piya-Anant (2003), Hagen (2006) and Ghroubi (2008) assessed PFMT alone as a treatment for prolapse, whilst Jarvis (2005) and Frawley (2007) focused on PFMT as an adjunct to surgery.

i) PFMT alone: Piya-Anant (2003) assessed the effect of PFMT in elderly women (aged 60 years or more) with genital (anterior) prolapse. This cluster RCT compared 324 control group women with 330 intervention group women; each group included women classified as having no prolapse, mild prolapse or severe prolapse. The intervention group received unspecified PFMT to strengthen the levator and perineal muscles and were instructed to exercise after one meal every day for 24 months. They were also given dietary and fluid advice. Women were followed up every six months for 24 months allowing comparison with baseline measurements. The main outcome measure in the study, worsening of genital prolapse, does not appear to have been determined using a recognised measure. No allowance appears to have been made in the study for the presence of other types of prolapse i.e. posterior vaginal wall prolapse or prolapse of the apical segment of the vagina.

Hagen (2006) conducted a feasibility study for an RCT of a PFMT intervention in 47 women (23 PFMT, 24 controls) with stage I or II prolapse of any type in two UK centres. The intervention consisted of five physiotherapy appointments over a 16-week period, with an individually-prescribed daily PFMT exercise programme. Control women received a prolapse lifestyle advice leaflet by post only. Outcome measures included: blinded prolapse assessment (POP-Q); prolapse-related symptom severity and quality of life via postal questionnaires; PFM strength (modified Oxford grading scale) (intervention group only).

Ghroubi (2008) conducted a trial in 47 women with stage I or II cystocele. Women were randomised to a conservative treatment group (PFM exercises plus advice on healthy living) or a non-treated group. Outcomes included clinical examination, the “Measurement of Urinary Handicap” (MUH) scale, urodynamic tests, the Ditrovie quality of life scale, patient satisfaction.

ii) PFMT and surgery: Jarvis (2005) investigated the effect of PFMT, bladder and bowel training on continence, quality of life and general health symptoms of 30 women undergoing surgery for UI and/or prolapse compared with 30 control women who received no training alongside their surgery. The intervention group received pre-operative training in PFMT exercises, and correct voiding and defaecation techniques with reinforcement post-operatively. There were no prolapse outcomes measured in this study. Results presented relate to the combined group of study women i.e. those having prolapse surgery, those having UI surgery and those having both.

Frawley (2007) compared physiotherapist-led pre- and post-operative PFMT versus usual care in 48 women undergoing prolapse repair surgery, with or without hysterectomy. Intervention comprised one pre-operative instruction session, and eight post-operative appointments, and a final appointment at nine months post-operatively. PFM strength was measured (manometry and modified Oxford grading...
scale) by a blinded investigator at four time points: preoperatively prior to randomisation, and three, six and 12 months post-operatively.

iii) Ongoing trials: In addition, there are three RCTs (two for PFMT alone, one for PFMT as an adjunct to surgery) and one feasibility study for an RCT (PFMT as an adjunct to pessary) ongoing at the time of this review. Following on from the feasibility study by Hagen (2006) a multi-centre trial of the same intervention, in women with stage I, II and III prolapse, is now underway in 17 UK centres (the POPPY Trial, ClinicalTrials.gov Identifier: NCT00476892 ), with additional international centres in New Zealand and Australia. Results are expected in 2010.

Bø and colleagues in Norway are undertaking a single blind RCT involving 100 women with stage I, II or III prolapse evaluating the effects of a PFMT intervention. The intervention spans a six month period, with weekly physiotherapy appointments for three months, then fortnightly appointments for three months, and a structured home training programme (the POP Study, ClinicalTrials.gov Identifier: NCT00271297). A case-control study is taking place simultaneously, including 50 women without prolapse, to assess risk factors for the condition. The results of this study are expected in 2008.

A RCT has just begun enrolling under the direction of the NIH-sponsored Pelvic Floor Disorders Network. This trial will compare two methods of suspending the vaginal vault in women undergoing vaginal surgery for POP and additionally will randomise half of the participants to adjunct post-operative PFM exercises and behavioural therapy and half to routine care. The analysis will assess whether such adjunct therapy improves both anatomic and symptomatic outcomes two years after surgery. The study is expected to be complete by 2012 (the OPTIMAL trial, ClinicalTrials.gov Identifier: NCT00597935).

A feasibility study (the PEPPY study) looking at the possible effects of PFMT with a vaginal pessary in situ is now underway in 17 UK centres (the POPPY Trial, ClinicalTrials.gov Identifier: NCT00476892 ), with additional international centres in New Zealand and Australia. Results are expected in 2010.

Outcome assessment was predominantly by self-reported questionnaire, and women knew the group they had been allocated to. Prolapse severity at follow-up was assessed by a gynaecologist who was blind to the group allocation of the woman. Blinding was not always successful as some women disclosed their group allocation during their assessment. Sufficient information on drop-outs was given. Ghroubi (2008), which was published very recently, is written in French with an English abstract. A translation has been requested in order to allow detailed description of the trial methods and findings.

ii) PFMT and surgery: In Jarvis (2005) randomisation was generated by a computer in balanced blocks of 20, and randomisation outcomes were stored in opaque envelopes separate from the clinic. It was stated that the physiotherapist assessing the women at follow-up was blind to their status. Sufficient information on drop-outs was given. No information on the randomisation methods was available from the published abstract of Frawley (2007). The PFM strength measurements were taken by a physiotherapist who was blind to the women’s group allocation. Numbers of drop-outs were adequately described.

2. Results

i) PFMT alone: Piya-Anant (2003) reported that PFMT was effective in elderly women who had a severe degree of genital prolapse. After 24 months of PFMT, the rate of worsening of genital prolapse was 73% in the control group and 27% in the intervention group (p=0.005). In the subgroup with ‘mild’ genital prolapse, the rate of worsening at 12 months was statistically significantly less for PFMT women than controls (p=0.02), but there was no difference between the groups at 24 months (p=0.1).

Hagen (2006) found that women in the PFMT group were more likely than controls to have an improvement in prolapse stage (Fisher’s exact test p=0.038). Intervention group women had significantly greater improvement by 26 weeks than controls in their prolapse symptom score (mean score decrease 3.5 versus 0.1, p=0.021). There were significant differences between the groups at both follow-up time points in perceived improvement in prolapse (20 weeks, p=0.001; 26 weeks, p=0.012); PFMT women were more likely to report their prolapse was better now than at the start of the study. A significant improvement in PFM strength was detected in the intervention group; mean muscle strength increased by 0.5 on the modified Oxford scale (95% CI 0.2 to 0.8, p = 0.008). However, PFM strength measures were not taken blinded to women’s group allocation.

Ghroubi (2008) found that immediately post-treatment, pelvic heaviness persisted in five women (19%) from the treatment group compared with fourteen (70%) in
the control group (p < 0.001). There were also significant differences in other outcomes, including quality of life and urodynamic measures. It was reported that 20 women from the intervention group retained benefits two years after the treatment had ceased.

**ii) PFMT and surgery:** Jarvis (2005) reported a significant improvement in both quality of life (improvement in score for treatment group 215, 95% CI 124 to 305 versus control group 47, 95% CI -26 to 121; p=0.004) and urinary symptoms (difference between groups in symptom score reduction 3.8, 95% CI 0.7 to 6.9; p=0.017) when pre-operative physiotherapy was given to women undergoing surgery for UI and/or prolapse compared with women who received no physiotherapy. There was no difference between the groups in SUI measured by pad test. Mean maximum PFM squeeze increased in the physiotherapy group by 2.7 cmH2O, and decreased in the control group (-1.8 cmH2O) (p=0.022). Frawley (2007) reported that despite the tendency towards improvement in the PFMT group over time, there were no significant differences in PFM strength scores between the controls and those who received PFMT at any of the post-operative time points.

Comparing the results for the two surgical trials [369, 371] it is interesting that one found an effect of PFMT on post-operative pelvic floor contraction pressure [369] while the other did not [371]. The latter appeared to have a more intensive intervention protocol (with one pre-operative and eight post-operative physiotherapy appointments up to nine months); however the former included teaching of voiding and defaecation techniques as well as a PFMT programme. In addition the trial populations were not identical, with some women having combinations of prolapse, hysterectomy and UI surgery. The sample sizes in both trials were small (n=60 and n=48 respectively).

**Summary**

Given the prevalence of POP and the fact that physical therapies, in particular PFMT, may already be part of the treatment offered to women in many centres [362] the lack of evidence of effectiveness is disconcerting. The results of further trials regarding the effectiveness of PFMT, which is costly in terms of therapist time, are awaited. These ongoing trials are large, have a control group, are randomised and use recognised objective measurements of prolapse severity, and thus will provide a high level of research evidence to inform practice. The effectiveness of PFMT used in conjunction with other treatments is another area where evidence is lacking [344] but trials to address this are also emerging.

Based on the evidence from one large trial, PFMT may prevent deterioration of anterior prolapse. However this trial had several weaknesses including its failure to utilise a recognised objective measurement of degree of prolapse and its restricted population (elderly women with anterior prolapse only). The results from two small trials provide some additional evidence of a positive effect of PFMT on prolapse symptoms and severity. In the next few years, the completion of two sizeable trials of PFMT for POP might provide a much stronger evidence base for clinical practice. (Level of Evidence: 2)

Pre- and post-operative PFMT may help to improve quality of life and urinary symptoms in women undergoing surgery for POP, but the findings regarding its effects on PFM strength are contradictory. The evidence available however is based on two small trials, one of which included women undergoing surgery for UI and/or prolapse. (Level of Evidence: 2)

**Reccomendations**

PFMT may help prevent deterioration in anterior prolapse, and may help improve prolapse symptoms and severity more generally (Grade of Recommendation: B). Further trials are needed to confirm these findings.

Preoperative PFMT may help improve quality of life and urinary symptoms in women undergoing surgery for prolapse (Grade of Recommendation: C). Larger trials are needed, and prolapse-specific measures should be primary outcomes in such trials.

Future studies of PFMT for POP should aim to reach a consensus on the optimal intervention programme prescribed in terms of the number of repetitions, type and duration of exercises and should also consider comparisons of individualised training with group training. There is also a need for studies of the effectiveness of physical therapies in comparison with surgery and vaginal pessaries.

**III. RINGS AND PESSARIES**

Pessaries aim to manage POP by supporting the pelvic area. These shaped devices are inserted into the vagina and rest against the cervix. They hold the prolapse inside the vagina, provide support to related pelvic structures and can relieve pressure on the bladder and bowel. Various shapes and sizes (Figure 9) and types (Figure 10) of pessary exist for use in the treatment of prolapse, a range of which is illustrated by Poma (2000) and Zeitlin (1992) [364, 373]. Modern pessaries are made from a variety of materials...
Figure 9: Range of pessaries (Courtesy of Mediplus Ltd, UK)

Figure 10: Types of pessaries
including rubber, clear plastic, soft plastic with metal reinforcements and silicone [373]. Until recently only a limited range of these has been available in some countries (e.g. the UK where often the choice is a ring or shelf).

Pessaries have been used for many years in the management of POP but their efficacy in treating this condition is unknown [374]. Surveys of pessary use have shown that 86% to 98% of gynaecologists/urogynaecologists prescribe pessaries [374, 375]. In the Cundiff (2000) survey of members of the American Urogynecologic Society 77% of physicians reported using pessaries as a first line therapy. Ninety percent of physicians believed that pessaries relieve symptoms associated with POP, while 48% felt that pessaries also had therapeutic benefit in addition to relieving symptoms.

Whilst there are identifiable trends in pessary use there are clear practice differences with respect to choosing a pessary for a specific patient. Similarly there are no clear prevailing removal regimes [375]. Many physicians receive little or no training in the use of pessaries [374] and have limited experience with pessary selection and fitting.

1. TREATMENT

Clinical experience suggests a substantial proportion of women with prolapse may be managed safely and effectively with a pessary [373, 376, 377]. Much of the evidence relating to pessaries originates from case reports describing complications arising from pessary use [378-381] and review articles that provide advice, primarily based on clinical experience, on the indications for pessary use, pessary selection, fitting, care and replacement [365, 373, 376, 377, 382-387].

A large number of observational studies relating to pessary use have been published. In addition, two completed intervention studies evaluating pessaries (one a before and after design [388], and one a RCT [389]) have recently been published, bringing some advances to research in this area.

1. QUALITY OF DATA

i) RCT: Cundiff (2007) reported a multi-centre crossover RCT, comparing a ring with support and a Gelhorn pessary for the treatment of symptomatic POP. One hundred and thirty four women were randomised; 71 to ring pessary with support and 63 to Gelhorn, followed by crossover to the second type of pessary, ring with support (n=54) or Gelhorn (n=54). Women had stage II or greater symptomatic prolapse and had no prior experience of a pessary. Forty eight percent had stage II, 42% stage III and 10% stage IV prolapse. The largest group (51%) had anterior prolapse. Mean age was 61 years, and most were parous and post-menopausal. There were no significant differences between groups in baseline characteristics. Participants were randomised to be fitted with one of the pessaries for three months, and then were fitted with the second pessary for a further three months. During each three-month period data were collected at one, six and 12 weeks from women who had a successful fit. At one year women had a final appointment to discuss pessary continuation and other treatment needs. Outcomes were measured at enrolment and three-months, including POP-Q, PFDI, PFIQ and a sexual function questionnaire.

Random allocation was by computer-generated random numbers using permuted blocks of variable size. Opaque, sealed envelopes were used to store the random allocation. Participants and clinicians were not blind to the allocation, but data were coded such that analysis was conducted blind.

ii) Non-randomised intervention studies: Lukban (2006) described a study of the effectiveness and safety of the Colpexin Sphere device in women (n=39) with prolapse beyond the hymenal ring [388]; all women had grade three or greater prolapse of at least one vaginal compartment (69% cystocele, 44% rectocele, 31% enterocele, 8% vault prolapse, 21% uterine prolapse). This is a spherical intravaginal device, similar to a pessary, which is placed above the levator musculature and requires active PFM contractions to keep it in place. The device has a string attached for easy removal and is available in six sizes. Its purpose is to reduce the prolapse while facilitating PFM strengthening which may treat co-existing bladder symptoms. Women were instructed to use the Colpexin Sphere only whilst in bed for the first week, and to use continuously thereafter, and were taught PFM exercises to be performed twice daily (Kegels and knee squeezes). The intervention period was 16 weeks. Outcome measures included prolapse stage (modified Baden and Walker classification system), PFM assessment (Brink Scale score), and a Pull Test to measure PFM tone and strength (a tensiometer is used to measure the force required to remove a 35mm sphere from above the levator plate). The small sample size, lack of control group and short follow-up were limitations of the study.

Kapoor (2004) reported on a cohort of 104 women attending a gynaecology service with symptomatic prolapse who completed the Sheffield POP symptom questionnaire [390]. Of these women 65 chose to have surgery and 39 chose to be fitted with a pessary. The baseline symptoms of these women were compared. Fernando (2006), using the same questionnaire, compared symptoms at one year follow-up between women (n=104) who chose surgery (n=48) and pessary (n=56) [391]. It is possible that these studies overlap as they take place at the same hospital.

iii) Observational studies: Several retrospective and prospective observational studies were identified that evaluated factors contributing to successful pessary fitting and usage, and/or the therapeutic impact of pessary use [390, 392-403].
Sulak (1993) evaluated the therapeutic usefulness of pessaries in a retrospective study of 101 women with pelvic relaxation. Wu (1997) performed a prospective study of 110 women with symptomatic POP to evaluate a protocol for pessary treatment. Handa (2002) described prospectively the course of POP amongst 56 women who used a supportive vaginal pessary for at least one year.

Both Hanson (2003) and Clemons (2004) conducted observational studies of 1043 and 100 women with prolapse respectively, to analyse the factors that contributed to successful pessary use. Hanson subsequently conducted further statistical modelling of their data and updated the study findings [397]. Clemons also published separately on the symptoms and patient satisfaction at two months of 73 out of the original 100 study women who had a successful pessary fit [398], and on continuation with pessary at one year of the sub-group who were satisfied users [399]. Mutone (2005) retrospectively reviewed the records of 407 women with symptomatic prolapse who had been fitted with a pessary in order to determine the factors influencing success at three weeks follow-up. Within the group of women 37% had previously undergone prolapse repair surgery. Bai (2005) reviewed the notes of 104 women who had been fitted with a pessary at one urogynaecology department and who were available for follow-up by questionnaire. Data on indications for pessary use, complications, satisfaction and frequency of removal were collected. Maito (2006) carried out a retrospective review of the notes of women who had been referred to a midwifery pessary clinic. Data on 120 women in whom pessary fitting was attempted were presented, including predictors of successful fitting and pessary continuation.

Fernando (2006) addressed the effectiveness of pessaries in alleviating symptoms associated with POP in a prospective study of 203 consecutive women attending a specialist urogynaecology unit.

Follow-up periods for observational studies varied from one week [396] to three years [393]. Only in some studies [394, 396, 398, 399] was a recognised measure of prolapse used i.e. POP-Q examination, to objectively assess and evaluate the prolapse. No consistent measure of pessary fitting “success” was used throughout studies. Commonly used questionnaires were the Sheffield POP symptom questionnaire, and the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ).

2. Results

i) RCT: Combining the two trial periods in a crossover trial by Cundiff (2007), there were complete data on the ring pessary from 94 women, on the Gellhorn from 99, and on both pessaries from 85. Results were presented graphically with no mean values reported. There were statistically significant improvements in the majority of PFDI and PFIQ scale scores for both pessaries, including the prolapse specific sub-scores (POPD1 for symptoms and POPIQ for impact). However there were no differences between pessaries in improvement in these two sub-scores (POPD1, p=0.99; POPIQ, p=0.29). Considering clinically significant differences in scores (improvement of greater than half the baseline standard deviation), all POPDI sub-scores showed clinically significant improvements for both pessaries. However only for the Gellhorn were there clinically significant improvements in impact of prolapse symptoms (POPIQ), and only then for the physical sub-score and the total POPIQ score. Women who were highly satisfied with the Gellhorn also had improvement in a range of symptoms including the POPDI score; no similar significant association was found for the ring pessary with support.

ii) Non-randomised intervention studies: Lukban (2006) evaluated use of the Colpexin Sphere in 39 women, of whom 27 completed the 16-week assessment and were included in data analysis. Twenty two women (82%) had an improvement in their prolapse of at least one vaginal compartment. No detail of the magnitude of this improvement was given. Seventeen women (63%) exhibited increased PFM function as measured by the Brink Scale total score; however the statistical significance of this improvement was not reported. The Pull Test force during contraction increased significantly (p=0.029) between baseline (mean 1.84lb, SD 1.04) and 16 weeks (2.14lb, SD 1.26). Displacement of the sphere with defaecation was a problem for 72% of women. Only two women (5%) experienced vaginal ulceration, and the problem was mild. Twenty five out of 27 women said they would recommend the device to others for the treatment of prolapse.

Two studies compared symptoms in women having surgery and women having a pessary. Kapoor (2004) found that generally the symptoms present before treatment did not differ between the groups, with the exception of low backache which was significantly more common in the group who then opted for surgery. The surgery group were also significantly younger and more likely to be sexually active. One year post-treatment Fernando (2006) found no significant differences in prolapse, bladder, bowel and sexual symptoms between women who had undergone surgery and those fitted with a pessary. The surgery group had been significantly younger at the outset but parity, ethnicity and menopausal status had been comparable.

iii) Observational studies: Study results show that pessary fitting ‘success’ rates ranged from 56% [393] to 75% [403] of women with POP. Higher success rates for specific types of prolapse (83% for uterine prolapse and 82% for cystocele) were recorded by
Hanson (2003). Comparison of fitting success rates by pessary type was difficult due to use of differing protocols for pessary selection within studies. Wu (1997) used ring pessaries in 96% of women who were successfully fitted. Similarly, ring pessaries were the primary choice of treatment in the studies by Handa (2002), Clemons (2004), Bai (2005) and Fernando (2006), whereas the Gelhorn pessary was primarily used in the study by Sulak (1993). The fitting protocol used by Mutone (2005) specified the ring pessary with support diaphragm in the first instance. Of women who had a successful pessary fitting, ring pessaries were used more often in women with stage II (100%) and stage III (71%) prolapse whereas Gelhorn pessaries were used more often with stage IV (64%) prolapse [396]. Hanson (2006) found significantly greater success with the ring, ring with support and Gelhorn pessaries than other type of pessaries (p<0.05), however only 54% of women in this study had prolapse (the remainder had UI).

Parameters reported as associated with a successful pessary fitting were often contradictory. Hanson (2003), Clemons (2004) and Mutone (2005) reported that patient age was not significantly related to the success of pessary fitting whereas Wu (1997) reported that women who were fitted successfully tended to be older (p<0.05). Mutone (2005) found that women classed as obese were significantly less likely to have a successful fi, whereas Maito (2006) found weight was not a predictor of successful pessary fit. Clemons (2004) reported no effect on fitting success of previous surgical intervention. Whereas Wu (1997) reported that a history of pelvic surgery reduced the probability of a successful pessary fitting from 79% to 67%, although this result was not significant (p=0.2). Mutone (2005) also showed a significant relationship between previous hysterectomy (p<0.001) or prolapse repair (p=0.010) and unsuccessful pessary fit. Similarly Maito (2006) reported that having a prior prolapse procedure or hysterectomy predicted unsuccessful fitting (p<0.001). Hanson (2006) found a higher fitting success rate in women with previous abdominal gynecotuary surgery (71%) compared to those with a history of gynecotuary surgery via the vaginal route (60%) (p=0.027). Fernando (2006) found 75% retained the pessary at two weeks, and that failure to retain was associated both with increasing parity and hysterectomy in a multivariate logistic regression analysis; site and type of prolapse did not affect success.

Current hormone use did not predict greater likelihood of fitting success [393, 396], whereas use of local oestrogen (with or without systemic HRT) was felt to play an important role in successful pessary fitting [395, 397]. Wu (1997) reported that women with SUI before pessary fitting had a significantly lower success rate (p=0.03), whereas Clemons (2004) did not find SUI to be a risk factor for unsuccessful fitting (p=0.60). Maito (2006) found no significant difference (p=0.50) in success rates between women with SUI (94%), POP (89%), or both (81%).

Increasing severity of prolapse was not associated with an unsuccessful pessary fit [393, 396, 400]. Neither was large genital hiatus [396, 400] nor severe vaginal atrophy [396]. Clemons (2004) however did find shorter vaginal length and wider vaginal introitus were associated with an unsuccessful fitting. Women with foreshortened vagina were not less likely to have successful fitting than those without in the study by Mutone (2005). Mutone (2005) also found that the location of prolapse was not associated with pessary success. Maito (2006) however found mild posterior prolapse to be a significant predictor of successful fit (p=0.002).

Comparison of long term pessary usage rates was difficult due to differing follow-up periods used in the studies reported. In Sulak (1993) the average length of use was 16 months. Maito (2006) reported continued pessary use of on average six months (range one to 17 months); discontinuation of pessary use was associated with severe posterior prolapse (p<0.04) after adjustment for age. Fifty percent of women continued to use the pessary at an unspecified follow-up period and 21% discontinued pessary use despite having no surgery [392]. In Wu (1997) 66% of those who used a pessary for more than one month were still users after 12 months and 53% were still users after 36 months. Thirty four percent of women in Handa (2002) continued pessary use for at least one year. Women with greater degrees of pelvic support loss were more likely to continue using the pessary than those with less support loss [392]. The main complaint of patients who discontinued using the pessary was dissatisfaction because symptoms were not adequately relieved or pessary use was inconvenient [392].

With regard to the effect of pessaries on POP symptoms and prognosis, 21.1% (95% CI -0.2% to 43.7%) of women had an improvement in stage of prolapse (measured via POP-Q with pessary removed) and none had worsening after using a pessary at least one year, although improvement was limited to women with anterior vaginal prolapse [394]. Four months after pessary insertion Fernando (2006) found, in the 97 women with successful fit who completed the four month questionnaire, significant improvements in all prolapse symptoms and in many urinary, bowel and sexual variables (change in Sheffield POP questionnaire responses from before pessary fitted to four month follow-up with pessary still in situ). In Sulak (1993) 82% of women still using the pessary at an unspecified follow-up period described their degree of satisfaction with their symptomatic relief as excellent. Clemons (2004) reported 92% (67/73) of women successfully fitted with a pessary were satisfied with
it at two months. All prolapse symptoms were significantly improved, and half of the baseline urinary symptoms had improved or resolved. However 21% of women without urinary symptoms at baseline developed de novo SUI. The 67 women who were satisfied at two months were evaluated at one year [399]. Fifty nine of these women were available for follow-up, 73% had continued with the pessary for at least one year, and 27% had discontinued (after a mean of 5.9 months) and underwent pelvic reconstructive surgery. Logistic regression analysis revealed that age <65 years (p<0.001), stage III or IV posterior vaginal wall prolapse (p=0.007), and desire for surgery at first visit (p=0.04) were independent predictors for discontinued pessary use and surgery.

Despite Cundiff (2000) reporting that use of pessaries was associated with potential complications no major complications were observed in the studies conducted by Sulak (1993) or Wu (1997). Bai (2005) reported 73% of women had complications such as bleeding or erosion, but that these were not severe and 70% said they were satisfied or very satisfied. Nineteen percent removed the pessary most often because of pessary slippage or discomfort. Based on clinical experience many authors advocate the use of local oestrogen to prevent or treat sores [377, 383-387, 396]. Indeed physicians thought that oestrogen was a necessary adjunct “most times” to pessary usage [374]. Differing advice however was apparent with regard to the frequency and amount of oestrogen applied.

**SUMMARY**

In the only RCT of pessaries identified, there was no difference in symptom relief for women between the Gellhorn and the ring with support; however greater clinically significant improvement in prolapse-related quality of life may have been achieved with the former (Level of Evidence: 2). Therefore, despite the fact that pessaries are commonly used in current practice to treat symptomatic POP there is almost no RCT evidence to support recommendations for their use. Whilst pessaries are cheap and complications are rare there is no consensus regarding various aspects of pessary management including indications for different types of pessary, appropriate choice of pessary, pessary fitting procedures, replacement intervals, follow-up care and treatment of complications. Similarly, there is relative little research on the therapeutic benefits of long term use of pessaries for POP although data suggest that they provide symptomatic relief and may prevent worsening of prolapse or indeed promote improvement in prolapse stage.

Pessaries and surgery may equally improve prolapse symptoms, but the types of women who choose these treatment options are likely to be different.

**RECOMMENDATIONS**

In a choice between the Gellhorn and the ring with support, either may improve prolapse symptoms and decrease their impact (Grade of Recommendation: B).

There are a rapidly increasing number of studies in this area; however there remains a pressing need for well-designed RCTs to examine the effects of using the wide variety of different pessaries in the treatment of POP. Such trials need to address optimal pessary effectiveness, including the symptomatic and therapeutic benefits of pessaries as well as the indications for use, pessary fit, replacement and care.

These studies need to adopt consistent protocols regarding choice of pessary and allow sufficient follow-up periods. There is also a need for studies to compare the effectiveness of pessaries with surgery, which is a more expensive option that may have additional morbidity, and with physical therapies. PFMT in conjunction with a pessary is an intervention which may warrant evaluation. It is not clear whether women would consent to being randomised to surgery or pessary; women might consider this if surgery was offered after a period of pessary use. If non-randomised studies comparing surgery and pessary are done, then efforts should be made to match the characteristics of the treatment groups.

**IV. COMPLEMENTARY AND ALTERNATIVE MEDICINES**

No studies have been found that evaluate the role of complementary and alternative medicines in the prevention and treatment of POP in women. It is not known what scope there might be for such therapies.

**V. SUMMARY**

Despite the prevalence of POP in women, which is increasing with the growing elderly population, there has been little attention paid to the effectiveness of interventions for the condition. There are encouraging signs of more rigorous research in this area, with the publication of four RCTs [370-372, 389] in this field since the 3rd ICI.

**1. RECOMMENDATIONS FOR PRACTICE**

There is no Level 1 Evidence, and generally insufficient Level 2 evidence on which to base recommendations for practice, and most recommendations are in effect hypotheses that need further testing in RCTs.
2. FUTURE RESEARCH DIRECTIONS

There is much scope for research on the effects of conservative therapies for POP in women. Research that is urgently needed, in the opinion of the committee members, is highlighted with the use of italics. There are a few recommendations that apply to all future studies in POP in women, namely:

- The assessment and measurement of POP be made in a standardised fashion using a validated outcome measure (such as the POP-Q examination).

- The assessment of prolapse symptoms is made in a standardised fashion. The choice of a single validated tool is however problematic at present.

a) Pelvic floor muscle training (PFMT)

- PFMT may help prevent deterioration of anterior prolapse, and may help improve prolapse symptoms and severity more generally (Grade of Recommendation: B) (Unchanged).

- Preoperative PFMT may help improve quality of life and urinary symptoms in women undergoing surgery for prolapse (Grade of Recommendation: C) (New).

b) Rings and Pessaries

- In a choice between the Gellhorn pessary and a ring with support, either may improve prolapse symptoms and reduce their impact (Grade of Recommendation: B) (New).

c) Rings and pessaries

- There remains a pressing need for well-designed RCTs to examine the effects of using the wide variety of different pessaries in the treatment of POP. Such studies need to:
  - Address optimal pessary effectiveness, including the symptomatic and therapeutic benefits of pessaries as well as the indications for use, pessary fit, replacement and care.
  - Adopt consistent protocols regarding choice of pessary.
  - Allow sufficient follow-up periods.

- There are no trials that address the following. Randomisation may not be appropriate in such studies but efforts should be made to match the characteristics of the treatment groups being compared. Comparisons of interest are:
  - Rings and pessaries versus surgery; surgery is a more expensive option that may have additional morbidity.
  - Rings and pessaries versus physical therapies.
  - Ring or pessary in conjunction with PFMT. (Note: Feasibility work for a larger RCT is currently underway: [http://www.wellbeingofwomen.org.uk/index.asp?PageID=279]).

b) Pelvic floor muscle training (PFMT)

- Studies are needed to fully investigate the role of physical therapies in the prevention of POP. Such studies should:
  - Consider the exact nature and timing of any physical therapies.
  - Ensure that the effects of lifestyle factors and other potential confounding variables are taken into account.

- Further trials are needed to add to the evidence regarding:
  - PFMT alone to improve or prevent deterioration in prolapse severity.
  - The role of PFMT as an adjunct to prolapse surgery.

- There are no trials that address the following comparisons of interest:
  - Low versus high intensity supervision of PFMT
  - Individual versus group PFMT.
  - PFMT versus surgery.
  - PFMT versus rings and pessaries.

a) Lifestyle interventions

- Studies are needed to fully investigate the association between occupation/heavy lifting, bodyweight, constipation and POP. These studies should ensure that:
  - Occupation, physical activity, bowel function and diet are assessed rigorously, using instruments with sound psychometric properties.
  - Potential confounding variables are considered.
  - Attempts are made to overcome some of the obstacles in research in this area such as recall bias inherent in assessing lifetime occupational history, or healthy worker bias which is a problem when attempting to compare POP in women currently employed in heavy labour type jobs versus others.

- Only when the links between various lifestyle factors and POP have been more clearly established can good RCTs be set up to investigate the effects that changes in these lifestyle factors can have on preventing POP.

- Anaemia is a treatable condition, either through diet or medication, and further research on its role in prevention of prolapse is warranted.

c) Complementary and alternative therapies

- Any developments in this area should be studied in RCTs.
SEARCH STRATEGIES

A: Urinary incontinence in women:

Lifestyle interventions

We searched Medline (languages English, Scandinavian, German) and the Cochrane Register of Controlled Trials from 1966-January, 2008 using the following keywords which were linked to “urinary incontinence” or “urination disorders” or “overactive bladder” or “urinary urgency”: lifestyle interventions, weight, obesity, weight loss, exercise, work, physical activity, lifting, smoking, tobacco, coffee, caffeine, posture, constipation, bowel function, fluids, fluid restriction, pulmonary status, cough, and diet.

Pelvic floor muscle training and weighted vaginal cones

This review drew on the search strategy developed for the Cochrane Incontinence Group. Relevant trials were identified from the Cochrane Incontinence Group Specialised Trials Register, which is also described under the Incontinence Group’s details in The Cochrane Library. The register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, The Cochrane Controlled Trials Register and hand searching of journals and conference proceedings. The trials in the Cochrane Incontinence Group’s Specialised Register are also contained in The Cochrane Controlled Trials Register (CENTRAL). There was no restriction on language of publication or publication status (that is full publication, grey literature, etc). The date of the last search was 4-10-2007.

Electrical Stimulation

Relevant trials were identified from the Specialised Register of Controlled Trials of the Cochrane Incontinence Group. The register contains trials identified from MEDLINE, CINAHL, the Cochrane Controlled Trials Register (CENTRAL) and handsearching of journals. Additional trials were sought from the reference lists of included studies and a broader search of computerized bibliographic databases (EMBASE, EXCERPTA MEDICA, DUTCH NATIONAL INSTITUTE OF ALLIED HEALTH PROFESSIONS), from 1980 – October 2007, was undertaken. In addition, published abstracts presented at the International Continence Society, the European Association of Urology, the American Urogynaecology Society, and the American Urological Association were reviewed from 2003 to 2007, and cross-referenced to find if a full-length report had been published. Keywords were incontinence, urinary incontinence, detrusor instability, detrusor overactivity, bladder, overactive bladder, stress incontinence, urge incontinence, mixed incontinence, urgency, frequency, nocturia, physiotherapy, physical therapy, conservative management, conservative therapy, non-surgical stimulation, electrostimulation, neuromuscular stimulation, electrical stimulation, electrotherapy, RCT’s, controlled trials, evaluation, effectiveness, efficacy, and outcomes.

Magnetic Stimulation

Relevant trials were identified from the Specialised Register of Controlled Trials of the Cochrane Incontinence Group. The register contains trials identified from MEDLINE, CINAHL, the Cochrane Controlled Trials Register (CENTRAL) and handsearching of journals. Additional trials were sought from the reference lists of included studies and a broader search of computerized bibliographic databases (EMBASE, EXCERPTA MEDICA, DUTCH NATIONAL INSTITUTE OF ALLIED HEALTH PROFESSIONS), from 1980 – October 2007, was undertaken. In addition, published abstracts presented at the International Continence Society, the European Association of Urology, the American Urogynaecology Society, and the American Urological Association were reviewed from 2003 to 2007, and cross-referenced to find if a full-length report had been published. Keywords were incontinence, urinary incontinence, detrusor instability, detrusor overactivity, bladder, overactive bladder, stress incontinence, urge incontinence, mixed incontinence, urgency, frequency, nocturia, physiotherapy, physical therapy, conservative management, conservative therapy, non-surgical stimulation, electrostimulation, neuromuscular stimulation, electrical stimulation, electrotherapy, RCT’s, controlled trials, evaluation, effectiveness, efficacy, and outcomes.

Scheduled voiding regimens

This review began with reports identified in the previous edition [281], which were predominantly obtained from MEDLINE, CINAHL, BIOSIS, and the Cochrane Register of Controlled Trials from February 1966 to January 2004. Keywords linked to urinary incontinence or overactive bladder consisted of: bladder, bladder training, habit training, timed voiding, behaviour therapy, toileting, rehabilitation, and therapy. This literature was updated by adding reports obtained using the same keyword searches in Pubmed from January 2004 to January 2008. Reference lists were searched from protocols and systematic reviews.
published on timed voiding, habit training, and bladder training by the Cochrane Collaboration, the Agency for Healthcare Policy and Research (United States) [256], review articles, and retrieved manuscripts.

To be considered for inclusion, studies had to meet the following criteria:

Prospective research design: randomised controlled or non-randomised controlled trials. If there were non available, then non-randomised cohort studies, case control studies, and case series were reviewed.

Types of participants: cognitively intact, non-institutionalised women and men with stress, urge, and mixed incontinence. Studies involving participants with catheters, urinary tract infections, interstitial cystitis or other pelvic pain syndrome, neurological disorders, or who were pregnant or immediate postpartum were excluded.

Type of intervention: timed voiding, habit training, and bladder training used in the management of urinary incontinence or lower urinary tract symptoms. Studies were excluded where it was not possible to establish any direct effects due to a specific scheduled voiding regimen. For example, studies that compared an intervention that used both bladder training and pelvic floor muscle training to another type of intervention such as drug therapy were excluded because it was not possible to determine the effect of bladder training alone.

Publication type: full published reports in English

B : Urinary incontinence in men:

Lifestyle interventions, pelvic floor muscle training and complementary therapies

We searched the Cochrane Incontinence Group Specialised Trials Register, MEDLINE, EMBASE, CINAHL, ERIC, the reference lists of relevant articles and conference proceedings of Wound Ostomy and Continence Nurses Society, International Continence Society, American Urological Association, Canadian Urological Association and Society for Urologic Nurses and Associates from 2004 at the time of the last ICI to January 2008. Search terms included ‘incontinence’, ‘male incontinence’, ‘prostatectomy/post prostatectomy’, ‘continence’, ‘pelvic floor/muscle exercises/therapy’, ‘biofeedback’, ‘quality of life’, ‘prostate surgery’, ‘urge incontinence’. Manuscripts in languages other than English were retrieved and translation obtained. Randomised or quasi randomised trials were included; case series were excluded.

For Complementary Therapies, the same electronic sources and years were used, applying the search terms “acupuncture” or “hypnosis” or “complementary therapies” or “alternative therapies” AND “urinary incontinence” or “urination disorders” or “overactive bladder” or “urinary urgency” or “uterine prolapse”. Manuscripts that included only children in the study population were excluded.

C : Pelvic organ prolapse:

Lifestyle interventions, physical therapies, rings and pessaries

Reports of RCTs evaluating the effect of lifestyle interventions, physical therapies and the use of rings and devices were obtained from a search of the Cochrane Incontinence Group specialised register. This register contains trials identified from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and handsearching of journals and conference proceedings. The date of the last search was November 2007.

Reports of other studies evaluating the effectiveness of the above treatments in the management of pelvic organ prolapse were obtained by searching MEDLINE (January 1966 to November 2007), PREMEDLINE (9 November 2007), EMBASE (1996 to November 2007), CINAHL (1982 to November 2007) and PEDro (November 2007). Key search terms were: prolapse, pelvic organ prolapse, uterine/uterus prolapse, vault prolapse, urogenital prolapse, cervical prolapse, pelvic prolapse, vaginal prolapse, rectocele, cystocele, urethrocele, enterocoele, proctocele, sigmoidocoele, pelvic dysfunction, pelvic disorder, pelvic relaxation, vaginal defects.

The UK National Research Register (November 2007) and ZETOC database of conference abstracts (November 2007) were also searched.
Acknowledgement
Jean and her committee gratefully acknowledge the editorial assistance and reference management provided by Tracey Norrish in preparing this work for publication.

REFERENCES


179. Tapp AJ S, Hills B, Cardozo LD: Randomised study comparing pelvic floor physiotherapy with the Burch...


287. Bales GT, Gerber GS, Minor TX, Mhoon DA, McFarland JM,


368. Frawley HC, Galea MP, Phillips BA, Bo K. The effect of a physiotherapy exercise program on pelvic floor muscle strength in women undergoing prolapse surgery. ICS Scientific Programme; Rotterdam, Netherlands. 2007.


375. Frawley HC, Galea MP, Phillips BA, Bo K. The effect of a physiotherapy exercise program on pelvic floor muscle strength in women undergoing prolapse surgery. ICS Scientific Programme; Rotterdam, Netherlands. 2007.


Committee 13

Surgical Treatment of Urinary Incontinence in Men

Chairman
S. HERSCHORN (Canada)

Members
H. BRUSCHINI (Brazil),
C.COMITER (USA),
P.GRISE (France),
T. HANUS (Czech Republic),
R. KIRSCHNER-HERMANNS (Germany)
| CONTENTS |
|------------------|------------------|
| I. INTRODUCTION |
| II. EVALUATION PRIOR TO SURGICAL THERAPY |
| III. INCONTINENCE AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER |
| IV. INCONTINENCE AFTER PROSTATECTOMY FOR BENIGN DISEASE |
| V. SURGERY FOR INCONTINENCE IN ELDERLY MEN |
| VI. INCONTINENCE AFTER EXTERNAL BEAM RADIOTHERAPY ALONE AND IN COMBINATION WITH SURGERY FOR PROSTATE CANCER |
| VII. INCONTINENCE AFTER OTHER TREATMENT FOR PROSTATE CANCER |
| VIII. TRAUMATIC INJURIES OF THE URETHRA AND PELVIC FLOOR |
| IX. CONTINUING PEDIATRIC PROBLEMS INTO ADULTHOOD: THE EXSTROPHY-EPISPADIAS COMPLEX |
| X. DETRUSOR OVERACTIVITY AND REDUCED BLADDER CAPACITY |
| XI. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE |
| XII. THE ARTIFICIAL URINARY SPHINCTER (AUS) |
| XIII. SUMMARY AND RECOMMENDATIONS |
| REFERENCES |
I. INTRODUCTION

Surgery for male incontinence is an important aspect of treatment with the changing demographics of society and the continuing large numbers of men undergoing surgery and other treatments for prostate cancer.

Basic evaluation of the patient is similar to other areas of incontinence and includes primarily a clinical approach with history, frequency-volume chart or bladder diary, and physical examination. Since most of the surgeries apply to patients with incontinence after other operations or trauma, other investigations such as radiographic imaging of the lower urinary tract, cystoscopy, and urodynamic studies may provide important information for the treating clinician.

Although prostatectomy for benign disease has become less frequent in many countries, the complication of incontinence is a rare but unfortunate occurrence that merits treatment. After a period of conservative therapy has been tried, surgical treatment, with implantation of the artificial urinary sphincter, has cured or improved 75-80% of sufferers. Injection therapy with agents such as collagen has helped 40-50% of men in the short term but fewer in the long term. New sling techniques have shown promising results in studies.

Radical prostatectomy for prostate cancer is performed far more frequently now than 10-15 years ago. Approximately 5-25% of patients will experience incontinence and of those a significant minority will require surgical treatment. The artificial sphincter has provided a satisfactory result in most cases with a positive impact on quality of life. Sling procedures are increasingly being reported to have a good outcome. Injectable agents have not shown durable long-term results but newer technologies such as volume-adjustable balloons have shown reasonably favourable early results in a number of reports.

With new data emerging stratification of treatment based on the degree of stress incontinence may become feasible.

Incontinence following radiation therapy, cryosurgery, high-intensity focused ultrasound, other pelvic operations and trauma is a particularly challenging problem because of tissue damage outside the lower urinary tract. The artificial sphincter implant is the most widely used surgical procedure but complications may be more likely than in other areas and other surgical approaches may be necessary. Unresolved problems from pediatric age and patients with refractory incontinence from overactive bladders may demand a variety of complex reconstructive surgical procedures. Other unique problems encountered are fistulae between the urethra and skin and the prostate and rectum. Surgical reconstructions in experienced hands are usually successful.

With extensive worldwide use of the artificial sphincter in the surgical management of male incontinence, its complications and their management are well known. Durability of the device is an important aspect that impacts on outcome and cost of treatment.

Although the literature is replete with well done cohort studies, there is a continuing need for prospective randomized clinical trials.

1. MATERIALS AND METHODS

The committee was charged with the responsibility of assessing and reviewing the outcomes of surgical therapy that have been published since the Third Consultation [1] for non-neurogenic male incontinence. Articles from peer-reviewed journals, abstracts from scientific meetings, and literature searches by hand and electronically formed the basis of this review. The outcomes were analyzed, discussed among the members of the committee and included in the chapter.

The incontinence problems were classified according to their etiology, i.e. either primarily sphincter or bladder related, and are listed in Table 1. Treatment of fistulae is covered separately.

Specific recommendations are made on the basis of published results and determined by the levels of evidence. Consensus of the committee determined the recommendations, which are found at the end of the chapter. Recommendations for future research are also included.
Table 1. Classification of surgically correctable problems

- **SPHINCTER RELATED**
  - Postoperative
    - Post-prostatectomy for prostate cancer
    - Post-prostatectomy for benign disease
    - TURP and radiation for prostate cancer
    - Post-cystectomy and neobladder for bladder cancer
  - Post-traumatic
    - After prostatomeanobanous urethral reconstruction
    - Pelvic floor trauma
  - Unresolved pediatric urologic incontinence
    - Exstrophy and epispadias

- **BLADDER RELATED**
  - Refractory urgency incontinence due to detrusor overactivity
  - Small fibrotic bladder

- **FISTULAE**
  - Prostatouretral (urethrorectal)
  - Urethrocutaneous

II. EVALUATION PRIOR TO SURGICAL THERAPY

Recommendations for evaluation prior surgery have not changed substantially from the last edition in 2005[1]. Before surgical treatment of the incontinent male is undertaken, the following evaluations should be done [2]. Basic evaluation includes history, physical examination (including neuro-urological examination: perineal sensation, anal tone, voluntary contraction and relaxation of the anal sphincter, bulbocavernous reflex [3], urinalysis, and postvoid residual urine. A frequency-volume chart [4], or bladder diary (indicating daytime and nighttime frequency of micturition, incontinence episodes, voided volumes, 24-hour urinary output, etc.) is also helpful. No clear guidelines can be found in the literature indicating the minimum number of days necessary to furnish reliable data for a voiding diary. According to Wyman et al. [5] the 7-day diary can be considered as the gold standard for voiding diaries. Schick et al.[6] demonstrated that a 4 day frequency-volume chart is the shortest one which still gives reliable results, as compared to the 7 day diary. The pad test quantifies the severity of incontinence. The 24-hour home test is the most accurate pad test for quantification and diagnosis of urinary incontinence because it is the most reproducible [7]. The 1-hour pad test is widely used because it is more easily done and standardized. A pad test may be helpful in quantifying leak in AUS failures. Postvoid residual urine is a good estimation of voiding efficiency [8,9]. These basic investigations are recommended in incontinent males prior to surgical therapy.

Blood testing (BUN, creatinine, glucose) is recommended only if compromised renal function is suspected or if polyuria (in the absence of diuretics) is documented by the frequency-volume chart [10]. Further evaluation should be adapted to the particular patient.

Cystourethroscoopy is useful to verify integrity of the urethral wall (anterior aspect of the distal sphincteric mechanism in post-TURP incontinence [11], erosion by the cuff of the artificial sphincter, voluntary contraction of the pelvic floor, etc.) and the status of the bladder (trabeculation, stone, diverticula, etc).

Imaging techniques include plain film of the abdomen (KUB or Kidneys, Ureters, Bladder), in cases of incontinence following artificial sphincter implantation when during the original procedure the hydraulic system was filled with contrast medium. A KUB immediately following sphincter implantation serves as a reference point for subsequent comparisons [12]. Figure 1 illustrates the case of a young spina bifida patient in whom an artificial sphincter has been implanted with the cuff around the bladder neck. After more than 10 years, he became suddenly incontinent. Second KUB compared to previous one clearly demonstrated fluid loss from the system. Contrast studies include cystography which may demonstrate an open bladder neck when bladder denervation is suspected [13] (e.g.: following abdominoperineal resection of the rectum). Cystourethrography may be used to demonstrate a fistula, stricture or urethral diverticulum eg., following healing of the urethral wall erosion caused by the cuff of the artificial urinary sphincter (Figure 2). Ultrasound is widely used not only to evaluate the upper urinary tract, but also to evaluate postvoid residual urine. The sensitivity of 66.7% and specificity of 96.5% when post-void residual is 100 ml or more is adequate for routine clinical use [14]. It has been shown to be cost-effective when compared to catheterization [15]. Other modalities, for example transurethral ultrasound [16] and magnetic resonance imaging of the external sphincter are still under development.

1. URODYNAMIC TESTING

In the opinion of the Committee a thorough urodynamic evaluation to characterize the underlying pathophysiology is useful prior to invasive therapy. However, there are factors that must be considered. In patients with incontinence secondary to radical prostatectomy who developed bladder neck stenosis, the urethral catheter can create obstruction giving false values for Valsalva leak point pressure. Sphincter weakness can be documented by the Valsalva [17] or cough [18] abdominal leak point pressure. Peschers et al. suggested that Valsalva
leak point pressure is significantly lower than cough leak point pressure [19]. However, its reproducibility has been studied almost exclusively in women. Catheter size seems to have a significant influence, but the correlation is extremely high between the test-retest leak point pressure when the same size of catheter is used [20,21]. In male patients, abdominal leak point pressure should be evaluated via a rectal catheter because a urethral catheter is much more likely to invalidate Valsalva leak point pressure measurements than it does in female [22]. It has become evident that bladder volume influences Valsalva leak point pressure, i.e. it decreases with bladder filling [23-25]. However, this observation is not consistent [26]. Unfortunately, there is no agreed standardization of the technique at the present time which somewhat limits its usefulness [27]. Measurement of leak point volume may also provide information on the functional capacity of the bladder [28].

Retrograde leak point pressure has been used to study incontinence following placement of an artificial sphincter [29,30]. It correlates with the lowest abdominal leak point pressure [31]. The intraoperative use of this technique has been proposed and this allows early recognition of intraoperative urethral injury and mechanical malfunction[32]. Electrophysiologic studies, mainly sphincter electromyography, may be useful to document denervation of the pelvic floor when nerve injury or neuropathology is suspected [33].

Detrusor function is best evaluated by multichannel urodynamics. Its main purpose is to detect detrusor overactivity and/or decreased compliance during bladder filling. It can be coupled with fluoroscopic imaging, video-urodynamics. It has also been proposed by some that fluoroscopy be replaced by transrectal ultrasound [34, 35]. Ultrasound measurement of bladder wall thickness was proposed as a better predictor of bladder outlet obstruction than uroflowmetry [36] but at present is controversial [37].

Non-invasive pressure-flow urodynamic evaluation based on Doppler ultrasound seems to have potential for diagnosing bladder outlet obstruction [38]. However invasive pressure-flow studies are still the gold standard in the incontinent male to rule out bladder outlet obstruction accompanied by detrusor overactivity [39] which in turn can cause incontinence.

In most recently published studies, urodynamic testing has been done prior to surgery [40-44]. Cystoscopy is frequently done as well [43, 45-49]. However there are some reports that questioned the value of urodynamics studies in predicting outcomes after
surgery. Thiel et al [50] found no evidence that patients with detrusor overactivity, low first sensation filling, decreased compliance or low bladder capacity had worse outcomes after artificial sphincter placement in 86 men. Trigo Rocha et al [51] also found that preoperative urodynamic findings such as detrusor overactivity, impaired detrusor contraction, low valsalva leak pressure, bladder outlet obstruction, and mildly reduced compliance did not lead to a bad outcome after artificial sphincter implantation.

The proposed evaluation of the incontinent male is summarized in Table 2.

### Table 2. Evaluation prior to surgical therapy

- History
- Physical examination
- Urinalysis
- Urine culture
- Post-void residual (by ultrasound)
- Voiding diary (2-7 days)
  - polyuria without diuretics: BUN, Creatinine, Glucose
- Pad-test
- Cystourethroscopy
- Urodynamics:
  - Multichannel urodynamics:
    - to characterize the incontinence and to detect detrusor overactivity, decreased compliance, and/or outflow obstruction

### Table 3. Evaluation prior to surgical therapy

- Polyuria without diuretics: BUN, Creatinine, Glucose
- Pad-test
- Cystourethroscopy
- Urodynamics:
  - Multichannel urodynamics:
    - to characterize the incontinence and to detect detrusor overactivity, decreased compliance, and/or outflow obstruction

### III. INCONTINENCE AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER

#### 1. PREVALENCE

Urinary incontinence occurring after radical prostatectomy (RP) is a significant problem. Although its rate has lessened [52] in these last few years primarily due to a better understanding of the pathophysiology and improvements in surgical technique, its prevalence has probably increased due to the dramatic increase of RP in developed countries which has lead to an overall increase in the number of patients affected.

Data from large multicenter studies and prostate cancer databases suggest that following RP, 1% to 40% of patients complain of persistent urinary incontinence. The incidence of post prostatectomy incontinence (PPI) depends on the definition of urinary incontinence and the length of follow-up [53-55]. In addition to numerous definitions of incontinence, the tools used to evaluate incontinence vary from validated questionnaires, to interviews from a data manager, to response to the surgeon’s inquiry.

Recent reports of large cohorts use definitions that include “total control/perfect continence”, “occasional leakage but no pad”, and “less than one pad”. Because 1/3 to 1/2 of men who do not wear pads will have occasional leakage of urine, it is important to distinguish among those men who leak enough to require pad use and those who do not, as it has been demonstrated that health related quality of life is strongly correlated with the level of incontinence and wearing one pad more significantly affects the quality of life than wearing no pad [56]. In addition, not all men who leak will elect to have further treatment. Most large cohort studies indicate that between 6% and 9% of patients undergo subsequent surgical treatment for PPI following prostate cancer surgery [57-60]. Several large cohort studies are listed in Table 3 [55, 61-74].

#### 2. RISK FACTORS

Reported risk factors for incontinence following radical prostatectomy include patient age at surgery, stage of disease, surgical technique including nerve sparing, preoperative bladder function and urinary continence status, prior radiation therapy, preoperative length of the membranous urethra, prior transurethral resection of the prostate (TURP), and vascular comorbidities. However, various studies have come to conflicting conclusions on specific risk factors. Risk factors for incontinence after TURP have not been as clearly defined, probably because the incidence is so low, making the accumulation of large prospective series of this type of incontinence difficult. However, previous brachytherapy does predispose to post-TURP incontinence (Section VII in this chapter).

Pre-operative urinary incontinence has been reported as a risk factor for post-operative SUI. While pre-operative lower urinary tract symptoms, including urgency incontinence and “overflow incontinence” may improve with de-obstruction secondary to extirpative surgery [75], pre-operative SUI does not improve following RP. Several recent cohort studies have demonstrated that pre-operative sphincteric insufficiency (demonstrated either the pre-existing clinical sign of SUI or the urodynamic finding of lower maximal urethral closure pressure) predicts post-operative SUI [76, 77]. Pre-operative bladder dysfunction can also contribute to post-operative incontinence. Pre-existing abnormalities of detrusor function may predispose to leakage following surgery, especially in the setting of neurogenic detrusor overactivity due to Parkinson’s disease, dementia or spinal cord injury [78].

Advancing age as a risk factor is supported by several studies [60, 75, 79-83]. Steiner, et al found no
correlation between age and continence status, but only 21 of the 593 patients were 70 years or older [84]. Others have found advancing age and the number of co-morbidities to have a negative impact on the recovering time for continence during the first year after radical prostatectomy [85] although the rate at one and two years did not seem to be significantly affected [86] Mohamad and colleagues reviewed 16,524 patients who underwent RRP in public hospitals, covering 95% of all procedures in Austria between 1992 and 2003. They found that increasing age was associated with an increased risk of future AUS implantation. In those aged 45-49, 0.5% were bothered enough by PPI to merit AUS placement, while those age 70-74 were five times as likely to undergo AUS placement for PPI. [87] Similarly, Rogers, et al demonstrated that age affected post-operative continence status following laparoscopic RRP. In those < 50 years old, 100% achieved 0-1 pad per day continence at 1 year, which decreased to 91% and 81% for those age 50-59 and > 60 yrs, respectively (p<0.01) [88]. Strasser and colleagues hypothesized that age related sphincteric changes may be responsible for the age-related increase in post-operative SUI, and successfully demonstrated a progressive reduction in sphincter striated muscle cells with age [16].

Most large series have found no correlation between the stage of disease and incontinence rates [80, 81, 89-91] Loeb and colleagues specifically demonstrated excellent continence rates even in high risk (high local stage) patients [92]. However, in certain cases, the stage of disease may affect the surgical technique (i.e. nerve sparing) and incontinence rates may be higher, but this appears to be a reflection on surgical technique and not disease stage [82].

Regarding surgical technique, the many parameters involved in continence may explain difficulties in understanding the benefit of certain technical points. Bladder neck preservation has been reported to improve continence at 3 months [90] no difference was found at 6 and 12 months [93, 94]. Nerve sparing has no significant impact according to Steiner et al. [84] and Lepor and Kaci [66] recently confirmed this. Others did find benefit [76]. In particular, Nandipati and

Table 3. Continence rates after radical prostatectomy according definition of continence, Definition 1: total control without any pad or leakage, Definition 2: no pad use but loses a few drops of urine, Definition 3: use no or one pad per day.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. pts.</th>
<th>Mean age (years)</th>
<th>Continence follow-up at 12 months</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>def 1</td>
<td>def 2</td>
</tr>
<tr>
<td>Kielb, et al [61]</td>
<td>90</td>
<td>59.6</td>
<td>76%</td>
<td>99%</td>
</tr>
<tr>
<td>Sebesta, et al [62]</td>
<td>675</td>
<td>&lt;65</td>
<td>43.7%</td>
<td>69.2%</td>
</tr>
<tr>
<td>Lepor and Kaci [63]</td>
<td>92</td>
<td>58.7</td>
<td>44.6%</td>
<td>94.6%</td>
</tr>
<tr>
<td>Olsson, et al [55]</td>
<td>115</td>
<td>65.2</td>
<td>56.8%</td>
<td>78.4%</td>
</tr>
<tr>
<td>Madalinska, et al [64]</td>
<td>107</td>
<td>62.6</td>
<td>33%</td>
<td>65%</td>
</tr>
<tr>
<td>Deliveliotis, et al [65]</td>
<td>149</td>
<td>66.5</td>
<td>92.6%</td>
<td>RPP</td>
</tr>
<tr>
<td>Harris, et al [66]</td>
<td>508</td>
<td>65.8</td>
<td>96%</td>
<td>RRP</td>
</tr>
<tr>
<td>Maffezzini, et al [67]</td>
<td>300</td>
<td>65.5</td>
<td>88.8%</td>
<td>RRP</td>
</tr>
<tr>
<td>Hofmann, et al [68]</td>
<td>83</td>
<td></td>
<td>74.7%</td>
<td>88%</td>
</tr>
<tr>
<td>Ruiz-Deya, et al [69]</td>
<td>200</td>
<td>63</td>
<td>93%</td>
<td>RPP</td>
</tr>
<tr>
<td>Augustin, et al [70]</td>
<td>368</td>
<td>63.3</td>
<td>87.5%</td>
<td>RRP</td>
</tr>
<tr>
<td>Anastasidis, et al [73]</td>
<td>70</td>
<td>65</td>
<td>67</td>
<td>RRP</td>
</tr>
<tr>
<td></td>
<td>230</td>
<td>64</td>
<td>72</td>
<td>LRP</td>
</tr>
<tr>
<td>Sacco, et al [74]</td>
<td>985</td>
<td>65</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>Jacobsen, et al [72]</td>
<td>172</td>
<td>64</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>61</td>
<td>83</td>
<td>50</td>
</tr>
<tr>
<td>Rassweiler, et al [71]</td>
<td>219</td>
<td>65</td>
<td>89.9%</td>
<td>RRP</td>
</tr>
<tr>
<td></td>
<td>219</td>
<td>64</td>
<td>90.3%</td>
<td>LRP</td>
</tr>
</tbody>
</table>
colleagues reported that in a cohort of 152 patients followed prospectively, bilateral nerve sparing surgery was associated with a shorter time to regain continence as well as improved long-term continence rates compared to non-nerve sparing surgery. They additionally found that increased age was a risk factor for post-prostatectomy incontinence.[95] Burkhard, et al. similarly demonstrated a positive effect of nerve-sparing surgery on post-operative continence. In a prospective cohort study of 536 patients, PPI developed in 1/75 (1.3%), 11/322 (3.4%), and 19/139 (13.7%) with attempted bilateral, attempted unilateral and without attempted nerve sparing, respectively. Attempted nerve sparing was in fact the only statistically significant factor influencing urinary continence after RRP in this cohort. [96]

Within the last decade, laparoscopic and robotic-assisted laparoscopic radical prostatectomy have become standard treatments for men with prostate cancer. At this time the body of available data on post-operative continence is limited, but it would appear that continence rates are similar between open and laparoscopic/robotic approaches. Several studies have compared the techniques either prospectively in non-randomized fashion, [72, 73] retrospectively, [97] or via limited meta-analysis [71, 98] and similar continence rates were found. Further prospective comparative studies with open surgery are needed.

Perineal prostatectomy is done by only a limited number of urologists but is still advocated for obese patients and the continence rate was reported as similar to the retropubic route [66, 99, 100].

3. PATHOPHYSIOLOGY

Post-prostatectomy incontinence, like any urinary incontinence, may be caused by bladder dysfunction, sphincter dysfunction or a combination of both. Urodynamic investigations are helpful to rule out bladder outlet obstruction or significant bladder dysfunction. In addition to incontinence symptoms, storage and voiding symptoms may be associated [99, 101]. Urodynamics demonstrated that the sphincter incompetence occurs as the sole cause in more than two thirds of patients, while isolated bladder dysfunction (detrusor overactivity, poor compliance, detrusor underactivity during voiding) is uncommon, occurring in less than 10% [102, 103]. However, sphincter and bladder dysfunction can coexist in at least one third of incontinent patients. Bladder dysfunction may occur de novo after prostatectomy perhaps induced by bladder denervation; may be caused by outlet obstruction, or may be related to pre-existing factors such as the age. Impaired detrusor contractility and poor compliance resolved in the majority of patients within 8 months [104].

Decreased sphincter resistance may be due to tissue scarring in some cases and reflected by a low urethral compliance, however this parameter is difficult to measure [102]. Scarring may lead to an anastomotic stricture evidenced by endoscopy or urethrography, and is clinically suspected when both incontinence and decreased force of stream coexist.

The pre-operative length of the membranous urethra determined on MRI has been shown to be significantly related to time to post-operative continence. When urethral length was greater than 12 mm, 89% of the patients were continent at one year, versus 77% with or less than this length [105]. Urodynamic studies revealed that a reduced functional urethral length was a predictive parameter of incontinence [76, 106, 107], Different components of the urethra may also be involved. The urethral intrinsic component responsible for passive continence as well as the extrinsic component responsible for active continence may be involved as has been demonstrated in a urodynamic alpha blockade test [108]. This may explain passive incontinence despite a high voluntary urethral pressure or that measured during an active squeeze by the patient. Post-operative disruption of the innervation of the posterior urethra may also be involved and can affect both motor and sensory functions [109, 110]. In clinical practice, urodynamic evaluation of a urethral weakness may be assessed by resistance to antegrade leakage (ALPP or VLPP), retrograde leakage, or profilometric measurement (MUCP) [111]. However no such parameters have been correlated to outcomes of treatments for the correction of post prostatectomy incontinence.

The state of a patient’s pelvic floor may also influence continence or return to continence after RP. Physiotherapy and pelvic floor rehabilitation have been shown to improve or enhance continence (decreased time to final continence level) in the post-operative period in two randomized studies, but only if such measures are instituted before or immediately after catheter removal [112, 113]. Maximum difference between physiotherapy and no treatment is achieved at 3 months, with almost no difference at 12 months. Another study showed that providing patients with instructions for pelvic floor muscle exercise alone was equivalent to biofeedback or electrical stimulation [114]. A randomized study in which randomization occurred 6 weeks after surgery showed no difference in continence at 6 months [115]. On the same note, studies in which physiotherapy was used as a treatment modality for established incontinence have shown more variable results [116-119].

4. SURGICAL AND MINIMALLY INVASIVE TREATMENTS

a) Urethral bulking agents

Urethral bulking is a minimally invasive treatment proposed for post prostatectomy incontinence, and theoretically works by adding bulk and increasing
coaptation at the level of the bladder neck and distal sphincter. It can be done in an office or outpatient setting in a retrograde or antegrade fashion. Several different agents have been used for urethral bulking in men including bovine collagen (Contigen®), and silicone macroparticles (Macroplastique®). All agents share the similar problems including the need for multiple injections, deterioration of effect over time, and very low cure rates.

For collagen, “success rates” for post-prostatectomy incontinence range from 36-69%, with 4-20% of patients reporting being dry [120-127]. Unfortunately, the end points in most of these studies are subjectively based, making comparisons difficult; however, it is clear that cure rates (total dryness) are low, and multiple injections are required to achieve modest rates of subjective improvement. There is no advantage of delivery technique (retrograde vs. antegrade). Several authors have identified factors which negatively affect results include extensive scarring or stricture formation, previous radiation, and high grade stress incontinence and low ALPP [121, 123, 124, 127]. One study reported more favorable results for collagen in treating incontinence after transurethral prostatectomy as opposed to radical prostatectomy (35.2% “social continence” versus 62.5%) [124]. It appears that collagen injection does not adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128]. Nor does collagen injection adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128]. Nor does collagen injection adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128]. Nor does collagen injection adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128]. Nor does collagen injection adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128]. Nor does collagen injection adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate [128].

Other bulking agents such as polydimethylsiloxane (Macroplastique®) have shown some initial success, but results also deteriorate over time. Bugel and co-workers treated 15 patients. They noted rapid deterioration after initial improvements with success rates of 40%, 71%, 33%, and 26% at 1, 3, 6, and 12 months respectively [131]. They also noted that a urethral closure pressure of at least 30 cmH2O was essential for success. Kylmala et al. prospectively studied 50 patients with mild to moderate SUI (average 48 cc on 1 hour pad test), with 12% achieving short-term continence following 1 injection, and an additional 20%, 18%, and 10% achieving continence with 2, 3, and 4 injections respectively. Follow-up, however, was limited to 3 months [132]. In a randomized trial of AUS versus Macroplastique injection in patients with minimal SUI (the vast majority had SUI following BPH surgery, with greater than 1/3 of the cohort suffering from SUI following RRP), Imamoglu and colleagues demonstrated no difference in success with AUS versus Macroplastique. However, in patients with more severe incontinence, AUS was superior, with minimal improvement following transurethral Macroplastique [47].

Several other bulking agents are currently used or are under investigation for female stress urinary incontinence, although there is minimal data on the use of these agents in men with post RP incontinence, it is certainly hoped that their effect will be better than those of currently available agents. These agents include carbon coated zirconium oxide beads (Durasphere®), hyaluronic acid dextranomer (Zuidex®), dimethyl sulfoxide/ethylene vinyl alcohol copolymer (Tegress®, Uryx™), hydroxylapatite spheres in carboxymethylcellulose carrier (Coaptite), and autologous muscle cells, stem cells, and fibroblasts. In a single institution series of 18 patients followed for an average of 4.2 months, injection of ethylene vinyl alcohol copolymer, (Tegress, C.R. Bard, Inc., Covington, GA) 41.1% of patients achieved at least a 50% improvement, but the complication rate was 58.8%. Accordingly, this compound is no longer available as an injectable agent [133].

Transurethral injection of living muscle stem cells to reconstitute the deficient urethral sphincter has recently been introduced. Mitterberger and colleagues demonstrated a 67% continence rate at an average of 1 year follow-up in a cohort of men suffering from PPI who were treated with transurethral ultrasound guided injections of autologous fibroblasts and myoblasts obtained from skeletal muscle biopsies [134]. An earlier report from the same group demonstrated that men with PPI achieved a 52% dry rate with injection of adult autologous stem cells, which was superior to a similar cohort of men treated with collagen injection [135]. However, it must be pointed out that there was a retraction issued by the editors of The Lancet [136] for a previous article on the treatment of female SUI with autologous cells published by the same group [137]. The project was investigated by the AGES PharmMed, a department of the Austrian Government’s Agency for Health and Food Safety. The editors stated that in their view “the conclusions of the official investigation pinpoint so many irregularities in the conduct of their work that, taken together, the paper should be retracted from the published record.”

Conclusion: Bulking agents remain the most minimally invasive treatment for post RP incontinence after conservative measures. All agents for which there is peer-reviewed data available, show only modest success rates with very low cure rates. Effects tend to deteriorate over time. It remains to be seen if improvements in outcomes can be achieved with alternative agents, or if the concept of urethral bulking has achieved its maximal benefit with the agents available now. (Level of evidence 3; Grade of recommendation C)

b) Male sling

The male sling procedure is based upon the concept of passive external urethral compression, and has recently emerged as a treatment for PPI. The male
sling is actually based on the concept similar to that described by Kaufman and associates in the early 1970's [138-140]. At that time a high rate of failure, septic complications and pelvic pain as well as the advent of the mechanical artificial urinary sphincter (AUS) led to the abandonment of the Kaufman prosthesis. Now with the higher prevalence of PPI and patient desire for less invasive surgery and a non-mechanical device the concept has been revisited. Procedures have been developed based on principles used to treat female stress urinary incontinence using biological and synthetic graft materials. These procedures rely on compression from the ventral side of the urethra rather than the circular compression caused by a natural or artificial sphincter. Therefore, most successful sling surgeries rely on a device that is placed under tension, occluding the urethra at rest, and during stress manoeuvres [141-143].

Schaeffer and Stamey described the bulbourethral sling which uses Dacron bolsters placed under the urethra, which are suspended to the anterior rectus fascia by sutures [144]. Data on this procedure are limited to retrospective analyses from the two authors who described the procedure: it has never gained widespread popularity. In the initial report from 2 centers, 64 patients were included and 56% were “dry” and 8% “improved” at a mean follow up of 22.4 months [144]. Almost one-third needed secondary retightening procedures and patients with radiation fared poorly. Subsequently, Clemens, et al reported a questionnaire-based study of 66 men from a single institution and 41% were cured and 51% improved but mean follow up was only 9.6 months [145]. They also reported that the bulbourethral sling did not cause significant outlet obstruction [146].

The long-term efficacy of the bulbourethral sling was evaluated in 2005, where 95 patients were followed retrospectively at an average of 4 years postoperatively. With follow-up questionnaires returned by 71 patients, the authors found that in patients who had undergone radiation, had worse outcomes with 14% dry and 43% requiring 1 or 2 or fewer pads daily. Those patients who had not had radiation treatment had a cure rate of 42% and 72% used only 0-2 pads per day for mild leakage [147]. Others have described a bulbourethral sling using a polypropylene mesh graft with or without a porcine dermis backing (presumably to reduce the risk of erosion) [48]. In two small studies of 9 [148] and 16 [48] patients cure rates range from 56-69% and failure rates from 22-25% at a mean follow up of 14 months. Recently, John described the bulbourethral composite suspension where porcine dermis is secured to the bulbospongious muscle and a 1 cm wide polypropylene sling is placed over this and passed through the retropubic space to emerge from two suprapubic incisions (similar to the tension free vaginal tape procedure in women) [48]. He reported a 69% cure and additional 6% improvement in 19 patients, with a mean follow up of 14 months. Eight intraoperative bladder perforations healed without complication.

Xu and colleagues described a bulbourethral composite suspension utilizing a suburethral polyester patch plus a narrow polypropylene tape passed from a perineal incision to a suprapubic incision. At an average of 28 months, 22 (85%) of 26 patients were successfully treated [149].

The most common method of sling fixation involves use of bone anchors. The bone anchored male sling (BAMS) has increased in popularity, as bone anchor fixation obviates the need for any suprapubic incision for suture passage and fixation. Since 2001, reports of the BAMS have become more prevalent in the literature. In 2001, Madjar, et al reported on 14 patients with post RP incontinence that underwent the procedure with a synthetic or cadaveric fascial sling [150]. At a mean follow up of 12.2 months, 86% were “cured” wearing none or 1 pad. Comiter reported a 76% cure and 14% "substantially improved" rate in 21 men with post prostatectomy incontinence using polypropylene mesh with a mean follow up of 12 months [129]. In a 2005 update, the same author reported that with a median of 48 months follow-up, 65% of patients remained pad free and 15% required 1 pad per day [151]. Urodynamic follow up in 22 men, revealed that the sling had no significant effects on voiding function and no man was obstructed postoperatively [152]. Onur and colleagues reported on 46 men with a mean follow-up of 17 months (6-26) [153]. They used different materials for the sling (allograft dermis, allograft fascia lata, porcine small intestine submucosal (SIS) graft, synthetic mesh, and a composite of synthetic and dermis). Overall they reported 41% of patients dry and 35% improved (50% reduction in the number of pads). All patients in whom allograft or xenograft alone were used failed. A 24-month update from that group revealed a patient satisfaction rate of 70% and a 74% improvement in leakage at a median of 24 months [154].

Several new slings have been introduced, with a common objective of overcoming the potential problem of overcorrection or undercorrection of continence. Transobturator slings have been introduced, [44, 155, 156] which rely more on rotation of the dorsal surface of the proximal bulbous urethra and indirect support of the sphincteric urethra, rather than direct compression of the urethral lumen [157]. However, small numbers of patients, with limited follow-up do not allow for adequate assessment of this new technique enjoying early popularity.

In an effort to overcome the problem of undercorrection, two “adjustable” slings have been introduced — the readjustable sling procedure (REMEEX), [158], and the “Argus” [159] In 48 patients reported in a Phase III multicenter trial of the Argus
sling, a 73% continence rate and additional 10% improvement rate was realized at an average of 7.5 months. Erosion and infection necessitated sling removal in 10% of patients. Adjustments were indicated for persistent incontinence as well as for urinary retention. In a prospective multicenter Phase II trial of the Male Remex System (MRS) adjustable sling, 51 patients were followed for an average of 32 months (range: 16-50). With 90% of patients requiring at least 2 adjustments, a continence rate of 64.7% was achieved, with an additional 19.6% realizing improvement over baseline [160].

Sling results are shown in Table 4 [40, 41, 48, 144, 147-154, 158-165].

1. COMPLICATIONS

Due to the small size of most reported cohort series of male sling patients, and due to the limited body of literature on the subject, the precise complication rate is not known. However, reports from the largest cohorts of patients reveal an infection rate ranging from 0-6%, and a urethral erosion rate of 0-2% [41, 151, 163]. Bothersome scrotal pain or numbness affects 16%-72% of patients post-operatively, but has been reported to resolve in all patients by 3 months [151, 165]. Reported rates of recurrent incontinence following sling surgery, amenable to revision surgery, are low (<5%) [41, 151, 154]. But the small sizes of the cohorts, and the limited follow-up of < 5 years prevent meaningful comparisons to the AUS at this time. Urinary retention is uncommon with male sling surgery, and may be avoided by excluding those patients with detrusor underactivity on pre-operative urodynamics [165, 166].

2. PREDICTORS OF SUCCESS

Several cohort studies have demonstrated that prior radiation therapy is associated with diminished efficacy of the male sling, probably due to urethral fibrosis and inadequate urethral coaptation [147, 153, 165]. In addition, the use of organic (resorbable) material is less efficacious than synthetic (permanent) sling material [153, 163, 165]. The treatment of male ISD with a suburethral sling requires tension which can only be maintained with the use of synthetic material. Pre-treatment severity of incontinence measured by the degree of leakage also appears to influence sling results. Several reports indicate that those with more severe leakage do not achieve similar continence rates when compared to those with milder leakage [153, 163, 165]. Fischer and colleagues were able to quantify, in prospective fashion, that leakage greater than 423 gm on pre-operative pad weight predicted an inferior outcome, compared to those men with less leakage on pre-operative pad weight test [41]. In their report, 62 patients with SUI were followed prospectively. All patients were rigorously evaluated with 24-hour pad test, urodynamics and validated incontinence questionnaires. Success was determined by the Patient Global Impression of Improvement. Overall, 36/62 (58%) of surgeries were successful at a mean follow-up of 15 months. The only preoperative predictive factor was 24-hour pad weight. If pad weight was less than 423 gm, there was a 6-fold greater success rate compared to those with a pre-operative pad weight of greater than 423 gm.

Finally, previous AUS placement and explantation predict sling failure [152, 163]. However, it is not clear if this is directly due to the urethral fibrosis and poor urethral coaptability, and/or if those patients simply suffer from more severe incontinence, which interferes with successful sling surgery.

CONCLUSION

In the intermediate term, the male sling appears to perform reasonably well. In the UK as well, the National Institute for Health and Clinical Excellence (NICE) has stated that current evidence on the safety and efficacy of slings appears adequate to support their clinical use [167].

The best candidates appear to be those with lower and moderate degrees of incontinence, who have not had previous radiation. While reported revision rates due to recurrent incontinence are quite low, longer follow-up is obviously needed before definitive comparisons to the AUS can be made. Nevertheless, in men with adequate detrusor contractility and mild to moderate degrees of SUI, or for patients demanding a less invasive procedure or non-mechanical device, a sling procedure is a reasonable alternative to artificial sphincter, although longer term outcome is unknown. (Level of evidence 3; Grade of recommendation C)

3. ADJUSTABLE BALLOONS

The adjustable balloon procedure is based upon the concept of passive compression of the urethra utilizing two balloons located on either side of the urethra. Balloons may be progressively inflated until there is optimal coaptation, thereby achieving continence. The biomaterial name ACT™ (Adjustable Continence Therapy) was originally conceived and developed for female stress urinary incontinence, and subsequently was applied to male incontinence. The proACT™ device was developed and reported in 2000 [168].

The device consists of a silicone elastomer balloon attached to an injectable titanium port via a silicone tube. A balloon is implanted on either side of the urethra, either under the bladder neck for post-radical prostatectomy incontinence, or under the veru montanum for post-TURP-incontinence. The ports are located subcutaneously in the scrotum, allowing simple access for percutaneous adjustment of the balloon volume. The implantation is performed under general or spinal anesthesia through a short perineal
### Table 4. Results of sling procedures in males with stress urinary incontinence

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. Patients</th>
<th>Mean Follow-up (months)</th>
<th>Sling type</th>
<th>Cured (%)</th>
<th>Improved (%)</th>
<th>Failed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thüroff [161]</td>
<td>22</td>
<td>10.3</td>
<td>Fascia sling with suprapubic and perineal approaches</td>
<td>63.6</td>
<td>9</td>
<td>27.3</td>
</tr>
<tr>
<td>Madjar, et al[150]</td>
<td>16</td>
<td>12</td>
<td>Synthetic or organic</td>
<td>86</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dikranian et al[40]</td>
<td>36 20</td>
<td>12 12</td>
<td>Organic Synthetic Synthetic</td>
<td>56 13</td>
<td>87 13</td>
<td>31 0</td>
</tr>
<tr>
<td>Ullrich &amp; Comiter [152]</td>
<td>36 25</td>
<td>25</td>
<td>Perineal (Invance®)</td>
<td>67 25</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Onur et al [153]</td>
<td>46</td>
<td>18</td>
<td>Synthetic or organic</td>
<td>41</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>John [48]</td>
<td>16</td>
<td>14</td>
<td>Polypropylene suspended suprapublically plus porcine skin collagen</td>
<td>69</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Stern et al[147]</td>
<td>75</td>
<td>48</td>
<td>Bulbourethral suspension</td>
<td>36</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Rajpurkar et al [154]</td>
<td>46</td>
<td>24</td>
<td>Synthetic or organic</td>
<td>37</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Comiter [151]</td>
<td>48</td>
<td>48</td>
<td>Synthetic</td>
<td>65</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Castle et al [163]</td>
<td>42</td>
<td>18</td>
<td>Synthetic</td>
<td>16</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Migliari et al. [148]</td>
<td>9</td>
<td>14</td>
<td>Polypepoylene needle suspension</td>
<td>55.6</td>
<td>22.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Cespedes &amp; Jacoby [162]</td>
<td>9</td>
<td>13</td>
<td>Perineal (Invance®)</td>
<td>66.7</td>
<td>11.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Schaeffer et al. [144]</td>
<td>64</td>
<td>18</td>
<td>Vascular graft bolsters with needle suspension</td>
<td>56</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Gallagher et al [164]</td>
<td>24</td>
<td>15</td>
<td>Synthetic</td>
<td>38</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Sousa-Escandon et al. [158]</td>
<td>6</td>
<td>18</td>
<td>Readjustable synthetic suprapubic and perineal</td>
<td>83.3</td>
<td>16.7</td>
<td>-</td>
</tr>
<tr>
<td>Moreno-Sierra et al. [159]</td>
<td>48</td>
<td>7.5</td>
<td>Argus -adjustable</td>
<td>73</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Romano et al.[160]</td>
<td>51</td>
<td>32</td>
<td>REMEEIX- adjustable</td>
<td>64.7</td>
<td>19.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Fischer et al.[41]</td>
<td>62</td>
<td>15</td>
<td>Perineal (Invance®)</td>
<td>34</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>Xu et al. [149]</td>
<td>26</td>
<td>28.3</td>
<td>Bulbourethral composite suspension</td>
<td>73</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Giberti et al[165]</td>
<td>36</td>
<td>41</td>
<td>Synthetic or organic</td>
<td>62</td>
<td>8</td>
<td>30</td>
</tr>
</tbody>
</table>
incision. A trocar covered with a U-shaped sheath is inserted up to the site of implantation, and then the balloon is pushed along inside the sheath. Fluoroscopic and urethroscopic guidance are used for the procedure. Transrectal ultrasound guided implantation [169] is a possible option. An isotonic medium with sterile water and contrast medium is prepared to fill the balloons with 2 ml during the initial procedure. Then, after a period of one month, the balloons are refilled with 1 ml of this solution at each period (maximum filling is 8 ml) until continence is achieved. The adjustment of the filling is volume limited and are carried out step by step in order to obtain a pseudo-capsule surrounding the balloons and therefore to minimize the risk of urethral erosion or migration. Results from 6 prospective studies [43, 46, 170-173] reported are shown in Table 5. Of 170 patients reported by Hubner [170] and Lebret [46], one-third became pad free. In other studies 70% of patients utilized 0-1 pads daily [46, 170-172]. Mean procedure time of 35 minutes was reported. Along with this improvement in pad use, there were parallel improvements in L-Qol quality of life score [46, 170, 171]. Based upon theses trials, the mean number of post-operative adjustments of the balloon was 3 to 5, with some patients requiring 6 to 8 refillings.

4. COMPLICATIONS

The most common peri-operative complications are urethral or bladder perforation, necessitating termination of the implant on the perforated side. However, contralateral implantation was not adversely affected, and repeat ipsilateral implantation was invariably achieved after healing of the urethral or bladder wall. Lebret et al. [46] reported a perforation rate of 10% and Hubner [43] reported a rate of 18% early in their series, but a lower urethral perforation rate in the most recent cases – illustrating a relatively short learning curve for optimal balloon placement near the urethral/bladder wall. Temporary urinary retention from presumed obstruction was reported at 5% [43]. Voiding was restored by removing fluid from the balloon.

Device explantation related to balloon failure, infection, erosion, or migration. The explantation rate ranged from 12 to 58% [43, 46, 170-173], but decreased with experience [43]. Device removal is straightforward, as a deflated balloon can be explanted transperineally. The only reported risk factor for failure and complications was prior external beam radiotherapy [46]. Kocjanic et al. [173] demonstrated a continence rate of 67% in non-radiated patients compared to 36% in radiated patients.

CONCLUSION

The proACT™ balloon technique appears to be a feasible procedure to improve the continence in short and median term, with better results occurring with more operator experience. Similar to the male sling procedure, appropriate candidates include those with mild to moderate leakage due to intrinsic sphincter deficiency, and no previous radiation. The benefit of an adjustable system should be weighed against the need for multiple sessions of refilling the balloon, and with reported rate of peri-operative and post-operative complications. Longer follow-up is needed before definitive comparison to male sling or artificial sphincter can be made. No recommendation is possible due to variable data on complication rates (12-58%). (Level 3, Grade D).

Table 5. Results and complications of six prospective series of Adjustable Balloons (proACT) in post-prostatectomy urinary incontinence

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Follow-up (mo)</th>
<th>Number of adjustments (balloon refilling)</th>
<th>Postoperative Complications with explantation (uni or bilateral)</th>
<th>Continence 0 or 1 pad/day</th>
<th>Complete Continence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hubner [170]</td>
<td>117</td>
<td>13 (3-54)</td>
<td>3 (1-15)</td>
<td>46 %</td>
<td>68 % (46/63)</td>
<td>35 % (22/63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>idem at 1 and 2 years</td>
</tr>
<tr>
<td>Trigo-Rocha [171]</td>
<td>23</td>
<td>22 (6-48)</td>
<td>5 (1-6)</td>
<td>17 %</td>
<td>65 % (15;23)</td>
<td></td>
</tr>
<tr>
<td>Hubner [43]</td>
<td>50 versus 50 (first pts /last pts)</td>
<td>20 vs 23</td>
<td>5 vs 4</td>
<td>58 % vs 24 %</td>
<td>52% vs 60 %</td>
<td></td>
</tr>
<tr>
<td>Cansino Alcaide [172]</td>
<td>69</td>
<td>22 (3-48)</td>
<td>2</td>
<td>12 %</td>
<td>70 %</td>
<td>14 %</td>
</tr>
<tr>
<td>Kocjancic [173]</td>
<td>64</td>
<td>20 (12-62)</td>
<td>3 (0-8)</td>
<td>17 %</td>
<td></td>
<td>67 %</td>
</tr>
<tr>
<td>Lebret [46]</td>
<td>62</td>
<td>6</td>
<td>4</td>
<td>31 %</td>
<td>71 %</td>
<td>30 %</td>
</tr>
</tbody>
</table>
c) Artificial urinary sphincter

The artificial urinary sphincter remains the most effective long term surgical treatment for post RP incontinence due to sphincteric insufficiency. However, due to the cost of the device, patient reluctance to have or inability to use a mechanical implant, and fear of complications, it is not ideal for all patients. In addition the development of less invasive techniques (as described above) potentially gives patients new options for treatment. Ultimately the choice of AUS will be based upon patient dexterity, economics, degree of incontinence and patient expectations from surgery.

The AUS has the longest track record of success in the treatment of PPI. Two studies have reported that about half of the patients with severe incontinence will undergo AUS implantation [174, 175]. However, these studies were conducted before male slings and bulking agents became popular. The success rates for AUS as defined by a continence status of zero to one pad per day range from 59% to 90% [176, 177], as shown in Table 6 [51, 176, 178-187]. Just as with reported rates of incontinence following prostate cancer surgery depend on the definition of incontinence, continence rates with the AUS can vary with the definition of continence, the method of evaluation, and the length of follow-up. The lowest rates are from patient administered questionnaires when pad free rates range from 10-72% [179, 188-192]. Nevertheless, high satisfaction rates of 87% to 90% are consistently reported, even without total continence [180, 184, 188].

One potential downside of the AUS is the need for periodic revisions in a number of patients. Revision and explantation rates due to mechanical failure, urethral atrophy, infection and erosion vary considerably among studies with respectively reports of 8-45% and 7-17% [192]. In a large cohort reported by Lai and colleagues [187], non-mechanical failure has decreased from 17% to 9% and mechanical failure decreased from 21% to 8% following introduction of the narrow back cuff and mean time to reoperation was 26.2 months (mean 2-68 months). With a Kaplan-Meier analysis, the overall 5 year expected product survival was 75%. Only 6% of devices failed mechanically, at an average of 68.1 months, with 75% of patients requiring no revisions at 5 years. Actuarial freedom from revision at 5 years was estimated at 50%-75%.

The long term efficacy of the AUS was demonstrated by Fulford et al who reported that at 10-15 year followup, [193] 75% of patients with an implanted AUS either still had or died with a functioning device. Revisions include replacement of the malfunctioning part, cuff replacement, repositioning or downsizing due to urethral atrophy, a second or tandem cuff [194, 195] or transcorporal cuff placement [196]. Transcorporal cuff placement, which involves inserting the cuff through the corporal bodies to avoid perforating the dorsal aspect of the urethra, can be particularly useful for patients with prior radiation or urethral erosion; however potency if present may be compromised. Some have advocated tandem cuffs not only as a salvage procedure, but also as a primary procedure for men with severe incontinence [197, 198]. However, O’Connor et al. recently reported no difference in continence outcome and a higher revision rate in patients undergoing double-cuff implant versus single-cuff after longer follow up [199].

Table 6. Results of the artificial urinary sphincter in post-radical prostatectomy incontinence.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. pts.</th>
<th>Follow-up (yrs.)</th>
<th>0-1 pad/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montague [178]</td>
<td>66</td>
<td>3.2</td>
<td>75%</td>
</tr>
<tr>
<td>Perez and Webster [176]</td>
<td>49</td>
<td>3.7</td>
<td>85%</td>
</tr>
<tr>
<td>Martins and Boyd [179]</td>
<td>28</td>
<td>2</td>
<td>85%</td>
</tr>
<tr>
<td>Fleshner and Herschorn [180]</td>
<td>30</td>
<td>3</td>
<td>87%</td>
</tr>
<tr>
<td>Mottet, et al [181]</td>
<td>96</td>
<td>1</td>
<td>86%</td>
</tr>
<tr>
<td>Madjar, et al [182]</td>
<td>71</td>
<td>7.7</td>
<td>59%</td>
</tr>
<tr>
<td>Klijn, et al [183]</td>
<td>27</td>
<td>3</td>
<td>81%</td>
</tr>
<tr>
<td>Haab, et al [184]</td>
<td>36</td>
<td>7.2</td>
<td>80%</td>
</tr>
<tr>
<td>Trigo Rocha, et al [51]</td>
<td>40</td>
<td>4.5</td>
<td>90%</td>
</tr>
<tr>
<td>Kim, et al. [186]</td>
<td>124</td>
<td>6.8</td>
<td>82%</td>
</tr>
<tr>
<td>Lai, et al. [187]</td>
<td>218</td>
<td>3.1</td>
<td>60%</td>
</tr>
<tr>
<td>Goldwasser [185]</td>
<td>42</td>
<td>1.2</td>
<td>82%</td>
</tr>
</tbody>
</table>
An increased revision rate has been reported for patients who received pelvic radiation [179, 200] but was not found in a recent series [177]. The results for continence for radiated patients are variable with some studies showing lower success rates [176, 200] while others do not [191]. It has been recommended that such patients have a lower pressure reservoir and/or longer period of deactivation time [179].

**CONCLUSION**

The AUS remains the gold standard for the treatment of PPI secondary to sphincteric insufficiency in patients with severe incontinence, and in those who have had external beam radiation treatment. It has the largest body of literature reporting long-term success. The long term success rates and high patient satisfaction seem to outweigh the need for periodic revisions in some patients. Intermediate term data with the male sling demonstrates that the sling is an alternative to the AUS in patients with mild-moderate SUI, provided that those patients have not failed previous AUS surgery, have not had radiation treatment, and have normal bladder contractility. Overall, the AUS remains the reference standard to which all other treatments must be compared. (Level of evidence 2; Grade of recommendation B)

**5. TIMING OF SURGICAL INTERVENTION**

There are no clear data on timing of a surgical intervention for the treatment of PPI, either with benign or malignant disease. Therefore, at present guidelines as to timing of the surgery cannot be formulated. A certain period of watchful waiting supplemented with conservative measures, particularly pelvic floor physiotherapy, seems to be a reasonable option. Thus, conservative management may be tried for periods of up to 6-12 months depending on whether there is any progress noted by the patient. In a prospective cohort study of men undergoing RRP, Lepor and Kaci63 demonstrated continued recovery of continence up to 24 months post-operatively, from 80.6% at 3 months to 95.2% at 12 months, plateauing at 98.5% at 24 months. Other cohort studies have demonstrated a plateau in continence rates at 12 months [201, 202]. Since continence may improve up to 12 months post-operatively, and possibly even until 24 months, it is generally recommended that behavioral/conservative management be utilized during the first year after prostate cancer surgery.

There have been some studies evaluating the effect of early interventional treatment for incontinence. Schneider and colleagues [203] demonstrated a beneficial effect on the earlier return to continence with early injection of periurethral bulking agent. Results were better in the subgroup of 34 patients that were injected early (mean 23 days post-operatively) compared to 10 patients treated at a mean of 26 months post-operatively. It could not be demonstrated, however, that long term continence is improved by early injection of bulking agent. Similarly, Jones and colleagues [204] demonstrated in a comparative cohort study of RRP patients treated either with or without a simultaneous suburethral sling, that sling placement at the time of RRP resulted in an earlier return to continence. There was no difference after 24 months. (Level of evidence 4; Grade of recommendation C)

**IV. INCONTINENCE AFTER PROSTATECTOMY FOR BENIGN DISEASE**

**1. INCIDENCE AND RISK FACTORS**

The incidence of urinary incontinence after prostatectomy for benign disease has been reviewed and described in the AHCPR “Benign Prostatic Hyperplasia” clinical Practice Guidelines [205]. The following percentages for stress incontinence and total incontinence, respectively, were reported:

- Open surgery (retropubic or transvesical prostatectomy): 1.9% and 0.5%.
- TUIP (transurethral incision of the prostate): 1.8% and 0.1%.
- TURP (transurethral resection of the prostate): 2.2% and 1.0%.

These figures were based on studies reported before 1990. Several other series were published after 1990. These series were reviewed for the 1st, 2nd, and 3rd International Consultations on Incontinence [1, 206, 207]. A clear description of the method of follow-up and assessment of the continence status was indicated in only about one third of these studies. The incidence of incontinence after open surgery, TURP, TUIP and HoLEP is low: the reported percentages ranged between 0 and 8.4%. Since the method of assessment of the continence status and the definition of incontinence is rarely stated it is actually not possible to make a distinction between simple stress incontinence and total incontinence. There is no clear indication that the incidence is affected by patient age or (resected) prostatic volume [206]. In a retrospective chart review from Wendt-Nordahl and colleagues [208], the incidence of incontinence following TURP was reported to have decrease over 17 years, from 3.3% in 399 patients operated on between 1987 and 1997, compared to 1.3% in 550 patients operated on from 1997-2004. Whether this statistically significant (p < 0.05) difference was due to improvement in surgical technique or patient characteristics is not clear, however both the earlier and later incontinence rates are consistent with those in the AHCPR and AUA guidelines reports.
In summary, the AUS is a successful surgical treatment option for post-prostatectomy incontinence. It is the most commonly performed surgery for post-prostatectomy incontinence, with the longest follow-up and therefore longest record of success. Level of evidence 2; Grade of recommendation B)

b) Injectable agents

Most series include post-prostatectomy incontinence after treatment for benign and malignant disease, with the majority after prostate cancer surgery. For collagen, “success rates” range from 36-69%, with 4-20% of patients reporting being dry [120-127]. Study results are inconsistent with both TURP [224] and radical prostatectomy [225] showing better outcomes. Other bulking agents such as polymethylsiloxane PDMS (Macroplastique®) have shown some initial success, but results also deteriorate over time. Bugel and co-workers treated 15 patients. They noted rapid deterioration of initial improvements with success rates of 40%, 71%, 33%, and 26% at 1, 3, 6, and 12 months respectively [131]. As mentioned previously in the section on post-radical prostatectomy incontinence Kylmala et al. prospectively studied 50 patients with mild to moderate SUI (average 48 cc on 1 hour pad test), with 12% achieving continence following 1 injection, and an additional 20%, 18%, and 10% achieving continence with 2, 3, and 4 injections respectively [132]. Follow-up, however, was only 3 months. In a randomized trial of AUS versus Macroplastique injection in patients with minimal SUI (the vast majority had SUI following BPO surgery, with less than 1/3 of the cohort suffering from SUI following RP), Imamoglu and colleagues demonstrated no difference in success with AUS versus Macroplastique. However, in patients with more severe incontinence, AUS was superior, with minimal improvement following transurethral Macroplastique [47]. There has also been some initial work with sphincteric injections of muscle stem cells [134, 135].

Bulking therapy fails in up to 75% of men. Of those who are improved only a minority actually becomes dry with short-term follow-up. Although bulking therapy may be slightly more efficacious in treating SUI following TURP compared to SUI following prostate cancer surgery, bulking is of limited value in those men with all but minimal SUI. (Level of evidence 3; Grade of recommendation C)

c) Male sling procedures

Since Frangenheim described his first successful urethral sling suspension for post-traumatic stress urinary incontinence in 1914, various sling materials and surgical methods have been reported [226]. Rectus fascia, as described by Frangenheim, has distinct advantages over alloplastic materials with respect to erosion and infection risks. Allograft off-the-shelf-materials like lyophilized fascia lata have a higher infection risk than does autologous fascia,
whereas the use of synthetic materials like polypropylene mesh or polytetrafluoroethylene slings are associated with a higher incidence of urethral erosion [227]. According to various published techniques, the sling can be placed either underneath the bladder neck, the urethral bulb or the membranous portion of the urethra. The principle of continence support is similar for all sling procedures and comprises passive compression of the urethra, which is dependent on the applied sling tension [161]. This mode of action favours sling procedures as a treatment option for intrinsic sphincter deficiency.

However, the sling tension needed for restoration of continence has not been standardized, with tensioning techniques ranging from perfusion sphincterometry, to a cough test, to visual approximation, [153, 228] and therefore the success of the procedure probably depends heavily to the surgeon’s experience and the degree of sphincteric incompetence. Overcorrection with consequent urinary retention (especially in the setting of detrusor underactivity) and undercorrection with persistent or recurrent incontinence are certainly possible, which may adversely affect continence, bladder emptying, and patient satisfaction. Published success rates are shown in Table 4 [40, 41, 48, 144, 147-154, 158-165].

Several new slings have been introduced, with a common objective of overcoming the potential problem of overcorrection or undercorrection of continence. Transobturator slings [44, 155, 156] rely more on rotation of the dorsal surface of the proximal bulbous urethra and indirect support of the sphincteric urethra, rather than direct compression on the urethral lumen [157]. However, small numbers of patients, with limited follow-up do not allow for adequate assessment of this new technique which is enjoying early popularity.

In an effort to overcome the problem of under-correction, two “adjustable” slings have been introduced — the readjustable sling procedure (REMEEX), [158], and the “Argus” [159]. In 48 patients reported in a Phase III multicenter trial of the Argus sling, a 73% continence rate and additional 10% improvement rate was realized at an average of 7.5 months. Erosion and infection necessitated sling removal in 10% of patients. Adjustments were indicated for persistent or recurrent incontinence as well as for urinary retention. In a prospective multicenter Phase II trial of the Male Remex System (MRS) adjustable sling [160], 51 patients were followed for an average of 32 months (range: 16-50). With 90% of patients requiring at least 2 adjustments, a continence rate of 64.7% was achieved, with an additional 19.6% realizing improvement over baseline.

---

**V. SURGERY FOR INCONTINENCE IN ELDERLY MEN**

With an increase in the aging population and improvements in anesthesia, availability of less invasive and shorter surgical procedures, reduced blood loss and reduced infection risk more aged patients are candidates for surgical treatment. Although every surgeon should be aware of those special risks in elderly patients which might require special peri-operative care, even in the very old well planned surgical procedures can be safe, and are justifiable, if it helps to improve continence and besides benefiting general health status leads to a better quality of life for the individual. Many studies have documented that the frequency of peri-operative complications increases with age [229]. This finding is not surprising given that the prevalence of significant co-morbid conditions is increased in the elderly [230]. It is however unclear whether the increased frequency of complications can be attributed to these co-morbid conditions or whether advanced age itself is an independent risk factor [231].

PubMed and Medline searches were conducted in May 2008 covering the time frame from 01.01.2004 to the present. The terms ‘surgery, male and urinary incontinence’ were used and the search was limited to English articles to update the previous comprehensive literature search done for the third edition of the ICI.

Data available are still sparse, since the search did not differentiate between fit and frail elderly. Since the latter are defined as patients with continuous severe impairment and/or co-morbidity, they are usually not candidates for surgical treatment.

Conflicting data are reported on age as an independent risk factor for incontinence after radical prostatectomy. In most reports, the patient’s age and preoperative urine leakage are predictive of postoperative urinary incontinence, whereas some came to the opposite conclusion [232]. Advancing age as a risk factor is supported by a number of studies [60, 79-83], Steiner, et al [84] found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older. However, Mohamad and colleagues reviewed 16,524 patients who underwent RP in public hospitals in Austria. They found that increasing age was associated with an increased risk of peri-operative complications [85] and with a higher incidence of peri-operative continence status following laparoscopic RP [88]. As mentioned above, Strasser and colleagues hypo-
thesized that age related sphincteric changes may be responsible for such age-related increase in post-operative SUI, and successfully demonstrated a progressive reduction in sphincter striated muscle cells with age [16].

Others have found that advancing age and number of co-morbidities have a negative impact on the speed of recovery of continence during the first year post radical prostatectomy [52, 85], but the rate at one or two years does not seem to be significantly affected [63]. Comparison of studies dealing with peri-operative risk of surgery in the elderly is complicated by the use of different definitions of diseases and outcomes, different modes of clinical care and diversity in the type of clinical procedure examined. Furthermore sub clinical diseases might not be detected and still may impose a risk factor. Although the overall frequency of peri-operative complications is increased in the elderly, it is still relatively low [233, 234].

Two frequently used options for incontinence in men after prostatectomy are injection therapy with bulking agents such as collagen and the placement of an artificial urinary sphincter. O’Connor et al. [235] concluded after having examined the outcome of primary artificial urinary sphincter in 29 men aged 75 years and older, that implantation of AMS Sphincter should not been denied to a patient simply on the basis of age. Thiel et al [50] found in their study of 86 men with artificial urinary sphincter surgery that older men conceived their improvement as less significant than younger men although the age difference between patients rated as ‘success’ and ‘failure’ was only two to three years and thus might not be clinically relevant. (Level of evidence 2 and 3; Recommendation Grade B)

Before implanting an artificial sphincter in a fit aged patient, mental status and dexterity have to be evaluated and discussed with the patient. No data could be found on how aging patients are able to manually operate and remember to use the artificial sphincter.

Most studies looking at these options for incontinence after treatment of localized prostate cancer did not look at age as an independent factor associated with certain complications [125, 128, 177, 236, 237]. Some investigators came to the conclusion that age does not predict treatment efficacy of bulking agents [126, 238]. (Level of evidence 3)

Recent series of slings with less than 2-year follow-up have shown satisfactory improvement rates, with results similar to those of the artificial urethral sphincter, although patient selection may be different. However, no stratification for age is available from the data.

TREATMENT OF DETRUSOR OVERACTIVITY

Therapy with intravesical neuromodulatory drugs such as capsaicin and resiniferatoxin as well as injection therapy with botulinum toxin has been extended to the treatment of non-neurological detrusor overactivity of the bladder after other treatment failed. These options are discussed in the section on Refractory Overactive Bladder (see below). No data were found on how these techniques work in aging bladders. Since detrusor contractility decreases with age [239] the incidence of bladder emptying problems might be expected to be higher in the elderly.

CONCLUSION

Age by itself should not preclude any patients from treatment. Although bulking agents are less invasive they have not yet been shown to be very effective. If co-morbidity, mental status and dexterity of the patient permit an invasive approach the implantation of an artificial sphincter, or a sling, should be offered to the patient. (Level of evidence 3; Grade of recommendation C)

VI. INCONTINENCE AFTER EXTERNAL BEAM RADIOTHERAPY ALONE AND IN COMBINATION WITH SURGERY FOR PROSTATE CANCER

The risk of incontinence after external beam radiotherapy (EBRT) for prostate cancer is variable and ranges from 0 to 18.8%. Lawton et al. [240] reported a risk of urinary complications of 7.7% in more than 100 patients, proportional to dose. Perez et al. [241] found incontinence in only 5 of 738 patients. Shipley et al. [242] reviewed more than 2500 cases with an incontinence rate of 0.5%. Similar incidences have been reported in more recent series. Madalinska et al. [64] reported an incidence of 6–7%. With three-dimensional conformal radiotherapy, Weil and colleagues [243] reported no incontinence in 168 consecutive patients and Hanlon et al. [244], in a series of 195 men, found that post treatment urinary symptoms were no different from a control group without cancer. With conformal radiotherapy, Sandhu et al. [245] reported a 9% incidence of stress incontinence in 110 patients. The impact of EBRT followed by prostatic boost, for a total of 66–70 Gy, was evaluated. Scalliet and co-workers [246] reported urinary incontinence in 16% of 230 patients, however, Fransson and colleagues [247] reported an increase in urinary incontinence on a patient-administered symptom bother scale 3 years after treatment in 153 men compared to pretreatment status. The increase was from a mean of 0, at the start to 2 out of 10 at 3 years. Poholzer et al. [248] reported incontinence in 18.8% of a group of 82 men who were surveyed 4.4 year after EBRT for prostate cancer. Furthermore urinary incontinence worsened from year 2 to year 6 in a cohort of 147 men treated with 3D conformal RT [249].
Pre-radiotherapy transurethral prostatectomy may be a risk factor for incontinence. Jonler et al. [250] reported an incontinence rate of 11% with pretreatment TURP. Green et al. [251] and Lee et al. [252] also reported a higher risk of incontinence with pretreatment TURP versus those without with 5.4% and 2% respectively. There are no series reported on the treatment of patients who only have incontinence after EBRT.

Salvage or adjuvant radiotherapy is frequently given after radical prostatectomy and the impact on continence is controversial. Petrovich et al. [253] reported no difference in incontinence in 2 cohorts of patients, one with and one without adjuvant radiation. In a follow-up study the same group reported no late toxicity [254]. Fontaine et al. also reported no change in continence status in 16 of 17 men after salvage radiation [255]. However, Petroski et al. reported that postoperative radiotherapy worsened continence in 26% of 129 patients followed for a median of 5 years [256]. On the other hand salvage radical prostatectomy following external beam radiotherapy has been has been generally reported to have a high incidence of urinary incontinence [257-259] possibly because of radiation induced fibrosis of the external sphincter [258].

**SURGICAL TREATMENT**

Results of surgical treatment of incontinence in this setting are based on retrospective clinical series. In the past the most commonly published treatment modality was the artificial urinary sphincter as therapy for sphincter damage. As discussed and referenced in the following paragraphs, the series published contain both patients who had and had not received radiotherapy and collagen injections have also been reported in case series.

There has been a higher reported revision rate for the artificial sphincter following radiotherapy (Table 7 [176, 177, 179, 187, 190, 200, 260, 261]) compared to low risk patients, 38% versus 22%. Although recent reports dispute the higher rate [177, 187]. However, generally this is due to a higher incidence of erosion and infection as well as urethral atrophy, possibly secondary to radiation induced vasculitic fibrosis of the urethra [179]. Radiation may also induce detrusor overactivity or poor compliance leading to urgency incontinence. Recurrence of bladder neck contracture may be more common [187]. Radiation was also identified as a co-morbidity associated with erosion [262]. However, good results are reported, and it is generally recommended that the cuff be inserted outside the radiated field [263].

Collagen injection has also been reported for incontinence after radical prostatectomy and adjuvant radiation [122, 126, 224, 264-266] or after salvage radical prostatectomy following radiotherapy [129,267]. Continence results are poorer compared to those without radiation [225]. Very few patients have been reported on with the use of Macro-plastique following radical prostatectomy and adjuvant radiotherapy.

The male perineal bone-anchored sling has been reported in patients following adjuvant RT. In Comiter’s group with the perineal compression sling 3/21 with radiation had no adverse sequelae [129]. Similarly in the series of Onur et al. radiation did not cause a worse outcome [153]. However, Schaeffer et al. reported that prior irradiation was the only identified factor that predisposed to failure. Their success rate following a single sling procedure was only 29% (2 of 7) for irradiated patients, and the corresponding rate for nonirradiated patients was 68% (39 of 57) [144]. They postulated that the sling acts by compressing and elevating the urethra, thereby increasing urethral resistance to abdominal pressures. Theoretically, radiation-induced fibrosis of the urethral and periurethral tissues would make compression and elevation more difficult by reducing tissue compliance and mobility.

**Table 7. The artificial sphincter for incontinence after radiotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Revision rate after radiotherapy</th>
<th>Continence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martins and Boyd [179]</td>
<td>34/81</td>
<td>38% for whole group</td>
<td>88%</td>
</tr>
<tr>
<td>Wang and Hadley [260]</td>
<td>16</td>
<td>25% (Infection and Erosion - 12.5%)</td>
<td>87%</td>
</tr>
<tr>
<td>Perez and Webster [176]</td>
<td>11/75</td>
<td>55%</td>
<td>63%</td>
</tr>
<tr>
<td>Gundian et al. [261]</td>
<td>15/56</td>
<td>22%</td>
<td>90%</td>
</tr>
<tr>
<td>Elliott and Barrett [190]</td>
<td>46/313</td>
<td>22%</td>
<td>-</td>
</tr>
<tr>
<td>Manunta et al. [200]</td>
<td>15/72</td>
<td>53% (Infection and Erosion – 20%)</td>
<td>73%</td>
</tr>
<tr>
<td>Gomha and Boone [177]</td>
<td>28/86</td>
<td>25% (Similar to a non-Radiated control group)</td>
<td>64%</td>
</tr>
<tr>
<td>Lai et al. [187]</td>
<td>60/176</td>
<td>20% versus 32% for non-radiated group</td>
<td>69%</td>
</tr>
</tbody>
</table>
In summary, despite the frequently reported higher incidence of complications of the artificial sphincter in post-prostatectomy patients after adjuvant radiation, it has provided acceptable treatment benefits. Collagen injections have yielded poor results. Although the data are limited, a perineal compression device may also be acceptable but suprapubic suspension bulbourethral slings may be less efficaceous. (Level of evidence 3; Grade of recommendation D)

**VII. INCONTINENCE AFTER OTHER TREATMENT FOR PROSTATE CANCER**

1. **BRACHYTHERAPY OF THE PROSTATE**

Brachytherapy is a form of radiation therapy in which radioactive materials are placed directly into the prostate gland. The incidence of incontinence following this modality is given in Table 8 [268-279] and was previously related to the treatment of post-brachytherapy retention of urine. Numerous series have reported retention to be associated with larger initial prostate volumes [280]. In a systematic review of brachytherapy series, Crook et al. [277] reported the incidence of retention to be 1-14%. Many patients require prolonged or permanent alpha blocker or TURP. The main risk factor for incontinence after brachytherapy is TURP. Hu and Wallner [274] reported on the incidence of urinary incontinence after TURP/TUIP following prostate brachytherapy for prostate cancer. Of the 10 patients who underwent the outlet relaxing procedures for refractory urinary obstruction, 7 developed some degree of permanent urinary incontinence. They surmised that the cause may be multifactorial and may include physical damage to the urinary sphincters and the radiation dose to the urethral region. Surgical therapy when required has included the artificial sphincter [275]. High dose brachytherapy that is administered over a short period of time may have reduced toxicity [281]. Urethrorectal fistula is another complication that has been reported in 1.8% of patients in a large U.S. medicare retrospective review [275]. Salvage brachytherapy leads to a higher rate of urinary tract complications [259].

2. **CRYOSURGICAL ABLATION OF THE PROSTATE**

Cryosurgical ablation of the prostate is used for clinically localized prostate cancer either as primary treatment or after unsuccessful external beam radiation therapy. The frequency of the main lower urinary tract complications are listed in Table 9 [282-294]. The artificial sphincter has been mentioned as one of the treatments for incontinence [293] Cryotherapy is an adverse factor for collagen injections. Urethrorectal fistulae can also occur in up to 5% of treated patients. Severe incontinence and fistulae that occasionally results may have to be treated with extirpative surgery and diversion [295].

3. **HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)**

Transrectal high-intensity focused ultrasound is emerging as another minimally invasive treatment for prostate cancer. HIFU destroys prostate cells by

---

**Table 8. Incontinence after brachytherapy for prostate cancer**

<table>
<thead>
<tr>
<th>Author</th>
<th>% Incontinence</th>
<th>% Post TURP</th>
<th>% No TURP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyer et al. [268]</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blasko et al. [269]</td>
<td>6</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Stock et al. [270]</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wallner et al. [271]</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kaye et al. [272]</td>
<td>4</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Blasko et al. [273]</td>
<td>13</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Hu and Wallner [274]</td>
<td>6</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>Benoit et al. [275]</td>
<td>6.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Merrick et al. [276]</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crook et al. [277]</td>
<td>5.6</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Talcott et al. [278]</td>
<td>105</td>
<td>83</td>
<td>39</td>
</tr>
<tr>
<td>Bottomley et al. [279]</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Implant plus external beam radiation
coagulative necrosis of the tissue without damaging the structures intervening between the transrectal probe and the target tissue [296]. Recent reports of efficacy also include morbidity. In a systematic review involving 37 articles/abstracts Rebillard et al. [297]. reported that stress incontinence occurs in 6-28%, urethra/bladder neck stenosis in 1-31%, and rectourethral fistula in 0-3% of treated patients. With improvements in techniques the risk of complications is decreasing [297].

4. INCONTINENCE AFTER NEOBLADDER CONSTRUCTION

The incidence of continence after neobladder construction following radical cystectomy for bladder cancer ranges from 85 to 100% during the day and 55 to 100% at night (Table 10 [298-310]). Most patients achieve daytime continence after one year and nighttime continence after 2 years. Most of the published reports do not comment on specific surgical management and imipramine is mentioned as treatment only occasionally. Martins and Boyd [179] reported on 8 patients treated with the AUS for persistent sphincter weakness incontinence. Six of these underwent revisions, 3 for infection and/or erosion and 3 for inadequate cuff compression. They cautioned against the use of the AUS and suggested alternatives such as intermittent catheterization at night. However, O’Connor and colleagues [311] reported a successful outcome, after AUS, with no complications in 5/5 men with incontinence after neobladder, with a mean follow-up of 22 months. The bone-anchored sling has been reported for one case [312]. Collagen has only been reported in women following neoblladder construction [313].

In summary there are not enough data upon which to recommend definitive surgical therapy, although the artificial sphincter looks reasonable. (Level of evidence 3; Grade of recommendation C-D)

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>% Incontinent</th>
<th>%Bladder outlet obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinohara et al. [282]</td>
<td>102</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Bahn et al. [283]</td>
<td>210</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Cox and Crawford [284]</td>
<td>63</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Wieder et al. [285]</td>
<td>83</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>Cohen et al. [286]</td>
<td>239</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Coogan and McKiel [287]</td>
<td>95</td>
<td>3.5</td>
<td>6</td>
</tr>
<tr>
<td>Sosa et al. [288]</td>
<td>1467</td>
<td>11</td>
<td>6.8</td>
</tr>
<tr>
<td>Long et al. [289]</td>
<td>145</td>
<td>83/2.0*</td>
<td>17.2</td>
</tr>
<tr>
<td>Pisters et al. [290]</td>
<td>150</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>Derakhshani et al. [291]</td>
<td>48</td>
<td>10.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Long et al. [292]</td>
<td>975</td>
<td>7.5</td>
<td>13</td>
</tr>
<tr>
<td>De la Taille et al. [293]</td>
<td>43</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Robinson et al. [294]</td>
<td>46</td>
<td>29 (urinary bother)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Previously radiated/not previously radiated

VIII. TRAUMATIC INJURIES OF THE URETHRA AND PELVIC FLOOR

Incontinence following posterior urethral injuries occurs in 0-20% of patients [314, 315] and is thought to be due to the extent of injury rather than to the method of management.

The data on surgical treatment are all retrospective case series and the most commonly published surgical therapy is the AUS. The series published contain both patients with and without traumatic injuries. Perez and Webster [176] reported on 27 patients after urethral or bladder neck strictures. The revision rate was 41% and the continence rate was 85%. In a subsequent report from this centre on reoperations the patients with traumatic injuries were not discussed separately [316]. In Montague’s [178] series 22 out of 166 patients had incontinence after trauma. He did not separate the results of this group from those of the other patients. Martins and Boyd [179] reported on only one patient out of 81 with a traumatic urethral injury. This patient was dry and required no revisions. Venn
at el. [263] reported on 2 with pelvic trauma out of a total of 70. (Level of evidence 3; Grade of recommendation C)

Bladder neck reconstruction by excising the scar and narrowing the calibre was reported by Iselin and Webster [317] in 6 patients who had incontinence with an open bladder neck on cystourethrography, following urethroplasty for traumatic strictures. Bladder neck closure with a Mitrofanoff catheterizable abdominal stoma has also been reported as treatment following severe urethral or bladder trauma [318] (Level of evidence 3; Grade of recommendation C)

For patients with severe bladder neck strictures and incontinence after prostate surgery Meulen et al. [319] and the group from Baylor [187, 320] reported on the use of a Urolume stent with a bulbar artificial sphincter. Alternative management with perineal urethroplasty and subsequent artificial sphincter placement in 6 patients was reported by Simonato et al. [321] (Level of evidence 3; Grade of recommendation C)

In summary, the AUS provides a reasonable outcome in appropriate cases. Since there are so few reports of alternative therapies the C recommendations were based primarily on expert opinion as to what is reasonable surgical therapy in very difficult cases.

Achieving continence and protecting the upper urinary tract are important goals of reconstruction in patients with exstrophy-epispadias complex. However, these tasks remain formidable challenge for pediatric urologists. Urinary incontinence [322, 323] and other voiding problems [324, 325] due to these congenital anatomical abnormalities are continuing problems into adulthood. Although quite a few publications on the exstrophy-epispadias complex have appeared in the literature over the past 7 years, the long-term follow-up data into adulthood are still lacking [322, 326], and there have been no significant changes in the management of urinary incontinence. Furthermore, the definition of continence differs between studies. Despite the devastating nature of this disease, there have been few studies addressing quality of life issue and psychological assessment in patients with exstrophy-epispadias complex. Lee et al. surveyed 208 patients of which only 24 were 18 years or older. They found that of those older than 20 years all women and but only 60% of males had close friendships [327].

Table 10. Continence after neobladder construction for bladder cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Follow-up (mo)</th>
<th>Day Continence (%)</th>
<th>Night Continence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcini et al. [298]</td>
<td>34</td>
<td>12</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>Cancrini et al. [299]</td>
<td>89</td>
<td>24</td>
<td>97 (22% with SUI)</td>
<td>83</td>
</tr>
<tr>
<td>Elmajian et al. [300]</td>
<td>266</td>
<td>24</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Studer et al. [301]</td>
<td>100</td>
<td>24</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>Benson et al. [302]</td>
<td>32</td>
<td>25</td>
<td>94</td>
<td>74</td>
</tr>
<tr>
<td>Abol-Enein and Ghoneim [303]</td>
<td>60</td>
<td>4</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Rogers and Scardino [304]</td>
<td>20</td>
<td>24</td>
<td>90</td>
<td>55</td>
</tr>
<tr>
<td>Hautmann et al. [305]</td>
<td>211</td>
<td>36</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Hautmann et al. [306]</td>
<td>363</td>
<td>57</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Steven and Poulsen [307]</td>
<td>166</td>
<td>32.4</td>
<td>100 (After 5 years)</td>
<td>100 (After 5 years)</td>
</tr>
<tr>
<td>Abol-Enein and Ghoneim [308]</td>
<td>353</td>
<td>38</td>
<td>93.3</td>
<td>80</td>
</tr>
<tr>
<td>Carrion et al. [309]</td>
<td>56 ileum</td>
<td>41</td>
<td>91</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>57 colon</td>
<td>41</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td>Nieuwenhuijzen et al. [310]</td>
<td>62</td>
<td>&gt;12</td>
<td>90</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>50 (sexuality preserving)</td>
<td>&gt;12</td>
<td>96</td>
<td>67</td>
</tr>
</tbody>
</table>
Published materials consist mainly of retrospective reviews of experience at various centers. Even major institutions struggle to gather large series of patients. Thus, we are still left with mainly level 3 evidence.

The management of the exstrophy-epispadias complex includes 2 principal aspects; initial management (primary treatment) and subsequent management of persisting incontinence. These 2 aspects are discussed separately. Based on the evaluation of the literature, recommendations are made at the end of this section.

I. INITIAL MANAGEMENT OF THE EXSTROPHY-EPISPADIAS COMPLEX

a) Staged repair versus one-stage primary repair

Staged surgical management of the exstrophy-epispadias complex (early closure with or without pelvic osteotomy, repair of epispadias and bladder neck reconstruction) has been the standard approach [323, 328-332] although the staged approach has undergone significant changes since first advocated by Jeffs et al [328]. Success rates for staged functional closure are high with continence rates reaching 75% to 90% [328-330]. However, these results were based on highly selected groups of patients and others failed to achieve such results. Continence rates of only 10% to 30% were reported with the staged approach [333, 334]. Complete primary repair described by Grady and Mitchell combined primary bladder closure with epispadias repair in one stage in neonates [335]. The idea was to optimize the chance for early bladder cycling and potentiate bladder development. It may also obviate the need for multistage repair of bladder extrophy including bladder neck reconstruction. Although acceptable short-term results were achieved, the procedure has been criticized in view of 50% incidence of antireflux surgery needed because of breakthrough urinary tract infections. A recent report from another institution has also shown that complete repair of exstrophy is feasible in neonates and older children after failed initial closure, with acceptable morbidity [336]. Urinary reflux was noted in 63% of renal units but did not require surgery in this series. There is short-term evidence of favorable outcome in newborns compared with older children [336]. However, we will have to wait for long-term results from those centers using this one-stage technique to know whether it is consistent in producing urinary continence and satisfactory sexual function.

The Mainz group has recommended primary urinary diversion (ureterosigmoidostomy, sigmoid rectal pouch, ileocecal pouch) with closure of the abdominal wall [337, 338]. The posterior urethra is closed as a seminal receptacle. While this approach is hardly used in North America, long-term reports have demonstrated excellent continence and upper tract preservation [337, 338]. Low pressure rectal reservoirs in children with bladder exstrophy have also provided excellent long-term outcome in continence (100%) and preservation of the upper tract (97%) [339]. However, prophylactic alkalinization does not prevent the long-term metabolic consequences. Subclinical metabolic acidosis and decreased linear growth are to be anticipated in more than 50% of patients, and moreover, significant bone demineralization is to be expected in all of these patients [339]. Thus, it is concluded that low pressure rectal reservoirs should be reserved for failed surgical reconstruction or patients presenting beyond the age suitable for reconstruction [339].

b) Bladder neck reconstruction

In a staged repair, bladder neck reconstruction is usually performed at age 4 to 5 years when the bladder gains enough capacity to provide for safe filling with good compliance and the child is ready to be dry and participate in a postoperative voiding program [328, 329]. The classic Young-Dees-Leadbetter technique has been modified in several ways [329, 332, 340]. The success of bladder neck reconstruction in both continence and emptying is highly dependent on the delicate balance between the bladder and outlet. Bladder capacity, contractility and outlet resistance are determinants of continence after bladder neck reconstruction [325]. A report from the Johns Hopkins group [329] describes that 77% of patients are completely dry by day and by night and voiding through the urethra without need for bladder augmentation or clean intermittent catheterization, and that another 14% have “social continence” (dry more than 3 hours during the day but still wet at night). Analysis of bladder capacity measurements under anesthesia, prior to bladder neck reconstruction, revealed that patients with a preoperative bladder capacity of greater than 85 cc had a better outcome [329]. However, subjective success with continence and emptying does not necessarily correlate with objective findings [325]. Despite near or total subjective continence (dry intervals of at least 2 to 3 hours) and “good voiding” in 18 patients, there were clinical (recurrent urinary tract infections, epididymitis and bladder stone) and urodynamic voiding problems in 72%, including flow rates of less than 10 ml/sec in 70%, postvoid residual more than 33% of capacity in 50% and acute urinary retention in 17% [325]. Another report from the Toronto group also highlights the extreme difficulty in achieving volitional voiding in an unselected extrophy population. Of 43 patients only 3 (7%) were voiding spontaneously through the native reconstructed urethra [341]. Similarly Burki et al. reported redo bladder neck reconstruction in 30 patients and all required intermittent catheterization [342]. Thus, perseverance in the pursuit of volitional voiding is more likely to result in repeatedly failed bladder neck
reconstruction and delay in the age at which continence is finally attained. Earlier recognition of the need for other storage improvement procedures such as bladder augmentation and/or appendicovesicostomy and bladder neck closure may facilitate the timing of achieving continence and self-esteem, and achieve a satisfactory result with fewer operative procedures [341].

c) Urodynamic evaluation

There are several reports on urodynamic evaluation in patients who underwent bladder neck reconstruction [343-345]. The majority of closed exstrophy bladders have normal filling dynamics before bladder neck reconstruction [344]. However, bladder abnormalities are very common after bladder neck reconstruction, with about 50% incidence of poor compliance and detrusor overactivity [343-345]. Detailed urodynamic investigation in patients with bladder exstrophy, after the first operation to create a functional bladder, is vital to guide the next step of management and to compare objectively the surgical outcome of reconstruction using different approaches.

d) The fate of the upper urinary tract

Preservation of the upper urinary tract is the most important goal in any form of lower urinary tract reconstruction. In several series of exstrophy patients, significant upper tract deterioration was noted in 22% to 26% of patients [323, 346, 347]. Because any type of outlet procedure that elevates the outlet resistance can be a potential cause of upper tract deterioration, upper and lower tracts should be monitored by ultrasound to measure the efficacy of bladder emptying and to look for subtle upper tract changes even in patients with a good bladder storage function who are undergoing any kind of outlet procedure.

2. MANAGEMENT OF PERSISTING INCONTINENCE

Regarding the management of persisting incontinence, there still remain considerable differences of opinion [337-339, 341, 347-352]. Various options are shown in Table 10. When planning the management of persisting incontinence, possible causes of incontinence should be thoroughly evaluated. Bladder and outlet storage function should be examined by detailed urodynamic investigation that allows for the individualization of treatment to optimize the chance of a successful outcome [345]. Multiple available reconstructive options may be considered to optimize continence outcome [353].

a) Augmentation cystoplasty

The late 1980s and early 1990s witnessed the more liberal use of bladder augmentation coupled with the option of a catheterizable appendicovesicostomy (Mitrofanoff procedure). The overall rate of bladder augmentation in patients with exstrophy-epispadias complex has been 22% to 40% [323, 325]. Preservation of the native bladder template has been emphasized by the Johns Hopkins group and others [330, 354]. This has two advantages, whether in the younger or older patients. First, using the template may decrease the amount of bowel needed for reconstruction. Second, if ureteral reimplantation is required, the bladder template is a better structure for reimplantation than a subtaenial tunnel of the bowel [330].

Stomach, ileum or colon can be used for bladder augmentation. Each type of augmentation has disadvantages that are inherent to the use of gastrointestinal segments, including metabolic derangement, urolithiasis [355], decreased linear growth [356], and hematuria-dysuria syndrome (in the case of stomach) [357]. A recent paper concludes that ileocystoplasty is safe and does not impact negatively on the linear growth or bone densities of patients with bladder exstrophy [358]. Gastrointestinal composite reservoirs, i.e. those made of a combination of stomach and other intestinal segments, may be considered to achieve electrolyte neutrality by contrasting electrolyte movements across the stomach and bowel [348].

b) Continent stoma

There are many surgical procedures, other than bladder neck reconstruction, to increase bladder outlet resistance, including injection of bulking agents and placement of bladder neck slings and artificial urinary sphincter [352]. Unfortunately, these outlet procedures have variable degrees of success with none being successful in all patients. It is not uncommon for some patients to undergo multiple procedures in an attempt to achieve continence. When these attempts fail, the creation of a catheterizable continent stoma with or without bladder neck closure is the preferred procedure to achieve continence [359]. Continence rate of 100% was achieved by bladder neck closure compared with continence rates of 56% by bladder neck reconstruction only and 67% by bladder neck reconstruction with augmentation and/or appendicovesicostomy [341]. However, the success of bladder neck closure is dependent in part upon patients’ compliance with intermittent catheterization [352]. In addition, those who have undergone bladder neck closure are at an increased risk for bladder stones [352].

c) Urinary diversion

Regardless of the type of continent urinary diversion used, most series demonstrate excellent success rates around 95% [359]. Based on the excellent continence rates achieved by urinary diversion
3. RECOMMENDATIONS

The published studies to date are retrospective case series with levels of evidence at best 3 with a grade of recommendation of C. The expert opinion of the Committee has resulted in the following recommendations regarding the evaluation and treatment of persisting incontinence in adulthood. (C)

- Patients with extrophy-epispadias complex should be evaluated and managed in specialized centers
- A universal definition of continence should be established
- Persisting incontinence should be evaluated with urodynamics and its treatment should be individualized based on urodynamic findings
- Life-long follow-up is mandatory in terms of continence, voiding efficiency, upper tract status and other urological complications
- Comparative studies, including quality of life and psychological assessment, should be undertaken if possible.

d) Outlet procedures

If the initial bladder neck reconstruction (original or modified Young-Dees-Leadbetter in many cases) fails and a low outlet resistance is the only cause of persisting incontinence, another outlet procedure is worth attempting. Option includes Kropp or Pippi Salle bladder neck reconstruction, injection of bulking agents, placement of bladder neck slings or an artificial urinary sphincter [352]. The presence of scarred tissue due to a previous surgery at the bladder neck may compromise the outcome. The value of the artificial urinary sphincter in dynamic control of outlet resistance in exstrophy patients is also questioned [323]. A vascularized gracilis muscle sling, to wrap around the compromised bladder neck of incontinent patients has been reported as salvage surgery [350]. Limited success has been reported with the use of bulking agents 361, 362.

3. RECOMMENDATIONS

X. DETRUSOR OVERACTIVITY AND REDUCED BLADDER CAPACITY

1. REFRACTORY URGENCY INCONTINENCE AND IDIOPATHIC DETRUSOR OVERACTIVITY

According to the Terminology Report of the International Continence Society the overactive bladder (OAB) syndrome refers to the symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia [363]. Detrusor overactivity (DO) was redefined to indicate the urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Idiopathic Detrusor Overactivity (IDO) exists when there is no defined cause and replaces the term “detrusor instability”. Neurogenic Detrusor Overactivity (NDO) is seen when there is a relevant neurological condition and replaced the term “detrusor hyperreflexia”. The criterion for considering detrusor overactivity as idiopathic is questioned, as Ahlberg et al found that 82% of patients initially considered idiopathic on careful searching actually had pathology potentially leading to the problem [364].

Idiopathic detrusor overactivity is a normal situation early in life. Children have urgency incontinence as a stage in acquiring bladder control. The incidence of detrusor overactivity during mid-life years (20 to 60) has been estimated as 10% [365]. In the asymptomatic elderly, detrusor overactivity once again becomes common, occurring in 50% of men over 70 [366]. In the symptomatic elderly, over 75 years old, it can reach 90% in men [367]. Detrusor overactivity may be a cause of severe storage symptoms such as frequency, nocturia, urgency and urgency incontinence. Conservative treatment of these symptoms such as bladder training and pharmacotherapy is discussed in other sections.

Magnetic stimulation may play a role in the non-invasive treatment of DO [368, 369]. Bradshaw et al. demonstrated an effect on cystometry of magnetic stimulation and found an improvement in urodynamic parameters but no consistent change in OAB symptoms [370]. Almeida et al. [371] in a prospective urodynamic controlled study of 91 women with UI, found an improvement on DO only in patients with initial bladder contractions <15 cm H2O. There are no other data available on the subject.

For symptoms that are refractory to conventional means, 4 interventional treatments have been reported: intravesical resiniferatoxin, botulinum-A toxin detrusor injections, neuromodulation, and bladder augmentation.
a) Resiniferatoxin

The use of intravesical neuromodulatory drugs such as capsaicin and resiniferatoxin was extended to DO of non-neurologic etiology after the suggestion that its etiology involved the enhancement of the C-fiber mediated spinal micturition reflex [372] and emerged as a minimally invasive procedure: the results are shown in Table 11 [373-380]. In spite of promising results, it is still considered experimental and more clinical studies are necessary for it to be licensed [381].

The mechanism of action is still under study. The mean bladder perception threshold is increased only in patients with clinical improvement [382]. The complexity of the mechanism is demonstrated by the presence of vanilloid receptors not only on sensory fibers but also in bladder urothelium and smooth muscle cells [379] and by ineffectiveness in treating an overactive bladder from idiopathic causes or suprapontine lesions with no vanilloid-sensitive fiber-mediated reflex [383]. It has been suggested that over expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response [384]. A well designed double-blind placebo-controlled study revealed no difference between placebo ethanol 10% saline solution and 50 nM resiniferatoxin, nevertheless both treatments showed improvement in symptoms of women with IDO [380]. Some placebo-controlled studies either did a quasi randomization [385] or did not explain how it was done [379]. Patients with increased bladder sensation without DO presented some improvement in symptoms in a small non placebo controlled series [386]. (Levels of evidence 1 – 4; Grade of recommendation D, two level 1 studies have contradictory conclusions [379, 384]

b) Botulinum-A toxin injection in the bladder

The minimal invasiveness of this method makes it very attractive but long term results in IDO are lacking (Table 12 [387-403]). The effects of its use are still not fully recognized [404], with possible systemic consequences [405-407], such as generalized muscle weakness in two patients treated for neurogenic bladder overactivity, and the development of resistance to the drug [408, 409]. The FDA made a public notification of adverse reactions linked to Botox use in February 2008, in approved and nonapproved usages. The agency is currently reviewing safety data from clinical studies to further communicate to the public its conclusions [410]. Most of the initial experience come from its use in neurogenic bladders [411-414], with favorable results. Information about its use in children is scarce [415]. A randomized study comparing the results of botulinum-A toxin injections to intravesical resiniferatoxin in NDO showed superior clinical and urodynamic benefit with the use of botulinum-A toxin [414]. The need for reinjections seems to be overcome by the significant improvement in quality of life of these patients [416], and is likely to be cost-effective [417]. The use of botulinum toxin B is less efficient, with a duration of action of about 10 weeks [418].

The optimal site of injections, including or not including the trigone, is still under debate [419]. Kuo in 2007 [399], published a study comparing the injections into the detrusor, suburothelial area, and bladder base, with the last location improving urgency but not increasing capacity. Most studies on idiopathic overactive bladder have been done in women [393, 394]. Data are lacking on dose, concentration, site(s), numbers of injections and long-term efficacy and side effects. Attempts to determine whether poor responders could be predicted from preoperative urodynamic parameters showed only a very high maximal detrusor pressure over 110 cm H2O as an unfavorable predictor when using 200 units [401]. Studies in women suggest a longer duration of action than its mere motor-nerve blocking potency can explain [394]. Therefore, a dual mechanism of action has been proposed: in addition to binding to cholinergic terminals, it might also affect afferent nerve transmission, thereby decreasing urgency [420, 421].

There are two commonly marketed forms of botulinum toxin-A (Botox and Dysport) and they require different doses to achieve similar results, in a proportion around 1:3 [422]. The first report using Dysport in refractory IDO was only recently published with similar results to Botox [393]. In a study using type A neurotoxin, purified by a procedure using a lactose gel column, improvements were seen in 89% of patients treated for incontinence due to IDO and NDO [396].

Many studies with botulinum toxin detrusor injection use different outcome measures for results and are variable for the presence of residual urine and the need for intermittent catheterization, but 6-75% of cases may present high post void residual urine [394, 396, 398, 401]. Besides being an alternative for treatment of refractory DO, currently available data do not show superiority of any specific treatment plan, and therapy options should be tailored to the specific patient and physician preference [423]. Higher doses such as 200 units in IDO resulted in incomplete emptying, necessitating intermittent catheterization in 6 out of 16 patients (37.5%) in one study [401]. Sahai suggests a careful follow up of the patients after the injections, starting IC in symptomatic patients if postvoid residual urine is more than 100-150 ml [424].

Many reports do not separate genders and mix neurogenic and idiopathic etiologies. A large number of publications are reviews of the literature [425-435]. There is one randomized double blind placebo controlled trial showing favorable difference against saline injections for frequency and incontinence, but not for urgency [401]. (Most levels of evidence 3, with one level 2; Grade of recommendation C)
<table>
<thead>
<tr>
<th>Author</th>
<th>No. (Gender)</th>
<th>Improvement</th>
<th>Duration of effect</th>
<th>Drug and dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruz et al. [373]</td>
<td>3 IDO (total of 16, including 3 males)</td>
<td>71% continence (overall total of 14) and 21% improvement</td>
<td>Up to 18 months</td>
<td>Capsaicin 125 ml of 30% alcohol in saline containing 1mM</td>
<td>Intense burning sensation</td>
</tr>
<tr>
<td>Kuo [374]</td>
<td>13 IDO (41 total) 18 previous TURP</td>
<td>5 (38.5%) 11 (61.1%)</td>
<td>2 to 9 months Average 5 months</td>
<td>RTX 10 ml of 100 nM RTX in 10% ethanol for 40 min</td>
<td>4 withdrew due to side effects. Significant worsening of emptying</td>
</tr>
<tr>
<td>Kuo [378]</td>
<td>(23) (19 ended)</td>
<td>(11 of 19) (58%)</td>
<td>10nM RTX weekly 3 to 4 times</td>
<td>Randomized double blind placebo controlled 6 withdrew after first instillation</td>
<td></td>
</tr>
<tr>
<td>Kuo et al. [379]</td>
<td>17 IDO</td>
<td>Vehicle 2(9) 22% RTX 5 (8) 63%</td>
<td>6 months</td>
<td>Vehicle or 4 weekly 10 nM RTX</td>
<td></td>
</tr>
<tr>
<td>Liu and Kuo [384]</td>
<td>28</td>
<td>14 (50%)</td>
<td>10 nM RTX weakly for 4 weeks</td>
<td>Transient receptor potential vanilloid subfamily 1 overexpressed in the responders</td>
<td></td>
</tr>
<tr>
<td>Palma et al [375]</td>
<td>25 females with idiopathic urgency incontinence</td>
<td>10 (40%) disappearance of urgency incontinence</td>
<td>1 month evaluation only</td>
<td>50 nM RTX</td>
<td>No mention of retention</td>
</tr>
<tr>
<td>Rios et al. [380]</td>
<td>58 females With IDO</td>
<td>43% RTX 35 % Placebo Vehicle Improvement - equal (p=0.439)</td>
<td>1 month first evaluation</td>
<td>50nM RTX or 10% ethanol saline solution</td>
<td>Randomized double-blind placebo controlled</td>
</tr>
<tr>
<td>Silva et al. [377]</td>
<td>13 IDO (2 men 11 women) (12 incont.)</td>
<td>11 improved (91%) in incontinence 3 (25%) dry</td>
<td>3 months follow-up</td>
<td>100 ml 50nM RTX solution 10% ethanol in saline for 30 min</td>
<td>No retention or other problems</td>
</tr>
<tr>
<td>Silva [385]</td>
<td>17 IDO (out of 23)</td>
<td>Vehicle 9 (39%) RTX 14 (60%)</td>
<td>Pre-test with vehicle only followed by RTX</td>
<td>Vehicle followed by 100 ml 50nM RTX (patients enrolled in 2005)</td>
<td>No separation of NDO and IDO</td>
</tr>
<tr>
<td>Yokoyama et al. [382]</td>
<td>10 (4 men) 5 (2 dry) 50%</td>
<td>3 months follow-up</td>
<td>100 ml 50nM RTX for 30 min</td>
<td>Neurometer before and at 30 days</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>No.</td>
<td>Type of patients</td>
<td>Dose</td>
<td>No. punctures</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>---------------------------------</td>
<td>------------</td>
<td>---------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Harper et al. 2003</td>
<td>39 (13 men and 26 women)</td>
<td>Neurogenic and idiopathic origin (not described separately)</td>
<td>200 idiopath 300 neurog</td>
<td>20 to 30 sparing the trigone Flex. cysto.</td>
<td>Increase max bladder volume 174 to 588 ml</td>
</tr>
<tr>
<td>Loch et al. 2003</td>
<td>30</td>
<td>Neurogenic and idiopathic</td>
<td>200 U</td>
<td>20 injections sparing the trigone</td>
<td>Significant improvement in 67% of the patients - &gt; residual urge</td>
</tr>
<tr>
<td>Radziszewski et al. 2002</td>
<td>12 (6 female and 6 male)</td>
<td>Only idiopathic</td>
<td>Up to 300 U</td>
<td>10-15 injections sparing the trigone</td>
<td>1 months follow-up 100% success no residual</td>
</tr>
<tr>
<td>Rackley et al. 2004</td>
<td>18 women</td>
<td>IDO</td>
<td>200-300 U (Botox)</td>
<td>Each 100 U in 1 cc saline, 0.1 cc injections</td>
<td>Improvement 40% frequency 30% urgency</td>
</tr>
<tr>
<td>Rapp et al. 2004</td>
<td>35 (29 females and 6 males)</td>
<td>6 neurogenic</td>
<td>300 U</td>
<td>30 injections including trigone</td>
<td>34% resolution 26% improvement</td>
</tr>
<tr>
<td>Kuo, 2004</td>
<td>30 (12 females and 18 males)</td>
<td>12 neurogenic</td>
<td>200 U</td>
<td>40 injections sparing the trigone</td>
<td>26% resolution 46% improvement</td>
</tr>
<tr>
<td>Chancellor et al. 2003</td>
<td>10 (2 males and 8 females)</td>
<td>Only idiopathic</td>
<td>100-300 U (Botox)</td>
<td>20-30 injections only in bladder base and trigone</td>
<td>80% improvement</td>
</tr>
<tr>
<td>Rajkumar et al. 2005</td>
<td>15 women</td>
<td>IDO</td>
<td>300 U (Botox)</td>
<td>30 ml – 30 injections</td>
<td>93% improvement</td>
</tr>
<tr>
<td>Popat et al. 2005</td>
<td>31 (18 women and 13 men)</td>
<td>IDO</td>
<td>200 U (Botox)</td>
<td>20 ml – 20 injections</td>
<td>57 % dry at 4 months</td>
</tr>
<tr>
<td>Kessler et al. 2005</td>
<td>11 patients (no gender information – 8 men in total of 22 patients)</td>
<td>IDO</td>
<td>300 U (Botox)</td>
<td>30 ml – 30 injections sparing the trigone</td>
<td>91% dry 5 months duration</td>
</tr>
<tr>
<td>Werner et al. 2005</td>
<td>26 women</td>
<td>Only IDO</td>
<td>100 U (Botox)</td>
<td>30 ml- 30 injections</td>
<td>65 % dry at 12 weeks 60% dry at 36</td>
</tr>
</tbody>
</table>
**c) Electrical stimulation and neuromodulation**

Electrical stimulation of the genital area was first used to control incontinence due to DO on an empirical basis for different etiologies [436]. Later, it was suggested that reflex sphincteric contraction induced by electrical stimulation can promote an inhibitory effect on detrusor activity, thus suppressing detrusor overactivity [437]. Many studies of external electrical stimulation for bladder inhibition of idiopathic urgency incontinence have been published, mainly in female patients [438-445]. The results vary from 45% to 85% success, with a mean of 38%, and 26% improved. Electrodes implanted in the pelvic floor, have not yielded good results [443].

Neuromodulation of sacral nerves has been reported as alternative therapy for urgency incontinence, urinary retention, and chronic pelvic pain. Good results have been published in treating neurogenic bladder dysfunction [446, 447]. The working mechanism of neuromodulation in the treatment of lower tract dysfunction is still unknown [448, 449]. A suggested mechanism is somatic afferent inhibition of sensory processing in the spinal cord [450, 451], therefore it may be a centrally acting treatment modality different from botulinum toxin, which is an end-organ therapy that specifically targets the bladder [452].

Long-term results suggest a sustained effect on restoring voiding in appropriately selected cases, but a revision rate of 42% at 5-year follow up remains a problem [453]. Its use in refractory idiopathic urgency incontinence has been limited to few patients, mostly women. Bosch and van Mastrigt reviewed 33 implanted women [454] presented results of chronic implantation in 15 women and 3 men, with an average age of 46 years. Significant improvements in voiding frequency, average voided volume, number of incontinence episodes and number of pads used were found, with no deterioration in response to stimulation with time. However, with subsequent experience in 14 men only 2 patients had a partial response and the rest ultimately failed [455]. Shaker and Hassouna [456] implanted 18 patients with refractory urinary urgency incontinence, but only 2 were in men. Groen, Bosch and van Mastrigt reviewed 33 implanted women and found no effect on urethral resistance and bladder contraction strength as consequence of the depressant effect of sacral (S3) nerve neuromodulation on detrusor overactivity [457]. Groenendijk et al. in a retrospective study for the Sacral Nerve Stimulation Study Group, reported urodynamic aspects of 111 patients implanted, but only 8 men were included [458]. They found a better result on urgency incontinence in patients without DO. The difference was not significant. This tendency was also found by South et al. in 67 women implanted [459]. Clinical or urodynamic values to predict the outcome of sacral nerve stimulation has been difficult do define. Evaluation of 19 women suggested that urethral instability seemed to be a good parameter to predict a favourable outcome [460].

Some studies do not specify the etiology of the DO and neurogenic and non-neurogenic causes are grouped together [456]. Some reports focus on technical or specific aspects of the procedure and the same patients may be included in different publications [458, 461, 462]. Implantation in children may be feasible in selected cases [463, 464] and poorer results are expected in older women [102]. The outcome in older men is unknown since there are no reports.

Table 13 [403, 453, 465-472] shows some recent studies.

Some reports are literature reviews [449, 473-475] or detail technical modifications [476, 477]. There is one systematic review on efficacy and safety of sacral nerve stimulation for urgency incontinence, but 13 of the articles analyzed are abstracts and it is also difficult to ascertain whether the same patients are included in different publications [478].

There are some publications with level 1[465, 466] or 2 [455, 468, 469] evidence and with a grade of recommendation D. However, due to relatively few men in the clinical trials, and poor results in one of the prospective trials, its general applicability to men with urgency incontinence may be limited. Level of evidence 3. Grade of recommendation D (due to lack of evidence)

**d) Surgical treatment by detrusor myectomy and augmentation**

Previously used treatments of surgical bladder denervation, open bladder transection, cystolysis, endoscopic phenol injections, hydrostatic bladder distention did not produce good results.

Bladder autoaugmentation or detrusor myectomy has been reported as an alternative to augmentation in neurogenic and non-neurogenic dysfunction. Table 14 [479-481] shows results of this treatment in patients with non-neurogenic detrusor overactivity. There are few long term results available [481]. Additional and longer term experience is still required to properly assess this procedure. (Level of evidence 3; grade of recommendation C-D)

Enterocystoplasty results are detailed in Table 15 [480, 482-488], which includes both male and female patients. Some publications are not clear about the type of surgery specifically done in IDO and about the gender [488]. Good results vary from 58% to 88%, with an average of 77%. Approximately 10 to 75% of patients require intermittent catheterization for bladder emptying. Ileum was the most frequently used bowel segment followed by sigmoid colon, although no scientific reason for the use of any particular segment was given. The surgery, as reported in other sections, has a significant complication rate and should be considered carefully when applying it to these patients. (Level of evidence 3; grade of recommendation C)
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Success (dry)</th>
<th>Improved</th>
<th>Control group</th>
<th>Study and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt et al. [465]</td>
<td>34</td>
<td>47%</td>
<td>29%</td>
<td>42</td>
<td>prospective randomized</td>
</tr>
<tr>
<td>Weil et al. [466]</td>
<td>21</td>
<td>56%</td>
<td>19%</td>
<td>23</td>
<td>prospective randomized</td>
</tr>
<tr>
<td>Bosch et al. [467]</td>
<td>34</td>
<td>38%</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(females)</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(males)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumar et al. [481]</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leng et al. [480]</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>49</td>
<td>38 (77.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*short term followup
**longer term follow-up of the same series, 45% required IC
2. REDUCED BLADDER CAPACITY

Fibrosis of the wall produces a low-volume low-compliant bladder, leading to diminished functional capacity. Symptoms of frequency and nocturia occur as a result of progressive decrease in bladder volume, but urinary incontinence may also be the consequence of a very small capacity, especially if accompanied by urethral weakness. The diagnosis can be suggested by the micturition chart, and confirmed by urodynamics. The causes can be congenital or acquired. Acquired causes include multiple surgeries, inflammatory processes (chronic cystitis, interstitial cystitis, tuberculosis, schistosomiasis, and chemical cystitis) or following radiation.

Bilharzial contracted bladder is a problem that is primarily limited to endemic areas in Africa and the Middle East. Schistosoma haematobium migrates to the veins of the vesical and pelvic plexuses, where the female begins to lay eggs, promoting a initial inflammatory response. As a result, granulomatous lesions form in the lamina propria. Mucosal reactions vary from hyperplasia to polypoid cystitis. A contracted bladder occurs in 2 % of cases [489]. Bladder augmentation seems to offer reasonable results in these cases.

Similarly, small fibrotic bladders due to other etiologies can be treated successfully with enterocystoplasty. The results of this surgery are presented in Table 16 [488, 490-516]. The results are similar in all etiologies except for radiation. The poorer results after radiation may be due to other tissue damage in the surgical area. New conformal techniques for radiotherapy may improve results in the future, so that the need for augmentation cystoplasty decreases.

Almost all of these studies do not distinguish bowel segments or separate males from females in reporting results. Therefore, it is not possible to correlate any particular aspect with the chance of success or failure. However, overall the results seem reasonably good with the exception of patients who have undergone radiation. (Level of evidence 3; Grade of recommendation C)

XI. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE

Urethrocutaneous or rectourethral fistula may have congenital, inflammatory, neoplastic or traumatic origin. It is important to recognize the varying etiology because each type may require different surgical strategy. All reports except one are retrospective case series. The report by Shakespeare et al. [517] is from a prospectively collected data base of patients treated with radiotherapy for prostate cancer. (Level of evidence 3; grade of recommendation C).

1. URETHROCUTANEOUS FISTULA (UCF)

a) Acquired UCF

Hidden foreign bodies have been described as a rare cause of both strangulation of the glans penis and urethrocutaneous fistula. Tash and Eid [518] presented the case of a 30-year-old man who developed a urethrocutaneous fistula and penile shaft necrosis after a condom broke during intercourse. Neither the patient nor several physicians could identify the retained ring of condom, which had been buried under newly epithelialized skin. He underwent removal of the foreign body under general anaesthesia, followed 5 months later by a formal urethrocutaneous fistula repair.

Table 15. Enterocystoplasty for treatment of refractory urgency incontinence due to detrusor overactivity (males and females)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Detrusor overactivity</th>
<th>Good or moderate result</th>
<th>Bowel segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasan et al. [482]</td>
<td>35</td>
<td>19</td>
<td>46 ileum</td>
</tr>
<tr>
<td>McInerney et al. [483]</td>
<td>50</td>
<td>44</td>
<td>13 colon</td>
</tr>
<tr>
<td>Bramble [484]</td>
<td>15</td>
<td>13</td>
<td>2 ileum</td>
</tr>
<tr>
<td>Sethia et al. [485]</td>
<td>11</td>
<td>9</td>
<td>ileum</td>
</tr>
<tr>
<td>Mundy and Stephenson [486]</td>
<td>40</td>
<td>30</td>
<td>ileum</td>
</tr>
<tr>
<td>Leng et al. [480]</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Edlund et al. [487]</td>
<td>25</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Blaiivas et al. [488]</td>
<td>9</td>
<td>9</td>
<td>Ileocaecal segment and ileum</td>
</tr>
<tr>
<td>Total</td>
<td>187</td>
<td>145 (78%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 16. Enterocystoplasty results for reduced bladder capacity

<table>
<thead>
<tr>
<th>Authors</th>
<th>Bilharziases cystitis</th>
<th>Tuberculous cystitis</th>
<th>Radiation cystitis</th>
<th>Unknown cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Success</td>
<td>Total</td>
<td>Success</td>
</tr>
<tr>
<td>Smith et al. [490]</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Kerr et al. [491]</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Zinnman and Libertino [492]</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dounis et al. [493]</td>
<td>-</td>
<td>-</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Lunghi et al. [494]</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Shawket and Muhsein [495]</td>
<td>8</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Whitmore and Gittes [496]</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Chan et al. [497]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shirley et al. [498]</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Goodwin et al. [499]</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Winter and Goodwin [500]</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fall and Nilsson [501]</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Goldwasser and Webster [502]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weinberg et al. [503]</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Novak [504]</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Sayegh and Dimmette [505]</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Beduk et al. [506]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kuo [507]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kawamura et al. [508]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hradec [509]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>El Otmany et al. [511]</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yamada et al. [512]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Miyano et al. [513]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blaivas et al. [488]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>de Figueirredo et al. [514]</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Yashi et al. [515]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lima et al. [516]</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>10</td>
<td>8 (80%)</td>
<td>136</td>
<td>123 (90%)</td>
</tr>
</tbody>
</table>
Urethroperineal fistula, as a complication of open perineal prostate cryosurgery, occurs as an immediate perioperative complication in 10.7% [519]. Thomas et al. [520] retrospectively evaluated 250 patients after radical perineal prostatectomy and revealed only 1 (0.4%) urethroperineal fistula. Fahal et al. [521] published an unusual complication of *mycetoma*. The patient had an infection with *Actinomadura madurae* that involved abdominal wall, perineum and urethra. This resulted in urinary extravasation with a urethrocrotanous fistula.

c) Management of UCF

The diagnosis of UCF is made by physical examination, retrograde urethrography (Figure 3), urethroscopy, fistulography, urethral ultrasound or color Doppler imaging. Urethral sonography provides additional information about any involvement of the surrounding tissue, location of vessels and associated abnormalities such as a periurethral abscess [522].

Treatment of UCF usually requires urethroplasty techniques with modifications involving fistula excision and multiple layer closure [523]. *(Level of evidence 3; Grade of recommendation C)*

2. RECTOURETHRAL FISTULAS (RUF)

Culp and Calhoon described five basic groups of RUF according to the etiology [524]: congenital, iatrogenic, traumatic, neoplastic, and inflammatory.

a) Congenital RUF

Endo et al. [525] described the results of the Japanese Study Group of Anorectal Anomalies (JSGA) to determine the relative incidence of specific types of these anomalies in Japan. They included discussion of RUF regarding the relationship between the fistula levels and the blind end of the rectum, low type deformity, rare types, and associated anomalies. A total of 1,992 patients (1,183 boys and 809 girls) registered from 1976 to 1995 were analysed according to the pathogenesis of anorectal malformation in the field of molecular genetics. They reported that more than 20% of RUF should be categorized as intermediate or low deformity from the position of the rectal pouch. A significant preponderance of Down’s syndrome in the deformities without fistulae suggests that investigation of associated anomalies and congenital diseases may provide further insights.

The purpose of Rintala’s study was to compare the long-term outcome of sacroperineal-sacroabdominoperineal pull-through (SP-SAP) to that of posterior sagittal anorectoplasty (PSARP). In boys with high anorectal anomalies, PSARP was superior to SP-SAP pullthrough in terms of long-term bowel function and faecal continence [526].

b) Acquired RUF

Acquired RUF may occur after pelvic trauma, surgery of the prostate or rectum, pelvic cancer, radiation (either external beam or brachytherapy), cryosurgery, prostatic hyperthermia, prostatic high intensity focussed ultrasound (HIFU), inflammatory bowel disease affecting rectum, or rarely prostatitis inflammation.

Benchekroun and co-workers [527] report a series of 11 RUF observed over a 25-year period. The etiologies were surgical trauma (5 cases), fracture of the pelvis (2 cases), inflammatory lesions (3 cases), and one fistula was congenital. Colostomy was performed in 2 patients, surgical closure of the fistula was performed in 7 patients: abdominoperineal (3 cases), perineal (2 cases), transperitoneal (1 case) or by transanospinhincteric incision (1 case).

In 1972 Smith and Veenema [528] reported their 20-year experience with 160 patients undergoing radical retropubic prostatectomy (RRP) with an incidence of 15 rectal injuries. Only 4 fistulas developed in this group.

The most common single cause of RUF in the series of 23 male patients published by Tiptaft et al. [529] was a fracture of the pelvis and iatrogenic causes (two cases after transurethral prostatic surgery, two cases after open prostatectomy, and three cases after urethral instrumentation (Table 17). Noldus et al. [530] reported 23 (3.9%) rectal injuries during 589 RRP and cystoprostatectomy procedures. Eastham and Scardino [531] summarized the incidence of rectal injury during RRP in 3834 patients with an average of 0.7% (range 0.2-2.9%). The incidence of RUF, as an immediate perioperative complication of open perineal prostate surgery, is 1.4 %.
Nyam et al. [532] reviewed records of all patients who were diagnosed with RUF between January 1981 and December 1995 and 16 males were identified. All patients were interviewed by telephone for follow-up. The mean age was 68 years and the mean follow-up was 80 months. Adenocarcinoma of the prostate in 15 patients and recurrent transitional cell carcinoma of the bladder in one patient were the underlying malignant diseases. Nine patients had had a RRP with 2 fistulas after radiation, 2 after brachytherapy, and 3 after a combination of radiation and brachytherapy. One patient formed a fistula after cystectomy and dilation of a stricture. This heterogenous group of patients received multiple therapies including initial colostomy (7 patients), transanal repair (2 patients), parasacral repair (2 patients), transperineal repair (2 patients), coloanal anastomosis (3 patients), and muscle transposition (3 patients). Four of the patients required a permanent stoma.

Badalament et al. [533] managed one patient (0.4%) with a urethrorectal fistula after cryoablation therapy for prostate cancer. Zippe [534] reviewed preliminary results of prostate cryosurgery and reported a 2 to 5% incidence of RUF. Porter [519] found a 2.5% rate of RUF in 210 patients after TRUS-guided prostate cryosurgery and no urethroperineal fistulae. Ismail et al. [535] reported the experience of using salvage targeted cryoablation of the prostate (TCAP) in 100 patients for the recurrence after radiotherapy. The mean follow-up was 33.5 months and RUF occurred in 1%.

Montorsi et al. [536] reported a RUF after transrectal prostatic hyperthermia (43 degree C) in patients with advanced prostatic cancer after multiple treatment sessions. The fistula was cured after a urethral catheter was left in place for one month.

Kleinberg et al. [537] summarized results of 31 patients with stage T1 or T2 prostatic carcinoma following CT guided transperineal I125 implants and reported that only one patient developed a prostatorectal fistula that was managed with an ileal conduit.

Fengler and Abcarian [538] published their experience of eight patients with RUF in the course of treatment of prostate cancer (3 fistulae after radiation therapy alone, 3 after prostatectomy and 2 after both surgery and radiation therapy). Larson et al. [539] evaluated 5719 patients after radiation for prostate cancer. Ten had documented RUF. Lane et al. [540] treated 21 men with RUF following primary external beam radiotherapy and one after adjuvant external beam radiation therapy for prostate cancer. Time from the last radiation treatment to fistula presentation was 6 months to 20 years. Four patients underwent proctectomy with permanent fecal and urinary diversion. Successful fistula closure was achieved in the 9 patients who underwent urethral reconstruction. Chrouser et al. [541] identified a total of 51 patients with a history of external beam radiation for prostate cancer that subsequently had a urinary fistula. Of 20 patients meeting inclusion criteria, 30% received external beam RT alone, 30% received brachytherapy and 40% had received combined external beam RT/brachytherapy. Most fistulas (80%) were from the rectum to the urinary tract with an average diameter of 3.2 cm. Of patients with rectal fistulas 81% had a history of rectal stricture, urethral stricture, rectal biopsy, rectal argon beam therapy or transurethral prostate resection after radiation. All patients with rectourethral fistulas who achieved symptomatic resolution required urinary and fecal diversion.

Shakespeare et al. [517] reviewed the potential factors in fistula development and identified three cases (0.2%) of RUF among 1456 patients treated with prostate brachytherapy (BT), occurring at 19-27 months following BT. All these patients had BT monotherapy and had been investigated with endoscopy and low rectal biopsy. They concluded that gastrointestinal specialists should not perform biopsy of the anterior rectum in patients who have had BT unless there is a very high clinical suspicion of malignancy. Marguet et al. [542] described 6 cases of RUF in patients treated with brachytherapy plus external beam radiotherapy for localized prostate cancer and subsequent rectal biopsies or rectal surgery. Four patients underwent hyperbaric oxygen therapy, which failed. Three patients underwent fecal diversion with gracilis interposition flaps, and two underwent pelvic exenteration. They also concluded that biopsy of rectal ulcers in the clinical setting of combined radiotherapy should not be performed.
Badalament et al. [533] managed one patient (0.4%) with a urethrorectal fistula after cryoablation therapy for prostate cancer. Zippe [534] reviewed preliminary results of prostate cryosurgery and reported a 2 to 5% incidence of RUF. Porter [519] found a 2.5% rate of RUF in 210 patients after TRUS-guided prostate cryosurgery and no urethroperineal fistulae. Ismail et al. [535] reported the experience of using salvage targeted cryoablation of the prostate (TCAP) in 100 patients for the recurrence after radiotherapy. The mean follow-up was 33.5 months and RUF occurred in 1%.

Montorsi et al. [536] reported a RUF after transrectal prostatic hyperthermia (43 degree C) in patients with advanced prostatic cancer after multiple treatment sessions. The fistula was cured after a urethral catheter was left in place for one month.

Chang et al. [543] published a case of prostatic malakoplakia masquerading as a rectal tumor due to formation of a fistulous tract to the rectal muscular layers. Cools et al. [544] reported a very uncommon type of fistula between the large bowel and the prostatic urethra due to Crohn’s disease. Felipetto et al. [545] described a prostatocutaneous fistula as a complication of pseudomonas prostatitis.

Transrectal high-intensity focused ultrasound (HIFU) destroys prostate cells by coagulative necrosis of the tissue. Recent reports of efficacy also include morbidity. Rebillard et al. [297] reported RUF in 0-3% in a review involving 37 articles/abstracts.

c) Diagnosis of RUF

RUF may be strongly suspected from the patient’s history (fecaluria, abnormal urethral discharge, pneumaturia, leakage of urine from the rectum during micturition). Rectal examination, proctoscopy, careful urethroscopy, intraurethral injection of methylene blue dye, radiopaque contrast agent placed into the bladder and then voided usually appears in the rectum on X-ray, are the most important diagnostic steps [522, 546] (Figure 4).

d) Therapy of RUF

Small fistulae may resolve spontaneously with urinary and/or fecal diversion. Therefore, an initial trial of conservative therapy is reasonable. Selected patients with chronic fistulas who are poor surgical candidates may also be managed conservatively with antibiotics, pads and symptomatic care. Timing of repair is often individualized, mainly according to the etiology, delay in diagnosis, size of fistula, whether it is the first or subsequent repairs, and the general condition of patient.

Diversion of urine (suprapubic cystostomy) is generally recommended as well as correction of any urethral stricture distal to the fistula. Fecal diversion, with colostomy is used by some as a mandatory part of double diversion or selectively by others. Gibbons [547] stressed the need for a diverting colostomy for 3-4 months.

However, as surgeons obtained more experience, bowel preparations became standardized, and effective antibiotics were developed, and the enthusiasm for colostomy diminished. Currently, colostomy is recommended in circumstances where antibiotics alone cannot control the inflammation and infection associated with the fistula or when the fistula involves radiated tissue. Low residue diet is also useful for healing. Suitable drainage (perineal and urethral splinting) is stressed.

e) Surgical Approaches

Surgical management for rectourinary fistulas remains a reconstructive challenge. Two-layer closure of the urethra and rectum with suture lines at right angles and with interposition of soft tissue (eg. omentum [548], gracilis muscle [549], or scrotal flap [550]) has been described. Surgical approaches include transabdominal, transvesical, or direct exposure of the RUF.

There are only a few guidelines to direct the surgeon to the most successful and least morbid technique. Rivera et al. [551] staged RUF as stage I—low (less than 4 cm from anal verge and nonirradiated), stage II—high (more than 4 cm from anal verge and nonirradiated), stage III—small (less than 2 cm irradiated fistula), stage IV—large (more than 2 cm irradiated fistula) and stage V—large (ischial decubitus fistula). Diverting colostomy was performed for stages
III to V 6 weeks before definitive therapy. Some of the patients in addition to the RUF will also have urethral strictures that have to be managed. Reconstruction of both aspects to restore functional anatomy is possible with complex reconstructions [552].

The surgical approaches including the numbers of reported patients are listed in Table 18 [524, 527-530, 538, 546, 550, 553-569].

1. PERINEAL APPROACH

In 1926, Young [553] dissected the rectum away from the sphincters, divided the fistula, closed the urethra, and mobilized the rectum further cephalad in such a fashion as to pull the affected rectum caudally out of the anus where it was then transected and discarded, suturing the proximal rectum to the anal skin. Subsequently Lewis, in 1947 [554], described suturing the levator muscle fibers together in the anterior midline when possible.

Goodwin et al. [555] reported a series of 22 RUF approached perineally. They extensively mobilized the rectum posteriorly and the bladder anteriorly through wide perineal exposure allowing interposition of the levator ani muscles between the urinary tract and rectum. Singh et al. [570] described the management of a delayed post-traumatic RUF repaired via transperineal access without rectal or sphincteric transgression. An example of a preoperative and postoperative urethrogram is in Figure 5. Pratap et al. [571] described a simultaneous perineal and abdominal approach in a series of 8 patients with traumatic perineal injuries who had both complex urethral disruptions and RUF.

2. POSTERIOR SAGITTAL APPROACH

Kraske in 1885 [572] described a posterior midline incision extending to the left paramedian aspect of the coccyx and sacrum that involved partial removal of the sacrum in addition to coccyectomy. His method did not involve division of the sphincters, but rather sweeping the rectum laterally to ultimately facilitate resection and reanastomosis of a tumour-bearing rectal segment, thereby preserving fecal continence. In 1962, Kilpatrick and Thompson [558] used this approach when the rectum was completely mobilized circumferentially proximal and distal to the fistula. The RUF was then divided, sparing as much as possible on the urethral aspect. The rectal part of the fistula was excised and closed in two layers, and the urethra was repaired and stented with a catheter.

3. POSTERIOR (PARASACROCOCCYGEAL) TRANSPHINCTERIC APPROACH

In 1969 Kilpatrick and Mason [560] updated this method and advocated a more radical method of dividing the rectal sphincters to give direct access to the RUF. The procedure (the York-Mason approach) is simpler than some complicated transabdominal or transperineal approaches to RUF. It is still used because it allows direct visualization of the fistula via parasacrococcygeal (transsphincteric) incision especially to fistulae in the mid to lower rectum [538]. After the skin incision the mucocutaneous junction is marked with sutures and the internal sphincter is exposed. Division of the sphincter mechanism and posterior rectal wall allows exposure of the fistula. Each sphincter muscle is tagged with color-coded sutures. The next step of this procedure is the incision around fistula, followed by excision of the fistulous tract exposing the catheter in the prostatic urethra. The undermining of rectal wall allows sufficient mobilization. After closure of the prostatic urethra it is recommended that the full-thickness rectal wall flaps are close in a "vest over pants" technique (Figure 6). It is important to make sure that the suture lines do not overlie each other. The procedure is completed by suture of the rectal wall and approximation of the sphincter muscles (Figure 7). Fengler and Abcarian [538] reported healing of RUF in all of 8 patients with the York-Mason approach. Bukowski et al. [562] managed 7 acquired recurrent RUF (3 after prostatectomy, 3 after trauma and 1 after perineal abscess) using York-Mason technique and a similar experience was described by Fournier et al. [561] in the management of a case of the urethro-prostato-rectal fistula after a gunshot wound.

Stephenson and Middleton [559] modified the York-Mason repair and reported their experience with posterior sagittal, transanal, transrectal repair of RUF in 15 patients. The transsphincteric, transanal surgical approach provides many advantages, including easy access and identification of the fistula tract, good surgical exposure, adequate resection back to well vascularized tissue, and access to several vascularized flaps for interposition between the repaired urinary and gastrointestinal tracts.

Culkin [565] reported preliminary experience with the transsphincteric, transanal surgical approach to correct acquired urethrorectal fistula in five men. Mean patient age was 56.6 years (range 37 to 72). The etiology was surgical (radical prostatectomy) in 3 cases, traumatic in 1 and idiopathic in 1. The time from the diagnosis of urethrorectal fistula to surgery was 4 weeks to 4 years. Five men underwent excision and closure of a urethrorectal fistula with diverting colostomy. In 4 men (80%) urinary continence subsequently returned with adequate sphincter tone, while in 1 (20%) with perineal trauma and active proctitis the fistula recurred 6 weeks after surgery.

Dal Moro et al. [573] reviewed a 15-year experience using the York-Mason posterior sagittal transrectal approach to iatrogenic RUF in 7 patients. In one patient with Crohn’s disease the fistula recurred 11 years after the first surgery. The colostomy remained in place only in one patient with Crohn’s disease and in another with ulcerative rectocolitis.
Table 18. Surgical approaches to rectourethral fistulas

<table>
<thead>
<tr>
<th>Approach</th>
<th>Author, Year</th>
<th>No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERINEAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Young, 1926 553</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Lewis, 1947 554</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Goodwin, 1958 555</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Culp and Calhoon, 1964 524</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Smith and Veenema,1972 528</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Youssef,1999 556 (perineal dartos flap)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Benchekroun,1999 527</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Ng, 2004 557(buccal graft)</td>
<td>27</td>
</tr>
<tr>
<td><strong>POSTERIOR - SAGITTAL</strong></td>
<td>Kilpatrick and Thompson, 1962 558</td>
<td>6</td>
</tr>
<tr>
<td><strong>POSTERIOR – TRANSSPHINCTERIC</strong></td>
<td>Stephenson,1996 559</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Kilpatrick and Mason, 1969 560</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Culp, 1964 524</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Fengler,1997 538</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fournier, 1996 561</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bukowski,1995 562</td>
<td>7</td>
</tr>
<tr>
<td><strong>TRANSANAL</strong></td>
<td>Vose,1949 563</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Parks and Motson, 1983 564</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tiptaft,1983 529</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Noldus,1997 530</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Culkin, 2003 565</td>
<td>5</td>
</tr>
<tr>
<td><strong>COMBINED (posterior transssphincteric anterior rectal wall advancement)</strong></td>
<td>Al-Ali,1997 546</td>
<td>16</td>
</tr>
<tr>
<td><strong>ANTERIOR TRANSANORECTAL</strong></td>
<td>Geceleter,1973 566</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Venable,1989 550</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zinman, 2003 567</td>
<td>22</td>
</tr>
<tr>
<td><strong>ENDOSCOPIC</strong></td>
<td>Wilbert, 1996 568</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bardari, 2001569</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 5: A. Cystogram demonstrates RUF caused by a TURP. Negative shadow from Foley catheter is seen in the bladder. B. Retrograde urethrogram after transperineal closure of RUF
Erickson et al. [574] reported a novel surgical technique used to repair a rectourethral fistula associated with two short-segment urethral strictures located in the anterior and posterior segments of the urethra in a patient with prior unsuccessful repairs. The anterior urethral stricture was reconstructed with a ventral onlay of buccal mucosa in the exaggerated lithotomy position. In a modified prone position, the rectourethral fistula was repaired using the transrectal transsphincteric (York-Mason) technique and the posterior urethral stricture with a radial forearm fasciocutaneous free flap which was anastomosed to the inferior gluteal artery and vein. The coexistence of a rectourethral fistula and distal urethral stricture requires simultaneous repair, because the urethral pressure from the distal obstruction may compromise fistula closure.

4. TRANSANAL APPROACH

Parks and Motson [564] popularized the addition of a full thickness local flap of anterior rectal wall as an adjunct to fistula repair through the intact anal canal (Figures 8 [575] and 9). They modified the transanal technique by denuding the rectal mucosa lateral and distal to the fistula, and mobilized the rectal wall away from Denonvilliers’ fascia proximal to the fistula for four centimeters. Tiptaft et al. [529] also used a special anal retractor for this surgery.

With the Latzko procedure the RUF is closed in three layers with absorbable suture. A transurethral catheter is placed for 3 weeks. Noldus et al. [530] reported 23 patients (3.9%) with urethral injury during 589 RP and cystoprostatectomies. Of these 23 patients, 12 developed a RUF. Seven fistulas closed spontaneously with prolonged catheter drainage. The remaining 5 fistulas were all successfully closed with the transanal Latzko procedure.

Al-Ali et al. [546] treated 30 men with RUF caused by war wounds. He used the method of posterior transsphincteric anterior rectal wall advancement as the treatment of choice. Double diversion (end sigmoid colostomy and suprapubic cystostomy) for one month was performed in all patients. Double diversion alone resulted in ‘spontaneous’ RUF healing in 47% of patients but 53% required reconstruction. Early repair was recommended for large fibrous fistulas. Undiversion was done after two months when the urethra and anorectal canals were normal.

5. ANTERIOR TRANSPHINCTERIC, TRANSANAL SURGICAL APPROACH (ASTRA)

In 1973 Gecelter [566] performed a midline perineal incision to gain access to the urinary tract after placing the patient in exaggerated lithotomy position. The sphincter was incised anteriorly, tag sutures carefully placed, and the rectal incision was carried to the fistulous tract, which was excised and repaired in multiple layers with transposition of tissue as available. Castillo et al. [576] reviewed their first 110 consecutive laparoscopic extraperitoneal radical prostatectomies and reported 3 RUF. Only one was cured with conservative management. The other 2 patients were repaired by anterior transsphincteric, transanal surgical approach (ASTRA)

6. ENDOSCOPIC APPROACH

Wilbert et al. [568] reported two patients with RUF who were repaired endoscopically transanally. The
Figure 8: Transanal repair of rectourethral fistula [575]. A. Elliptical incision of the rectal mucosa around the fistula. B. Denudation of the rectal mucosa. C. Fistula closed with absorbable suture. D. Rectal mucosal flap sutured with absorbable suture.

Figure 9. A. Retrograde urethrogram of a 55 year-old man who underwent a radical prostatectomy. He complained of fecaluria and urine per rectum. This shows urethral contrast in the rectum through a rectourethral fistula (Black arrow). B. Intraoperative photograph of transanal rectourethral fistula repair. The anus is held open by the ring retractor to permit direct access to the fistula. C. Intraoperative view of the rectal mucosal sutures in the rectourethral fistula repair. D. Retrograde urethrogram 3 months after transanal rectourethral fistula repair. There is no contrast entering the rectum from the urethra. The patient’s suprapubic tube was removed and his colostomy was reversed.
patients were positioned prone and the rectoscope mounted to the operating table was inserted into the rectum. The fistula was visualized and the opening excised to the level of the perirectal tissues with cautery. The rectal wall was mobilized full thickness with scissors and closed primarily in two layers with a microscope. The patient was then placed in lithotomy position and the urethral side of the fistula was coagulated and injected with fibrin.

Bardari et al. [569] used cyanoacrylic biological glue to close one prostato-perineal fistula complicating an abdominoperineal resection of rectum and one persistent neobladder-ileal fistula. The biologic sealant was administrated endoscopically through an open-end 6F ureteral catheter. Quinlan et al. [577] presented the case of an iatrogenic fistula in a 71-year-old man treated by a transanal endoscopic microsurgical (TEM) approach, without recourse to a stoma. Bochove-Overgaauw et al. [578] reported successful repair of 1 of 2 RUF with transanal endoscopic microsurgery (TEM). The RUF occurred after laparoscopic radical prostatectomy.

7. Other modifications

Youssef et al. [556] successfully treated 12 male patients who presented with RUF from 1990 to 1997 using the perineal subcutaneous darts flap procedure. The RUF resulted from crush pelvic injury in 6 cases, gunshot wounds in 2, and post prostatectomy in 4. The fistula was associated with a urethral stricture in 4 cases. A perineal approach was used and combined with a transsymphseal approach in the 4 patients with posterior urethral stricture. They interposed a subcutaneous darts flap as a tissue flap between the repaired rectum and urethra. No leakage or perineal collection developed and there was no fistula recurrence. Follow-up ranged from 9 to 42 months. This technique of a perineal subcutaneous darts flap may fulfill the principles for successful repair of RUF. Varma et al. [579] also concluded that darts muscle interposition is a straightforward technique that can result in successful fistula repair, but should not be used in immunocompromised patients or after radiation therapy.

Felipetto et al. [545] used human fibrin sealant (Tissucol) to close a prostato-cutaneous fistula (as a complication of pseudomonas prostatitis). Venkatesh and Ramanujam [580] prospectively studied the efficacy of autologous fibrin glue for closure of recurrent anorectal fistulas. Overall success rate was 60% however patients with acquired immunodeficiency syndrome who had fistulas associated with the urinary tract failed to respond.

Finally Chirica et al. [581] reported their experience with coloanal sleeve anastomosis (Soave procedure) as a salvage procedure for complex rectourinary fistulas after radical prostatectomy or followed anterior resection for rectal cancer after radiochemotherapy. All eight patients had a temporary ileostomy, which was successfully reversed in 7.

f) Summary

A review of recent literature shows an increasing number of papers describing treatment. All available studies are retrospective cases and case series (level 3 evidence). There are many causes of these fistulas described in the literature but there is a lack of valid epidemiologic data about the incidence of UCF and RUF. The diagnostic algorithm has not changed in many years.

The aim of the surgical approach is the closure of all types of fistulas. While spontaneous closure and success with a one-stage procedure has been reported, most cases to date involve 3 stages (double diversion, closure technique, and undiversion). An endoscopic approach using biological sealants is promising. Only a few urologists and general surgeons have gained wide experience in the management of UCF or RUF. No single procedure has yet proved to be best or universally applicable. Conservative treatment is generally ineffective in the management of large RUF. Surgical intervention offers symptomatic relief and improved quality of life in most patients. All reports are still only retrospective case series (Level of evidence 3; grade of recommendation C).

XII. THE ARTIFICIAL URINARY SPHINCTER (AUS)

Different devices designed to control urinary incontinence in the male go back to the middle of the 18th century [582]. Since then research eventually produced external and implantable devices. The gold standard today is considered to be the artificial urinary sphincter (AUS) designed by F.B. Scott, W.E. Bradley, and G.W. Timm in 1973 [583]. The original model underwent a number of modifications, but the basic principle remained the same. It consists of a fluid filled hydraulic system with a cuff around the urethra, a pressure regulating balloon and an activating device, the pump, placed in the scrotum.

1. Availability and cost

The results of an e-mail survey among urologists and gynecologists were previously published in the 3rd ICI, whereby members of the International Continence Society asking them if the AUS was available in their country; and if so, what was the price of the device (in US dollars). About 10% of the members responded by email from 31 countries. The price varied from $4000 to $10,000 USD. The high price in some countries at the time (Georgia, Hong-Kong, Romania and Saudi Arabia) precluded its use. Very few gynecologists implant the sphincter, probably since the majority of patients receiving the device are male.
2. INDICATIONS

The indication for AUS placement is for the treatment of SUI due to ISD that is persistently bothersome despite 6-12 months of active conservative management. As the most common cause of SUI in men is iatrogenic injury during prostate cancer surgery, it follows that the most common indication for AUS is post-prostatectomy incontinence (PPI). The use of the AUS for the treatment of PPI varies regionally. For example, within the United States, state-by-state use of the AUS ranges from 1% to 10% of all RRP patients, with an average of 6% of RRP patients ultimately undergoing AUS implantation. In 2005, 4,426 AUS units were sold in the United States, which represents approximately 1 unit per every 3 U.S. urologists [584]. Nearly half of all AUS implantations in the U.S. were indicated for SUI following prostate cancer surgery [184, 193, 263, 585, 586]. The remaining 50% of units are used for patients with neurogenic disorders (such as spina bifida or neurogenic ISD), for those with incontinence after transurethral resection of the prostate, and for females with ISD following failed sling surgery.

Previous radiotherapy to the pelvis is not a contraindication for AUS placement in males, [587] as the ultimate outcome seems to be similar in men whether or not they have received radiation therapy [236], although a higher incidence of urethral atrophy, erosion and infection requiring surgical revision has been reported in irradiated patients compared to those not irradiated (41% vs 11%). Despite this observation, long term continence and patient satisfaction appear not to be adversely affected in the irradiated male patient [236]. Unlike in men, previous external beam radiation is a relative contra-indication for implantation in females due to a considerably higher erosion rate [263].

The compressive effect of the AUS is temporarily relieved when the patient squeezes the scrotal/labial pump, transferring fluid from the urethral cuff to the pressure-regulating balloon. Subsequently, the bladder can then empty either by bladder contraction and/or by abdominal straining. Accordingly, patients voiding with the Valsalva manoeuvre because of an underactive or neurologically acontractile bladder, do not seem to be at an increased risk of complications [588]. It should also be noted that patients with previous anti-incontinence procedures show a significantly higher explantation rate [589].

Clinical experience suggests that enterocystoplasty or gastrocystoplasty can be done simultaneously with the implantation of the AUS [590, 591]. However, AUS placement at the time of cystoplasty is associated with earlier infections, especially during the first 3 years post-operatively [592]. In the long-term (> 3 years) the infection rate is the same whether the AUS is implanted after or at the time of cystoplasty, AUS can also be successfully implanted in patients after bladder substitution [311], and in those with locally recurrent prostate cancer with a relatively good prognosis [593], or those with severe post-radical prostatectomy Stricture in whom a stent has been placed previously [320].

Finally, advanced age is not a contra-indication to AUS placement. A retrospective analysis by O’Connor and colleagues of a cohort of men over age 75, revealed excellent success rates, with 21 of 29 men (72%) achieving successful continence. Revision rate was 14% at an average of 5 years follow-up, with 14% requiring explantation, and 21% requiring device deactivation due to deterioration in overall health precluding proper use of the AUS at an average of 47 months after placement [235].

3. SURGICAL TECHNIQUES

The original technique of implantation is illustrated in Figure 10. The cuff of the sphincter around the bulbous urethra is placed via a midline perineal incision, while the pressure regulating balloon and the scrotal pump are inserted via a separate inguinal incision. A relatively new surgical approach has been described using a single, upper transverse scrotal incision which allows the placement of all 3 components of the system, the cuff, the pump in a scrotal pouch, and the reservoir behind the fascia transversalis [223]. Alternatively, the pressure-regulating balloon may be placed through a separate inguinal incision, with the cuff and control pump placed via a single trans-scrotal incision, with the connections among scrotal pump, balloon reservoir, and urethral cuff tubing made in the usual inguinal incision. While the trans-scrotal approach potentially minimizes the invasiveness of the AUS surgery, by limiting the surgical approach to a single incision [223], a few reports have revealed that surgical success might be diminished compared with perineal cuff placement and abdominal balloon reservoir placement [594, 595]. Henry and colleagues [596] noted in their retrospective analysis of patients treated with a perineal versus trans-scrotal AUS over a 17-year period (mean follow-up not given), the former group had a completely dry rate of only 28%, versus 57% in the perineal group (p<0.03). Beyond the difference in “completely dry” rate, social continence was also better in the perineal versus scrotal surgery (73% versus 60%). Thus the perineal approach for initial artificial urinary sphincter implantation appears to control male stress incontinence better than the trans-scrotal approach.

The trans-scrotal approach appears particularly useful for simultaneous placement of an AUS and inflatable penile prosthesis through a single incision, with Kendirci and colleagues [596] reporting a urethral erosion rate of 9%, an overall revision rate of 14%, and a social continence rate of 100% in 22 patients at 17 months average follow-up. Sellers, et al. [597] recommend the simultaneous surgery for cost-efficacy.
Figure 10: A. With the patient in lithotomy position, a perineal incision is made behind the scrotum to expose the bulbar urethra. B. The urethra is mobilized circumferentially within the bulbospongiosus muscle and the measuring tape is used to obtain the cuff size. C. The belt-like cuff is positioned around the urethra. D. A right lower quadrant (RLQ) abdominal incision is made and the extraperitoneal space is entered lateral to the rectus muscle for insertion of the reservoir. E. After reservoir insertion the cuff is pressurized with fluid. F. A scrotal space is created under the dartos and the pump is inserted (held with a Babcock clamp).
They demonstrated a $7,000 cost savings when both devices were implanted simultaneously through a scrotal approach, compared to staged implantation with 2 separate surgeries.

The trans-scrotal approach is also useful for revision surgery. Van der Horst and colleagues [598] described AUS revision through a trans-scrotal approach, with addition of a second cuff distal to the primary cuff. In addition, Comiter [166] described the trans-scrotal approach for placement of an AUS following previous perineal sling surgery. In the case of suboptimal continence following sling surgery, placing the AUS cuff distal to the sling through a scrotal incision allows the surgeon to avoid the previous operative field, minimizing dissection through potentially scarred tissue; secondly, it leaves the proximally placed sling as a partially effective compressive device proximal to the AUS cuff.

4. COMPLICATIONS

Complications following implantation of the AUS can be divided into the broad categories of incontinence, erosion and/or infection, and unusual complications. While the number of AUS procedures performed varies geographically throughout the world, especially within the United States. Certain “centers of excellence” perform substantially more procedures than do community hospitals [584]. However, the total number of procedures done in a given center does not seem to be a determining risk factor for complications. Comparable erosion/infection rates have been reported from centers with fewer than 50 or more than 100 cases [206]. This suggests that erosion and infection may be more closely related to the physiologic state of the host rather than the experience of the surgical team, provided standard precautions are strictly applied.

a) Incontinence

Incontinence following implantation of an AUS can result from (1) alteration in bladder function, (2) atrophy of the urethra, or (3) mechanical failure of the device. These causes may co-exist.

1. ALTERATION IN BLADDER FUNCTION

This situation has been reported principally in patients with neurogenic bladder dysfunction, especially in children [599-604]. These changes include de novo involuntary detrusor contractions, decrease in bladder compliance, and the development of a high pressure system, causing incontinence, hydronephrosis and ultimately renal failure. Modifications in detrusor behavior (including its consequences on the upper urinary tract) occur in up to 57% of cases [599-610]. It should be pointed out, however, that there has never been a published report of hydronephrosis following implantation of an AUS for incontinence after prostatectomy [611]. The best candidates for sphincter implantation are those with a low pressure, relaxed, and compliant bladder but an incompetent urethral sphincter [608].

2. ATROPHY OF THE URETHRA

This may occur at the cuff site secondary to long-term mechanical compression of the periurethral and urethral tissues. It is not often reported and some
authors do not even mention it as a possible cause of AUS failure [237, 263, 611]. About 4 months following implantation, cuff efficiency diminishes, presumably because pressure atrophy occurs in every patient to some extent [612]. The incidence of urethral atrophy leading to revision varies from 3% to 9.3% [178, 184, 187, 586, 609, 613-615]. This atrophy can be lessened with nocturnal deactivation of the cuff [616].

3. MECHANICAL FAILURE

This includes perforation of one of the components with loss of fluid from the system, air bubbles or organic debris within the system causing inadequate function of the pump, disconnection of the tubes, or kinking of the tubes. Introduction of “kink-free” tubing has virtually eliminated this last complication.

The incidence of these complications varies widely with ranges from 0% [613] to 52.5% [193] with the longest follow-up. In this latter study, the cuff seemed to be the most vulnerable part of the system (22 cuff failures in 18 patients, most of them occurring during the first 2 to 3 years following implantation), followed by pump failure (6 times in 4 patients). Blockage is an exceptional event, occurring only once in 61 patients followed from 10 to 15 years [193]. In a recent publication from Baylor [187], chronicling a 13-year experience with the AUS, mechanical failure occurred at an average of 68.1 months postoperatively. An unusual mechanical complication has been reported recently. The locking tab became displaced distally into the cycling portion of the cuff preventing the fluid from flowing into the cuff surrounding the urethra [617].

4. EROSION AND/OR INFECTION

Erosion and infection are two major complications that almost invariably necessitate removal of the prosthesis. Their incidence may be reported separately, or more commonly as a single complication. The incidence of these complications varies from 0% to 24.6% [178, 263, 586, 602, 608, 609, 613-615, 618, 619]. Most recent large series report an incidence of infection and erosion generally less than 8% [51, 186, 187, 198, 237, 611, 620, 621]. As would be expected, the highest incidence has been reported with the longest follow-up (10-15 years) [178]. Lai and colleagues [187] from Baylor recently reported that erosion occurred at an average of 19.8 months postoperatively rather than in the peri-operative period. Previous surgery [622] at the site of cuff placement increases the risk of erosion. This, however, may be decreased by delayed cuff activation [623]. Some authors, however, did not find an increased incidence of complications when a new cuff was implanted at the site where several months before a cuff has been removed for infection or erosion [624]. Other risk factors include urethral catheterization and urethral endoscopic manipulations with an activated sphincter in place [625].

A likely etiology of early erosion is intra-operative laceration of the urethra when dissecting it from the corpora cavernosa, where a difficult anatomical plane exists. Intraoperative recognition of urethral injury can be facilitated by retrograde perfusion sphincterometry using a flexible cystoscope [32]. While recognition of a urethral injury may alert the surgeon to the necessary termination of the procedure, urethral erosion may still occur without a known urethral laceration [626].

As mentioned above, while the majority of authors consider previous radiotherapy a risk factor for increased infection and erosion, it is not a contraindication to implantation of an AUS in the male patient with PPI [177, 179, 200, 236, 237, 260, 627]. Overall patient satisfaction is similar in those who have been irradiated, compared to those who have not been [177, 188, 236]. Furthermore, the degree of satisfaction does not diminish with an increased number of surgical revisions [192, 628].

5. RARE COMPLICATIONS

Several unusual, although rare complications have been recently reported in the literature, such as the intravesical migration of the reservoir with secondary stone formation in the bladder [629], or a giant urethral diverticulum at the site of a previously removed cuff because of erosion and urinary extravasation [630].

5. DURABILITY OF AUS COMPONENTS

When defining durability of one of the components or the AUS as a whole, one should distinguish between explantation of the device due to device malfunction (e.g. leak in one of the components) or complications caused by an otherwise properly functioning sphincter unit (e.g. erosion by the cuff, infection at the site of implantation, etc.). This distinction is rarely made in the literature. Durability of a device is defined as the time elapsed during which no mechanical problem alters the normal function of the device. This should exclude the second group from further analysis.

There are very few references in the literature pertaining to the length of time a device functioned normally before its removal due to mechanical failure. In a multicenter trial, for neurogenic bladders, conducted in France [609], the authors mention that the “mean operational life” of the sphincter was 56 months (range 3-118 months). Haab et al [184] analyzed 68 patients and noted that the mechanical failure rate dropped from 44.4% to 12.4% since modifications were made to the device, mainly the cuff component. Survival time of these components was not provided. Similar conclusions can be drawn from a series from the Mayo Clinic [190] where the modification of the cuff design (narrower back) resulted in a significant drop of the reoperation rate at 5 years. In the “narrow back” group 17% (31/184) required reoperation. In that cohort, non-mechanical failure decreased from 17% to 9% and mechanical failure
decreased from 21% to 8% following introduction of the narrow back cuff [190]. Mean time to reoperation was 26.2 months (mean 2-68 months). Using Kaplan-Meier statistical analysis for this group of patients, the overall 5 year expected product survival was 75%. In Lai’s report regarding Baylor’s recent 13-year experience with the AUS, only 6% of devices failed mechanistically, at an average of 68.1 months, with 75% of patients requiring no revisions at 5 years [187]. In a review, Venn et al [263] analysed the outcome of 100 patients in whom an artificial urinary sphincter was implanted for more than 10 years. Thirty-six percent of them still had the original sphincter and were continent at a median follow-up of 11 years. The bulbocavernous function, as compared to the bladder neck cuff provided a slightly better continence rate at 10 years, 92% and 84%, respectively. The lowest erosion rate occurred with the bulbocavernous function. Device survival rate at 10 years was 66% in this series.

In a series of 30 boys with spina bifida Spiess et al [631] found that the mean lifetime of all AUS was 4.7 years, with no statistically significant difference in sphincter survival of those inserted at the bladder neck or the bulbous urethra (4.6 and 4.9 years, respectively). A sharp drop was observed at 100 months with only 8.3% of the original sphincters still functioning beyond this point. In a series of 35 adolescents with neurogenic voiding dysfunction implanted with a bladder neck cuff over an 11-year period, with an average follow-up of 5.5 years, Lopez Pereira and colleagues [632] reported a 20% mechanical failure rate, with an additional 8.6% erosion rate. Adverse bladder storage changes developed in 31.8% of patients, who thereby required augmentation cystoplasty. However, continence was achieved in 91.4% of individuals. Ruiz and colleagues [633] followed 19 adolescents for an average of 80 months who were implanted with bladder neck cuffs over a 14 year period for reasons other than spina bifida. They reported a mechanical failure rate of 26.3%, an infection/erosion rate of 15.8%, and a revision rate of 26.3%. However, even in this very high risk group, a continence rate of 87% was achieved despite this high complication rate. It might be useful to consider patients with ‘primary adequate function’ when no revision is necessary to achieve continence separately from those with ‘additional procedure-assisted adequate function’, where one or more revisions are necessary to obtain favourable outcome. Klijn et al. [183] showed in their series of 27 men who became incontinent after a radical prostatectomy that at a mean follow-up of 35 months, 81% of the patients achieved satisfactory continence. The 5-year ‘primary adequate function’ and ‘additional procedure-assisted adequate function’ rates, based on the Kaplan-Meier curves, were 49% and 71%, respectively. The median time to failure for the ‘primary adequate function’ group was 48 months, the median time to definitive failure of ‘additional procedure-assisted adequate function’ was more than 72 months.

In other recent series, the global long term (2 to 7.7 years) revision rate, for any of the above mentioned reasons varies between 16% and 50% [186, 187, 191, 192, 628, 632-635]. In Webster’s recent report [628] of 554 implantations over a 10 year period, (i.e. performed since the 1987 device modification), he noted a mechanical failure rate of only 31/554 (5.5%). Non-mechanical failure was 88/554 (15.9%), with 63/554 (11.3%) due to urethral atrophy and 21/554 (3.8%) due to cuff erosion. Of the total cohort, 21.4% required at least one revision surgery, while 78.6% did not. Of those 119 patients who required re-operation, 76.5% required no further treatment (similar to the non-reoperation rate of the initial cohort), while 23.5% required re-operation for either mechanical or non-mechanical failure. Five-year durability of the AUS following primary or secondary implantation was comparable, with 80% for the initial placement, and 88% following revision surgery. Similarly, continence status was comparable, with 90% of primary and 82% of revision patients achieving 0-1 pad per day urinary control. Patients with neurological deficit seem to have a higher risk of non-mechanical failure and the overall continence rate may be poorer compared to non-neurologic patients [29].

6. Diagnostic Procedures Related to Artificial Sphincter Failure

The diagnostic evaluation of urinary incontinence after the placement of the AUS is critical for the management of these patients and represents a challenging problem for the urologist. Several diagnostic and management algorithms have been proposed, some relatively simple, others more complex [29, 30, 200, 206, 610, 636-638]. Figure 11 shows an algorithm to investigate and treat the male patient with a previously functioning AUS who becomes incontinent.

Physical examination should exclude infection at the site of the cuff or the scrotal/labial pump. Difficulty compressing the pump suggests tube kinking, fluid loss or an obstructed system.

Plain X-rays of the abdomen or pelvis may show fluid loss, if the system is filled with radio-opaque solution [639, 640] (Figure 1). Alternatively, sonography of the pressure regulating balloon may show volume loss. It is necessary to obtain a baseline film at the discharge of the patient from the hospital for subsequent comparison because radiographic imaging of the balloon does not detect changes until at least 50% of its volume has been lost [12].

Cystometry or complete urodynamic study will demonstrate changes in bladder behavior following insertion of the AUS as described above. Cystourethrogram could eventually demonstrate a urethral diverticulum at the site of previous cuff erosion (Figure 2). Endoscopy will disclose any urethral erosion by the cuff (Figure 12).
Figure 11: Algorithm for managing incontinence after AUS placement
Retrograde perfusion sphincterometry has been reported to diagnose the loss of compressive pressure in the urethral cuff [29]. It is done by infusing fluid from the meatus in a retrograde fashion. If the AUS cuff is functional and the urethral is intact there should be no flow when the pressure equals the AUS balloon pressure. This technique can also be used intraoperatively to detect urethral perforation or to adjust the pressure in the cuff [32]. This seems to be more useful than urethral pressure profile (UPP) [606].

Intraoperative electrical testing, using an ohmmeter [619, 637] has been described to determine the site of fluid leakage from the system. This test can be helpful to avoid the need to change the whole system, and allow replacement of the leaking part only.

7. TREATMENT OF COMPLICATIONS

As outlined above, complications directly related to the presence of an artificial sphincter can be divided into categories: incontinence from alteration in bladder function, urethral atrophy, and/or mechanical failure, and infection/erosion. The treatment of each of these complications deserves comment, as no detailed reference can be found in the literature dealing with the treatment of these complications.

a) Alterations in bladder function

De novo (or pre-existing) detrusor overactivity can be treated with parasympatholytics. In a small proportion of patients systemic side effects will prevent the use of these drugs; there might also be some medical contraindications, or the drug may be ineffective. Other options such as bladder augmentation or enterocystoplasty may be considered. To date no report can be found where implantation of an artificial sphincter resulted in the deterioration of the upper urinary tract in a neurologically normal post-prostatectomy patient [188, 611]. It has been reported that enterocystoplasty performed together with the placement of an AUS in the same operative session does not increase the morbidity of the procedure and does not affect the success rate [590]. However, in a recent review of 286 patients Furness et al. [641] demonstrated an infection rate of 14.5% and 6.8% with simultaneous and staged procedures, respectively. Catto, et al. [592] however, showed that while infections may occur earlier with simultaneous procedures, the ultimate infection rate is no different when augmentation cystoplasty and AUS placement separately or simultaneously. No clear urodynamic guidelines exist to select patients who need bladder augmentation in combination with an AUS [612], although small voided volumes with reduced cystometric capacity, poor compliance, or severe detrusor overactivity after failed medical treatment would suggest the need.

b) Atrophy of the urethra

Several therapeutic options exist to increase cuff pressure around the atrophied urethral wall: changing the balloon reservoir for one generating a higher pressure, downsizing the cuff diameter [12, 179, 642], or increasing the amount of fluid in the system. Another approach consists of placing the cuff inside the corporal tunica albuginea on the dorsal aspect of the urethra (transcorporal). This allows a safer mobilization of the urethra and adds some supplementary bulk of tissue to the circumference of the urethra, possibly decreasing the risk of erosion [196]. It should be mentioned, however, that there is a risk of reduced erectile function with this technique. The vast majority of such patients, however, already suffer from erectile dysfunction secondary to the prostate cancer surgery. Guralnick reported a retrospective chart review of 31 patients with an average of 17 months follow-up after trans-corporal cuff placement for varied indications (previous erosion, urethral atrophy, radiation). The vast majority of patients (84%) realized 0-1 pad per day leakage post-operatively, with no device erosions or infections, while 3 patients (9.7%) required revision surgery for malfunction. Overall, 29 of 31 had erectile dysfunction prior to the procedure, and only 1 of 2 had deterioration of his erectile function post-operatively. Magera and Elliott [643] reported their results of 18 patients who underwent tandem cuff transcorporal salvage surgery. Ten patients had only the distal cuff placed transcorporally, while 18 had both cuffs placed transcorporally. Infection occurred in 1 patient (5.5%), and erosion occurred in 1 patient (5.5%), while 69% reported that they were very
improved or extremely improved with respect to continence at an average of 26 months follow-up. The implantation of a double-cuff AMS 800 has become more popular, as a primary procedure in the totally or severely incontinent patient [197, 644], or as a salvage procedure, by adding a second cuff, following a failed previous single cuff [194, 195, 644]. Dimarco’s group [195] and others have shown excellent results with the addition of a second urethral cuff, placed 1.5–2.0 cm distal to the primary cuff. Alternatively, a circumurethral wrap of an organic bulking agent can be fitted, with subsequent placement of the AUS cuff over the biologic external urethral bulking agent [645]. Early reports of primary double cuff placement did not demonstrate any significant increase in morbidity with the double-cuff as compared with the single cuff system [197], and patient satisfaction also seems to be higher [198] at an average of 21-41 months follow-up. However, with longer follow-up (58-74 months), the same group [199] reported that the complication rate was higher in men with primary double-cuff placement (55% versus 28%), and there were no significant differences in overall continence and QOL measures.

c) Mechanical failure
As with any device, mechanical failure can be expected with the AMS 800 AUS. The treatment involves surgical replacement of the failed component and reconnecting the system.

d) Infection
With overt infection the accepted treatment option is removal of the entire device and appropriate antibiotics. A second system can be subsequently implanted with equally good results [623]. It has been demonstrated, however, that immediate reimplantation of a new AUS after the removal of an infected, but not eroded, prosthesis can be a valid option with an overall success rate of 87% [646]. In 2007, AMS introduced the InhibiZone-coated artificial urinary sphincter (rifampin and minocycline hydrochloride coating) [643].

e) Erosion
In case of urethral erosion by the cuff, the “offending” cuff must be removed. No clear guidelines exist whether removal of the whole system is superior to removal of the cuff alone but it must be assessed for infection. If infection is present the whole device should be removed. Reservoir erosion into the bladder has been described following the removal of an eroded cuff [629]. Furthermore, it is not known whether it is necessary to allow the urethra to heal over a catheter versus surgical repair. The former risks diverticulum formation (Figure 2), and the latter may increase the amount of the periurethral fibrosis. This might compromise success of a new cuff. However, the new cuff should be positioned away from the erosion site. In case of the erosion of one of the cuffs of a double system removal of the eroded cuff can successfully convert a double-cuff system into a single cuff system [647]. It is logical that intra-operative urethral injury may precipitate cuff erosion if unrecognized. However, Petrou and colleagues [628] showed that early postoperative cuff erosion can occur even when no laceration is demonstrated by intraoperative intraurethral instillation of indigo carmine.

8. CONSENSUS PROTOCOL FOR FOLLOW-UP OF PATIENTS WITH AUS
As complications continue to be seen for years after implantation [648], it is helpful to have a structured follow-up plan. However, no standardized recommendations are available in the literature.

The consensus upon which the members of this subcommittee agreed and which is based on expert opinion are as follows:

1. Perioperative antibiotics are recommended. Gram-negative enteric bacteria and Staphylococcus epidermidis are the most frequently encountered microorganisms in infected prostheses [625].
2. Hospital stay should be kept to a minimum.
3. Urethral catheters, if inserted, should be withdrawn within 24-48 hours of surgery and the preoperative continence management continued.
4. In general the sphincter device should not be activated immediately postoperatively. In the initial period scrotal oedema and pain prevent patients from manipulating the pump adequately. When this subsides after 6 to 8 weeks the device can be activated. Earlier activation may also be acceptable. Irradiated patients may benefit from a longer initial period of deactivation, up to 12 weeks [179]. Nocturnal deactivation should be considered in high-risk patients 178.
5. Patients are reviewed at 3 months after activation to ensure the device is working adequately, and to assess the continence status.
6. Long-term follow-up is different in the neurogenic and non-neurogenic patient. With time, alteration in bladder function may jeopardize renal function in the neurogenic patients. Periodic ultrasound evaluation of the upper urinary tract and monitoring of renal function is essential. If changes occur, urodynamic studies should be done to rule out detrusor overactivity. In non-neurogenic patients, periodic ultrasound may not be necessary.
7. When changes in the continence status occur, diagnostic procedures depicted in Figure 11 should be considered. (Level of evidence 3; Grade of recommendation B-C)
XIII. SUMMARY AND RECOMMENDATIONS

1. EVALUATION

Prior to surgery a basic patient evaluation should consist of history and physical examination, urinalysis and postvoid residual urine (Level of evidence 1-2; grade of recommendation A). A voiding diary is helpful to assess functional capacity and total urine output (Level of evidence 1-2; grade of recommendation B). Pad tests may be useful in certain circumstances (Level of evidence 1-2; grade of recommendation B). Blood testing (BUN, creatinine, glucose) is recommended if compromised renal function is suspected or if polyuria (in the absence of diuretics) is documented. Additional testing with cystoscopy and appropriate imaging of the urinary tract are also helpful in guiding therapy (Level of evidence 2-3; grade of recommendation B). The committee felt that multichannel urodynamics are useful prior to invasive treatment for incontinence. (Level of evidence 3; grade of recommendation C)

2. INCONTINENCE POST-PROSTATECTOMY FOR BPO AND POST-RADICAL PROSTATECTOMY FOR PROSTATE CANCER

After a period of conservative management, which may also be from 6 to 12 months, the artificial sphincter is the preferred treatment for properly selected men who have stress incontinence after radical prostatectomy with the longest record of safety and efficacy. Male slings are an alternative with intermediate data support their safety and efficacy in men with more moderate degrees of PPI, although long-term data are beginning to accumulate. However, the literature contains results on many different kinds of slings. Injectable agents are a less effective option for some men with mild to moderate incontinence. (Level of evidence 3; grade of recommendation C)

3. AGE

Age is not a restriction for surgical treatment of urinary incontinence. Cognitive impairment and lack of dexterity may be restrictions for the artificial sphincter and must be determined preoperatively. (Level of evidence 3-4; grade of recommendation C)

4. INCONTINENCE FOLLOWING OTHER TREATMENTS FOR PROSTATE CANCER

The artificial sphincter is most widely used but radiation may be a risk factor for an increase in complications. Slings have variable results after radiation. Injectable agents have not been successful in this setting. (Level of evidence 3; grade of recommendation C)

5. INCONTINENCE FOLLOWING PELVIC TRAUMA

The artificial sphincter is most widely reported. Bladder neck reconstruction has also been reported on a limited basis. (Level of evidence 3; grade of recommendation C)

6. INCONTINENCE IN ADULT EPISPADIAS-EXSTROPHY COMPLEX

Patients should be treated in centres of excellence. A patient-directed approach should be taken. The choices include further bladder neck reconstructive surgery, bladder neck closure, bladder reconstruction or diversion with bowel. The data are insufficient for a specific recommendation. Transition is important between the pediatric and adult urologist. Life-long follow-up is mandatory in terms of continence, voiding efficiency, upper tract status and other urological complications. (Level of evidence 3; Grade of recommendation C)

7. REFRACTORY URGENCY INCONTINENCE AND DETRUSOR OVERACTIVITY

Botulinum toxin-A bladder injections is a minimally invasive treatment with some efficacy. Neuromodulation is a treatment option with success reported in a limited number of male patients. Detrusor myectomy has also been reported to be successful in a small number of male patients. Augmentation cystoplasty is potentially successful in controlling symptoms but may be associated with unacceptable side effects. Urinary diversion is a final option. (Level of evidence 3; grade of recommendation C)

8. REDUCED CAPACITY BLADDER

Augmentation cystoplasty has been successful in most etiologies apart from radiation. (Level of evidence 3; grade of recommendation C)

9. URETHROCUTANEOUS FISTULA AND RECTOURETHRAL FISTULA

Etiologic factors causing acquired urethrocutaneous fistulae are demonstrated by clinical, endoscopic and imaging studies. Surgical reconstruction is applied as required. Similar diagnostic maneuvers are applied to rectourethral fistulae. In those that do not close with or without temporary urinary and fecal diversion, surgical reconstruction may be carried out. Most repairs are now carried out after prior fecal diversion. Various techniques are available for closure and can be done in collaboration with colorectal surgeons. (Level of evidence 3; grade of recommendation C)

10. MANAGEMENT OF AUS COMPLICATIONS

Incontinence may result from alteration in bladder function, urethral atrophy, or mechanical malfunction. Infection and/or erosion of components demand surgical removal of all or part of the prosthesis. A treatment algorithm is presented to aid in management and in follow-up of patients. (Level of evidence 3; grade of recommendation C)
11. NEW TECHNOLOGIES

Evidence for the adjustable balloons is accruing and the early high complication rate appears to have been resolved. However, more evidence is required before specific recommendations can be made. (Level of evidence C; grade of recommendation D)

FUTURE RESEARCH DIRECTIONS

- New technologies, bulking agents, sling materials, prosthetic devices should continue to be evaluated
- Accuracy in reporting of early research results is mandatory
- Mechanisms of post-prostatectomy incontinence and device effects need further research

CLINICAL TRIAL RECOMMENDATIONS

- Randomized trials (AUS and slings)
- Standardized workup and outcome measures including QoL
- Complete reporting of complications and outcomes especially those of slings
- Reporting of procedures to salvage failures
- Long-term results (>2 years)
- Standardized reporting of durability

REFERENCES


56. Litwin MS, Pasta DJ, Yu J, Stoddard ML, Flanders SC. Urinary function and bother after radical prostatectomy


116. Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomized controlled


271. Wallner K, Roy J, Zelefsky M, Fuks Z, Harrison L. Fluoroscopic visualization of the prostatic urethra to


378. Kuo HC. Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int. May 2005;95(7):1023-1027.


424. Sahai A. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int. Feb 2006;97(2):413.

438. Trsinar B, Kraij B. Maximal electrical stimulation in
437. Tanagho E. Concepts of neuromodulation. Neurourol
435. Smith CP, Somogyi GT, Chancellor MB, Appell RA. A
434. MacDonald R, Fink HA, Huckabay C, Monga M, Wilt TJ.
444. Nakamura M, Sakurai T, Sugao H, Sonoda T. Maximum
electrical stimulation for urge incontinence. Urol Int.
443. Merrill DC. The treatment of detrusor incontinence by
442. McGuire EJ, Zhang SC, Horwinski ER, Lytton B.
441. Fall M. Does electrostimulation cure urinary
440. Nakamura M, Sakurai T, Tsubamoto Y. Tada Y. Bladder
inhibition by electrical stimulation of the perilan skin. Urol
439. Ho MH, Lin LL, Haessler AL, Bhatia NN. Intravesical
438. Apostolidis A, Fowler CJ. The use of botulinum
437. Shaker HS, Hassouna M. Sacral nerve root
436. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP,
et al. Urodynamic evaluation of sacral neuromodulation
435. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP,
et al. Results of sacral neuromodulation therapy for
434. Bosch JL, Groen J. Disappointing results of
433. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP,
et al. Urodynamic evaluation of sacral
432. Bosch JL, Groen J. Sacral nerve stimulation for
431. Apostolidis A, Fowler CJ. The use of botulinum
effectiveness and adverse effects. Spinal Cord. Aug
430. Dmochowski R, Sand PK. Botulinum toxin A in the
429. Patterson JM, Chapple CR. Botulinum toxin: a case for bladder botulinum toxin application. Urol Clin
428. MacDonald R, Fink HA, Huckabay C, Monga M, Wilt TJ.
427. Nakamura M, Sakurai T, Sugao H, Sonoda T. Maximum
electrical stimulation for urge incontinence. Urol Int.
426. Patel AK, Patterson JM, Chapple CR. The emerging
518. Nakamura M, Sakurai T, Tsujimoto Y, Tada Y. Bladder
inhibition by electrical stimulation of the perilan skin. Urol


Committee 14

Surgery for Urinary Incontinence in Women

Chair
A.R.B. Smith (U.K)

Members
R. Dmochowski (USA),
P. Hilton (U.K),
E. Rovner (USA),
C.G. Nilsson (Fin)

Consultants
F.M. Reid (U.K),
D. Chang (USA)
## CONTENTS

<table>
<thead>
<tr>
<th>INTRODUCTION</th>
<th>VI. COMPLICATIONS OF SURGERY FOR DETRUSOR OVERACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. SURGERY FOR STRESS INCONTINENCE</td>
<td>VII. NEUROMODULATION</td>
</tr>
<tr>
<td>II. CONFOUNDING VARIABLES</td>
<td>VIII. URETHRAL DIVERTICULUM</td>
</tr>
<tr>
<td>III. STRESS INCONTINENCE WITH PROLAPSE</td>
<td>IX. NON-OBSTETRIC URINARY FISTULAE</td>
</tr>
<tr>
<td>IV. COMPLICATIONS OF SURGERY FOR STRESS INCONTINENCE</td>
<td>X. OUTCOME MEASURES</td>
</tr>
<tr>
<td>V. SURGERY FOR DETRUSOR OVERACTIVITY</td>
<td>IX. ARTIFICIAL URINARY SPHINCTER IN WOMEN</td>
</tr>
<tr>
<td>REFERENCES</td>
<td></td>
</tr>
</tbody>
</table>

---

1192
INTRODUCTION

Surgeons have been criticised for the lack of rigour with which they have analysed their results. This chapter highlights the progress made, particularly in surgery for stress incontinence where more randomised controlled trials have been reported, and illustrates areas where more studies are needed. The section on outcome measures illustrates that whilst the measurement of subjective and objective outcome may clarify the value of an operation some standardisation of outcome measures is required in order to meaningfully compare different procedures.

I. SURGERY FOR STRESS INCONTINENCE

1. PROCEDURES EXCLUDING MID-URETHRAL TAPES

The practice of surgical treatment for stress urinary incontinence has changed dramatically over the last decade; the number of procedures undertaken appears to be increasing, and the shift in relative numbers of different procedures has been remarkable. In England between 1997-’98 and 2005-’06 the annual number of operations undertaken for stress urinary incontinence (SUI) increased by 28%, despite over 90% reduction in the numbers of colposuspension and needle suspension procedures, and 50% reduction in bladder neck buttress, sling and urethral bulking procedures. The increase was entirely due to the rapid dissemination of the Tension-free Vaginal Tape (Gynecare®, Ethicon, Somerville, NJ) in 1998, and similar minimally invasive synthetic sub urethral sling procedures subsequently (Hilton, 2008) [1]

Whilst these trends may be in line with currently available evidence, other changes in practice seem to proceeding in advance of high quality evidence; the drivers behind such changes in practice have recently been reviewed (Hilton, 2008)[1].

In their systematic review published in 1996, Black and Downs drew attention to the deficiencies of the literature available at the time (Black & Downs, 1996, Downs & Black, 1996) [2,3]. In particular they highlighted the difficulties posed by case definition and the uniformity of surgical technique both between and within surgical teams, the problem of variations in outcome measures used, the handling of confounding variables, the generalisability or external validity of the results, and the lack of statistical power in most studies. Most systematic reviews published since on the topic of surgery for incontinence in general or relating to individual surgical procedures have made similar comments regarding the quality of available evidence. Hence recommendations must be made not only on the amount of evidence available, but on the quality of that evidence. Several systems for grading the quality of studies have been proposed, including that initially presented by Black and Downs (Black & Downs, 1996, Downs & Black, 1996) [2,3], and that proposed by the GRADE group (Grading of Recommendations Assessment, Development and Evaluation) in their publications (Atkins et al., 2004a, Atkins et al., 2004b, Atkins et al., 2005) [4,5,6] and on their website, http://www.gradeworkinggroup.org. A recent series of articles in the BMJ explain the GRADE system in more detail (Guyatt et al., 2008a, Guyatt et al., 2008b, Guyatt et al., 2008c) [7,8,9].

The duration of follow-up is another factor affecting the validity of comparison between studies of efficacy and safety. In the first edition of this consultation, it was suggested that short term surgical follow-up should be considered as being up to 3 months, medium term from 3 to 12 months, and long term over 12 months (Mattiasson et al., 1999) [10]. There are occasions when case reports or short-term trial follow up and the early presentation of outcomes may be not only appropriate but also indeed mandatory. If serious unexpected adverse events come to light during early experience with procedures, colleagues and patients must be made aware. Where significant differences in efficacy or safety outcomes become apparent before the end of a study, it may be ethically unacceptable to continue randomisation. It is unlikely however that these factors are at play in the majority of studies of less than a year follow-up. In a recent review on long-term studies of pelvic floor dysfunction Hilton found that of 127 papers published in the last 25 years on
incontinence or pelvic organ prolapse (POP) which included the phrase ‘long term’ in their title or abstract, follow-up periods ranged from 1 to 14 years, with a mean of 59.5 months in those investigating surgical treatments (Hilton, 2008) [1]. Whilst highlighting some of the difficulties inherent both in undertaking and interpreting long-term studies, he argued for longer-term studies of high quality, and for a change in definition of ‘long-term’ to imply outcome at 5 years or more (Hilton, 2008) [1].

a) Search strategy

This section is based on electronic searches of Medline, EMBASE, CINHAL, the Cochrane database of systematic reviews, and the NICE website (www.nice.org.uk) references included in identified reviews were evaluated separately. Hand searching of recent (Jan-Apr 2008) issues of American, European and British journals in urology, gynaecology and urogynaecology was undertaken, to capture recent publications not yet included in the online databases. ICS, IUGA, AUA and AUGS conference proceedings for 2007 were also reviewed. It was assumed that trials presented earlier than this would be in press if they were of sufficient quality and maturity to justify inclusion; hence older abstracts have not been considered here. A total of 5331 references were identified; excluding duplicates, there were 3650 unique references. Of these 762 were of relevance to this review of non-tape procedures. Search terms used included the following:

URINARY INCONTINENCE; URINARY INCON- TINENCE, STRESS/; ((stress$ or mix$ or urg$ or urine$) adj3 incontinen$); SURGICAL PROCEDURES, OPERATIVE/; SURGICAL PROCEDURES, MINIMALLY INVASIVE/; UROGENITAL SURGICAL PROCEDURES/; GYNECOLOGIC SURGICAL PROCEDURES/; UROLOGIC SURGICAL PROCEDURES/; UROGENITAL SYSTEM/su [Surgery]; URINARY TRACT/su [Surgery]; URETHRA/su [Surgery]; VAGINA/su [Surgery]; BLADDER/su [Surgery]; LIGAMENTS/su [Surgery]; ((urethra$ or vagina$ or bladder$) adj surg$); (colposuspension$ or colpo suspension$) or vescicosuspension$ or urethrosuspension$ or urethrocystosica$ adj3 susp$; (urethrocystopexy$ or cystourethropexy$ or urethrocervicopexy$); (bladder$ adj3 buttress$); colpoplication$; burch$; (marshall$ or marchetti$ or krantz$ or mkm$); (paravagina$ or pubococcygeal$) adj3 repair$; (obturator$ adj3 shelf$); ((bladder$ or neck$ or needle$) adj3 susp$); ligament fixation$; (pereyra$ or stamey$ or raz$ or gitte$) adj3 (susp$ or procedure$); colporraph$; ((anterior$ or vagina$) adj3 repair$); (pacey$ or kelly$ or kennedy$); SURGICAL MESH/; (slings$ adj3 (procedure$ or operat$)); ((bladder$ or surgical$ or synthetic$ or biological$ or autologous$) adj3 (slings$ or tape$ or mesh$)); ((urethra$ or suburethra$ or midurethra$ or mid urethra$ or transurethra$ or trans urethra$ or transurethra$ or midurethra$ or midurethra$ or suprapubic$ or supratubular$ or suprapubic$ or pubovaginal$ or pubo- vaginal$ or transvaginal$ or intravaginal$ or lyodura$) adj3 (sling$ or mesh$ or implant$) bologna$; ingelman sundberg$; ‘PROSTHESSES AND IMPLANTS’/; INJECTIONS/; ((urethra$ or suburethra$ or midurethra$ or mid urethra$ or transurethra$ or periurethra$ or endourethra$ or endo urethra$) adj3 (inject$ or agent$ or bulk$)); injectable$; (injection$ adj3 ther$); (bulk$ adj3 agent$) contig$; COLLAGEN/; macroplastique$; exp SILICONES/; microparticulate$; HYALURONIC ACID/; hyaluronan ther$; act balloon$; CARBON$; carbon particle$ POLYTETRAFLUORETHYLENE/; BIOCOMPATIBLE MATERIALS/; URINARY SPHINCTER, ARTIFICIAL/; ((artificial$ or prosthete$) adj3 (urinary or genitourinary or urethra$ or bladder$) adj3 sphincter$); limit to humans; limit to female.

Relatively little high-level evidence has been published on the basis of new research since the last consultation; where available, level 1 and 2 evidence has been included in this update. Systematic reviews had already been published by the Cochrane Collaboration (Moehrer et al., 2000, Bezerra et al., 2001, Glazener & Cooper, 2001, Pickard et al., 2003, Glazener & Cooper, 2004) [11-15], and others have been developed or updated since (Bezerra et al., 2005, Lapitan et al., 2005, Dean et al., 2006a, Keegan et al., 2007) [16-19]. The National Institute for Health and Clinical Excellence (NICE) in England has published a clinical guideline on all aspects of urinary incontinence in women, including sections on surgical treatment (National Institute for Health & Clinical Excellence, 2006b, based on systematic reviews undertaken by the National Collaborating Centre for Women’s and Children’s Health (National Collaborating Centre for Women’s & Children’s Health, 2006). NICE has also published guidance on a number of individual procedures through its Interventional Procedures Programme (National Institute for Health & Clinical Excellence, 2003, 2005a, b, 2006a). http://www.nice.org.uk

b) Anterior colporrhaphy.

The term ‘anterior colporrhaphy’ tends to be used generically to describe procedures for both anterior vaginal wall prolapse and for SUI. When used to treat SUI, in addition to the reconstruction of the pubocervical fascia, it is conventional to use some form of plicating sutures to support and/or elevate the urethra and/or bladder neck. Many variations have been described often lending eponymous titles to the procedures e.g. Kelly, Kennedy, Pacey. The heterogeneity of procedures adds to the difficulties of evaluation of anterior colporrhaphy or vaginal repair procedures as a group. The place of anterior colporrhaphy in management of POP is covered elsewhere.

1194
Case series indicate a wide range of continence rates following anterior colporrhaphy, ranging between 31% and 100% (Jarvis, 1994) [20] [EL=3]. Accepting variation in the procedures undertaken, the duration of follow-up considered, and the outcomes reported, cohort studies that include anterior colporrhaphy consistently show it to be associated with lower cure rates than the comparators (usually colposuspension or Marshall-Marchetti-Krantz procedure (MMK)); cure rates reported from cohort studies are 21% to 70% (National Collaborating Centre for Women's & Children's Health, 2006) [EL=3]. Accepting variation in the procedures undertaken, the duration of follow-up considered, and the outcomes reported, cohort studies that include anterior colporrhaphy consistently show it to be associated with lower cure rates than the comparators (usually colposuspension or MMK); cure rates reported from cohort studies are 21% to 70% (National Collaborating Centre for Women's & Children's Health, 2006) [EL=3].

Several reviews of greater or lesser degrees of rigour have included anterior colporrhaphy; these include the previous editions of this chapter (Jarvis et al., 1999, Smith et al., 2002, Smith et al., 2005), and those of Jarvis (Jarvis, 1994) [20], Black (Black & Downs, 1996, Downs & Black, 1996) [2,3], the American Urological Association (Leach et al., 1997) [24], Cochrane (Glazener & Cooper, 2001) [13], and NICE (National Collaborating Centre for Women's & Children's Health, 2006, National Institute for Health & Clinical Excellence, 2006b).

Many randomised trials are presented (with published abstracts) or published (as full peer-reviewed papers) on several occasions, usually with increasing duration of follow-up. The 10 trials reported in the Cochrane review of anterior vaginal repair appear as 27 abstracts or papers (Glazener & Cooper, 2001) [13]. Two of these trials, despite being undertaken over 20 years ago, have not yet appeared as full papers (Quadri et al., 1985, Stanton et al., 1985b) [25,26]; the latter are therefore not included in the more recent NICE report.

Ten randomised trials are considered here (Table 1), comparing anterior colporrhaphy with pelvic floor muscle training (Klarskov et al., 1986) [27], colposuspension (Bergman et al., 1989a, Bergman et al., 1989b, Bergman & Elia, 1995, Berglund & Lalos, 1996, Liapis et al., 1996a, Liapis et al., 1996b, Berglund et al., 1997, Kammerer-Doak et al., 1999, Klutke et al., 1999, Colombo et al., 2000, Lalos et al., 2000) [28,30], needle suspension, (Bergman et al., 1989a, Bergman et al., 1989b, Bergman & Elia, 1995, Klutke et al., 1999, Di Palumbo, 2003) [28-30,37,39], MMK (Liapis et al., 1996b) or TVT (Meschia et al., 2004) [40] (some studies having 3 intervention arms).

Excluding cases that may have appeared in more than one report, 967 women were included in these studies, 346 undergoing anterior colporrhaphy. Cure rates of 31% to 88% are reported, with anterior colporrhaphy consistently showing what are both statistically and clinically poorer outcomes than surgical comparators [EL=1].

Few trials provide follow-up beyond 12 months, although mean follow-up is provided at periods between 1 and 14 years in different studies. Where serial outcome is provided the results indicate lack of longevity. Subjective outcomes fell from 80% at 1 year to 60% at 5-7 years in one study (Berglund & Lalos, 1996, Lalos et al., 2000) [31,38] [EL=2], and combined subjective and objective cures fell from 80% at 3 months to 63% at 1 year and 37% at 5 years in another (Bergman et al., 1989a, Bergman & Elia, 1995) [28,30] [EL=2].

The view of the first edition of this consultation was that the major indication for bladder buttress in contemporary practice must be the patient who prefers to sacrifice some chance of becoming continent for a reduced risk of complications (Jarvis et al., 1999) [21]. Subsequent editions found no new literature to justify a change to that view (Smith et al., 2002, Smith et al., 2005) [22,23].

The previously expressed view of the American Urological Association was that anterior repairs are the least likely of the four major operative categories (anterior repair, suburethral sling, colposuspension, long needle suspension) to be efficacious in the long-term (Leach et al., 1997) [240]. The Cochrane review of anterior vaginal repair, whilst finding insufficient data to allow comparison with physical therapies, needle suspension, suburethral slings or laparoscopic retropubic suspensions, felt that there was evidence to indicate that anterior vaginal repair was less effective than open abdominal retropubic suspension in the treatment of primary urodynamic stress incontinence (SUI). The beneficial effect of the abdominal approach...
<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Klarskov et al., 1986) [27]</td>
<td>RCT</td>
<td>PFMT</td>
<td>16/50 (7:9)</td>
<td>1y</td>
<td>43% vs. 78% (S – cured or improved)</td>
<td>2</td>
<td>AC or colpo depending on defect identified; only AC incl. here</td>
</tr>
<tr>
<td>2 (Bergman et al., 1989a) [28]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>107/127 (35:38:34)</td>
<td>1y</td>
<td>63% vs. 89% vs. 65% (o) &lt;0.05 colposuspension vs. others</td>
<td>2</td>
<td>Data only reported for completers.</td>
</tr>
<tr>
<td>(Bergman &amp; Elia, 1995) [30]</td>
<td></td>
<td>Needle suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (Bergman et al., 1989b) [29]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>298/339 (99:101:98)</td>
<td>1y</td>
<td>69% vs.87% vs.70% (o) ≤0.02 colposuspension vs. others</td>
<td>2</td>
<td>All vag. hysterectomy &amp; repair. Number randomised unclear; 339 ‘eligible’, and 41 lost to follow-up.</td>
</tr>
<tr>
<td>(Klutke et al., 1999) [36]</td>
<td></td>
<td>Needle suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (Berglund &amp; Lalos, 1996) [31]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>45 (15:30)</td>
<td>1y</td>
<td>47% vs. 67% (o)</td>
<td>2</td>
<td>Those with poor PF contraction excluded from repair group; no detail of randomisation given.</td>
</tr>
<tr>
<td>(Berglund et al., 1997) [34]</td>
<td></td>
<td></td>
<td>43/45 (14:29)</td>
<td>5-7y</td>
<td>71% vs. 64% (o)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Lalos et al., 2000) [38]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (Liapis et al., 1996a) [32]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>81</td>
<td>3y</td>
<td>57% vs.88% (o); p&lt;0.001</td>
<td>2</td>
<td>These 2 papers appear to cover the same study; one describes 2 arms at 3 years, the other 3 arms at 5 years.</td>
</tr>
<tr>
<td>6 (Liapis et al., 1996b) [33]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>161/170 (50:54:51)</td>
<td>5y</td>
<td>56% vs. 89 vs. 67% (o) ≤0.001 colposuspension vs. others</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MMK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (Kammerer-Doak et al., 1999) [36]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>35/35 (16:19)</td>
<td>1y</td>
<td>31% vs. 89% (o) RR 0.15 (95% CI 0.04 to 0.59)</td>
<td>2</td>
<td>Anterior colporrhaphy in 100% vs. 16%; paravaginal repair in 6% vs. 42%.</td>
</tr>
<tr>
<td>8 (Colombo et al., 2000) [37]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>68/71 (33:35)</td>
<td>≥8y</td>
<td>42% vs. 74% (o) OR 3.9 (95% CI 1.3 to 12.5), p=0.02</td>
<td>2</td>
<td>Vag. or abdo. hysterectomy also done; post repair in 100% vs. 34%</td>
</tr>
<tr>
<td>9 (Di Palumbo, 2003) [39]</td>
<td>RCT</td>
<td>Needle suspension</td>
<td>80/80 (52:28)</td>
<td>9m-4.5y</td>
<td>73% vs. 86% (o); p&lt;0.01</td>
<td>2</td>
<td>2:1 randomisation; wide range of FU</td>
</tr>
<tr>
<td>10 (Meschia et al., 2004) [40]</td>
<td>RCT</td>
<td>TVT</td>
<td>50/50 (25:25)</td>
<td>2y</td>
<td>56% vs. 92% (o); p&lt;0.01</td>
<td>2</td>
<td>Recruited patients with ‘occult’ SUI</td>
</tr>
</tbody>
</table>
appeared to be longer lasting, whether or not the women had associated prolapse, and there appeared to be a greater need for repeat surgery for incontinence after vaginal repair. Although there was a higher incidence of prolapse after abdominal operations, this did not require surgical correction more often. Since postoperative surgical morbidity, quality of life measures, and economic outcomes were poorly reported, the alternative treatments could not be compared in other ways. They concluded that the use of anterior vaginal repair in the treatment of urinary incontinence should be restricted to women deemed unsuitable for alternative treatments (Glazener & Cooper, 2001) [13] [EL=1]. Given the recent developments in less invasive surgical approaches to SUI, it seems unlikely that one could identify a group of women who are suitable for anterior colporrhaphy yet who would be deemed unsuitable for some more effective alternative. Although we were not able to identify studies directly comparing of anterior colporrhaphy with mid-urethral tape procedures in the treatment of overt stress urinary incontinence, one randomised trial compared anterior colporrhaphy (including endopelvic fascial plication) with tension-free vaginal tape (TVT) in 50 women with stage II anterior wall prolapse and ‘occult SUI’ (Meschia et al., 2004) [40]. They found both subjective (96% vs. 64%; p=0.01) and objective (92% vs. 56%; p=0.01) continence rates to be significantly higher following insertion of TVT, with no increase in post-operative voiding problems or irritative symptoms [EL=2]. The recent NICE guidance makes a high level recommendation that anterior colporrhaphy should not be used for the treatment SUI (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b) [EL=1]. We found no new high quality evidence published on anterior colporrhaphy since this latter review; indeed we found no new evidence of any level that considered the place of anterior colporrhaphy in the treatment of SUI incontinence in the absence of POP.

**Summary**

Anterior colporrhaphy is comparable in effectiveness to needle suspension, and less effective than open colposuspension in the treatment of SUI; its effectiveness deteriorates substantially with time [EL=2]. Although the evidence is less robust, it appears to be less effective than the minimally invasive mid-urethral tape procedure (TVT) in the management of ‘occult’ SUI [EL=2].

**Recommendation**

**Anterior colporrhaphy should not be used in the management of SUI alone. [Grade A]**

c) **Open colposuspension (Figure 2)**

The general reviews of incontinence surgery cited earlier all included open colposuspension of the Burch type (Burch, 1961, Burch, 1968) [41,42] amongst their considerations (Jarvis, 1994, Black & Downs, 1996, Downs & Black, 1996, Leach et al., 1997, Jarvis et al., 1999, Smith et al., 2002, Smith et al., 2005, National Collaborating Centre for Women’s & Children’s Health, 2006)[20,23, 24,21-23]; the Cochrane database includes a specific review of the procedure (Lapitan et al., 2005) [17]. The latter includes details of 39 trials 12 of which were available only as abstracts, although otherwise there was virtually complete overlap with the systematic reviews from which the NICE guidance was formulated (National Collaborating Centre for Women’s & Children’s Health, 2006). One of those studies previously only available in abstract form has recently been published (Carey et al., 2006) [43], and two others have further publications with health economic considerations or longer term follow-up (Dumville et al., 2006, Ward et al., 2008)[44,45].

There have been only two newly published randomised trials including colposuspension since previous systematic reviews (Albo et al., 2007, Sivasloglu et al., 2007)[46,47]. In total we examined 33 published randomised trials, seven trials comparing open colposuspension with the anterior colporrhaphy, (Bergman et al., 1989a, Bergman et al., 1989b, Bergman & Elia, 1995, Berglund & Laos, 1996, Liapis et al., 1996a, Liapis et al., 1996b, Berglund et al., 1997, Kammerer-Doak et al., 1999, Klutke et al., 1999, Colombo et al., 2000, Laos et al., 2000)[28,38], four with the MMK procedure (Colombo et al., 1994, Liapis et al., 1996b, Quadri et al., 1999, McCrery & Thompson, 2005) [48,33,49,50], six with needle suspension (two of which also had an anterior colporrhaphy arm) (Mundy, 1983, Bergman et al., 1989a, Bergman et al., 1989b, German et al., 1994,

![Figure 2: Open colposuspension illustrating sutures elevating para-urethral fascia towards Cooper's ligament](image)
Open colposuspension has been shown to be an effective surgical treatment for stress incontinence.

In common with other procedures there is some loss of efficacy with time.

Recommendations:

Open retropubic colposuspension can be recommended as an effective treatment for primary stress urinary incontinence, which has longevity. [Grade A]

Although open colposuspension has to a large extent been superseded by the less invasive mid-urethral tapes, it should still be considered for those women in whom an open abdominal procedure is required concurrently with surgery for SUI. [Grade D]

d) Marshall-Marchetti-Krantz (MMK) procedure

Only level 3 evidence relating to the MMK procedure was consider in the last edition of this consultation (Smith et al., 2005) [23]. Fifty eight papers, predominantly retrospective case series, published between 1951 and 1998 were reviewed, including 3238 patients. Cure rates were largely subjectively defined and averaged 88%. In many studies it was not possible to say whether procedures were carried out for primary or recurrent SUI; those that did specify gave success in 92% in primary procedures and 84% in recurrent cases (Smith et al., 2005) [23].

The MMK procedure itself has not been subject to formal Cochrane review, although two studies were identified where MMK was considered as a comparator in the review of open colposuspension (Colombo et al., 1994, Liapis et al., 1996a) [48,32], and one where the index procedure was of the MMK type rather than Burch type (Henriksson & Ulimsten, 1978) [84]. (Lapitan et al., 2005) [17]. The systematic review underlying the NICE guidance on urinary incontinence (National
Table 2. Published level 1 & 2 evidence relating to open colposuspension for the treatment of stress urinary incontinence

Notes: patient numbers are given as total no. followed up or analysed / total no. recruited (no. in index group: no. in comparator group)

SS = sample size; ITT = intention to treat

<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj) effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mundy, 1983)</td>
<td>Quasi-RCT</td>
<td>Needle suspension</td>
<td>51/51 (26:25)</td>
<td>Min 1y</td>
<td>Success 88% vs 76% (s)</td>
<td>2</td>
<td>Quasi-RCT - by alternation. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>2 (Bergman et al., 1989a)</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>107/127 (38:35:34)</td>
<td>1y</td>
<td>89% vs. 63% vs. 65% (o) p&lt;0.05 colposuspension vs. others</td>
<td>2</td>
<td>Data only reported for completers. No ss calculation</td>
</tr>
<tr>
<td>(Bergman &amp; Elia, 1995)</td>
<td>RCT</td>
<td>Needle suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Bergman &amp; Elia, 1995)</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>64/78 cured at 1y above</td>
<td>5y</td>
<td>82% vs. 37% vs. 43% (o) p≤0.05 colposuspension vs. others</td>
<td>2</td>
<td>Data only on those cured at 1y. No ss calculation</td>
</tr>
<tr>
<td>3 (Bergman et al., 1989b)</td>
<td>RCT</td>
<td>Needle suspension</td>
<td>298/339 (101:99:98)</td>
<td>1y</td>
<td>87% vs. 69% vs. 70% (o) p≤0.05 colposuspension vs. others</td>
<td>2</td>
<td>All vag. hysterectomy &amp; repair. Number randomised unclear; 339 'eligible', and 41 lost to follow-up.</td>
</tr>
<tr>
<td>(Klutke et al., 1999)</td>
<td>RCT</td>
<td>Needle suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (Colombo et al., 1994)</td>
<td>RCT</td>
<td>MMK</td>
<td>80/80 (40:40)</td>
<td>2-7y</td>
<td>80% vs. 65%; p=ns (o)</td>
<td>2</td>
<td>Wide range of FU times (differed between groups). No ss calculation</td>
</tr>
<tr>
<td>5 (German et al., 1994)</td>
<td>RCT</td>
<td>Needle suspension</td>
<td>50/50 (24:26)</td>
<td>12-44m</td>
<td>71% vs. 58%; 86% vs. 53% for 29 primary procedures; p&lt;0.05</td>
<td>2</td>
<td>Randomisation not stated; analysis not clear if ITT; range of FU mean 2y.</td>
</tr>
<tr>
<td>6 (Berglund &amp; Lalos, 1996)</td>
<td>RCT</td>
<td>Pubococcygeal repair</td>
<td>45 (30:15)</td>
<td>1y</td>
<td>67% vs. 47% (o)</td>
<td>2</td>
<td>Those with poor PF contraction excluded from repair group; no detail of randomisation given.</td>
</tr>
<tr>
<td>(Berglund et al., 1997)</td>
<td>RCT</td>
<td>Needle suspension</td>
<td>43/45 (29:14)</td>
<td>5-7y</td>
<td>64% vs. 71% (o)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Lalos et al., 2000)</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>81</td>
<td>3y</td>
<td>88% vs.57%; p&lt;0.001 (o)</td>
<td>2</td>
<td>These 2 papers appear to cover the same study; one describes 2 arms at 3 years, the other 3 arms at 5 years.</td>
</tr>
<tr>
<td>7 (Liapis et al., 1996a)</td>
<td>RCT</td>
<td>MMK</td>
<td>161/170 (54:50:51)</td>
<td>5y</td>
<td>89% vs. 56 vs. 67% (o) p≤0.001 colposuspension vs. others</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8 (Liapis et al., 1996b)</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (Athanassopoulos &amp; Barbalias, 1996)</td>
<td>Quasi-RCT</td>
<td>Needle suspension</td>
<td>51/51 (27:24)</td>
<td>8-27m</td>
<td>74% vs. 71%; p=ns (o)</td>
<td>2</td>
<td>Quasi-RCT – randomised by DoB. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>Study references</td>
<td>Type</td>
<td>Comparator</td>
<td>N/N (n1:n2)</td>
<td>FU</td>
<td>Cure (obj or subj)/ effect size</td>
<td>EL</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>------------</td>
<td>-------------</td>
<td>----</td>
<td>-------------------------------</td>
<td>----</td>
<td>----------</td>
</tr>
<tr>
<td>10 (Colombo et al., 1996) [55]</td>
<td>RCT</td>
<td>Paravaginal repair</td>
<td>36/36 (18:18)</td>
<td>2y</td>
<td>100% vs. 61%; p=0.004 (o)</td>
<td>2</td>
<td>No ss calculation, but discontinued recruitment early for ethical reasons.</td>
</tr>
<tr>
<td>11 (Enzelsberger et al., 1996) [56]</td>
<td>RCT</td>
<td>Sling (dura mater)</td>
<td>72/72 (36:36)</td>
<td>32-48m</td>
<td>86% vs. 92%</td>
<td>2</td>
<td>No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>12 (Su et al., 1997) [69]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>92/92 (46:46)</td>
<td>6m</td>
<td>96% vs. 80%; p=0.044 (o)</td>
<td>2</td>
<td>Part preference, part randomised; sample size calculation req’d. 152.</td>
</tr>
<tr>
<td>13 (Gilja et al., 1998) [54]</td>
<td>RCT</td>
<td>Needle suspension Transvaginal colpo</td>
<td>146/204 (56:46:44)</td>
<td>3y</td>
<td>89% vs. 80% vs. 86%; p=ns (o)</td>
<td>2</td>
<td>No ss calculation; 28% lost to FU.</td>
</tr>
<tr>
<td>14 (Kammerer-Doak et al., 1999) [35]</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>35/35 (19:16)</td>
<td>1y</td>
<td>89% vs. 31% (o) RR 0.15 (95% CI 0.04 to 0.59)</td>
<td>2</td>
<td>Ant. colporrhaphy in 16% vs. 100%; paravaginal repair in 42% vs. 6%. No ss calculation.</td>
</tr>
<tr>
<td>15 (Quadri et al., 1999) [49]</td>
<td>RCT</td>
<td>MMK</td>
<td>30/30 (15:15)</td>
<td>1y</td>
<td>53% vs. 93%; p=0.017 (o)</td>
<td>2</td>
<td>No ss calculation.</td>
</tr>
<tr>
<td>16 (Colombo et al., 2000) [37]</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>68/71 (35:33)</td>
<td>≥8y</td>
<td>74% vs. 42% (o) OR 3.9 (95% CI 1.3 to 12.5), p=0.02</td>
<td>2</td>
<td>Vag. or abdo. hysterectomy also done; post repair in 100% vs. 34%.</td>
</tr>
<tr>
<td>17 (Sand et al., 2000) [57]</td>
<td>RCT</td>
<td>Sling (Gore-tex)</td>
<td>28,36/37 (19:17)</td>
<td>3m/33-116m</td>
<td>90% vs.100%; p=ns (o - 3m) 85% vs. 100%; p=ns (o - longer-term)</td>
<td>2</td>
<td>Only 28 in longer-term FU; concurrent procedures in 21% vs. 12%.</td>
</tr>
<tr>
<td>18 (Patthy et al., 2001) [70]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>74/74 (40:34)</td>
<td>18m</td>
<td>85% vs. 88%; p=ns (o+s)</td>
<td>2</td>
<td>No ss calculation.</td>
</tr>
<tr>
<td>19 (Demirci &amp; Yucel, 2001) [58]</td>
<td>Quasi-RCT</td>
<td>Sling (rectus fascia)</td>
<td>34/46 (17:17)</td>
<td>1y</td>
<td>88% vs. 94%; RR 2.00; 95% CI 0.20, 20.04 (o)</td>
<td>2</td>
<td>Quasi-RCT - by alternation. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>20 (Cheon et al., 2003) [71]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>90/90 (43:47)</td>
<td>1y</td>
<td>86% vs. 85%; p=ns (o)</td>
<td>2</td>
<td>37% vs. 15% underwent concomitant hysterectomy.</td>
</tr>
<tr>
<td>21 (Ankardal ai et al., 2005) [72]</td>
<td>RCT</td>
<td>Lap colpo (sutures)</td>
<td>184/211 (63:49:72)</td>
<td>1y</td>
<td>92% vs. 90% vs. 63% (o) p&lt;0.05 open vs. mesh</td>
<td>2</td>
<td>Unclear randomisation; all pts randomised to Burch or lap colpo (mesh) also included in separate multicentre study (Ankardal et al., 2004). Only completers analysed.</td>
</tr>
<tr>
<td>22 (Ustun et al., 2005) [73]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>52/52 (26:26)</td>
<td>3-24m</td>
<td>81% vs. 81%; p=ns</td>
<td>2</td>
<td>Many concurrent procedures - varied between groups.</td>
</tr>
</tbody>
</table>
Table 2. Published level 1 & 2 evidence relating to open colposuspension for the treatment of stress urinary incontinence (Continued) Notes: patient numbers are given as – total no. followed up or analysed /total no. recruited (no. in index group: no. in comparator group) SS = sample size; ITT = intention to treat

<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (McCreery &amp; Thompson, 2005) [50]</td>
<td>RCT</td>
<td>MMK</td>
<td>138/7 (66:72)</td>
<td>6-60m</td>
<td>59% vs. 49%; p=0.02 (s+o)</td>
<td>2</td>
<td>No. randomised not clear; all had concurrent paravaginal repair.</td>
</tr>
<tr>
<td>24 (Ward et al., 2002) [65] (Ward et al., 2004) [67] (Ward et al., 2008) [45] (Manca et al., 2003) [134]</td>
<td>RCT</td>
<td>TVT</td>
<td>316/344 (146:170)</td>
<td>6m, 2y, 5y</td>
<td>57% vs. 66%; (95% CI for diff.–4.7%, +21.3%) (missing = fail) (o at 6m) 81% vs 80% (OR 1.67, 95% CI 0.59 to 2.06) (o at 2y) – completers analysis 81% vs 90% (OR 0.47, 95% CI 0.16 to 1.4) (o at 5y) – completers analysis</td>
<td>1</td>
<td>8% dropout after randomisation before surgery (colpo&gt;TVT). 88% FU at 6m, 71% at 2y and 51% at 5y.</td>
</tr>
<tr>
<td>25 (Liapis et al., 2002) [64]</td>
<td>Quasi-RCT</td>
<td>TVT</td>
<td>71/171 (36:35)</td>
<td>2y</td>
<td>84% vs. 86%; p=ns (o)</td>
<td>2</td>
<td>Quasi-RCT – alternation; no ss calculation</td>
</tr>
<tr>
<td>26 (Wang &amp; Chen, 2003) [66]</td>
<td>RCT</td>
<td>TVT</td>
<td>90/108 (41:49)</td>
<td>12-36m</td>
<td>82% vs. 76%; p=ns (o)</td>
<td>2</td>
<td>SS calculated on obstructive outcome rather than cure.</td>
</tr>
<tr>
<td>27 (El-Barky et al., 2005) [68]</td>
<td>RCT</td>
<td>TVT</td>
<td>50/50 (25:25)</td>
<td>3-6m</td>
<td>72% vs. 72%; p=ns (s)</td>
<td>2</td>
<td>Randomisation not stated; analysis not clear if ITT. No ss calculation</td>
</tr>
<tr>
<td>28 (Bai et al., 2005) [60]</td>
<td>RCT</td>
<td>TVT</td>
<td>92/92 (33:31:28)</td>
<td>1y</td>
<td>88% vs. 87% vs. 93%; p&lt;0.05 for sling vs. others</td>
<td>2</td>
<td>Disparities between text and tables. No ss calculation</td>
</tr>
<tr>
<td>29 (Kitchener et al., 2006) [74] (Dumville et al., 2006) [44]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>242/291 (147:144)</td>
<td>2y</td>
<td>70% vs. 80% (o)</td>
<td>1</td>
<td>5 had no op., &amp; 12 changed op. after randomis’n. Objective data on 83%.</td>
</tr>
<tr>
<td>30 (Carey et al., 2006) [43]</td>
<td>RCT</td>
<td>Lap colpo</td>
<td>164/200 (88:76)</td>
<td>3-5y</td>
<td>78% vs. 72%; p=0.22 (o at 6m) 80% vs. 69%; p=0.38 (s at 2y)</td>
<td>2</td>
<td>Telephone interview at 3-5y; results ‘similar’ to 24m</td>
</tr>
<tr>
<td>31 (Tennstedt &amp; Urinary Incontinence Treatment Network, 2005) [81] (Albo et al., 2007) [46] (Richter et al., 2008) [63]</td>
<td>RCT</td>
<td>Sling (rectus fascia)</td>
<td>520/655 (329:326)</td>
<td>2y</td>
<td>49% vs. 66% (p&lt;0.001) (s+o)</td>
<td>1</td>
<td>50% concomitant surgery for POP, 79% outcome assessment at 2 years.</td>
</tr>
<tr>
<td>32 (Sivaslioglu et al., 2007) [47]</td>
<td>RCT</td>
<td>TOT</td>
<td>63, 100/100 (61:49)</td>
<td>1y &amp; 2y</td>
<td>80% vs.86%; p=0.4 (o at 1y) 84% vs. 88%; p=0.6 (o at 2y)</td>
<td>2</td>
<td>No ss calculation. Only 63 FU at 2y</td>
</tr>
</tbody>
</table>
Collaborating Centre for Women’s & Children’s Health, 2006) identified two further RCTs comparing MMK with open colposuspension (Quadri et al., 1999, McCrery & Thompson, 2005) [49,50]. We have not identified other level 1 or 2 evidence relating to MMK (see table 3). The Cochrane review found that whilst results at early follow-up were not significantly different, both subjective and objective cure were significantly better after the Burch procedure than after MMK at one to five years after surgery (RR 0.44; 95%CI 0.25 to 0.77) (Lapitan et al., 2005) [17] [EL=1]. One of the additional studies identified in the review underlying the NICE guidance showed significantly better subjective and objective results from MMK at 1 year (negative stress test 93% vs. 53%; p=0.02) (Quadri et al., 1999) [49] [EL=2]; the other showed significantly better subjective outcomes from colposuspension at a mean follow-up of 2 years (59% vs. 49%; p=0.02) (McCrery & Thompson, 2005) [50] [EL=2]; neither reported longer term outcome.

Other longer term follow up data are limited, and of poor quality. Six studies looking specifically at long-term outcome found cure rates averaging 58% at periods between 4 and 15 years (McDuffie et al., 1981, Colombo et al., 1998, Czaplicki et al., 1998, Luna et al., 1999, Hegarty et al., 2001, Demirci et al., 2002) [85-90]. Two studies showing trends over time in 204 and 81 patients respectively reported cure in 90% at year one, 86% and 57% at five years, and 72% and 28% at 10 years (McDuffie et al., 1981, Czaplicki et al., 1998) [85,87] [EL=3].

Summary:

Although short-term results indicate comparable cure rates to colposuspension, there is limited evidence that longer-term outcome is poorer following MMK [EL=1], and declines further over time [EL=3]. The previous edition of this consultation found no reason to support the continued use of MMK over colposuspension; there is no new evidence to indicate a change in this view.

Recommendation:

The MMK procedure is not recommended for the treatment of SUI. [Grade A]

e) Needle suspension procedures (Figure 3)

Several endoscopic and non-endoscopic bladder neck needle suspension procedures have been described since the original report of Pereyra (Pereyra, 1959) [91]; modifications include those described by Stamey (Stamey, 1973) [92], Gittes (Gittes & Loughlin, 1987) [93], and Raz (Raz et al., 1992) [94]. The procedures have been considered appropriate for either primary or recurrent SUI in particular where open retropubic suspension procedures were unsuitable, such as in frail or elderly women or where colposuspension may be technically difficult because of poor vaginal mobility.

Table 3. Published level 1 & 2 evidence relating to Marshall-Marchetti-Krantz procedure for the treatment of stress urinary incontinence

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Comparator</th>
<th>Type</th>
<th>FU</th>
<th>Cure (obj or subj effect size)</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henriksson &amp; Ulmsten, 1978 [84]</td>
<td>Qua-RCT</td>
<td>RCT</td>
<td>3m</td>
<td>100% vs. 100% (o)</td>
<td>2</td>
<td>Qua-RCT - by alternation. No ss calculation; analysis not clear if ITT. No apparent overlap with Lapitan et al. (2005) [17] 2 arms at 3 years.</td>
</tr>
<tr>
<td>Liapis et al., 1996b [33]</td>
<td>RCT</td>
<td>RCT</td>
<td>5y</td>
<td>67% vs. 69% &amp; 76% (o)</td>
<td>2</td>
<td>Apparent overlap with Lapitan et al. (2005) [17] 2 arms at 3 years.</td>
</tr>
<tr>
<td>Colombo et al., 1994 [48]</td>
<td>RCT</td>
<td>RCT</td>
<td>3y</td>
<td>59% vs. 73%, p&lt;0.01 (o)</td>
<td>2</td>
<td>No ss calculation.</td>
</tr>
<tr>
<td>Quadri et al., 1999 [49]</td>
<td>RCT</td>
<td>RCT</td>
<td>1y</td>
<td>93% vs. 53%, p&lt;0.01 (o)</td>
<td>2</td>
<td>No ss calculation.</td>
</tr>
<tr>
<td>McCrery &amp; Thompson, 2005 [50]</td>
<td>RCT</td>
<td>RCT</td>
<td>6-60m</td>
<td>49% vs. 59%, p&lt;0.02 (o)</td>
<td>2</td>
<td>No randomised; no clear all had concurrent paravaginal repair.</td>
</tr>
</tbody>
</table>

Notes: patient numbers are given as –no. followed up or analysed /total no. recruited (analysed no. in index group: analysed no. in comparator group)
or capacity, from atrophic change, previous surgery, or radiotherapy.

The review by Jarvis was based largely on low level evidence, with only seven out of the 213 surgical studies reviewed being randomised. He identified data from 3553 women undergoing endoscopic or non-endoscopic bladder neck needle suspension with an average subjective cure rate of 79% and objective cure rate of 71% (Jarvis, 1994) [20] [EL=2].

The Cochrane review of needle suspension procedures (Glazener & Cooper, 2004) [15] and the systematic review underlying the NICE guideline on urinary incontinence (National Collaborating Centre for Women’s & Children’s Health, 2006) both included the same ten RCTs describing six different needle suspension procedures, 1983, (Palma et al., 1988, Bergman et al., 1989a, Bergman et al., 1989b, Hilton, 1989, Stein & Weinberg, 1991, German et al., 1994, Bergman & Elia, 1995, Athanassopoulos & Barbalias, 1996, Gilja et al., 1998, Klutke et al., 1999, Di Palumbo, 2003) [95,28,29,96,29,97,52,30,53,54,36,39]. We did not identify any more recent high level evidence relating to this group of procedures (see Table 4). No studies were identified comparing needle suspension with sham treatment or non-surgical treatments; one small study compared with a sling procedure, seven with colposuspension, and three with anterior repair; two others compared different needle suspension procedures or different sutures. The needle suspension procedures were found to be less effective than colposuspension based on subjective outcome within one year of surgery (RR for failure 1.70, 95% CI 1.11 to 2.60); and after the first year (29% vs. 16% failure; RR for failure 2.00, 95% CI 1.47 to 2.72); there were no clear differences between the procedures for any of the other outcome measures examined, although the confidence estimates around estimates were wide. The performance of needle suspension and anterior colporrhaphy appeared similar in terms of subjective cure rates after 12months (RR 0.86, 95%CI 0.64 to 1.16) and voiding dysfunction, whether the women had prolapse in addition to stress incontinence or not [EL=1].

Only low level evidence is available to judge long-term outcomes. Cure rates of 31%-68% have been reported at 4-5 years (Hilton & Mayne, 1991, Bergman & Elia, 1995, Reid & Parys, 2005) [98,30,99] and 20%-33% at 10 years (Trocmak et al., 1995, Mills et al., 1996) [100,101]. Unpublished results from the Leeds group showed 80% cures at 1 year (n=186), declining to 45% at 2 years, 18% at 4 years, and to only 6% at 10 years (n=17) (Jarvis et al., 1999) [21] [EL=3].

A later development of the needle suspension procedures, introduced in an attempt to improve the longevity of results, was the use of bone anchors for the suspensory sutures. Bone-anchored cystourethropexy has not been subject to RCT, although two versions, the ‘Vesica®’ and ‘In-Tac®’ procedures, have been reviewed by the NICE Interventional Procedures Programme (National Institute for Health & Clinical Excellence, 2003). They highlighted the poor long-term outcomes, and concluded that current evidence of the safety and efficacy of bone-anchored cystourethropexy is not adequate to support the use of this procedure in routine clinical practice [EL=2].

Although we found no new high level evidence regarding needle suspension procedures, there is continuing concern not only about long-term efficacy, but also about long-term complications which continue to emerge. These include suture migration into the urinary tract, and chronic infective complications from the implanted buffers and/or bone anchors (Goldberg et al., 2004, Gregorakis et al., 2006, Smith & Rovner, 2006) [102-104]; osteomyelitis of the pubic bones has been reported to occur in 1.3% in one series (Goldberg et al., 2004) [102] [EL=3].

**Summary:**

High level evidence indicates that needle suspension procedures are as effective as anterior colporrhaphy, but less effective than colposuspension even in the short-term [EL=1]. Long-term studies indicate lack of longevity even of the initial modest results; long-term complications remain a concern [EL=3].

**Recommendation:**

**Endoscopic and non-endoscopic bladder neck needle suspension procedures, with and without bone-anchors are not recommended for the treatment of SUI. [Grade A]**

**f) Paravaginal repair**

The paravaginal defect repair was first described by White in the early part of the 20th century, as a vaginal procedure (White, 1909, 1912) [105,106]. It has since
<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mundy, 1983) [51]</td>
<td>Quasi-RCT</td>
<td>Colposuspension</td>
<td>51/51(25:26)</td>
<td>Min 1y</td>
<td>Success 76% vs 88% (s)</td>
<td>2</td>
<td>Quasi-RCT - by alternation. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>2 (Palma et al., 1988) [95]</td>
<td>RCT</td>
<td>MMK</td>
<td>50/70 (40:30)</td>
<td>2-56m</td>
<td>50% vs. 77%; RR 2.14; 95% CI 0.98, 4.69 (o)</td>
<td>2</td>
<td>Unclear randomisation; FU duration wide &amp; diff for 2 groups.</td>
</tr>
<tr>
<td>3 (Hilton, 1989) [96]</td>
<td>RCT</td>
<td>Sling (porcine dermis)</td>
<td>20/20 (10:10)</td>
<td>2y</td>
<td>80% vs. 90% (o - at 3m)</td>
<td>2</td>
<td>Included only USI with vaginal narrowing unsuitable for colpo.</td>
</tr>
<tr>
<td>4 (Bergman et al., 1989a) [28]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>107/127 (34:38:35)</td>
<td>1y</td>
<td>65% vs. 89% vs. 63% (o) $p&lt;0.05$ colposuspension vs. others</td>
<td>2</td>
<td>Data only reported for completers.</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (Stein &amp; Weinberg, 1991) [87]</td>
<td>RCT</td>
<td>Goretex vs. Prolene sutures</td>
<td>20/24 (9:11)</td>
<td>6m</td>
<td>100% vs. 73%; RR 0.17; 95% CI 0.01, 2.94 (S)</td>
<td>2</td>
<td>3 different suspension procedures in series; no ss calculation.</td>
</tr>
<tr>
<td>6 (German et al., 1994) [52]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>50/50 (28:24)</td>
<td>12-44m</td>
<td>58% vs. 71%, 53% vs. 86% for 29 primary procedures; $p&lt;0.05$</td>
<td>2</td>
<td>Randomisation not stated; analysis not clear if ITT; range of FU mean 2y.</td>
</tr>
<tr>
<td>7 (Bergman et al., 1989b) [29]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>298/339 (98:101:99)</td>
<td>1y</td>
<td>70% vs.87% vs.89% (o) $p&lt;0.02$ colposuspension vs. others</td>
<td>2</td>
<td>All vag. hysterectomy &amp; repair. Number randomised unclear; 339 eligible, and 41 lost to follow-up.</td>
</tr>
<tr>
<td></td>
<td>Ant. colporrhaphy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (Athanassopoulos &amp; Barbalias, 1996) [53]</td>
<td>Quasi-RCT</td>
<td>Colposuspension</td>
<td>51/51 (24:27)</td>
<td>8-27m</td>
<td>71% vs. 74%, $p=ns$ (o)</td>
<td>2</td>
<td>Quasi-RCT – randomised by DoB. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>9 (Gilja et al., 1998) [54]</td>
<td>RCT</td>
<td>Colposuspension</td>
<td>146/204 (46:56:44)</td>
<td>3y</td>
<td>80% vs. 89% vs. 86%, $p=ns$ (o)</td>
<td>2</td>
<td>No ss calculation; 28% lost to FU</td>
</tr>
<tr>
<td>10 (Di Palumbo, 2003) [39]</td>
<td>RCT</td>
<td>Ant. colporrhaphy</td>
<td>80/80 (28:52)</td>
<td>9m-4.5y</td>
<td>86% vs. 73% (o); $p&lt;0.01$</td>
<td>2</td>
<td>2:1 randomisation; wide range of FU</td>
</tr>
</tbody>
</table>
been described using either abdominal (Richardson et al., 1976) [107] or laparoscopic approaches (Richardson et al., 1997) [108]. There is little high level evidence on these procedures, and the available studies are often confounded by the use of combined procedures.

Only one RCT has been published which included abdominal paravaginal defect repair in a comparison with open colposuspension in women with SUI and grade 1 urethrocystocele (Colombo et al., 1996) [55]. Although this study was included in the Cochrane review of colposuspension, it was felt that this study was too small, and the data insufficient to draw conclusions. Thirty six women were recruited, and although no sample size calculation is included in the paper, recruitment was terminated when it was felt no longer ethical to randomise patients. The majority of women in both groups also underwent hysterectomy during the laparoscopic procedure (Scotti et al., 1996, Bruce et al., 1999) [109,110], 70% to 93% following the laparoscopic procedure (Ostrzenski, 1998, Miklos & Kohli, 2000) [111,112], and 43% to 89% following the vaginal procedure (Mallipedi et al., 2001, Clemons et al., 2003)[113,114]. Only one small series has been published more recently, indicating a cure rate of 93% for prolapse and 80% for SUI in 20 women treated by abdominal paravaginal repair alone compared to cures in 100% of 10 women treated by paravaginal plus incontinence surgery, at a mean follow-up period of 40 months [EL=3].

Several small case series with limited follow-up and largely subjectively defined outcome were reviewed in the last edition of this consultation. Cure rates of 80% to 94% were found following the abdominal procedure (Scotti et al., 1998, Bruce et al., 1999) [109,110], 70% to 93% following the laparoscopic procedure (Ostrzenski, 1998, Miklos & Kohli, 2000) [111,112], and 43% to 89% following the vaginal procedure (Mallipedi et al., 2001, Clemons et al., 2003)[113,114]. Only one small series has been published more recently, indicating a cure rate of 93% for prolapse and 80% for SUI in 20 women treated by abdominal paravaginal repair alone compared to cures in 100% of 10 women treated by paravaginal plus incontinence surgery, at a mean follow-up period of 40 months [EL=3].

Summary:

There is limited evidence that abdominal paravaginal defect repair is less effective than open colposuspension [EL=2].

Recommendation:

Paravaginal defect repair is not recommended for the treatment of SUI alone. [Grade A]

9) Laparoscopic colposuspension (Figure 4)

The Cochrane review of laparoscopic colposuspension has been updated since the last edition of this consultation; it now includes details of 22 RCTs that including laparoscopic colposuspension (Dean et al., 2006a) [18], 14 more than their initial review (Moehrer et al., 2000) [11]. Of these 22 trials, ten compared laparoscopic colposuspension with open colposuspension (Su et al., 1997, Burton, 1999, Summitt et al., 2000, Fathy et al., 2001, Morris et al., 2001, Cheon et al., 2003, Ankardal et al., 2004, Ankardal et al., 2005, Carey et al., 2006, Kitchener et al., 2006) [69,115,116,70,117,71,118,72,43,74], and eight with minimally invasive mid-urethral slings (Persson et al., 2002, Ustun et al., 2003, Maher et al., 2004, Paraiso et al., 2004, Valpas et al., 2004, Mirosh & Epp, 2005) [119-124]; the remainder examined different aspects of the laparoscopic technique (one vs. two sutures (Persson & Wolner-Hanssen, 2000) [125], sutures vs. Mesh (Ross, 1996, Zullo et al., 2001, Ankardal et al., 2005) [126,127,72] and transperitoneal vs. extraperitoneal approach to laparoscopy (Wallwiener et al., 1995 [128]). Seven compared laparoscopic colposuspension with Tension-free Vaginal Tape®, and these have been published separately (Dean et al., 2006b) [129]. Seven were only available as abstracts at the time of the systematic review underlying the NICE guidance on urinary incontinence, and hence were not considered in their report (National Collaborating Centre for Women’s & Children’s Health, 2006). Eight of the ten studies comparing laparoscopic colposuspension with open colposuspension were included along with eight retrospective cohort studies in a recently published meta-analysis (Tan et al., 2007) [130]. We identified two further RCTs on laparoscopic colposuspension (Piccione et al., 2001, Ustun et al., 2005) [131,73]; in addition one study previously only in abstract form has recently been published (Carey et al., 2006) [43], and two have further publications with longer-term follow-up (Jelovsek et al., 2008) [132] or cost-effectiveness data (Valpas et al., 2006) [133]. Details of the 15 published studies (22 papers) are given in table 5.
<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj) effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Wallwiener et al., 1995)</td>
<td>RCT</td>
<td>Transperitoneal vs. extraperitoneal</td>
<td>22 (7:7)</td>
<td>1-12m</td>
<td>92% (s+o)</td>
<td>2</td>
<td>Mixture of suturing/stapling techniques; outcomes not separately evaluable.</td>
</tr>
<tr>
<td>2 (Ross, 1996)</td>
<td>RCT</td>
<td>Sutures vs. mesh/staples</td>
<td>69/69 (35:34)</td>
<td>1y</td>
<td>91% vs. 94%; RR 0.97; 95% CI 0.85, 1.11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3 (Su et al., 1997)</td>
<td>RCT</td>
<td>Open colpo</td>
<td>92/92 (46:46)</td>
<td>6m</td>
<td>80% vs. 96%; p=0.044 (o)</td>
<td>2</td>
<td>Part preference, part randomised; sample size calculation req’d 152.</td>
</tr>
<tr>
<td>4 (Persson &amp; Wolner-Hanssen, 2000)</td>
<td>RCT</td>
<td>2 single bite vs. 1 double bite sutures</td>
<td>161/? (83:78)</td>
<td>1y</td>
<td>83% vs. 58%; p&lt;0.001</td>
<td>2</td>
<td>Enrolment curtailed early after interim analysis</td>
</tr>
<tr>
<td>5 (Piccione et al., 2001)</td>
<td>RCT</td>
<td>Sutures vs. mesh/staples</td>
<td>53/60 (27:26)</td>
<td>1 &amp; 3y</td>
<td>89% vs. 75% (o - at 1y) 70% vs. 42%(o - at 2y) 58% vs. 38% (o – at 3y); p&lt;0.05</td>
<td>2</td>
<td>Only completers analysed in 2001 paper; ITT used in 3 year follow-up.</td>
</tr>
<tr>
<td>6 (Fatthy et al., 2001)</td>
<td>RCT</td>
<td>Open colpo</td>
<td>74/74 (34:40)</td>
<td>18m</td>
<td>88% vs. 85%; p=NS (s+o)</td>
<td>2</td>
<td>No ss calculation.</td>
</tr>
<tr>
<td>7 (Persson et al., 2002)</td>
<td>RCT</td>
<td>TVT</td>
<td>68/79 (31:37)</td>
<td>1y</td>
<td>87% vs. 89% RR 0.98; 95% CI 0.82, 1.16</td>
<td>2</td>
<td>270 approached; 79 randomised. Study designed to examine costs.</td>
</tr>
<tr>
<td>8 (Cheon et al., 2003)</td>
<td>RCT</td>
<td>Open colpo</td>
<td>90/90 (47:43)</td>
<td>1y</td>
<td>85% vs. 86%; p=NS (o)</td>
<td>2</td>
<td>15% vs. 37% underwent concomitant hysterectomy</td>
</tr>
<tr>
<td>9 (Ustun et al., 2003)</td>
<td>RCT</td>
<td>TVT</td>
<td>46/46 (23:23)</td>
<td>3-24m</td>
<td>83% vs. 83%; RR1.00; 95% CI 0.77, 1.30 (s+o)</td>
<td>2</td>
<td>No information on randomisation; no allowance for variation in FU</td>
</tr>
<tr>
<td>10 (Valpas et al., 2003)</td>
<td>RCT</td>
<td>TVT</td>
<td>121/128 (51:70)</td>
<td>1y</td>
<td>57% vs. 86% (95% CI for diff. 12.7, 43.9); p=0.000 (o)</td>
<td>2</td>
<td>Lap. colpo with mesh. SS calculation required 176.</td>
</tr>
</tbody>
</table>
Table 5. Published level 1 & 2 evidence relating to laparoscopic colposuspension for the treatment of stress urinary incontinence Notes: patient numbers are given as – total no. followed up or analysed /total no. recruited (no. in index group: no. in comparator group) SS = sample size; ITT = intention to treat

<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (Paraiso et al., 2004)(^{12}) (Jelovsek et al., 2008)(^{13})</td>
<td>RCT</td>
<td>TVT</td>
<td>71/72 (35:36)</td>
<td>12-43m 12-88m</td>
<td>97% vs 81% (o – at median 18m) 43% vs. 52% (s – at median 65m)</td>
<td>2</td>
<td>SS 130; recruitment stopped early because of slow recruitment. 63 (88%) FU at 1y; 33 (46%) at 2y</td>
</tr>
<tr>
<td>12 (Ankardal et al., 2005)(^{14})</td>
<td>RCT</td>
<td>Open colpo</td>
<td>184/211 (49:63:72)</td>
<td>1y</td>
<td>90% vs. 92% vs. 63% (o) p&lt;0.05 open vs. mesh</td>
<td>2</td>
<td>Unclear randomisation; all pts randomised to Burch or lap colpo (mesh) also included in separate multicentre study (Ankardal et al., 2004). Only completers analysed.</td>
</tr>
<tr>
<td>13 (Ustun et al., 2005)(^{15})</td>
<td>RCT</td>
<td>Open colpo</td>
<td>52/52 (26:26)</td>
<td>3-24m</td>
<td>81% vs. 81%; p=ns</td>
<td>2</td>
<td>Many concurrent procedures - varied between groups</td>
</tr>
<tr>
<td>14 (Kitchener et al., 2006)(^{16}) (Dumville et al., 2006)(^{17})</td>
<td>RCT</td>
<td>Open colpo</td>
<td>242/291 (144:147)</td>
<td>2y</td>
<td>80% vs. 70% (o)</td>
<td>1</td>
<td>5 had no op., &amp; 12 changed op. after randomis’n. Objective data on 83%</td>
</tr>
<tr>
<td>15 (Carey et al., 2006)(^{18})</td>
<td>RCT</td>
<td>Open colpo</td>
<td>164/200 (76:88)</td>
<td>3-5y</td>
<td>72% vs. 78%; p=0.22 (o at 6m) 69% vs. 80%; p=0.38 (s at 2y)</td>
<td>2</td>
<td>Telephone interview at 3-5y; results ‘similar’ to 24m</td>
</tr>
</tbody>
</table>
Studies included in the Cochrane review had different lengths of follow-up, although eight studies had follow-up in the region 6 to 18 months. In comparison with open colposuspension they found subjective cure rates to range from 58% to 96% in the open and 62% to 100% in the laparoscopic group within the 18 months follow up, with a non-significant 5% lower relative subjective cure rate for laparoscopic colposuspension (RR 0.95, 95% CI 0.90 to 1.00) (Dean et al., 2006a) [18] [EL=1]. The two studies with follow-up at five years or beyond unfortunately remain unpublished and available in abstract form only. Both these studies were relatively small, and their results are inconsistent, one finding better subjective outcome from the laparoscopic procedure (Morris et al., 2001) [117], and one favouring the open procedure (Burton, 1999) [117]; the methodology of this latter study in particular has been questioned [EL=2].

Overall, the objective cure rate as judged by cough stress testing or pad test within 18 months was statistically significantly lower following laparoscopic colposuspension (RR 0.91, 95% CI 0.86 to 0.96) [EL=1]. Between 18 months and five years there was no significant difference (RR 1.01, 95% CI 0.88 to 1.16); again however, there was heterogeneity with one small trial greatly favouring open procedure (Burton, 1999) [115] and the other favouring laparoscopic (Morris et al., 2001) [117] [EL=2]. When objective cure was judged by urodynamic investigations there was a significantly higher success rate following open colposuspension (RR 0.91, 95% CI 0.85 to 0.99).

Cost effectiveness was assessed in only one trial (Dumville et al., 2006, Kitchener et al., 2006) [44,74]. This study showed that whilst laparoscopic surgery produced greater quality adjusted life years (QALYs), there was an additional cost when compared to open surgery. The differential mean cost was GBC 372 (95% credibility interval [CrI]; 274–471), and at 6 months QALYs were slightly higher in the laparoscopic arm relative to the open arm (0.005; 95% CrI: −0.012 to 0.023). The cost of each additional QALY in the laparoscopic group or incremental cost-effectiveness ratio (ICER) was £74,400 at 6 months, but reduced to £9,300 by 24 months, in view of a further increase in QALYs, but no additional costs (assumed) (Dumville et al., 2006) [44] [EL=1]. Earlier studies have shown TVT™ to be dominant in cost effectiveness terms over both open (Manca et al., 2003) [134] and laparoscopic colposuspension (albeit using a mesh technique) (Valpas et al., 2006) [133] [EL=1].

In comparison with minimally invasive mid-urethral slings there was no statistically significant difference in subjective cure rates within 18 months (RR 0.91, 95% CI 0.80 to 1.02) [EL=1]. The definition of objective cure varied widely between studies, although overall the objective cure rate was higher for minimally invasive mid-urethral slings than laparoscopic colposuspension (RR 0.92, 95% CI 0.85 to 0.99) [EL=1].

Studies comparing different laparoscopic techniques found that two sutures either side of the bladder neck resulted in higher subjective (RR 1.37, 95% CI 1.14 to 1.64) and objective (RR 1.42, 95% CI 1.14 to 1.77) cure rate than one (Persson & Wolner-Hanssen, 2000) [125] [EL=2], and that sutures resulted in higher subjective (RR 1.28, 95% CI 1.11 to 1.47) and objective (RR 1.20, 95% CI 1.07 to 1.35) cure rate than mesh (Ross, 1996, Piccione et al., 2001, Zullo et al., 2001, Ankardal et al., 2005) [126,131,127,72] [EL=1].

The conclusion from the Cochrane review was that the currently available evidence suggests that laparoscopic colposuspension may be as effective as open colposuspension two years postoperatively (Dean et al., 2006a) [18]. The systematic review specific to laparoscopic colposuspension and TVT™ concluded that the evidence so far appears to favour the latter as the minimal-access technique of choice for USI (Dean et al., 2006b) [129]. In both cases however the authors indicated that the place of laparoscopic colposuspension in clinical practice could not be clearly defined without further long-term results.

It should also be noted that much of the published research in this area is from individuals with enthusiasm and skill in laparoscopic surgery; their results should not necessarily be seen as being generalisable to the urogynaecological/urological community at large. The NICE guidance includes amongst its recommendation that laparoscopic colposuspension is not recommended as a routine procedure for the treatment of SUI in women, but that the procedure should be performed only by an experienced laparoscopic surgeon working in a multidisciplinary team with expertise in the assessment and treatment of UI (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b); this same point is emphasised in the meta-analysis from Tan and colleagues (Tan et al., 2007) [130] [EL=4].

**Summary:**

Laparoscopic colposuspension shows comparable subjective outcome, but poorer objective outcome than both open colposuspension and TVT™ in the short to medium term; longer term outcomes are unknown [EL=2]. It may not be good value for money when compared with open colposuspension in the short term (i.e. first 6 months following surgery), but it could be a cost-effective alternative over 24 months [EL=1]; other comparisons however suggest that minimally invasive mid-urethral tape procedures may be dominant in health economic terms.
Urethral bulking agents have been used for the treatment of SUI in women for the past 3 decades. A variety of substances have been reported to be safe and effective in this context including bovine glutaraldehyde cross linked (GAX) bovine collagen (Contigen®), polytetrafluoroethylene (Teflon®), polydimethyl-siloxane elastomer (Macroplastique®), porcine dermal implant (Permacol®), carbon-coated zirconium beads (Durasphere®), non-animal stabilized hyaluronic acid/dextranomer NASHA/Dx (Zuidex®), calcium hydroxyapatite (CaHA; Coaptite®), ethylene vinyl alcohol (Uryx®; Tegress®) and autologous tissues such as fat, chondrocytes, and myoblasts. Each of these different agents has variable biophysical properties that influence tissue compatibility, tendency for migration, radiographic density, durability and safety. The ideal urethral bulking agent has not yet been identified.

Most urethral bulking agents are injected transurethrally or periurethrally, in a retrograde fashion under direct cystoscopic guidance although implantation devices have been developed which potentially obviate the need for this. There is no universally accepted injection route, technique, equipment or anaesthetic regimen. The optimal location for injection has not been defined and reported injection locations have included anywhere between the mid-urethra and the bladder neck. The optimal volume of material for injection during a single session, ideal site orientation for injection, or the optimal number of reinjection sessions for any given agent (until clinical “failure” has been determined) has not been defined. Long term success may not correlate with the endoscopic appearance at the conclusion of the injection session or certain preoperative urodynamic parameters.

The exact mechanism by which urethral bulking agents exert their effects on continence has not been defined although an obstructive effect or an improved hermetic effect has been suggested (Dmochowski & Appell, 2000) [135]. Although initially it was thought that urethral bulking agents would be most effective in patients with intrinsic sphincter deficiency (ISD) alone, subsequent reports have suggested clinical efficacy in patients with urethral hypermobility (Herschorn et al., 1996, Steele et al., 2000, Bent et al., 2001) [136,137,138].

The Cochrane review of periurethral injection therapy has been updated since the last edition of this consultation (Keegan et al., 2007) [19] and now includes 12 RCTs including bulking agents in at least one arm; this is five additional trials over the previous review (Pickard et al., 2003) [14], although five do not exist as full peer-reviewed publications and are available only as conference abstracts. One double blind study compared autologous fat with a placebo (Lee et al., 2001) [139]. Two studies compared injection with open surgery; one collagen therapy with bladder neck suspension, sling or Burch colposuspension (Corcos et al., 2005) [140], the other silicon particles with pubovaginal sling (Maher et al., 2005) [141]. Eight studies compared two different bulking agents; two compared GAX collagen with silicon particles (Macroplastique®) (Anders et al., 2002, Appell et al., 2005) [142,143]; two compared GAX collagen with carbon particles (Durasphere®) (Lightner et al., 2001, Andersen, 2002) [142,145] two compared with calcium hydroxyapatite (Coaptite®), coaptite with collagen (Dmochowski et al., 2002a, Appell et al., 2005) [146,143]; one study compared GAX collagen with ethylene vinyl alcohol (Uryx®) (Dmochowski et al., 2002b) [147]; a single study compared porcine dermal implant (Permacol®) with silicon injection (Macroplastique®) (Bano et al., 2005) [148] and one study compared periurethral and transurethral injection techniques (Schulz et al., 2004) [149]. We identified only one further RCT comparing calcium hydroxyapatite with bovine dermal collagen (Mayer et al., 2007) [150] (see table 6).

The Cochrane group felt the available trials were small, generally of only moderate quality, and the limited data available were not suitable for meta-analysis in view of the wide confidence intervals around all estimates.

The study comparing urethral bulking with a saline placebo (Lee et al., 2001) [139] found cure or improvement in 21% in both groups 3 months after the final injection (RR 0.98; 95% CI 0.75 to 1.29), with no significant change from baseline in UI score or in pad weight. One woman died from fat embolism (EL=1).

The two studies comparing urethral bulking with conventional surgery found significantly better objective outcome in the surgical groups, although not in subjective cures or patient satisfaction (Corcos et al., 2005, Maher et al., 2005) [140,141] [EL=2].
<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj) / effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Lee <em>et al.</em>, 2001) [139]</td>
<td>DB-RCT</td>
<td>Autologous fat vs. Placebo (saline)</td>
<td>68/68 (35:33)</td>
<td>3m</td>
<td>22% v.s 21%; p=ns (s)</td>
<td>2</td>
<td>Re-injection up to 3monthly</td>
</tr>
<tr>
<td>2 (Lightner <em>et al.</em>, 2001) [144]</td>
<td>DB-RCT</td>
<td>Carbon coated zirconium beads (Durasphere) vs. Bovine collagen (Contigen)</td>
<td>235/355 (115:120)</td>
<td>9-30m</td>
<td>37% vs. 35%; p=ns (s)</td>
<td>2</td>
<td>33% lost to FU; only completers analysed.</td>
</tr>
<tr>
<td>3 (Andersen, 2002) [145]</td>
<td>RCT</td>
<td>Carbon coated zirconium beads (Durasphere) vs. Bovine collagen (Contigen)</td>
<td>46/52 (25:21)</td>
<td>18-36m</td>
<td>40% vs. 14%; p=ns (s)</td>
<td>2</td>
<td>Both injected transurethrally. No information on randomisation, allocation concealment, or blinding.</td>
</tr>
<tr>
<td>4 (Schulz <em>et al.</em>, 2004) [149]</td>
<td>RCT</td>
<td>Transurethral vs. Periurethral injection of hyaluronic acid/dextran copolymer (Zuidex)</td>
<td>34/40 (17:17)</td>
<td>12m</td>
<td>3/17 (18%) vs. 1/17 (6%); p=ns (s)</td>
<td>2</td>
<td>Re-injection up to 3monthly. 20 pts terminated study early owing to recurrent or persistent UI.</td>
</tr>
<tr>
<td>5 (Bano <em>et al.</em>, 2005) [148]</td>
<td>RCT</td>
<td>Silicone particles (Macroplastique) vs. Porcine dermal collagen (Permacol)</td>
<td>48/50 (25:25)</td>
<td>6m</td>
<td>38% vs. 60%</td>
<td>2</td>
<td>Silicone transurethral; collagen largely periurethral. No details of randomisation; unclear whether ITT analysis used; No statistical analysis reported.</td>
</tr>
<tr>
<td>6 (Maher <em>et al.</em>, 2005) [141]</td>
<td>RCT</td>
<td>Silicone particles (Macroplastique) vs. Sling (rectus fascia)</td>
<td>45/45 (23:22)</td>
<td>6m</td>
<td>9% vs. 81%; p&lt;0.0001</td>
<td>2</td>
<td>Silicone injected transurethrally.</td>
</tr>
<tr>
<td>7 (Corcos <em>et al.</em>, 2005) [140]</td>
<td>RCT</td>
<td>Surgery (left to surgeon’s choice &amp; experience)</td>
<td>133 (66:67)</td>
<td>12m</td>
<td>52% vs. 55%; mean difference: –3.71% (95% CI –20.61, +13.2); p=ns</td>
<td>2</td>
<td>Glutaraldehyde cross-linked (GAX) collagen; up to 3 injns at 1month intervals. 15 withdrew after randomisation; ITT analysis</td>
</tr>
<tr>
<td>8 (Mayer <em>et al.</em>, 2007) [150]</td>
<td>SB-RCT</td>
<td>Calcium hydroxyapatite (Coaptite) vs. Bovine dermal collagen (Contigen)</td>
<td>231/296 (131:100)</td>
<td>12m</td>
<td>83 (63.4%) vs. 57 (57%) improved by 1 Stamey grade; p=0.34 (s)</td>
<td>2</td>
<td>22% lost to FU; unclear assignment numbers; limited outcomes; improvement only, no measure of ‘cure’. Up to 5 injns over 6m.</td>
</tr>
</tbody>
</table>
All results from studies comparing different agents had wide confidence intervals. Silicone particles (Anders et al., 2002, Ghoniem et al., 2005) [142, 151], calcium hydroxyapatite (Dmochowski et al., 2002a, Appell et al., 2005, Mayer et al., 2007) [146, 143, 150], ethylene vinyl alcohol (Dmochowski et al., 2002b) [147], and carbon spheres (Lightner et al., 2001, Andersen, 2002) [144, 145] gave improvements equivalent to collagen [EL=2]. Porcine dermal implant gave improvements comparable to silicone at six months (Bano et al., 2005) [148] [EL=2]. A comparison of periurethral and transurethral methods of delivery of the bulking agent found similar outcome but a higher rate of early complications in the periurethral group (Schulz et al., 2004) [149] [EL=1].

Many published case series exist in the literature describing each of the bulking agents mentioned here: 50 of these are reviewed in the systematic review forming the basis of the NICE guidance (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b). The methodological problems surrounding these are even greater than those of the RCTs described, and they provide little useful additional data to inform practice.

Several periurethral bulking agents have been associated with the formation of periurethral pseudocysts (Abdelwahab & Ghoniem 2007., Hartanto et al 2003., Sweat & Lightner 1999., Petrou et al 2006., Hagemeier et al 2006., Madjar et al 2006) [152, 153, 154, 155, 156, 157]. These collections may result in a variety of symptoms including pain, voiding dysfunction and urinary retention. Definitive treatment consists of transurethral resection, transvaginal needle aspiration or transvaginal resection.

Summary:
The evidence of benefit from urethral bulking agents is limited, and appears to be temporary. The only placebo controlled randomised study found similar symptomatic improvement with both placebo and autologous fat [EL=1]. Greater symptomatic improvement was observed after conventional surgery, although these advantages may need to be seen against likely higher risks [EL=2]. There is no evidence that any one bulking agent has advantage over any other [EL=2]. There are no available data comparing urethral bulking agents with non-surgical treatments or with other minimal access surgical techniques.

Recommendations:
If urethral bulking agents are to be used, women should be made aware that repeat injections are likely to be required to achieve efficacy, that efficacy diminishes with time, and is inferior to that of conventional surgical techniques; they should also be aware of alternative minimally invasive procedures. [Grade B] Newly developed

---

i) ‘Traditional’ sling procedures (Figure 5)
The term ‘traditional’ sling procedures is used here, in line with the terminology used in the latest Cochrane review, (Bezerra et al., 2005) [16] to distinguish open sling procedures more usually placed at the region of the bladder neck, from the newer minimal access mid-urethral tape procedures.

Sling procedures have been in use since the beginning of the twentieth century. Many variations in the technique have been described although it is unclear which of these materially influence the outcome. The majority of sling procedures have involved a combined abdomino-vaginal approach, although totally abdominal procedures are described. Suspended or ‘sling on a string’ methods have been developed in order to reduce the invasiveness of the procedure, and to shorten the length of sling material. As with needle suspension procedures, bone anchoring has been used as an alternative form of sling suspension.

Sling materials vary widely, and whilst perhaps having only limited effect on initial efficacy, may have considerable impact on the longevity of procedures,

Figure 5 : The Aldridge sling employing rectus sheath fascia
or the associated morbidity. Materials may be synthetic or biological; the latter include autograft (rectus fascia, fascia lata, round ligament, dermis, vaginal skin, and gracilis, levator, and rectus muscles), allograft (fascia, dermis and dura mater) and xenograft (porcine dermis and small intestinal mucosa, bovine fascia and pericardium). Both biological and synthetic sling materials are analysed together in the Cochrane review, although these were considered separately in the systematic review underlying the NICE guidance on urinary incontinence (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b). NICE has also published a non-systematic review of biological sling procedures under its Interventional Procedures Programme (National Institute for Health & Clinical Excellence, 2006a).

The Cochrane review included 13 RCTs describing a total of 760 women of whom 627 were treated with sub urethral slings; four of these are available only in abstract form and remain unpublished as full peer-reviewed papers. Five of the trials compared sub urethral slings with open abdominal retropubic suspension (Henriksson & Ulfsten, 1978, Enzelsberger et al., 1996, Sand et al., 2000, Demirci & Yucel, 2001, Fischer et al., 2001) [84,56-58,158], and one compared sub urethral slings with Stamey needle suspension (Hilton, 1989) [96]. In six trials, different types of sub urethral sling were compared with each other (Barbalias et al., 1997, Lucas et al., 2000, Shin et al., 2001, Arunkalaivanan & Barrington, 2003, Kondo et al., 2003, Viseshsindh et al., 2003) [159-164]. Nine different sling materials were included (Teflon, polytetrafluoroethylene, prolene, porcine dermis, lyophilised dura mater, fascia lata, vaginal wall, autologous dermis and rectus fascia). There were no comparisons of sub urethral sling with anterior repair, laparoscopic retropubic suspension, urethral bulking agents or artificial urinary sphincter. One trial compared surgery (including slings) with anticholinergic medication. The systematic review underlying the NICE guidance on urinary incontinence (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b) included three further RCTs comparing pubovaginal sling with TVT ((Lucas et al., 2004, Bai et al., 2005, Wadie et al., 2005) [165,60,166] and open colposuspension (Bai et al., 2005) [60], or other sling procedures (Lucas et al., 2004) [165]. We identified a further publication of longer-term outcomes from one of the included RCTs (Guerrero et al., 2007) [167] and one new study (Tennstedt & Urinary Incontinence Treatment Network, 2005, Albo et al., 2007, Mallett et al., 2008, Richter et al., 2008) [61,46,62,63]. Hence material from 15 RCTs is considered here (see table 7).

In comparison with open colposuspension the objective cure rate from sling operations was not significantly different within the first year (RR 0.19; 95% CI 0.02 to 1.53) or on longer follow-up (RR 0.49; 95%CI 0.17 to 1.42) [EL=1]. Other outcomes were not analysable in the Cochrane review. The most recent, and by far the largest and most rigorous RCT of colposuspension and fascial sling randomised 655 women of whom 520 were assessed at 24 months; this was not included in the Cochrane review. This showed significantly better combined subjective and objective outcome in terms of any incontinence 38% vs. 47% (p=0.01) and SUI 49% vs. 66% (p<0.001) from the sling procedure; adverse events in general (47% vs.63% (p<0.001) and voiding difficulty in particular (14% vs. 2%, p<0.001) were more common in sling group (Albo et al., 2007) [46] [EL=1].

Only one small trial is available to allow comparison between sling (porcine dermis) and needle suspension (Stamey) in a group of women unsuitable for abdominal colposuspension because of vaginal narrowing secondary to either previous interventions or atrophic change (Hilton, 1989) [96]. Although there were no differences in objective cure rates at 3 or 24 months, peri-operative complications (RR 4.50; 95% CI 1.28, 15.81) and length of hospital stay (RR 13.00; 95% CI 5.00, 21.00) favoured the needle suspension procedure [EL=2].

In the Cochrane review, trials comparing rectus fascia with other materials heavily weighted the comparison different types of sling (Bezerra et al., 2005) [16]. Failure rates were similar both in the short (RR 0.96; 95% CI 0.59, 1.55) and long-term (RR 0.69; 95% CI 0.41, 1.16).

1. Synthetic slings

A silicone sling material reinforced with woven polyethylene terephthalate (Dacron®) was described by Stanton and colleagues (Stanton et al., 1985a) [26]. No high level evidence relating to procedures utilising this material was identified; three case series reported outcomes in 124 women (Stanton et al., 1985a, Korda et al., 1989, Duckett & Constantine, 2000) [26,168,169]. The subjective cure rate was 79% at mean follow-up of 15 months in one series, and both subjective and objective cure rates were 83% at 3 months in another. Intra-operative complications were common, including haemorrhage requiring blood transfusion (6%) and vaginal, bladder or urethral perforation (7% each). The need for sling adjustment or removal because of sinus or fistula formation was found in all series, and sling removal was required in 5 out of 7 patients (71%) in one series (Duckett & Constantine, 2000) [169] [EL=3].

Three small controlled trials evaluated a polytetrafluoroethylene (PTFE – Gore-Tex®) sling in comparison to open colposuspension (Sand et al., 2000, Culligan et al., 2003) [57,59], rectus fascial sling (Barbalias et al., 1997) [159], and vaginal wall
Table 7. Published level 1 & 2 evidence relating to traditional sling procedures for the treatment of stress urinary incontinence

Notes: patient numbers are given as – total no. followed up or analysed /total no. recruited (no. in index group: no. in comparator group)

SS = sample size; ITT = intention to treat

<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Henriksson &amp; Ulmsten, 1978) [84]</td>
<td>Quasi-RCT</td>
<td>Sling (Zoedler, vaginal) vs. MMK</td>
<td>30/30 (15:15)</td>
<td>3m</td>
<td>100% vs. 100% (o)</td>
<td>2</td>
<td>Quasi-RCT - by alternation. No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>2 (Hilton, 1989) [96]</td>
<td>RCT</td>
<td>Sling (porcine dermis) vs. Stamey needle suspension</td>
<td>20/20 (10:10)</td>
<td>2y</td>
<td>90% vs. 80% (o - at 3m) 90% vs. 70% (s - at 2y)</td>
<td>2</td>
<td>Included only USI with vaginal narrowing unsuitable for colpo.</td>
</tr>
<tr>
<td>3 (Enzelsberger et al., 1996) [56]</td>
<td>RCT</td>
<td>Sling (dura mater) vs. Colposuspension</td>
<td>72/72 (36:36)</td>
<td>32-48m</td>
<td>92% vs. 86%</td>
<td>2</td>
<td>No ss calculation; analysis not clear if ITT.</td>
</tr>
<tr>
<td>4 (Barbalias et al., 1997) [159]</td>
<td>RCT</td>
<td>Sling (Goretex) vs. Sling (rectus fascia)</td>
<td>48/48 (16:32)</td>
<td>6m &amp; 30m</td>
<td>88% vs. 81% (s – at 6m) 88% vs. 65% (s – at 12m)</td>
<td>2</td>
<td>No baseline data reported per treatment group, no analysis of results.</td>
</tr>
<tr>
<td>5 (Lucas et al., 2000) [160]</td>
<td>RCT</td>
<td>Sling (rectus fascia) – standard (20cm long) vs. Sling-on-a-string (9–10cm long)</td>
<td>165/168 (81:84)</td>
<td>12m &amp; 25-60m (mean 42m)</td>
<td>84 vs. 84%; p=ns (s – at 12m) 40%-53% vs. 36%-51% on sensitivity analysis; p=ns (s at mean 42m)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6 (Sand et al., 2000) [57]</td>
<td>RCT</td>
<td>Sling (Gore-tex) vs. colposuspension</td>
<td>28,36/37 (17:19)</td>
<td>3m/33-116m</td>
<td>100% vs.90%; p=ns (o - 3m) 100% vs. 85%; p=ns (o - longer-term)</td>
<td>2</td>
<td>Only 28 in longer-term FU; concurrent procedures in 21% vs. 12%</td>
</tr>
<tr>
<td>7 (Choe et al., 2000) [170]</td>
<td>Quasi-RCT</td>
<td>Sling (PTFE - MycroMesh) vs. Sling (vaginal wall)</td>
<td>40/40 (20:20)</td>
<td>12-27m</td>
<td>95% vs 75% (s+o – at mean 22m)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8 (Demirci &amp; Yucel, 2001) [58]</td>
<td>Quasi-RCT</td>
<td>Sling (rectus fascia) vs. colposuspension</td>
<td>34/48 (17:17)</td>
<td>1y</td>
<td>94% vs. 88%; RR 2.00; 95% CI 0.20, 20.04 (o)</td>
<td>2</td>
<td>Quasi-RCT - by alternation. No ss calculation; analysis not clear if ITT.</td>
</tr>
</tbody>
</table>
### Table 7. Published level 1 & 2 evidence relating to traditional sling procedures for the treatment of stress urinary incontinence

**Notes:** patient numbers are given as – total no. followed up or analysed /total no. recruited (no. in index group: no. in comparator group) (Continued)

**SS = sample size; ITT = intention to treat**

<table>
<thead>
<tr>
<th>Study references</th>
<th>Type</th>
<th>Comparator</th>
<th>N/N (n1:n2)</th>
<th>FU</th>
<th>Cure (obj or subj)/ effect size</th>
<th>EL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Viseshsindh et al., 2003)</td>
<td>RCT</td>
<td>Sling (rectus fascia) vs. Sling (vaginal wall)</td>
<td>26/26 (15:11)</td>
<td>3-12m</td>
<td>93% vs. 100%; p=ns</td>
<td>2</td>
<td>lack of details re randomisation, analysis of results.</td>
</tr>
<tr>
<td>(Arunkalaivanan &amp; Barrington, 2003)</td>
<td>RCT</td>
<td>Sling (porcine dermal collagen – Pelvicol) vs. TVT</td>
<td>128/142 (74:68)</td>
<td>6-24m &amp; median 36m</td>
<td>85% vs. 89% (s – at median 12m)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Abdel-Fattah et al., 2004)</td>
<td>RCT</td>
<td>Sling (porcine dermal collagen – Permacol)</td>
<td>70, 97/139 (33:31:40)</td>
<td>12m</td>
<td>88% vs. 80% vs. 76% (s – 6m) 81% vs. 83% vs. 53% (s – at 12m)</td>
<td>2</td>
<td>260 required from SSC; 139 recruited; FU data available from 97 at 6 months &amp; 70 at 12 months. Permacol arm of trial stopped early because of results of interim analysis.</td>
</tr>
<tr>
<td>(Lucas et al., 2004)</td>
<td>RCT</td>
<td>Sling (rectus fascia sling-on-a-string (8–10cm long) vs. TVT</td>
<td>45/45 (22:23)</td>
<td>6m</td>
<td>81% vs. 9%, p&lt;0.0001</td>
<td>2</td>
<td>Silicone injected transurethrally.</td>
</tr>
<tr>
<td>(Maher et al., 2005)</td>
<td>RCT</td>
<td>Sling (rectus fascia) vs. Silicone particles (Macroplastique)</td>
<td>92/92 (28:31:33)</td>
<td>1y</td>
<td>93% vs. 87% vs. 88%; p&lt;0.05 for sling vs. others</td>
<td>2</td>
<td>Disparities between text and tables. No ss calculation.</td>
</tr>
<tr>
<td>(Bai et al., 2005)</td>
<td>RCT</td>
<td>TVT</td>
<td>53/53 (25:28)</td>
<td>6m</td>
<td>92% vs. 92%; p=ns (o – at 1 week)</td>
<td>2</td>
<td>No SS calculation; appears underpowered; cure determined at first FU visit.</td>
</tr>
<tr>
<td>(Wadie et al., 2005)</td>
<td>RCT</td>
<td>Sling (rectus fascia) vs. TVT</td>
<td>520/655 (326:329)</td>
<td>2y</td>
<td>66% vs. 49% (p&lt;0.001) (s+o)</td>
<td>1</td>
<td>50% concomitant surgery for POP; 79% outcome assessment at 2 years.</td>
</tr>
</tbody>
</table>
sling (Choe et al., 2000) [170] (total n = 124). In a RCT against open colposuspension, although the groups were different at baseline in terms of the proportion with detrusor overactivity (DO), cure rates with PTFE were not significantly different from open colposuspension at 2.5 years (objective 100% vs. 85%; subjective 84% vs. 93%) (n = 36) (Sand et al., 2000, Culligan et al., 2003) [57, 59] [EL=2]. In a RCT against fascial sling the combined objective and subjective cure rates were 88% and 81%, respectively, at 6 months (Barbalias et al., 1997) [159]. A quasi-randomised comparison with vaginal wall sling gave no statistical analysis, but found combined subjective and objective cure in 95% vs. 75% at mean follow-up of 22 months (Choe et al., 2000) [170] [EL=2]. Again, the need for sling removal is common, reported in up to 31% (median 8%) in a review of case series within the systematic review underlying the NICE guidance on UI (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b) [EL=3].

Only low level evidence is available to evaluate slings made of polyester (Mersilene®). Four case series evaluated a Mersilene® sling with follow-up from a mean of 2 years to 5 years (Kersey, 1983, Kersey et al., 1988, Guner et al., 1994, Young et al., 2001) [171-174]. Subjective cure rates across the studies ranged from 50% to 96% (median 84%). The objective cure rate in 52 women followed-up at 5 years in one study was 94%, compared to 95% at 1 year (although this only represented a quarter of the women treated) (Young et al., 2001) [174] [EL=3].

2. BIOLOGICAL SLINGS

Nearly all RCTs of biological slings compare the autologous rectus fascial sling procedure with a range of other surgical interventions. RCTs evaluating dura mater and porcine dermal slings were also identified.

i) Rectus fascial sling

One RCT compared autologous rectus fascial sling with periurethral silicone injection in women with stress UI secondary to ISD in whom conservative treatment had failed. At 6 months, no significant differences were seen between groups in subjective cure or satisfaction, QOL (UDI-6, IIQ). Significantly more women undergoing sling surgery were objectively cured on the basis of urodynamic assessment (81% vs. 9%; p=0.0001), but duration of the procedure, catheterisation, inpatient stay, and time to return to normal activities were significantly longer. A survey of two-thirds of the women at 5 years found no statistically significant differences between groups in urinary symptoms or in satisfaction with surgery (n = 45),557 [EL=2].

Open continence surgery (a suspension procedure in 46% and fascial sling in 54%) was compared with periurethral collagen in women with stress or mixed UI in a further RCT. Again there were no significant differences in patient satisfaction or QOL (SF-36, IIQ) between groups at 1 year. Using intention-to-treat analysis there was no significant difference in continence rates at 1 year (52% collagen, 55% surgery); if only the 89% of women who underwent the randomised intervention were considered, the continence rate with surgery was significantly higher (72% vs. 53%; p=0.01). The incidence of adverse effects was significantly higher in the surgery group: urinary retention 13% versus 2%, transient voiding difficulty 36% versus 17%, UTI 6% versus 0% (n = 133) (Corcos et al., 2005) [140] [EL=2].

Three RCTs have compared autologous rectus fascial sling with TVT involving a total of 284 patients (Bai et al., 2002, Lucas et al., 2004, Wadie et al., 2005) [175,165,166]. Cure rates at 12 months (symptom-free +/- negative stress test in the different studies) were 83%, 87%, and 88% following TVT and 81%, 82% and 93% following rectus fascial sling; one of these trials also had a colposuspension arm, which had a 12 month cure rate of 88% (Bai et al., 2002) '175', and one a porcine dermis sling arm with a cure rate of only 53% (Lucas et al., 2004) [165] [EL=1/2]. One quasi RCT compared autologous rectus fascial sling with a self-fashioned polypropylene sling in 50 women, with similar findings (Kuo, 2001) [176] [EL=2].

One RCT compared rectus fascial and PTFE slings in women with stress UI, 92% of whom had had prior continence surgery. Combined objective and subjective cure rates were 81% and 88%, respectively, at 6 months. No complications were reported in the fascial sling group, whereas urethral erosion, recurrent UTI and de novo DO were very common with PTFE (n = 48) (Barbalias et al., 1997) [159] [EL = 1].

Rectus fascial and vaginal wall slings were compared in one RCT and two non-randomised retrospective studies (Kaplan et al., 1996, Visesshindhu et al., 2003, Rodrigues et al., 2004) [177,164,178]. All were considered to be of poor quality. The RCT reported high subjective cure, and satisfaction rates (80–100%), with median follow-up of 7 months (n = 26). (Viseshshindhu et al., 2003) [164] [EL=2]. The non-randomised studies reported similar ‘success’ rates with both interventions, ranging from 80% to 97%, with follow-up of 21 months, and 70 months versus 45 months (n = 232, n = 79) [EL=2].

One RCT compared two techniques of fascial sling in 168 women with urodynamic stress UI 89% of whom had had prior continence surgery. Women underwent a standard fascial sling procedure or a ‘sling on a string’ (a shorter sling mounted on each end with a nylon thread). At 1 year, subjective cure rates were 84% using both techniques. Satisfaction and changes in IIQ scores were also similar in both groups, whereas improvements in UDI scores were greater with the standard approach (adjusted for differences in baseline
et al. (Lucas et al., 2000) [160]. A further follow-up of women in this study was recently reported at 5 to 7 years (Guerrero et al., 2007) [167]. There were no significant differences in symptoms of SUI or UUI between groups, with 40%-53% vs. 36%-51% reporting SUI in sensitivity analysis [EL=1].

Case series of autologous rectus fascial sling were reviewed within the systematic review underlying the NICE guidance on urinary incontinence (National Collaborating Centre for Women’s & Children’s Health, 2006, National Institute for Health & Clinical Excellence, 2006b). Ten series including a total of 1280 women were considered. Studies had a mean or median duration of follow-up between 2 and 6 years; in three studies, maximum follow-up of 15–18 years was reported. Subjective cure rates ranged from 26% to 97% (median 81%); and cure that included subjective and objective elements 73% to 95%. Satisfaction rates of 86% and 92% were reported in two studies.

**ii) Dura mater sling**

One RCT compared dura mater sling with open colposuspension in 72 women with SUI after hysterectomy. The combined objective and subjective cure rates were 92% versus 86%, at about 3 years. Significantly more women in the sling group had voiding difficulty or retention postoperatively, both of which were common, and more women developed rectocele in the colposuspension group. Bladder perforation and de novo urgency were common in both groups. Time to spontaneous voiding was significantly longer in the sling group (n = 72) (Enzelsberger et al., 1996) [56] [EL=1].

**iii) Porcine dermis sling**

One small RCT compared a porcine dermis sub urethral sling with the Stamey needle suspension procedure in 20 women with stress UI who were considered unsuitable for colposuspension. At 2 years, subjective cure rates were 90% versus 70%. Intraoperative blood loss and postoperative infection were significantly more common in the sling group. Other common complications in both groups were bladder injury and de novo DO (n = 20) (Hilton, 1989) [96] [EL=2].

One RCT comparing porcine dermis sling (Permacol®) with TVT™ found no significant differences operating time, hospital stay, complication rates, or subjective cure at 1 year (85% vs. 89%) (Arunkalaivanan & Barrington, 2003) [162] nor in cure (88% vs. 82%) or satisfaction at 3 years, assessed by mailed questionnaire (77% vs. 80%) (Abdel-Fattah et al., 2004) [179] [EL=1]. One can only speculate why this study found comparable results between Permacol® and TVT™, whereas the 3-arm trial cited above found such significantly poorer results from Permacol® to require the premature curtailment of recruitment (Lucas et al., 2004) [165].

**iv) Autograft vs. allograft vs. xenograft**

Seven non-randomised studies compared the outcomes of autologous and allograft slings in a total of 786 women with SUI; one also compared both interventions with a xenograft material (porcine dermis). All were retrospective reviews, each with differences in duration of follow-up for the interventions evaluated (between 3 months and 3 years), with drop-out rates of 4% to 34%; between 16% and 82% in different studies underwent other concomitant surgeries; all were considered to be of poor quality (Wright et al., 1998, Brown & Govier, 2000, Soergel et al., 2001, Flynn & Yap, 2002, O’Reilly & Govier, 2002, Almeida et al., 2004, McBride et al., 2005, Simsiman et al., 2005) [180-187] [EL=2].

Four of these studies compared autologous with allograft (cadaveric) fascia lata. Three of these studies reported similar results for all outcomes (subjective cure, satisfaction, and UDI-6, IIQ-7 and SEAPI scores) (Wright et al., 1998, Brown & Govier, 2000, McBride et al., 2005) [180,181,186]; the fourth study reported significantly higher cure rates in the autologous group (Almeida et al., 2004) [185] [EL=2].

In three studies that compared autologous rectus fascia or fascia lata with allograft fascia lata, two found a significantly higher cure rate in the autologous group(Soergel et al., 2001, Simsiman et al., 2005) [182,187]; the other found no significant differences in cure rate, although satisfaction rates were higher in the autologous group after 2 years follow-up(Flynn & Yap, 2002) [183]. In the study with a xenograft arm, cure rates were significantly higher with autograft material (Simsiman et al., 2005) [187] [EL=2].

**Summary:**

The conclusion of the Cochrane review was that data on sub-urethral sling operations remain too few to adequately address the effects of this type of surgical treatment. They highlight the fact that many studies fail to address appropriate outcome measures to address the broader effects of the surgery, such as general health status and health economics. They also emphasise that reliable evidence on which to judge whether or not sub-urethral slings are better or worse than other surgical or conservative management is currently not available.

Autologous rectus fascial sling is the most widely evaluated biological sling, which is an effective treatment for SUI and has longevity [EL=1]. Limited data suggest that pubovaginal sling using porcine dermis is also effective [EL=1], although data relating to other biological slings are few, and generally of poor quality. There is limited evidence that rectus fascial sling may be as effective as or more effective than open colposuspension, although adverse events and voiding difficulty in particular may be more common [EL=1]. There is no high level evidence of a
difference in efficacy between biological and synthetic sling materials, although adverse events may be more common following the use of synthetic materials for 'traditional' sling procedures [EL=3]. There is no high level evidence of a difference in efficacy between different biological sling materials, although those studies that find a difference all favour autologous materials [EL=2].

**Recommendations:**

Autologous fascial sling is recommended as an effective treatment for stress urinary incontinence, which has longevity. [Grade A]

Further high quality research is required to clarify the place of 'traditional' sling procedures in relation to other procedures, and to establish the optimum sling materials. [Grade D]

### 2. MID-URETHRAL TAPES

The Tension-free Vaginal Tape (TVT) procedure for treatment of female urinary stress incontinence was first introduced by Ulmsten et al. in 1996. The development of the TVT operation was an attempt to support the middle portion of the urethra instead of restoring anatomy and correct urethral hypermobility at the bladder neck.

The idea of supporting the "mid-urethra" derived from discoveries of several research projects conducted during the last thirty years. Zaccharin already in 1968 [581] and DeLancey in 1994 [582] showed that the pubourethral ligaments inserted at the mid-urethra and that the urogenital diaphragm also was more close to the middle portion of the urethra than the bladder neck.

Owman et al. 1978 found that the most densely innervated portion of the urethra was the middle part and Huisman in 1983 [583] in histological studies showed that the mid-urethra had the most abundant vascularisation.

When Westby et al. 1982 [584] in radiographic studies showed how the urine stream was interrupted at the mid-urethra on holding in continent women and Asmussen et al. 1983 [585] showed that the maximal urethral closure pressure was situated at the mid-urethra it became apparent that focus on the mid urethra might bring improvement in the performance of incontinence surgery.

Prospective observational cohort studies revealed that placing a macroporous, monofilament polypropylene tape at the mid urethra resulted in cure rates between 80-90 % in primary cases of stress incontinence (Ulmsten et al 1996, Ulmsten et al 1998, Nilsson 1998, Ulmsten et al 1999, Nilsson et al 2001) [188-192], in recurrent cases (Rezapour and Ulmsten 2001, Kuuva and Nilsson 2003) [193, 194], in mixed incontinence cases (Rezapour and Ulmsten 2001) [607] and in an unselected group of women including primary, recurrent and mixed incontinence as well as women with intrinsic sphincter deficiency (Nilsson and Kuuva 2001) [195]

a) RCT:s comparing TVT with traditional incontinence operations (Figure 6)

Only around 12 randomized clinical trials comparing TVT with traditional incontinence procedures have been published in peer reviewed journals. Five of these compare TVT with open colosuspension (Ward et al. 2002, Liapis et al. 2002, Wang et al 2003, Bai et al. 2005, El-Barky et al. 2005) [65,64,66,60,68], four compare TVT with laparoscopic colposuspension (Persson et al. 2000, Ustun et al. 2003, Parasol et al. 2004, Valpas et al. 2004) [119,120,122,123], two compare TVT with a fascial sling (Bai et al. 2005,Wadie et al. 2005) [60,166] and one compares TVT with no treatment (Campeau et al. 2007) [196]. These articles are listed in Table 1. A limitation to the conclusions that can be drawn from the results obtained in these studies is the fact that most of the trials include only 23 -50 patients in each arm with no mention of power calculations. The trials by Ward et al. 2002, 2004, 2008 [65,67,64] and Valpas et al. 2004 [123] enrolled a greater number of patients and included power calculations, but neither reached the required number of patients.

*Figure 6: The tension free vaginal tape (TVT)*
b) TVT vs Colposuspension

Four of the studies comparing TVT with open colposuspension used objective outcome measures for defining cure: 1 hour pad test (Ward et al. 2002, 2004, 2008, Liapis et al. 2002, Wang et al. 2003) [65,67,45,64,66], cystometry (Ward et al. 2002) [65] and a stress test (Ward et al. 2002, 2004, Bai et al. 2005) [65,67,60]. The study by El-Barky et al 2005 [68] only used subjective outcome measures. None of these studies found any statistical differences in objective cure rates between the two operations. The cure rate varied between 63 and 87 % in the TVT groups and between 51 and 90 % in the open colposuspension groups. The time period of follow-up was between 3 and 24 months in all five trials except the 5 years extension of the Ward et al. 2008 study. This five years report is, however, hampered by a 58 % lost to follow-up in the TVT group and a 67 % lost to follow-up in the colposuspension group. Subjective cure was mostly poorly defined and validated quality of life questionnaires was only used in the Ward et al. 2002 [65] study finding no difference in subjective cure between the TVT and the colposuspension groups.

Operation time, hospital stay and time for resuming normal activity was significantly shorter in the TVT groups (Ward et al. 2002, Liapis et al. 2002, El Barky et al. 2005) [65,64,68]. The percentage of intra-operative bladder perforations was significantly greater in the TVT group in than the colposuspension group, 9 % and 3 % respectively, in the Ward et al. 2002 study while El Barky et al. 2005 reported no perforations in the colposuspension group and two in the TVT group (< 0.05). Wound infections were more common in the colposuspension group (<0.05).

Significantly more patients experienced delayed voiding in the colposuspension group in the Ward et al. 2002 [65] study and in the 2 years follow-up report of the same study there were significantly more patients in the colposuspension group needing intermittent self catheterization (<0.0045) and surgery for pelvic organ prolapse (<0.0042) than in the TVT group.

c) TVT vs Fascial sling

The study by Bai et al. 2005 [60] actually compared TVT with both open colposuspension and a fascial sling and found that at 3 and 6 months follow up there was no difference in cure rate between the operations, but at 12 months the fascial sling operation had a significantly higher cure rate of 92.8% than the colposuspension and TVT operations, 87.8% and 87.0% respectively. No difference in cure rates was found between the TVT and the fascial sling operations in the study by Wadie et al.2005 [166]. In an interesting study by Campeau et al. 2007 [196] elderly women over the age of 70 years were randomized either to immediately receive TVT surgery or had to wait for 6 months for surgery. Follow-up at 6 months by different quality of life questionnaires revealed highly significantly (<0.0001) higher quality of life in the operated women, even though 22.6% experienced bladder perforation and 12.9% urinary retention as a result of the surgery.

d) TVT vs laparoscopic colposuspension

Laparoscopically performed colposuspension has been compared with the TVT operation in four randomized trials (Persson et al. 2000, Ustun et al. 2003, Paraiso et al. 2004, Valpas et al. 2004) [119,120,122,123] and with modified mid-urethra tape procedures as the transobturator route of tape placement (TOT) and tape placement retropubically by an abdominal approach (SPARC) in two trials: TOT by Sivaslioglu et al. 2007 and SPARC by Foote et al. 2006197.

In the studies comparing TVT, TOT or SPARC with laparoscopic colposuspension objective cure was assessed by a pad test in 2 of the six studies (Persson et al. 2000, Valpas et al. 2004) [119,123], by a stress test in four of the studies (Ustun et al. 2003, Paraiso et al. 2004, Valpas et al. 2004, Sivaslioglu et al. 2007) [120,122,123,47] while the criteria for cure or improvement was rather unclear in the study by Foote et al. 2006 [197]. The trial by Valpas et al. 2004 [123] with the greatest number of patients enrolled showed a significantly higher objective and subjective cure rate in the TVT group than in the laparoscopic colposuspension group (<0.0001), while the other studies showed similar cure rates for both procedures ranging between 72.9% and 96.8% in the TVT groups and between 58.8% and 87% in the laparoscopic colposuspension groups.

Although laparoscopically performed colposuspension is regarded as a less invasive operation than the open colposuspension the mid-urethra tape procedures had significantly shorter operating time (<0.001), hospital stay (<0.001) and time for resuming normal activity (<0.01 -0.001) than the laparoscopic colposuspension.

e) Metanalyses of TVT vs other procedures

Novara et al. 2007 [586] published a meta-analysis of randomized controlled trials comparing Tension-free mid-urethral slings with other surgical procedures for treatment of stress incontinence. They concluded by meta-analysis that the TVT procedure outperformed the Burch colposuspension and that the efficacy of the TVT was similar to pubo-vaginal slings. A review by Dean et al. 2006 [18] including seven randomized trials comparing laparoscopic colposuspension with TVT found an overall objective cure rate within 18 months of follow-up to be significantly higher in the TVT group.
f) RCTs comparing TVT with modifications of the retropubic tape placement

The favorable results obtained with the TVT operation have resulted in several modifications of the procedure and the use of different tape materials. These retropubic modifications have been poorly clinically evaluated and only seven randomized studies comparing these with the TVT have been published. Three trials compare the TVT with the Supra Pubic Arc Sling (SPARC) which utilizes a polypropylene tape material, but differs from the TVT by approaching the mid-urethra from an abdominal incision (Tseng et al 2004, Adonian et al. 2005, Lord et al. 2006). [198,199,200] The study by Lord et al. including 147 TVT and 160 SPARC cases showed a significantly higher subjective cure rate in the TVT group. They also found that the SPARC procedure was significantly more often associated with tape erosion and was more difficult to adjust with the need of tape loosening in the operating theater than the TVT procedure (<0.002). Tseng et al.[198] reported a 12.9 % of bladder perforation in the SPARC group with none in the TVT group. The difference was not statistically significant in this small study with only 31 patients in each group, but the authors stated it to be clinically significant.

One study compares TVT with an allogenic graft material made from acellular porcine collagen, the Pelvicol. Arunkalaivanan et al.[162] report on the results in two articles, the 12 months results in 2002 and the 36 months results in 2004. Outcome was assessed in both reports by a postal questionnaire and found no difference in subjective cure rate between the groups of 68 TVT operations and 74 Pelvicol operations.

Three trials compare TVT with the Intra Vaginal Sling (IVS) procedure, which utilizes a multifilament, miniporous polypropylene tape material (Rechberger et al. 2003, Lim et al. 2005, Meschia et al. 2006) [201-203]. In the study by Meschia et al. including 95 patients in each group the objective cure rate was 85% for the TVT and 72% for the IVS and the subjective cure rate was 87% and 78% respectively, with no difference between groups. There was a 9% erosion rate during the 2 years of follow-up in the IVS group, with none in the TVT group. Rechberger et al found no difference between the groups in their 13 months follow-up of 50 patients per group. Lim et al. [77] compared TVT with both IVS and SPARC, with 65 patients in each group. The subjective cure rates between 6 and 12 months of follow-up were 87.9% in the TVT group, 81.5% in the IVS group and 72.4% in the SPARC group, the differences not being significant. They found a significantly greater rate of tape protrusion in the SPARC group compared to both TVT and IVS (<0.04). Most concerning is the report by Balakrishnan et al. 2007 [587] in which they followed the subgroup of IVS patients of the Lim et al [202]. study for up to 30 months and found that 13% had sling erosions requiring sling removal and that of the 29 patients (47%) of the initial IVS group who were seen 12 to 34 months post-operatively 24% experienced sling erosion with sinus formation and requiring sling removal.

The meta-analysis by Novara et al. 2007 [586] concludes that the TVT is more effective than both the IVS and the Sparc.

g) RCT:s comparing TVT with transobturator tape placement (Figure 7)

The retropubic placement of the mid-urethra tapes has been associated with the risk of bladder injury, the rates varying between 0.8% and 21 % in different reports (Wang 2004, Andonian et al. 2005) [204,199]. Two systematic registries on the rates of complications associated with the TVT operation have been published, one from Finland including the first 1455 operations performed nation-wide and one from Austria including 2795 operations (Kuuva and Nilsson 2002, Tamussino et al. 2001) [205,206].

The rates of bladder perforation were 3.8% and 2.7% respectively. To avoid bladder injuries Delorme in 2001 [588] introduced a modified tape procedure in which the tape was brought to support the mid-urethra from inside the thighs through the obturator foramen on both sides, the so called outside-in transobturator tape procedure (TOT). De Leval in 2003 [589] further modified the procedure to be an inside-out procedure called the Tension-free Vaginal Tape-Obturator (TVT-O).

The original retropubic TVT has been compared with the inside-out TVT-O in six randomized trials (Zullo et al. 2007, Meschia et al.2006, Liapis et al. 2006, et al. Laurikainen et al 2007, Araco et al. 2008, Rinne et al. 2008) [207,203,208,209,210], and with the outside-in TOT in two trials (Andonian et al. 2007, Porena et al. 2007) [212,213] Wang et al. 2006 [590] compared the TOT with SPARC and found no difference in cure rate or rates of complications between the group of 31 TOT patients and 29 SPARC patients.
Five of the studies comparing TVT with TVT-O included power calculations either for detection of differences in cure rates and complication rates (Meschia et al. 2006, Laurikainen et al. 2007, Rinne et al. 2008) [203,209,211], or only for detection of differences in complications (Zullo et al. 2007) [207]. The study by Liapis et al [208] reported no power calculations. No differences in the overall objective or subjective cure rates were seen between the TVT and the TVT-O procedures during follow-up periods of 6 to 12 months. The only statistically significant difference in objective cure rate was seen in the Araco et al. [210] report where a stratification between mild and severe stress incontinence had been made. They found a significantly higher cure rate in the TVT patients with severe stress incontinence than in the TVT-O patients with the same condition: 100% versus 66% cure respectively (<0.001).

Somewhat contradictory results concerning complications arise from the trials. The reports by Meschia et al.[203] and Laurikainen et al., [209] including 3-4 times more patients than the reports by Zullo et al. [207] and Liapis et al. [208] show either no differences in the overall number of complications or a significantly higher rate of overall complications in the TVT-O group (Laurikainen et al.). It is not clear from the Zullo et al. study, which showed a higher complication rate for the TVT, how the overall complication rate was calculated.

The two trials comparing TVT with TOT (Porena et al. 2007, Andonian et al.2007) [213,212] found no difference in cure rates between the procedures. There were no differences in complication rates between the procedures in the Porena et al. report, while Andonian et al. reported significantly greater rates of complications in the TOT than in the TVT group.

Two trials have compared the inside-out procedure (TVT-O) with the outside-in procedure (TOT). But and Faganelj 2007 [591] included 60 patients in each group and found no difference in subjective cure rate between the procedures at 4 months follow-up, 90.7% for the TVT-O and 88.7% for the TOT respectively. Lee et al. 2008 [592] concludes that in their underpowered study no differences in objective or subjective cure rate was seen and no differences in complication rates.

h) Metanalyses
The meta-analysis by Novara et al 2007 [586] found overlapping cure rates with the retropubic and transobturator procedures. A meta-analysis by Latthe et al. 2007 [593] also arrived at equal cure rates for both the retropubic and transobturator route of mid-urethra tape placement the follow-up period though being only 2-12 months. There seems to be no difference in complications between the TVT procedure and the transobturator procedures.

CONCLUSION
There is evidence that the retropubic TVT is more effective than the Burch colposuspension and equally effective as traditional fascial sling operations (Level 1/2).

Operation time, hospital stay and time to resume normal daily activity is shorter with the TVT than with colposuspension. Post-operative voiding problems and need for urogenital prolapse surgery are more commonly associated with colposuspension, while bladder perforation is more commonly associated with TVT (Level 1/2).

TVT is more effective than the IVS and the SPARC procedure (Level 1/2).

Retropubic and transobturator placement of monofilament tapes at the mid-urethra perform equally at a short term follow-up of 6 to 12 months and overall complication rates are comparable (Level 1/2) (Table 7 a).

II. CONFOUNDING VARIABLES

1. AGE
Although there is extensive historical reporting of efficacy and low morbidity associated with various sling technologies, the affect of age on outcomes is relatively undefined. The affect of aging on the lower urinary tract includes a higher rate of detrusor overactivity, as well as, urge incontinence and intrinsic sphincteric deficiency. In addition, older patients are more likely to have had prior interventions, and may, therefore, may have a higher rate of peri-urethral fibrosis and/or other abnormalities in the area tissues surrounding the lower urinary tract. The presence of multiple co-morbidities may also affect overall surgical outcome, including creating the possibility for increased complication and prolonged post-operative course. Variable rates of success have been reported by numerous authors [214,215,216].

When evaluating mid-urethral slings in older women, the definition of age is controversial. The most extensive study of older patients is that of Gordon [217], who evaluated 460 consecutive women undergoing transvaginal tape (TVT). By characterization of age (greater than 70 years), 157 (34%) were considered to be elderly. These patients underwent pre-operative and three-month post-operative urodynamic outcomes, as well as symptom appraisal. All patients were followed for at least twelve months, with a mean follow-up of 26 months. In the older age population, there was a greater prevalence of mixed incontinence (31%), when compared to the younger patients (23%). In addition, concomitant pelvic organ prolapse surgery was undertaken in a greater percentage of the older patients (84%), when
Table 7a. Studies comparing TVT with modifications of retro-pubic and obturator procedures

<table>
<thead>
<tr>
<th>Reference</th>
<th>Years</th>
<th>Type of operation</th>
<th>No of Pts</th>
<th>Duration of follow-up</th>
<th>Power calculation</th>
<th>Lost to f-u</th>
<th>cure rate</th>
<th>cure rate</th>
<th>Significans</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward et al 2002</td>
<td>2002</td>
<td>TVT vs OC</td>
<td>175/169</td>
<td>6 mos</td>
<td>yes, nr</td>
<td>66/57</td>
<td>na</td>
<td>na</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ward et al 2004</td>
<td>2004</td>
<td>TVT vs OC</td>
<td>175/169</td>
<td>2 yrs</td>
<td>yes, nr</td>
<td>63/51</td>
<td>na</td>
<td>na</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ward et al 2008</td>
<td>2008</td>
<td>TVT vs OC</td>
<td>175/169</td>
<td>5yrs</td>
<td>yes, nr</td>
<td>81/90</td>
<td>91/90</td>
<td>na</td>
<td>2-jan</td>
<td>2</td>
</tr>
<tr>
<td>Liapis et al 2002</td>
<td>2002</td>
<td>TVT vs OC</td>
<td>36/35</td>
<td>2yrs</td>
<td>no</td>
<td>84/86</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Wang et al 2003</td>
<td>2003</td>
<td>TVT vs OC</td>
<td>49/49</td>
<td>22 mos</td>
<td>no</td>
<td>92/93</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bai et al 2005</td>
<td>2005</td>
<td>TVT vs OC</td>
<td>31/33</td>
<td>12 mos</td>
<td>0/0</td>
<td>87/87.4</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>El-Barky et al 2005</td>
<td>2005</td>
<td>TVT vs OC</td>
<td>25/25</td>
<td>3-6 mos</td>
<td>no</td>
<td>72/72</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Persson et al 2002</td>
<td>2002</td>
<td>TVT vs LBC</td>
<td>38/32</td>
<td>12 mos</td>
<td>yes, nr</td>
<td>89/87</td>
<td>57/52</td>
<td>na</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ustun et al 2003</td>
<td>2003</td>
<td>TVT vs LBC</td>
<td>23/23</td>
<td>3 mos</td>
<td>no</td>
<td>82.6/82.6</td>
<td>82.6/82.6</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Paraiso et al 2004</td>
<td>2004</td>
<td>TVT vs LBC</td>
<td>36/36</td>
<td>12 mos</td>
<td>no</td>
<td>86/86</td>
<td>na</td>
<td>0.05</td>
<td>1</td>
<td>favors TVT</td>
</tr>
<tr>
<td>Valpas et al 2004</td>
<td>2004</td>
<td>TVT vs LBC</td>
<td>70/51</td>
<td>12 mos</td>
<td>yes, nr</td>
<td>85.7/56.9</td>
<td>82.5/58</td>
<td>0.001</td>
<td>1</td>
<td>favors TVT</td>
</tr>
<tr>
<td>Bai et al 2005</td>
<td>2005</td>
<td>TVT vs sling</td>
<td>31/28</td>
<td>12 mos</td>
<td>0/0</td>
<td>87/92.8</td>
<td>0.05</td>
<td>2</td>
<td>favors sling</td>
<td>2</td>
</tr>
<tr>
<td>Wadie et al 2005</td>
<td>2005</td>
<td>TVT vs sling</td>
<td>28/25</td>
<td>1 week</td>
<td>no</td>
<td>93/92</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Campeau et al 2007</td>
<td>2007</td>
<td>TVT vs no treatment</td>
<td>31/27</td>
<td>6 mos</td>
<td>yes, nr</td>
<td>77.4/81.4</td>
<td>na</td>
<td>no</td>
<td>0.0001</td>
<td>1 favors TVT</td>
</tr>
<tr>
<td>Foote et al 2006</td>
<td>2006</td>
<td>SPARC vs LBC</td>
<td>49/48</td>
<td>27 mos</td>
<td>yes, nr</td>
<td>87.1/83.8</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sivaslioglu et al 2007</td>
<td>2007</td>
<td>TOT vs SPARC</td>
<td>49/51</td>
<td>2 yrs</td>
<td>no</td>
<td>87.5/87</td>
<td>87.5/83.8</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adonian et al 2004</td>
<td>2005</td>
<td>TVT vs SPARC</td>
<td>43/41</td>
<td>12 mos</td>
<td>no</td>
<td>95/83</td>
<td>na</td>
<td>no</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lord et al 2006</td>
<td>2006</td>
<td>TVT vs SPARC</td>
<td>147/154</td>
<td>6 weeks</td>
<td>yes</td>
<td>87.1/76.5</td>
<td>na</td>
<td>no</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arunkalaivanan et al 2003</td>
<td>2003</td>
<td>TVT vs Pelvicol</td>
<td>68/74</td>
<td>12 mos</td>
<td>no</td>
<td>74/76</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abdel-Fattah et al 2004</td>
<td>2004</td>
<td>TVT vs Pelvicol</td>
<td>68/74</td>
<td>36 mos</td>
<td>no</td>
<td>88.3/82.4</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rechberger et al</td>
<td>2003</td>
<td>TVT vs IVS</td>
<td>50/50</td>
<td>4-18 mos</td>
<td>no</td>
<td>88/80</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lim et al 2005</td>
<td>2005</td>
<td>TVT vs IVS</td>
<td>65/65</td>
<td>6-12 weeks</td>
<td>no</td>
<td>82.8/83.9</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mescia et al 2006</td>
<td>2006</td>
<td>TVT vs IVS</td>
<td>95/95</td>
<td>24 mos</td>
<td>yes</td>
<td>87/78</td>
<td>na</td>
<td>no</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zullo et al 2006</td>
<td>2007</td>
<td>TVT vs TVT-O</td>
<td>35/37</td>
<td>12 mos</td>
<td>yes</td>
<td>91/89</td>
<td>na</td>
<td>na</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mescia et al 2006</td>
<td>2006</td>
<td>TVT vs TVT-O</td>
<td>114/117</td>
<td>6 mos</td>
<td>yes</td>
<td>92/92</td>
<td>na</td>
<td>na</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Liapis et al 2006</td>
<td>2006</td>
<td>TVT vs TVT-O</td>
<td>46/43</td>
<td>12 mos</td>
<td>0/0</td>
<td>89/90</td>
<td>73.9/76.7</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Laurikainen et al 2007</td>
<td>2007</td>
<td>TVT vs TVT-O</td>
<td>136/131</td>
<td>2 mos</td>
<td>yes</td>
<td>98.5/95.4</td>
<td>na</td>
<td>no</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Araco et al 2008</td>
<td>2008</td>
<td>TVT vs TVT-O</td>
<td>120/120</td>
<td>12 mos</td>
<td>yes, nr</td>
<td>100/66</td>
<td>na</td>
<td>0.001</td>
<td>1 favors TVT</td>
<td>2</td>
</tr>
<tr>
<td>Rinne et al 2008</td>
<td>2008</td>
<td>TVT vs TVT-O</td>
<td>136/131</td>
<td>12 mos</td>
<td>yes</td>
<td>90/93</td>
<td>na</td>
<td>no</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Andonian et al 2006</td>
<td>2007</td>
<td>TVT vs TOT</td>
<td>80/78</td>
<td>12 mos</td>
<td>yes</td>
<td>86/83</td>
<td>na</td>
<td>no</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Intra-operatively, the rates of blood loss between older and younger patients were similar, although there were fewer bladder perforations encountered in the elderly patients. Post-operative complications such as wound infection and urinary tract infection were similar between the two groups but older patients experienced age-related problems at a greater rate, including pulmonary embolism (two), DVS thrombosis (one), pneumonia (one), and cardiac arrhythmia (two). There was no increased risk of device erosion or extrusion in the older patients. There was also no significant difference between the two groups in post-operative voiding dysfunction although one patient in the older group did require urethrolysis. Failure to cure SUI was not encountered to any greater extent in the older population and rates of post-operative urge incontinence were also similar. A higher rate of de novo urge incontinence was encountered in the older patients (18% versus 4%). Small studies have documented the higher rates of de novo urgency in older patients [218].

In one study the authors analyzed the potential influence of urethral hypermobility (as defined as Qtip test < 30 degrees) [219]. Of those patients with no hypermobility, 71% were cured, compared with 62% of patients with hypermobility. They identified a similar post-operative outcome, but with a somewhat extended post-operative outcome, as compared to the younger population. Considering the overall impact of voiding dysfunction and other complications in overall quality of life, Walsh, using King's Health Questionnaire, noted that younger patients (defined as less than 70 years) experienced a greater improvement following stress incontinence surgery than older patients (defined as 70 years and older) [219]. In addition, older patients had a higher rate of pre-operative detrusor overactivity than younger patients (24% versus 8%), and also had a higher rate of post-operative voiding dysfunction (as defined by a positive Q-tip test) [219].

### Table 7a. Studies comparing TVT with modifications of retro-pubic and obturator procedures

<table>
<thead>
<tr>
<th>Reference</th>
<th>Years</th>
<th>Type of operation</th>
<th>No of Pts</th>
<th>Duration of follow-up</th>
<th>Power</th>
<th>Lost to f-u</th>
<th>Cure rate</th>
<th>Significans</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al 2005</td>
<td>2004 (204)</td>
<td>SPARC vs TOT</td>
<td>29/31</td>
<td>9 mos</td>
<td>yes</td>
<td>na</td>
<td>98.3/98.3</td>
<td>no</td>
<td>2</td>
</tr>
<tr>
<td>But et al 2007</td>
<td>2007 (591)</td>
<td>TVT-O vs TOT</td>
<td>60/60</td>
<td>4 mos</td>
<td>no</td>
<td>0/0</td>
<td>90.7/88.7</td>
<td>no</td>
<td>2</td>
</tr>
<tr>
<td>Lee et al 2008</td>
<td>2008 (592)</td>
<td>TVT-O vs TOT</td>
<td>50/50</td>
<td>12 mos</td>
<td>no</td>
<td>0/0</td>
<td>86/92</td>
<td>no</td>
<td>2</td>
</tr>
</tbody>
</table>
2. RACE

There are clear differences in the prevalence of SUI among racial groups (Dooley, Kenton et al. 2008) [594], (Anger, Saigal et al. 2006) [221] however whether these differences have implications in the treatment of SUI, especially the surgical treatment of SUI, is unclear. Racial disparities in the US may exist among patients undergoing surgery for SUI. In one study in US women over the age of 65, Caucasians and Hispanics were more likely to be diagnosed with SUI and undergo sling surgery for the condition as compared to non-whites (Anger, Rodriguez et al. 2007) [232]. One other study suggested that US Caucasians are 5x more likely to undergo SUI surgery than blacks (Waetjen, Subak et al. 2003) [223]. However, non-whites are approximately twice as likely to suffer complications as a result of the surgery (Waetjen, Subak et al. 2003) [223] (Anger, Rodriguez et al. 2007) [222]. Whether this is due to actual racial differences or other factors such as disparities in health care services is unclear. Race does not appear to be related to symptom severity or bother in those undergoing SUI surgery (Kraus, Markland et al. 2007) [224] and does not appear to be independently associated with quality of life outcomes (Ragins, Shan et al. 2008) [595] or surgical outcomes (Daneshgari, Moore et al. 2006) [226].

There is little data on whether a particular surgical approach is more effective or is associated with more morbidity in any given racial group as compared to another. The small amount of underpowered data available suggests that race does not independently predict for failure following SUI surgery (Richter, Diokno et al. 2008) [63].

3. OBESITY

There are no prospective randomized studies that have examined obesity as an independent variable across different anti-incontinence surgical procedures or within the same procedure. Obesity has been studied only retrospectively in case series as a risk factor for success or morbidity in stress incontinence surgery (Level 4 evidence).

There are no prospective, randomized trials that suggest superiority of one surgical technique over another in the obese population. Recent studies have focussed on complication rates and outcomes from mid-urethral tapes; the analysis of the influence of obesity is therefore divided into mid-urethral tapes and other surgeries.

a). Other surgeries

Several studies have suggested increased failure rates among obese patients undergoing needle bladder neck suspensions (O’Sullivan DC et al 1995) [227], (Lo TS et al 2003) [228], (Varner RE et al 1990) [596] or retropubic suspensions (Alcalay M et al 1995) [82], (Brieger G & Korda A 1992) [230] (Kjolhede 2005) [231]. In contrast a retrospective study of anti-incontinence surgery in 198 women demonstrated that overall continence did not correlate with obesity in patients undergoing anterior colporrhaphy, anterior colporrhaphy with needle bladder neck suspension or Burch colposuspension although cure rates were markedly better in those in the Burch colposuspension cohort overall (Zivkovic F et al 1999) [597]. One small case series suggested that fascial slings are effective in the morbidly obese patient (Cummings JM et al 1998) [233]. In this study, 2/4 patients failed bladder neck suspension surgery whereas there were no failures in the 12 patients undergoing fascial slings.

b). Mid-urethral tapes

1. COMPLICATIONS OF SURGERY

A review of the influence of obesity on pelvic floor disorders (Jerod Greer W et al 2008) [234] identified seven studies which compared the complications of tension free vaginal tape (TVT) surgeries between 251 obese and 700 non-obese patients. Bladder injury was the only complication reported consistently enough for metaanalysis in six of the studies. The overall perforation rates were 1.2% in the obese group and 6.6% in the non-obese group (p=0.015 ; OR 0.277, 95% confidence interval 0.098-0.782). Only one of the studies demonstrated a difference in TVT complications (Skriapas et al 2006) [235]. A higher risk of immediate post-operative complications was reported in morbidly obese women (BMI>40) compared to non-obese women (BMI<30) : 48.4% in the morbidly obese compared to 38.5% in the non-obese. Complications observed in the morbidly obese but not in the non-obese included minor wound haematoma (n=2), deep vein thrombosis (n=2), pneumonia (n=1) and cardiac arrhythmia (n=1) whilst there was no differences in blood loss, operating time, hospital stay or length of time catheterised post-operatively. Jerod Greer W et al also noted that although TVT surgery on the obese patient is perceived to be more difficult by surgeons there is no evidence from a review of seven additional TVT studies that complications such as blood loss and visceral injuries is higher in obese patients. Even when a significantly longer operating time was reported this was not associated with a higher complication rate (Rogers R et al 2006) [236].

2. EFFICACY

Although several studies comparing outcome from TVT in obese and non-obese women report similar efficacy Jerod Greer et al 2008 found that metanalysis of seven studies which included 453 obese and 1,186 non-obese women revealed a significant difference in cure rates (81% vs 85% =<0.001 ; OR 0.576, 95% confidence interval 0.426-0.779). Most of these studies are limited by their length of follow up (6-24 months).
Longer term follow up might be expected to reveal a progressive increase in the difference in cure rate between the obese and non-obese. Furthermore, Hellberg et al 2007 [598] reported that the failure rate appears to rise more when the BMI is >35 compared to >30.

There are no studies, prospective or retrospective, that have suggested obesity has a positive or favourable influence on outcome in stress incontinence surgery.

4. PSYCHIATRIC ILLNESS

Despite the obvious association between psychological or personality factors and satisfaction with treatment, minimal research has been done on the influence of such factors on subjective or objective surgical success. Black et al. found women undergoing stress incontinence surgery in the United Kingdom to be demographically similar to the general population, although mental health status was not specifically compared (Black NA et al 1996) [237]. Baseline symptom impact correlated positively with mental health, symptom severity, poorer socioeconomic status, and youth.

In a study of 45 women who underwent retropubic cystourethropexy or pubococcygeal repair, baseline lower neuroticism correlated with subjective and pad test cure at one year (Berglund A et al 1997) [34]. Higher extraversion correlated with subjective but not objective cure. Depression decreased in women objectively cured, but not those improved/failed; the decrease in depression in those subjectively cured did not reach statistical significance. Baseline somatic anxiety, psychic anxiety, and psychasthenia (obsessive-compulsive) characteristics were higher in women subjectively failed/improved than those cured or than a reference group. The multiple comparisons and small sample size in this study make some chance associations likely. The same subjects analyzed in a different study showed the cured group to have a higher baseline degree of social integration than the improved group (Berglund A et al 1996) [31]. No differences were found in baseline or follow-up intimate relationship measures.

Öbrink et al. detected above-average levels of neuroticism and depression in women who reported failure of their continence surgery without objective urine loss at 10 to 20 year follow-up (Öbrink A et al 1979) [238]. Below-average levels were found in women with objective but not subjective failure. In 63 women who underwent a Burch procedure, symptomatic improvement was associated with fewer sleep disturbances and less tension (Rosenzweig BA et al 1991) [240]. Subjectively persistent incontinence was associated with more depression and sleep disturbance.

There is Level 3 evidence that psychological factors impact on subjective and objective surgical outcomes in different ways. No data inform psychological interventions to improve the outcome of persistent incontinence or its impact.

5. ACTIVITY

There is no evidence on the influence of post-operative activity on the cure rate or risk of recurrence of stress incontinence after surgery.

6. PREVIOUS CONTINENCE SURGERY

As indicated in the review of procedures above, cure rates following surgery for SUI vary between 20% and 100%; for many procedures, whilst initial results may be good, long-term outcomes indicate variable recurrence rates. The mechanisms underlying initial failure and later recurrence may be quite different, although it would be counter-intuitive if prior surgery were not a significant confounding factor in the outcome of second-line treatment for SUI. The majority of studies reporting on surgery for SUI are however limited to primary cases; many others do not specify whether cases were primary or recurrent, or are inadequately powered to undertake subgroup analysis in this respect. In the review published by Jarvis less than half the reported patients were specified as primary or recurrent (Jarvis, 1994) [20]. Jarvis was however able to extract some useful data on the outcome of surgery recurrent SUI, and found that the objective results for traditional sling (mean 86.1%; 95% CI 82.4-89.8%), colposuspension (mean 82.5%; 95% CI 76.3-88.7%) and endoscopic needle suspension procedures (mean 86.4%; 95% CI 72.4-100%) were better than other procedures, with sling having the narrowest confidence intervals (Jarvis, 1994) [20].

The previous consultation suggested that women should be advised that other procedures for recurrent stress incontinence have been shown to have a lower success rate than the same procedures used in primary SUI (although it was also pointed out that preliminary data on the TVT procedure suggested similar cure rates in both primary and recurrent cases) (Smith, et al., 2005) [23]. Amaye-Obu & Drutz undertook a retrospective review of 118/198 women treated for recurrent SUI over a 12 year period. Overall, they found similar subjective and objective cure rates for the various procedures examined, but found the cure rate following colposuspension was lower in women with more than one previous unsuccessful procedure, whereas the results following slings were maintained in women who had undergone 2 previous failed operations (colposuspension 81%, 25% and 0%, sling 77%, 73% and 38%, for 1, 2, and 3 previous unsuccessful procedures respectively) (Amaye-Obu & Drutz, 1999) [241] [EL=3]. It should be noted that the number of patents with >2 previous procedures in this series was very small.
a) Open colposuspension for recurrent SUI

Case series reporting the outcome of colposuspension for the treatment of recurrent SUI after previous surgical treatment have shown variable results, with an objective cure rate at median follow-up of 9 months of 81% and 86% in two studies (Maher, et al., 1999, Bidmead, et al., 2001) [80,81], but 61% and 65% at 5-15 years in two studies using a Kaplan-Meier analysis (Alcalay, et al., 1995, Thakar, et al., 2002) [82,83] [EL=3]. The latter study in particular found no correlation between outcome and age, past hysterecestomy, number of previous incontinence procedures, parity, body mass index or blood loss at operation (Thakar et al, 2002) [83].

b) Laparoscopic colposuspension for recurrent SUI

As noted above, one small RCT reported in abstract form only compared laparoscopic colposuspension and TVT in the treatment of recurrent SUI found similar success, complication and re-operation rates, although TVT was associated with reduced operating time, hospital stay and return to normal activity (Maher, et al., 2004) [121] [EL=2].

- Traditional sling procedures for recurrent SUI

Despite the supportive conclusions of Jarvis (see above) (Jarvis, 1994) [20], and the fact that the biological slings have traditionally been seen by many as treatment of choice for recurrent SUI, the Cochrane review on traditional sling procedures reported that the data on sub urethral sling operations remain too few to address the effects of this type of surgical treatment. They felt that reliable evidence on which to judge whether sub urethral slings are better or worse than other forms of management was not currently available; in particular they made no comment on the application of sling procedures in the management of recurrent SUI (Bezerra, et al., 2005) [16] [EL=1]. In the review of procedures we have identified a number of recently published RCTs examining the effect of sling procedures; none however adequately address the question of sling procedures for recurrent SUI.

Since the last consultation a number of small case series have been published describing a variety of sling procedures applied to women with recurrent SUI. Petrou & Frank reported 86% subjective cures following repeat pubovaginal sling; it should be noted however that 3/14 women suffered significant post-operative complications, and only 50% were considered objectively cured at mean follow-up of 17 months (Petrou & Frank, 2001) [242] [EL=3]. Kane & colleagues reported 92% (12/13) subjective and objective cures following a bone-anchored pubovaginal sling procedures at median 2 year follow-up(Kane, et al., 1999) [243] [EL=3]. A retrospective series of 72 fascia lata slings found 90% subjective cures at minimum follow-up of 6 months (Breen, et al., 1997) [244] [EL=3]. Finally, a series of in-situ vaginal wall sling procedures was compared with a historical control group of traditional polytetrafluoroethylene sling operations in the treatment of recurrent SUI; both objective (35% vs. 88%) and subjective (61% vs. 93%) were significantly poorer in the index cases(Su, et al., 1999) [245] [EL=3].

c) Mid-urethral tapes for recurrent SUI

In the previous consultation very limited data were available on the use of tape procedures in the treatment of recurrent SUI. Two cohort studies reported comparable cure rates in recurrent SUI to those in primary cases at mean follow-up of 9 months (Rardin, et al., 2002) [246] and 4 years respectively (Rezapour & Ulmsten, 2003) [193] [EL=3]. Since then only one RCT and a number of case reports have addressed the issue of mid-urethral tapes in the management of recurrent SUI.

One small RCT comparing laparoscopic colposuspension and TVT in the treatment of recurrent SUI found similar success, complication and re-operation rates, although TVT was associated with reduced operating time, hospital stay and return to normal activity (Maher et al, 2004) [121] [EL=2]; this study is still only available in abstract form.

In a prospective series of 51 women treated with TVT for recurrent SUI, the objective cure rate was reported to be 90% and subjective cure rate 80% at a two-year follow-up (Kuuva & Nilsson, 2003) [194]. Liapis et al reported a small series with 12 month follow-up; the overall cure rate was 70%, although they described greater success in those with urethral hypermobility (90%) than those with a fixed urethra (33%) (Liapis, et al., 2004) [239] [EL=3].

The use of repeat TVT has been reported to be successful in patients with persistent or recurrent SUI after an initial TVT procedure (Riachi, et al., 2002, Villet, et al., 2002) [247,248] [EL=3]. Other small case series or reports have examined the effect of shortening the original tape, claiming comparable success rates to those reported from re-operation (Villet et al, 2002, Lo & Lee, 2004, Paick, et al., 2004, Nam, et al., 2007) [248,249,250,251] [EL=3].

One case series described five patients with SUI persisting or recurring after transobturator tape procedures successfully managed by a retropubic tape (Moore, et al., 2007) [252] [EL=3].

Summary

The role of previous continence surgery as a confounding factor is poorly understood, and further high level evidence is needed in this area.

It is received wisdom that most continence procedures when used in recurrent stress incontinence will have a lower success rate than the same procedures used...
in primary SUI. It has been suggested that results may be even poorer following several failed procedures. There is limited low level evidence to support this latter contention [EL=3].

Short-term follow-up suggests that the results of open (and laparoscopic colposuspension) in recurrent SUI may in fact be comparable to those in primary cases; long term results from ‘survival analysis’ suggest a greater fall off in cures following the application of colposuspension in recurrent SUI [EL=3].

Previous meta-analysis has suggested that the results from traditional slings are as good as or better than other procedures. In primary SUI (or series where the surgical history is not specified) slings appear to have longevity. Limited low level evidence suggests high success rates in recurrent SUI; high level evidence and long-term follow-up are not available in this patient group [EL=3].

Limited low level evidence suggests that TVT is associated with a similar success rate in recurrent SUI to that seen in primary cases [EL=2/3].

This seems to apply whether TVT is applied following a previously unsuccessful TVT, other mid-urethral tape procedures, or other forms of continence surgery [EL=3].

There are not sufficient data on tape shortening or re-tensioning to evaluate these procedures.

**Recommendation**

**Women undergoing surgery for the treatment of recurrent SUI should be aware of the uncertain log-term outcomes. [Grade B]**

Whilst only limited low level evidence is available currently, colposuspension, traditional biological slings and retropubic mid-urethral tape procedures are recommended in the management of recurrent SUI. [Grade B]

8. SEVERITY AND DURATION OF SYMPTOMS

Severity of SUI is difficult to measure accurately. It is tied to many factors including ambient physical activity of the patient, urethral function, and voiding frequency among others. Commonly utilized objective and subjective severity measures include pad tests and/or pad counts, urethral function tests, questionnaires, voiding diaries, quality of life scores, and bother indices. In the few prospective trials that have measured outcomes using a variety of different measurements, surgical success rates vary widely depending on the parameter (Ward, Hilton et al. 2004; Albo, Richter et al. 2007) [67,46]. Each of these outcomes is associated with significant limitations as an isolated measure and furthermore these parameters only modestly correlate with each other (Albo, Wruck et al. 2007) [46]. When comparing outcomes across SUI procedures, baseline severity is rarely considered and may not be comparable across trials leading to confounding factors when trying to compare procedures.

Symptom duration, especially as regards SUI treatment, is rarely reported in intervention trials. The inherent problem in reporting this data is recall bias by the patient in remembering the duration of symptoms prior to intervention. Therefore, whether duration of SUI symptoms correlates with surgical success or morbidity is unclear.

9. DETRUSOR OVERACTIVITY AND STRESS INCONTINENCE

The previous edition of this consultation found only level 3 evidence to support their conclusion that women who have detrusor overactivity (DO) pre-operatively are less likely to have a favourable outcome from surgery for SUI.
Much of the data on the effect of symptomatic urge urinary incontinence (UUI) on the outcome from surgery for SUI is based on women with overactive bladder syndrome (OABS), rather than on the pre-operative urodynamic finding of DO. There are no prospective randomised trials which compare the outcome of surgery in women with and without DO. Early case series of colposuspension in DO reported cures rates as low as 24-43% (Stanton, et al., 1978, Milani et al, 1985, Lose, et al., 1988) [277,254,261] [EL=3]. Colombo et al performed a retrospective cohort study and compared 44 stress incontinent women with DO with a matched group of women with stress incontinence and a stable bladder (Colombo, et al., 1996) [55]. They reported a cure rate of 95% in the stable group compared to 75% in the unstable group two years after surgery [EL=3].

Choe et al. demonstrated a comparable outcome after sling procedures performed in stress incontinent patients with or without OABS, although only 26% of in their mixed incontinence group actually had DO (Choe, et al., 2008) [267] [EL=3]. A number of studies have examined slightly different aspects of detrusor function in urodynamically mixed incontinence. In a retrospective study of 98 women treated by colposuspension, or needle suspension procedures, Pow-Sang et al demonstrated that ‘high pressure’ DO was associated with a poorer outcome than in patients with stable bladders or those with ‘low pressure’ overactivity (Pow-Sang, et al., 1986) [262] [EL=3]. A retrospective review of 36 women who underwent a sling procedure for stress incontinence and Valsalva induced DO revealed a cure rate of stress incontinence of 92% and urge incontinence of 75% (Serels, et al., 2000) [263] [EL=3]. Koonings et al. demonstrated that in women with mixed incontinence where bladder contraction is preceded by urethral relaxation, there is a more than 90% chance that bladder overactivity will disappear after successful operation for stress urinary incontinence (Koonings, et al., 1988) [264] [EL=3].

We have only identified a further four evidence level 3 studies published since the last consultation, and these are summarised as follows. In a cohort study of 340 women treated by traditional bladder neck sling or minimally invasive mid-urethral sling, Botros et al found that more patients in the mid-urethral sling group had resolution of their DO (38% vs. 15%, p<0.001), and fewer developed de novo overactivity than in the bladder neck sling group (29% vs. 62%, p=0.002) (Botros, et al., 2005) [265] [EL=3].

In a retrospective cohort study of 51 women undergoing TVT for combined urodynamic stress incontinence and DO, Duckett & Tamilselvi found resolution of overactivity in 47% and subjective cure of urge symptoms in 63% at a minimum of six months follow-up; stress incontinence was objectively cured in 92% (Duckett & Tamilselvi, 2006) [266] [EL=3].

In a series of 192 women undergoing sub urethral sling procedures, patient satisfaction was reported by 98% of 106 with normal detrusor function pre-operatively, 82% of 50 with underactive or acontractile detrusor function, and 75% of 36 patients with pre-operative DO (p<0.05) (Kuo, 2007) [599] [EL=3].

Choe et al. reported a retrospective cohort of 549 women treated by TVT; 180 had OABS in addition to SUI pre-operatively; 132 of these were seen for follow-up at 3 months. Based on a 3-day frequency-volume chart and a questionnaire responses complete resolution of OABS was seen in only 24%. Perhaps surprisingly, the rate of resolution was significantly higher in those with DO preoperatively than in those with stable bladders (37% vs. 18%; p=0.021) (Choe, et al., 2008) [267] [EL=3].

Summary

It has long been accepted that women who have detrusor overactivity pre-operatively are less likely to have a favourable outcome from surgery for SUI than those with pure USI [EL=3]. The rate of resolution of stress incontinence in women with mixed USI and DO is not significantly from that seen in those with pure USI [EL=3]. Rates of ‘cure’, or resolution of OABS or urodynamic findings ranging from 24% to 90% have been reported in women with mixed USI and DO [EL=3].

This wide range of treatment effect may be due to differences in surgical techniques or in methodology and outcome assessment [EL=4].

Although a number of women may develop new symptoms of OABS or so-called de novo DO following surgery for USI, such surgery should not be considered contraindicated in women with mixed symptoms of SUI and OABS or mixed urodynamic findings of USI and DO, provided that patients are fully counselled about possible outcomes [EL=4].

Recommendations

Surgery for USI should not be considered contraindicated in women with mixed symptoms of SUI and OABS or mixed urodynamic findings of USI and DO. [Grade B]

All patients undergoing surgery for stress urinary incontinence should be appropriately counselled to allow realistic expectations of outcome; this is particularly important in those with mixed symptoms or mixed urodynamic. [Grade B]
10. URETHRAL OCCLUSIVE FORCES

The influence of urethral function defined by leak point pressure or maximum urethral closure pressure is difficult to define on account of the large variation in outcome measures employed. Furthermore, other variables such as urethral mobility are often not controlled. Intrinsic sphincteric deficiency (ISD) is usually defined as a leak point pressure of < 60 or maximal urethral closure pressure (MUCP) of < 20. Rezapour reported a four-year outcome follow-up for patients undergoing TVT with ISD [193]. Of the 49 patients, only eight had immobile urethras. None of the patients with immobile urethras were cured, although three were noted to be improved. Paic also reported lower cure rates in patients with low leak point pressures, given no substantial differences in urethra hypermobility [250]. Urethral hypermobility has been predictive of mid-urethral sling success by some authors [269], whilst low leak point pressures have not been predictive of success by other authors [270,271]. It would appear that a low leak point pressure is less predictive of outcome on this data when compared to the presence or absence of urethral hypermobility.

11. SURGEON’S EXPERIENCE

Several factors independent of the patient characteristics might affect the outcome of incontinence surgery. Such are the experience of the surgeon as a surgery performing physician, experience of the surgeon in performing a given procedure, experience of the team and the hospital within which the surgery is performed. These issues have not been studied within randomized trials or in a prospective way.

In a report by Gormley et al (2002) [272] no effect of surgeon’s grade of experience or teaching status of the hospital was seen when performing pubovaginal sling procedures. There are a few reports looking at the learning curve of surgeons performing the TVT operation. The overall impression is that bladder perforations and retention symptoms occur more often during the first 15 to 50 TVT operations than later on. In a nationwide report on the introduction of the TVT procedure in Finland, where the learning curve of every single surgeon was included it was found that performance improved after the first 15 operations (Kuuva and Nilsson 2002) [273] Groutz et al (2002) [274] reported a dramatic decrease in the rate of bladder perforations from 40% in the first 10 patients to 10% in the next 10 patients and in the last 10 of a total of 30 patients operated on by a newly trained experienced urogynaecologist no further bladder perforations occurred. Lebret et al (2001) [275] reported a similar decline in the rate of bladder perforation from 22% in the first 50 patients to 8% in the next 50 patients. McLennan et al (2005) [276] analyzed the bladder perforation rate in 278 TVT operations performed by 23 residents performing a mean number of 12 operations each and found a linear decrease in perforation rate from 34% in the first 5 patients to 26% in the last five of 15 patients.

There is no robust literature on how many procedures need to be performed to maintain skills nor is there evidence on whether surgical skill or experience influences the cure rate rather than the complication rate although a correlation might be expected.

III. STRESS INCONTINENCE WITH PROLAPSE

1. URINARY INCONTINENCE AND PROLAPSE

Women who present with urinary incontinence as their primary symptom may also have pelvic organ prolapse which may be symptomatic or asymptomatic. The decision as to whether the prolapse should be treated surgically at the same time as the incontinence is determined by the symptoms and bother the prolapse produces to the patient and the influence that the prolapse surgery may have on the outcome of the surgery for the incontinence. The following clinical scenarios may present:

a) Stress urinary incontinence with prolapse
b) Urgency incontinence with prolapse
c) Prolapse with urinary incontinence (See Prolapse Chapter)

Where the prolapse is symptomatic it will be a matter of subjective opinion whether the incontinence or the prolapse is more significant (rather than a pathological diagnosis). If the treatment selection is based on subjective assessment it follows that the outcome from treatment must be based on subjective rather than objective measures.

a) Stress incontinence with prolapse

Women who present with stress incontinence commonly have deficient support of the anterior vaginal wall. Significant prolapse is generally defined anatomically as the presenting part of the prolapse reaching to within a cm of the hymenal remnant. Symptomatic prolapse may be more or less prominent. Milani et al (Milani 1985) [254] (Level 3) noted that the presence of vaginal prolapse preoperatively led to a lower cure rate of stress incontinence with either the Burch colposuspension or the MMK procedure; the greater the severity of the prolapse, the greater the reduction in cure rate. In a RCT Colombo et al (Colombo 2000) [37] compared Burch colposuspension with anterior colporrhaphy in women with stress urinary incontinence and Grade 2-3 anterior vaginal wall prolapse and found that the Burch colposuspension was better in controlling stress incontinence but that cystocele recurred in 34% of
patients. The cure rate for cystocele with anterior colporrhaphy was high (97%) but stress incontinence cure rate was very low. The authors concluded that neither operation was recommended for combined stress incontinence and advanced cystocele.

Gordon (Gordon et al 2001) [600] prospectively followed 30 patients short-term who underwent TVT at the same time as surgery for severe genitourinary prolapse. No patients had postoperative symptoms of stress incontinence despite 3 patients (10%) having positive postoperative stress tests. De novo detrusor overactivity occurred in 13% of subjects. A RCT compared types of anti-incontinence procedure performed with prolapse surgery, endopelvic fascia plication and TVT. (Meschia 2004) [40] (Level 1). This study included 50 women and demonstrated that adding a TVT results in higher 2-year objective continence rate than endopelvic fascia plication at the urethrovesical junction (92% vs. 56%, respectively; p<.01). The subjective cure rates were 96% for TVT compared to 64% for suburethral plication. Time for resumption of spontaneous voiding, rates of urinary retention, de novo urge incontinence, and complications did not differ between the groups. Despite negative cystometrograms, de novo urge incontinence symptoms were reported in 12% of the TVT group compared to 4% of the suburethral plication group (p=.66). Although not statistically significant, the authors recommend that data from a larger series are required to define the risk: benefit ratio between TVT and endopelvic fascia plication.

The TVT procedure combined with vaginal reconstruction resulted in 85% to 95% cure rates for urodynamic stress incontinence in a prospective cohort (Huang 2003) [278] and case series (Partoll 2002)279. Huang et al (Huang 2003) [278] reported urinary urgency and voiding dysfunction rates of 10% and 11%, respectively. Voiding difficulties and post void residuals of > 100 ml were treated with urethral dilatation. The authors did not report any cases of long-standing urinary retention.

b) Urgency incontinence with prolapse

The effect of anterior vaginal wall prolapse on bladder function and the influence of surgical repair are much debated. Digesu et al (2007) [280] reported on a 12 month prospective cohort study of ninety three women who had a standard anterior fascial repair for cystocele. Post-operatively, urinary frequency resolved in 60%, urgency resolved in 70% and urge incontinence resolved in 82% illustrating that anterior repair appears to resolve the majority of overactive bladder symptoms. Similar findings were reported in a prospective cohort study of prolapse repair in elderly women by Foster RT Sr et al (2007) [281]. They also noted that vaginal reconstructive or obliterator surgery produced a similar improvement in urinary symptoms at 12 months after surgery.

CONCLUSIONS

There is Level 2/3 evidence that when prolapse repair surgery is performed at the same time as a TVT to treat stress incontinence, the cure rate for the stress incontinence is not adversely affected.

There is Level 3 evidence that treatment of prolapse by constructive or obliterator surgery improves overactive bladder symptoms.

IV. COMPLICATIONS OF SURGERY FOR STRESS INCONTINENCE

1. EVIDENCE
2. INCIDENCE OF COMPLICATIONS
3. PREVENTION OF COMPLICATIONS
4. OPERATIVE EXPERIENCE
5. CHOICE OF APPROACH
6. OTHER RISK FACTORS
7. COMPLICATIONS RELATED TO SUI SURGERY
a) Intraoperative
   1. URINARY TRACT INJURY
      i) Urethra
      ii) Bladder
      iii) Ureter
   iv) Bleeding and vascular injury
v) Bowel injury
b) Postoperative complications
   1. VOIDING DYSFUNCTION AND URINARY RETENTION
   2. VAGINAL EXTRUSION AND URINARY TRACT EROSION
   3. NERVE INJURY
   4. BONE ANCHOR RELATED COMPLICATIONS
   5. SEXUAL DYSFUNCTION
   6. OTHER POSTOPERATIVE COMPLICATIONS
   8. PERIURETHRAL BULKING AGENTS
1. EVIDENCE

There are very few randomized, prospective studies adequately powered to assess differences in complications between operative procedures. Because the reported incidence of most complications is quite low, adequate powering of randomized clinical studies would necessitate extraordinarily large numbers of patients. Current literature does not permit such an analysis although national registries may be one such source of this information in the future. Most of the available evidence is from case series, non-cohort comparative trials or underpowered randomized trials. Meta analysis and underpowered clinical trials may give some information on the incidence of particular complications, but comparing the relative risk of complications across various procedures of a similar nature is difficult and may be misleading based on available data.
The field of incontinence surgery, and especially stress urinary incontinence (SUI) surgery has rapidly transformed over the past several years. The types of SUI procedures being performed has evolved from transvaginal needle suspensions and retropubic suspensions to various types of slings, most commonly the midurethral polypropylene slings. This shift has implications for the types of complications seen in contemporary practice. Therefore the emphasis in this section will be in review of the midurethral sling procedure and its many derivatives. It is important to note that much of the data regarding these complications is immature. It is possible that over time the incidence of various types of complications or unforeseen additional types of complications may occur.

2. INCIDENCE OF COMPLICATIONS

The overall incidence of intraoperative and postoperative complications is difficult to ascertain. Much of the available literature derives from a single centre experiences, national registry data, case series or case reports. In addition, the reporting of surgical complications by individual investigators is not mandatory, is often selective, and is defined by the investigator. Furthermore, the incidence and type of complications reported in the literature are, for the most part, derived from academic medical centres. Complications arising in community practices may be wholly different. Central databases such as the FDA MAUDE website are voluntary and accurately determining complication rates based on such data is not possible for a variety of methodological reasons.[282]. In addition, there is no generally accepted standard categorization, or nomenclature for the reporting of surgical complications for urinary incontinence (UI) surgery although it has been suggested [283,24]. One such paradigm was developed by the AUA SUI Guidelines Panel which divided complications into 6 categories: transfusions, general medical, intraoperative, perioperative, subjective, and those complications requiring surgery [24]. Unfortunately this taxonomy has not been widely adopted. A system for the grading of severity of surgical complications has also been developed [284] and utilized in the UI literature [46] but it does not provide a mechanism for classification of specific complications in the genitourinary tract. Complications vary in severity and associated morbidity (i.e. a postoperative UTI vs. transvaginal erosion and extrusion of a synthetic sling material are not equivalent in severity but are weighted equally in the overall complication rate of a given procedure) As a result of these deficiencies an omission of the reporting of a given complication by an investigator is considered consistent with its lack of occurrence. Whether this method of accounting reflects accurately on the trial or on clinical practice is not clear. Finally, the definition of exactly what constitutes a complication is unclear. There are particular complications that are dichotomous or categorical: they either occur or they do not (e.g.: bowel injury, urinary tract injury, sling extrusion). However, other potential complications such as bladder outlet obstruction and dyspareunia are graded on a spectrum and not well defined. This lack of standardization permits considerable variability in the reporting of complications. For example, excessive bleeding is considered by most surgeons to be a complication but some bleeding is commonly encountered in the performance of most anti-incontinence procedures. However, the quantity of bleeding that must occur for it to be considered a complication is not standardized. Bleeding as a complication has been defined variably in the literature as a volume of blood loss (e.g. >200cc), development of a postoperative hematoma, peri- or postoperative hypotension, the requirement for transfusion, or even hemorrhagic shock and death.

Notwithstanding the limitations noted above, the incidence of complications varies widely between studies. Case reports and case series likely underestimate the actual incidence of some complications especially major complications [285]. In some series for certain groups of patients undergoing UI surgery, the complication rate may approach 40-50% if UTI's and urgency symptoms are defined as complications [286,287]. The AUA SUI Guidelines Panel reported that each of the 6 categories of complications occurred in 2-16% of patients across the 4 types of procedures covered in the meta-analysis: slings, retropubic suspensions, transvaginal sus-pensions and anterior repair. In a review of midurethral sling procedures, Boustead et al noted that the complication rate in published series ranged from 1-40% [288]. Taub et al used the Nationwide Inpatient Sample (a national database in the US) of over 147,000 patients who underwent surgery for SUI from 1988 to 2000 and found an overall complication rate of 13% [289]. Waetjen et al estimated a complication rate of 18% from the 1998 National Hospital Discharge Survey and the 1998 National Census including data on over 135,000 patients undergoing surgery for SUI [223]. On review of a sampling of the Medicare database from 1999-2001, Anger et al found that 12.5% of patients undergoing a sling developed a surgical or urological complication in the first 3 months following surgery [221].

3. PREVENTION OF COMPLICATIONS

Although most complications related to the surgical treatment of female urinary incontinence are treatable and, for the most part reversible, the optimal scenario is to prevent or minimize the potential for an adverse outcome. Certain preoperative factors may influence the risk of intraoperative or postoperative complications. Most have not been studied in a controlled fashion.
4. OPERATIVE EXPERIENCE
Operative experience with a given procedure has been cited as an important factor contributing to the risk of complications. Proper training and subsequent maintenance of skills is important not only in optimizing outcomes, but in minimizing complications. The number of cases necessary to gain competence with a given procedure is unknown and likely varies with the nature of the surgery, the learning environment and the skill of the surgeon. For the experienced and practicing surgeon, the NICE guidelines from the UK recommend that a minimum of 20 cases per year per surgeon for each incontinence procedure is necessary to maintain skills [290] this document further states that if fewer than 5 of a particular procedure are done by an individual surgeon per year, then local clearance and oversight, or alternatively referral to another centre may be necessary [290].

Kuuva et al reviewed a nationwide database on midurethral slings and noted that operative complications varied inversely with surgical experience (Level 3) [273] These authors reported that the risk of bladder perforation during a transvaginal midurethral sling varied with the experience of the operating surgeon in doing the procedure. Surgeons performing more than 80 procedures had almost 50% fewer perforations than those with less than twenty cases experience and these authors also noted that complications decreased per surgeon after completing 15 procedures. McClennan et al reported that the risk of perforation of the urinary bladder during TVT decreased with increasing surgical experience in a residency training program (Level 3) [276]. In a prospective Dutch study of TVT procedures, there was an increased risk of complications in teaching hospitals as compared to non-teaching hospitals as well as an increased risk of complications during a surgeon's second 10 procedures as compared to their first 10 procedures or >20 procedures (Level 2) [291]. Alternatively, Anger et al, in review of a large national database found no correlation between surgical experience and risk of surgical complications in patients undergoing SUI surgery (Level 3) [601].

5. CHOICE OF APPROACH
The relative risks of each complication between the various types of surgery being performed, especially within a single category such as midurethral slings, regardless of approach (e.g. the risk of bleeding in a transobturators vs. suprapubic vs. transvaginal approach), is difficult to assess due to the small number of randomized controlled trials between procedures and the relative low frequency of the event (complications). In a large meta-analysis in 1997, the AUA SUI Guidelines Panel reported that slings and retropubic suspensions were associated with a higher risk of complications such as bleeding and obstruction than anterior repairs and needle bladder neck suspensions (Level 1) [24].

There are few prospective randomized trials comparing complications. Ward and Hilton compared Burch to TVT and found that the risk of intraoperative complications such as bladder perforation was higher in the TVT group whereas the risk of postoperative complications such as delayed voiding was greater in the Burch group (Level 1) [65]. The Urinary Incontinence Treatment Network (UITN) completed a randomized controlled trial comparing Burch colposuspension to autologous rectus fascia pubovaginal sling (Level 1) [46]. There was no overall difference in total serious adverse events between groups (13% vs. 10%, p=0.20, sling vs. Burch, respectively) but surgical interventions for the treatment of voiding dysfunction only occurred in the sling group (19 interventions in the sling group vs. none in the Burch group). Overall adverse events (including most commonly UTIs) occurred more often in the sling group. (63% vs. 47%, p<0.001, sling vs. Burch, respectively). A small prospective study compared autologous fascial sling to TVT in 53 patients with SUI and found no difference in complications between the groups at 6 months follow-up (Level 2) [166].

There have been a few randomized trials comparing some combination of TOT (transobturator), TVT (transvaginally placed retropubic tape), and SP (suprapubically placed retropubic) urethral tapes. Zhu et al found no difference in complication rates or urinary retention in 56 women randomized to either TVT or TOT (Level 2) [292] as did Lee et al with 120 patients quasi-randomized to either procedure [293]. Laurikainen and colleagues noted that a TOT approach was associated with more complications than TVT but this difference was not considered clinically significant by the authors [209]. However, Liapis et al noted more overall complications in patients undergoing TVT (11/46) as compared to TOT (2/43) in a randomized trial between these two procedures [208]. At a median follow-up of 9 months, Wang et al noted no significant difference in complications between 60 patients randomized to TOT or SP urethral tapes although there was a non-significant trend for increased thigh pain and vaginal extrusion in the TOT group (Level 2) [591]. In a prospective trial, David-Montefiore et al found similar complication rates in patients randomized to TVT (8/42) or TOT (5/46) although the types of complications differed between the groups (see below) [294].

With respect to a transobturator approach, two studies have demonstrated equivalently low complication rates between the outside-in vs. inside-out approach (Level 2) [295,296].

6. OTHER RISK FACTORS
There are many patient factors which may potentially impact on the risk of complications in a given patient including aetiology and type of urinary incontinence, age, medical co morbidities, preoperative sexual function, the presence of associated conditions such
as vaginal prolapse, and prior abdominal, pelvic or anti-incontinence surgery. In one prospective study of over 800 patients undergoing TVT, Schraffordt Koops et al noted an overall 6.2% incidence of complications and identified several risk factors including menopausal state, previous prolapse surgery (but not prior incontinence surgery), mode of anaesthesia, and having the procedure done in a teaching hospital (Level 2) [291].

Identifying preoperative patient risk factors such as prior surgery, age, and obesity that consistently predict for intraoperative and postoperative complications has also been difficult. Much of the existing literature is conflicting (Level 3) [297]. For example, some authors have found that prior pelvic or incontinence surgery predicts for intraoperative bladder injury during midurethral sling (Level 2-3) [286, 298,206,257], while others have not (Level 2) [301]. This variability may be due to the type of prior SUI surgery: prior retropubic surgery such as Burch or MMK may lead to retropubic scarring and a risk of bladder injury whereas a prior transvaginal operative such as a Kelly plication wherein the retropubic space is not violated, may not [257]. Advanced age is not a contraindication to anti-incontinence surgery.

However surgery in the advanced elderly (>80 y.o.) may be associated with some increased morbidity as compared to the “young” elderly (Level 3) (65-80 y.o) [299] and may be associated with higher rates of postoperative urge incontinence, bladder outlet obstruction and surgical failure as compared to younger patients (Level 3) [300]. Rogers et al demonstrated no increased risk of intraoperative or postoperative complications in obese patients (BMI>30) as compared to the non-obese patients undergoing a variety of SUI surgeries in a prospective nested cohort study.(Level 2) [301] This supports the conclusion of other prior studies [233,302]. One study noted that individuals with a BMI>26.5 were at increased risk of bladder perforation during TVT but that overall outcomes were not affected [303].

7. COMPLICATIONS RELATED TO SUI SURGERY

a) Intraoperative Complications

1. URINARY TRACT INJURY

During SUI surgery, the urethra, bladder or, much more rarely, the ureters may be injured. The key to the management of each of these injuries is immediate recognition and repair. Long term sequelae resulting from unrecognized urinary tract injury can be devastating to the patient.

i) Urethra

Intraoperative urethral injury during UI surgery is rarely reported. It may occur during the initial transvaginal dissection, during trocar placement for midurethral sling procedures, needle placement for transvaginal suspensions, or during cystocele repair. Failure to recognize the injury or failure to repair it properly risks urethrovaginal fistula, erosion of sling material into the urethral lumen postoperatively, infection, and other potential problems (Level 4). The risk of urethral injury may be as high as 4 fold greater in the transobturator approach as compared to the TVT/retropubic approach [290] however this data is based on a single literature review and thus indirect comparisons and not randomized control trial data.

In the event of a planned synthetic sling in the setting of a concomitant intraoperative urethral injury, it is probably advisable to repair the urethra and abort the sling procedure until the urethra is completely healed (Level 4).

An autologous sling may be considered a safer alternative than a synthetic sling at the time of a urethral injury as an anti-incontinence procedure but there is little data to support this notion (Level 4). The urethra is rarely injured during retropubic surgery as the middle and distal thirds are protected by the symphysis pubis.

ii) Bladder

The potential for bladder injury may vary with the choice of operative approach. Albo et al reported a trend toward more bladder injuries in the colposuspension group as compared to the sling group (10/329 vs. 2/326, colposuspension vs. sling respectively) in the UITN study [46]. The risk of bladder injury during midurethral sling is probably higher with a retropubic approach as compared to a transobturator approach although randomized trial data are minimal in this regard (Figure 8).

Figure 8 : Mesh erosion into the bladder following TVT
In one literature review, the risk of bladder injury may be as much as 6 fold higher in the TVT/retropubic approach as compared to the transobturator approach [290]. The incidence of bladder perforation during TVT has been reported in 0-8% of patients (Level 3) [273,317,291,206,65]. Hodroff et al reported an overall bladder perforation rate of 6.7% in 445 patients undergoing a SP midurethral tape procedure and Deval et al reported an incidence of 10.5% in 104 patients (Level 3) [304, 286]. Davila et al reported no bladder perforations in over 200 patients undergoing a TOT sling (Level 3) [305].

Barber et al retrospectively compared over 200 patients undergoing TVT to a similar number of patients undergoing TOT (Level 3) [306] and found that the incidence of bladder perforation in the TVT group was 5% while there were no such injuries in the TOT group. Several small prospective RCT’s have reported a trend towards a greater risk of bladder perforation during TVT as compared to TOT (Level 2) [209, 208,307]. Nevertheless, there are multiple reports of bladder injury during transobturator midurethral slings [308,309] and thus this potential complication must be considered.

The relative risk of bladder perforation with a transvaginal vs. suprapubic approach to retropubic midurethral slings is, as of yet, unclear. While one retrospective study noted a high bladder perforation rate with a suprapubic approach (29% vs. 4%, suprapubic vs. transvaginal, respectively) (Level 3) [310], others have not (Level 2) [200].

In one small randomized prospective trial comparing transobturator to retropubic midurethral slings, bladder perforation was noted only in the retropubic cases (4/42, 9.5%) whereas vaginal injury was noted only in the transobturator cases (5/46, 10.9%) [294].

Redo incontinence surgery may be associated with a higher risk of urinary tract injury in patients undergoing midurethral sling surgery. Jeffry et al reported a bladder perforation rate during TVT of 71.4% vs. 7.6% in patients with prior surgery vs. those without (Level 3) [298]. Likewise, in patients undergoing SPARC, Deval et al reported a 36.6% vs. 7.5% urinary tract injury rate in those with vs. those without a history of prior surgery (Level 3) [286]. The risk of bladder perforation in the Austrian TVT national registry was 4.4% in patients with prior surgery but only 2% in those without prior surgery (Level 3) [206]. However, LaSala et al reported that prior abdominal hysterectomy or BMI >26.5, but not prior anti-incontinence surgery, was associated with an increased risk of intraoperative cystotomy during TVT (Level 3) [303]. Nevertheless, in one series, the surgical results in those with an intraoperative bladder perforation during TVT appear to be no different from those without such a complication provided that the perforation is recognized intraoperatively and corrected (Level 3) [303]. It is possible that the type of prior surgery has a significant impact on the risk of bladder perforation with such operations as Burch colposuspension in which there is considerable dissection in the retropubic space posing a potentially greater risk than prior anterior repair where no such dissection is performed (Level 3) [257].

iii) Ureter

Ureteral injury during incontinence surgery is very uncommon. The ureter may be kinked or obstructed during Burch or MMK procedures or during bladder neck sling procedures. With the advent of midurethral slings, these injuries are rare given the expected location of the sling at the level of the midurethra. In the UITN trial of Burch vs. autologous fascial sling, there were 2 ureteral injuries and both occurred in the Burch group [46].

iv) Bleeding and vascular injury

The risk of bleeding during SUI surgery can be minimized, but not entirely eliminated by good operative technique. Multiple blood vessels traverse the deep pelvis including large venous channels in the retropubic space.Named vessels in the obturator fossa, along the pelvic sidewall including the iliac vessels, and within the vascular pedicle of the bladder are at risk for injury especially during vaginal incontinence surgery due to lack of direct visualization of these structures during passage of trocars or needles (Figure 9).

Major vascular injury can quickly lead to life threatening haemorrhage if not recognized intraoperatively and may result in large retropubic hematomas postoperatively [311,312]. Leach et al reported bleeding complications requiring transfusion in 5% of colposuspensions, 4% of slings, 3% of needle suspensions and 3% of anterior repairs. (Level 1) [24]

Figure 9 : Abdominal wall haematoma after laparoscopic surgery
These differences were not statistically significant. In a series of over 5000 midurethral slings reported on by the Austrian Working Group for Urogynaecology, bleeding problems were reported in 2.7% of cases (Level 3) [313]. Only 0.8% of patients required intervention for bleeding with the vast majority of cases managed conservatively without operative intervention. Less than 1% of patients required transfusions. Kuuva et al reported a 1.9% incidence of bleeding >200cc in over 1400 TVT cases (Level 3) [273]. RCT’s comparing TOT to TVT and SP urethral tapes show no significant difference in bleeding complications between approaches (Level 2) [307,208,209]. There was no significant difference in complications related to bleeding between the colposuspension group and the sling group in the UITN report from Albo et al (3/329 vs. 1/326, p=0.62, colposuspension vs. sling respectively) [46].

**v) Bowel injury**

There exist multiple reports of bowel injury during urinary incontinence surgery [314,308,304]. Fortunately this is a rare and very infrequently reported complication. Bowel injury may occur during the retropubic dissection for a Burch or MMK especially in reoperative surgery, during entry into the retropubic space during an autologous pubovaginal sling, or during passage of needle passers or trocars during midurethral slings. These can be devastating complications leading to sepsis, abscess and even death [308].

**b) Postoperative complications**

1. **VOIDING DYSFUNCTION AND URINARY RETENTION**

Bladder outlet obstruction (BOO) may occur following SUI surgery. This presents as prolonged complete urinary retention, persistently elevated post-void residual urine volume or, as variably bothersome and poorly categorized lower urinary tract symptoms including combinations of recurrent urinary tract infections, obstructive symptoms and urinary urgency or urge incontinence.

Historically the prevalence of postoperative voiding difficulties lasting greater than 4 weeks occurs in 3-7% of patients undergoing Burch procedures, 4-8% of those undergoing transvaginal needle suspensions and 3-11% of pubovaginal slings [24]. Permanent urinary retention was estimated to be <5% across all procedures by these same authors.

The prevalence of voiding dysfunction, including urinary retention and de novo urgency and urge incontinence, following midurethral slings ranges from approximately 2%-25% (Level 2-3) [315-317, 320,367,318,319,295,286,206,205]. Surgical intervention for voiding dysfunction and urinary retention has been reported in 0-5% of patients undergoing midurethral slings (Level 2-3) [304, 206,319,295,367]. Randomized prospective studies have shown short term voiding difficulties following TVT appear less likely than following Burch (Level 1) [85] and pubovaginal slings (Level 2) [168]. Dietz found TOT to be less “obstructive” than TVT based on flow rates and ultrasound (Level 3) [321]. In one multicenter retrospective study, transobturato slings had fewer “obstructive” complications than retropubic midurethral slings (Level 3) [322] and another retrospective study compared TVT to TOT and found that fewer patients in the TOT group required urethralysis or anticholinergic medications in the postoperative period implying less obstruction (Level 2) [306]. Alternatively, one randomized trial comparing SP midurethral tapes to TOT demonstrated no difference in postoperative voiding dysfunction (Level 2) [204].

The diagnosis of urethral obstruction following SUI surgery is difficult and based on a combination of clinical parameters. In some patients, cystoscopy and videourodynamics may be helpful. However, there is no universally agreed method of making a diagnosis of postoperative urethral obstruction which prevents a true assessment of the incidence of this complication.

Management options for prolonged postoperative voiding difficulties include repeated voiding trials, initiation of intermittent urethral catheterization, and incision of the sling or urethralysis. As many cases of postoperative voiding dysfunction will spontaneously resolve, the ideal timing for surgical intervention has not been defined. Early intervention may result in high rates of recurrent SUI in patients in whom the voiding dysfunction may have resolved spontaneously given enough time. Alternatively, subjecting the patient to ongoing irritative lower urinary tract symptoms, UTI’s or CIC due to ongoing obstruction is not optimal. Some authors have recommended conservative therapy for postoperative voiding dysfunction for up to 3 months prior to attempting surgical revision [323]. However, a prolonged time to intervention for BOO may be associated with long term, potentially irreversible bladder dysfunction even following successful urethralysis [324, 325].

Transvaginal sling incision is often successful in reversing obstruction from a pubovaginal or midurethral sling (Level 2) [326-328]. For patients who fail transvaginal incision, or who underwent a non-sling procedure as the cause for their BOO, a urethralysis may be performed [329,330]. Via a transvaginal or retropubic approach [221,329,331], the retropubic space is entered and the urethra is sharply dissected off the posterior surface of the symphysis pubis and freed from the surrounding scar. The limbs of the sling or other retropubic attachments are isolated and divided in the retropubic space. Lateral attachments to the pelvic sidewall are incised as needed for those who previously underwent a Burch or paravaginal repair. A transvaginal, suprameatal approach to urethralysis has also been described and may be
particularly applicable to those patients previously undergoing an MMK [331].

Recurrence of SUI symptoms following urethrolysis or sling incision may occur in 15-20% of patients [328,332].

2. **VAGINAL EXTRUSION AND URINARY TRACT EROSION**

Vaginal extrusion refers to the finding of exposed sling material in the vaginal cavity postoperatively, whereas erosion implies the finding of material within the lumen of the urinary tract at some time interval postoperatively (Figure 10) which was clearly documented as not being within the urinary tract at the time of surgery. Both extrusion and erosion may lead to long term voiding dysfunction despite removal of the sling material.[333].

Extruded material may be located in the midline at the incision line or at the anterolateral vaginal wall. Midline extrusions imply wound dehiscence or defective healing whereas lateral extrusions may be due to an unrecognized vaginal wall perforation or injury at the time of sling placement (Level 4) [334].

Extrusion of material may be related to surgical technique, host factors, wound healing, infection, or the physical properties of the implanted material such as pore size or monofilament vs. multifilament construction [335,336]. Pore size or the specific weave of a mesh may be related to the intrinsic ability of a material to resist infection by allowing migration of host fibroblasts and macrophages into the interstices of the mesh to eliminate bacteria [336]. Certain woven mesh products may have a pore size or interstices below a critical size which may predispose to infection.

There is a paucity of randomized trials comparing monofilament to multifilament (polyfilament) mesh. One randomized trial found 9 extrusions in a multifilament sling group as compared to none in the monofilament group (TVT) (Level 2) [203] and another trial reported higher extrusion rates with a multifilament as compared to two other monofilament products [588]. A case control study comparing a monofilament to a multifilament mesh reported a several fold increase in urethral erosions in the multifilament group as compared to the monofilament group [337]. However, Rechberger et al noted no difference in extrusion rate in an RCT comparing monofilament to multifilament mesh. (Level 2) [201]. Several case series have suggested that the risk of extrusion with multifilament or other types of treated mesh is significant and may occur in 9-20% of cases (Level 4) [338-342,588]. The reported rate of mesh extrusion from case series using monofilament sling materials has been reported as between 0-5% [291,273,203,65,343,304].

Extrusions should be treated expeditiously. Some small extrusions may heal with conservative management including the application of topical oestrogen creams (Level 4) [343]. The size of an extrusion which can be managed non-operatively is not well defined nor is the time frame after which surgical intervention should be pursued. Larger extrusions can be managed with copious irrigation and secondary closure in the operating room. Some patients with large extrusions which are unable to be secondarily closed or who have already failed secondary closure should undergo excision and removal of the extruded sling (Level 4).

Urinary tract erosion may occur with synthetic, biologic or autologous materials [344,345]. The risk of sling erosion into the urethra is extremely low. In several national databases, the urethral erosion rate for TVT has been reported to be less than 1% [346,273,206,291]. One retrospective series demonstrated no urethral injuries with TOT-I or TOT-O [334].

This complication is managed operatively. Whether urinary tract erosion occurs as a result of a “missed” urinary viscus perforation at the time of surgery, or occurs as a result of migration of the material into the urinary tract sometime following surgery, is unclear. Patients may complain of irritative lower urinary tract symptoms, recurrent UTI’s, haematuria, dysuria as well as pelvic pain. The definitive diagnosis of urinary tract erosion is usually made endoscopically and treatment may involve endoscopic [347,348] or open removal of the eroded mesh.

3. **NERVE INJURY**

Several nerves traverse through the deep pelvis as well as superficially within the lower abdominal soft
tissues. These nerves are at risk for injury during female incontinence surgery during positioning of the patient or during the surgical procedure.

Lithotomy position may result in stretch or compression injury to the femoral nerve as can retractor placement during retropubic UI surgery. Femoral nerve compression may occur at the level of the inguinal ligament due to flexion of the hip joint [349]. This results in sensory changes to the anterior thigh or in more severe cases weakness of hip flexion. Severe abduction and external rotation of the thigh should be minimized during positioning to avoid this complication. The peroneal nerve can be injured by direct compression while in the lithotomy position. Lateral direct pressure on the peroneal nerve between the stirrup at the lateral aspect of the knee joint and the fibular head for a prolonged period of time may result in a peroneal nerve palsy and foot drop [349]. This injury may also occur with compression of the fibular head against the stirrup holder, especially candy cane stirrups as the leg rotates externally after placement in the holders.

The ilioinguinal and iliohypogastric nerves may be injured by sling harvest during autologous rectus fascia pubovaginal sling, trocar placement or dissection [350,357].

4. Bone anchor related complications

Bone anchors (BA) were popularized as an alternative method of suture fixation during stress urinary incontinence surgery such as pubovaginal slings and transvaginal needle bladder neck suspensions. Rackley et al estimated the prevalence of BA related infections in female pelvic reconstructive procedures as approximately 0.6% [351]. However, the complications associated with BA’s can be devastating including pelvic abscess and osteomyelitis of the symphysis pubis. There are numerous reports of bone anchor related complications associated with female incontinence surgery in the urologic, gynaecological and orthopaedic scientific literature [352-355]. Once diagnosed, osteomyelitis related to BA’s requires operative exploration and removal of the bone anchor.

5. Sexual Dysfunction

Postoperative female sexual dysfunction (FSD) was reported in between 2-8% of female patients undergoing SUI surgery in the AUA Female SUI Guidelines Panel [24]. The difference between procedures was not statistically significant. There are several questionnaires that have been utilized to assess FSD [356]. Use of these disease-specific questionnaires may yield a higher incidence of FSD than previously reported in many series which may be up to 20% [356,357] however not all contemporary series report such findings [358].

Dyspareunia is one form of sexual dysfunction and it may occur following UI surgery. Vaginal anatomy is altered by SUI surgery. The vaginal axis can be shifted changing the angulation of the vaginal canal. Circumferential narrowing of the vagina may occur due to excessive trimming of vaginal wall during prolapse surgery or as a result of aberrant scarring. Dissection along the anterior vaginal wall may result in nerve injury and neuroma formation. Sling erosion may also result in dyspareunia. Other poorly understood factors contributing to postoperative sexual dysfunction may exist. For example in some series 4-5% of patients following TVT or IVS slingplasty experienced decreased libido [359,356]. The reason for this decreased libido is unclear.

6. Infection and UTI

Multiple cases of pelvic abscesses have been reported with anti-incontinence surgeries including midurethral slings [360,361,363,282,364-365]. These consist mostly of case reports (Level 4).

There is inconsistent reporting of the prevalence urinary tract infection following anti-incontinence surgery. This may be due to issues with definitions and cause and effect.

7. General Medical complications and other postoperative complications

The incidence of significant morbidity from non-urinary tract medical conditions is unknown. As with any surgical procedure, there exists an undefined risk due to anaesthesia, associated cardiac and pulmonary morbidities such as postoperative myocardial infarction or pulmonary embolus. Older age and medical co morbidities may be associated with an increased risk of general medical and non-urological complications in older patients undergoing UI surgery as compared to younger patients [300].

Likewise the risk of death is unknown as this is an exceedingly rare complication in UI surgery. The AUA SUI Guidelines Panel estimated the risk of death following anti-incontinence surgery as 5/10,000 cases based on data from hysterectomy series [24].

Urinary fistula following SUI surgery is quite rare. Nevertheless, an unrecognized and unrepaird intraoperative injury to the ureter, bladder or urethra may result in ureterovaginal, vesicovaginal or urethropalvaginal fistula.

De novo vaginal prolapse may occur following anti-incontinence surgery and has been associated with colposuspension procedures including vault prolapse and posterior vaginal wall prolapse.

8. Periurethral bulking agents

(Figure 11)

In general, the morbidity associated with periurethral injectable agents is low. UTI, short term voiding dysfunction including urinary retention and haematuria
have been reported with all of the periurethral injectable agents. Stothers et al looked at complications related to intraurethral bovine collagen injection in a large series of patients (Level 3) [366]. In 337 patients injected with intraurethral collagen, approximately 20% of patients had at least one minor complication. The most common reported complication was de novo urge incontinence in 12.6%, followed by haematuria in 5% and urinary retention in 1.9%. Other bulking agents have demonstrated similar adverse event trials (Level 2) [148,144,150,149].

With respect to approach, periurethral injection has been noted to be associated with more complications including urinary retention and postoperative voiding dysfunction as compared to transurethral injection of bulking agents in one randomized trial of a dextran/hyaluronic acid compound (Level 2) [149,144].

Randomized controlled trials have compared bovine collagen to carbon coated beads as well as calcium hydroxylapatite. Lightner et al demonstrated a similarly minimal long term complication rate between collagen and carbon coated beads with a higher incidence of short term urinary retention and urgency in the carbon coated bead group (Level 1) [144]. Mayer et al noted no difference in short or long term complications in a randomized prospective trial comparing collagen and calcium hydroxylapatite (Level 1) [150]. Finally, there was no significant difference in short or long term complications in a randomized trial comparing porcine collagen to silicone (Level 2) [148].

Periurethral bulking agents including silicone [140] and collagen [141] have been compared to surgery in 2 randomized prospective trials. In both trials morbidity due to surgery was significantly greater than that associated with the injectable agent (Level 2).

Distal and systemic migration of polytef [368,369], and carbon coated beads [370] has been reported. The long term ramifications of these synthetic materials in the lymph nodes, lungs, brain and other organs are unknown. One bulking agent has been noted to have a high rate of erosion into the urethral lumen and has been recently withdrawn from the US marketplace.[371]

**V. SURGERY FOR DETRUSOR OVERACTIVITY**

The presumed aetiology of overactive bladder is detrusor overactivity [372]. Symptomatically, only 1/3 of patients with overactive bladder have associated urinary incontinence [373]. Many of these patients can be successfully treated with a combination of non-surgical measures including behavioural modification, pelvic floor physiotherapy and pharmacological therapy (see chapter on Conservative Management of Urinary Incontinence). Surgical therapy of non-neuropathic overactive bladder incontinence is generally reserved for those patients who have failed an adequate trial of these measures [374,375]. Overall, there are few studies on the surgical therapy of non-neurogenic detrusor overactivity urinary incontinence.[376,377]

Surgical interventions for urinary incontinence related to neurogenic detrusor overactivity incontinence are covered elsewhere (see chapter on Neuropathic Bladder).

### 1. ENDOSCOPIC APPROACHES

#### a) Endoscopic bladder transaction

Endoscopic bladder transaction is modelled after an open procedure, designed, in part to denervate the bladder by circumferential endoscopic incision proximal to the bladder neck. There are few reports of its use and this procedure is now rarely, if ever, performed.

**Level I evidence:** There is no Level 1 evidence regarding this modality in the therapy of non-neurogenic detrusor overactivity incontinence.

**Other evidence:** Parsons et al reported endoscopic bladder transaction as an effective technique of treating symptomatic bladder instability (Level 4 evidence) [378]. Subsequent reports (Level 4 evidence) [379,380] have been less favourable.

#### b) Hydrodistension or Bladder Overdistension

Bladder overdistension was originally described by Helmstein et al for the treatment of bladder cancer [381] but has also been cited as potential therapy for the treatment of some types of voiding dysfunction, including interstitial cystitis. Several reports have described its application towards the treatment of...
detrusor overactivity. In practice, this procedure is performed under general or regional anaesthesia and utilizes a hydrostatic column of fluid under high pressure infused into the urinary bladder and left indwelling for a variable period of time. The mechanism by which this therapy purportedly treats detrusor overactivity is not well understood.

**Level I evidence:** There have been no randomized controlled trials, double blind trials or cohort studies which have examined the effects of bladder overdistension for non-neurogenic detrusor overactivity incontinence.

**Other Evidence:** There are only a few reports on hydrodistention for the therapy of detrusor instability or non-neurogenic detrusor overactivity incontinence. The existing literature consists of primarily small retrospective case series with brief follow-up and subjective outcome parameters (Level 4 evidence).

Of the few favourable reports on hydrodistention for urinary incontinence, Ramsden reported that 41/51 patients (80.4%) had substantial improvement or were free of urinary symptoms at a follow-up of 13 months [382]. Dunn et al noted that 19/20 patients with urge incontinence or severe urgency and frequency were either improved or cured following bladder distention [383]. Corroborative objective outcomes data such as pad tests or voiding diaries were lacking in both of these studies. In contrast, Delaere and colleagues reported on 63 patients with involuntary bladder contractions on uroflowmetry and urge incontinence undergoing prolonged bladder distention [384].

Results were tabulated according to symptomatic outcome. Continence was not a primary outcome measure. At 1 year follow-up 11% of patients were cured and 21% improved. Whitfield noted that none of 11 patients with detrusor instability treated with a classical Helmstein balloon bladder overdistension “reverted” to a normal cystogram although 6/11 noted some symptomatic improvement [385]. Poor results were also seen by Pengally and colleagues in whom only 4/46 patients noted symptomatic improvement following hydrodistention [386]. Of the 43 patients undergoing postoperative urodynamics in this study, none had “conversion” to a stable detrusor on uroflowmetry.

Long-term follow-up studies demonstrating an objective or durable response to this modality of therapy for detrusor overactivity incontinence are lacking. Outcome measures have included mostly subjective patient assessments done in a retrospective fashion. Validated general or disease specific quality of life instruments have not been utilized to assess outcomes in these patients.

Bladder rupture, haematuria, infection, voiding dysfunction, and urinary retention are potential risks of bladder overdistention.

c) **Transvesical Phenol Injection**

Transvesical phenol injection is performed by endoscopic injection of a 5%-6% aqueous phenol solution in the region of the trigone of the bladder. The mechanism by which phenol exerts its favourable effects is purported to be via chemical denervation (neurolytic agent) [387].

**Level I evidence:** There are no randomized, double blind, placebo controlled studies that have examined the efficacy of subtrigonal phenol or compared it to another therapy for detrusor overactivity incontinence.

**Other evidence:** Several uncontrolled studies have examined the effects of subtrigonal phenol injection for the treatment of both non-neurogenic and neurogenic detrusor overactivity (Level 4 evidence). Initial studies suggested that this therapy was safe and effective in the short term with response rates of between 58-83% [388-391]. Better response rates were seen in neurogenic as compared to non-neurogenic voiding dysfunction, especially in patients with multiple sclerosis [389,390]. In one study, neurogenic bladder patients had a markedly greater response rate (82%) as compared to younger (<55 years old) non-neurogenic patients (14%) [391]. Subsequent studies with longer-term follow-up have not reproduced these results. Chapple and colleagues reported that only 4 out of 24 patients derived any ongoing benefit from phenol injection at 6 months follow-up [392], whereas Ramsay and colleagues reported a subjective response rate of only 14% in 41 patients at a mean follow-up of 13.7 months [393]. Wall et al reported a 29% initial response rate with all patients eventually failing at up to 4 years follow-up [394]. A similar long term failure rate was seen by Rosenbaum et al where only 1 out of 60 patients maintained a satisfactory result at 2 years [395].

Overall an 11.3% complication rate has been attributed to subtrigonal phenol injection including urinary retention, fistula and significant haematuria [392].

**Recommendation:**

Current evidence suggests that women with refractory non-neurogenic detrusor overactivity do not gain long term benefit from endoscopic bladder transaction, bladder overdistension, or transvesical phenol injection. Clinical use of these modalities is not recommended for this indication. (Grade C)

2. **OPEN SURGICAL INTERVENTIONS**

a) **Ingelman-Sundberg Denervation**

In 1959 Ingelman-Sundberg described an operation for the treatment of urge incontinence that selectively divided the preganglionic pelvic nerves near the inferior surface of the bladder through a transvaginal approach.
This involved considerable dissection near the cervix and bilateral transection of the pelvic nerves in this region.

**Level I evidence:** There have been no randomized controlled trials, double blind trials, sham-controlled studies, or cohort studies which have examined the effects of Ingelman-Sundberg denervation for the treatment of non-neurogenic detrusor overactivity incontinence.

**Other evidence:** Hodgkinson et al reported good results with this procedure in a case series of 23 patients, with 12 patients subjectively cured and an additional 9 improved (Level 4 evidence) [396]. The results of a modified Ingelman-Sundberg procedure by Cespedes and colleagues suggested a 64% cure of urge incontinence in carefully selected patients at a mean follow-up of 14.8 months [397]. In this case series (Level 4 evidence) the authors preselected the 25 patients based on a satisfactory clinical response to a transvaginal injection of local aesthetic in the region of the trigone. Westney and colleagues reported long term results with the same modified Ingelman-Sundberg procedure in a case series of 28 women (Level 4 evidence) [398]. Using the same preselection criteria as Cespedes et al, these authors noted a 54% cure of urge incontinence and a 68% cure/improved rate at a mean follow-up 44.1 months.

One randomized prospective trial compared 96 patients with mixed urinary incontinence treated with a transobturator midurethral sling (TOT) alone vs. those treated with a TOT combined with an Ingelman-Sundberg procedure. Objective surgical response rate was significantly higher in the TOT plus Ingelman-Sundberg group than in the TOT alone group (84.8% vs. 62.8%; p=0.019) [399]. Complications in both groups were similar although operative times were longer in the combined surgery group.

Complications associated with the Ingelman-Sundberg procedure have included ongoing voiding dysfunction, bleeding, and transient urinary retention.

**b) Sacral rhizotomy**

This procedure is primarily performed in the neuropathic bladder population and is discussed further elsewhere (See chapter on Neuropathic bladder).

**c) Enlargement (augmentation) cystoplasty**

1. **Enterocystoplasty**

Augmentation cystoplasty has been used for many years with varying degrees of success for refractory detrusor overactivity and related incontinence. Indications for enterocystoplasty (other than non-neurogenic detrusor overactivity) include small capacity bladders due to fibrosis, tuberculosis, radiation, or chronic infection, neurogenic detrusor overactivity, poor bladder compliance, as well as others [400-403]. Virtually any portion of the GI tract can be utilized for enterocystoplasty with each segment having its own unique favourable properties as well as inherent complications [403,404]. There is no ideal segment for all cases. Incorporation of bowel into the lower urinary tract results in decreased bladder contractility and an interval increase in the volume to first involuntary bladder contraction during cystometry. Technically, the surgeon must be aware that the selected bowel segment should contain a suitable length of mesentery to reach into the deep pelvis for a tension free anastomosis between bowel and bladder. During enterocystoplasty, there is no general agreement on whether it is more favourable to bivalve the bladder sagittally or transversely. However, it is ideal to create the broadest possible opening in the bladder and thereby create the widest possible anastomosis between bladder and bowel resulting in the most spherical configuration possible. The bowel is divided and detuberalised on its antimesenteric side prior to anastomosis to maximally reduce peristaltic contractions. The goal of enterocystoplasty is to create a high capacity, low-pressure reservoir during the filling/storage phase of the micturition cycle. When successful, and properly combined with other concomitant reconstructive procedures (i.e. ureteroneocystostomy, slings, artificial urinary sphincters, etc.), enterocystoplasty protects the upper urinary tract from pressure-related injury, infection and reflux while ideally providing complete urinary continence.

**Level 1 evidence:** There have been no randomized controlled trials, double blind or sham-controlled trials or cohort studies which have examined the effects of enterocystoplasty for the treatment of non-neurogenic detrusor overactivity incontinence or directly compared it to another therapy for the same indication.

**Other evidence:** There are only a small number of reports in the literature that have examined the results of enterocystoplasty in adult patients with non-neurogenic detrusor overactivity incontinence. These include only case series (Level 4 evidence). One series comprised solely females [405] with the remaining series including both males and females as well as varying numbers of neuropathic bladder patients [379, 406-412] (See Table 8). Outcome measures have included mostly non-validated questionnaires and subjective patient assessments. Validated general or disease specific quality of life instruments have not been widely utilized to assess outcomes in these patients.

Awad et al reported on a series of 51 female patients undergoing augmentation cystoplasty for refractory non-neurogenic bladder related incontinence [405]. 18% of patients continued to have disabling symptoms of urinary incontinence, and only 53% of patients classified themselves as “happy” with the outcome of the surgery. One series noted a deterioration in
outcomes over time [376]. In this mixed series, symptomatic improvement was reported in 83% of non-neurogenic patients at 3 months postoperatively, but decreased to just 58% at last follow-up (mean follow-up 38 months). In contrast, 92% of neuropathic bladder patients in this series reported a “good” or “moderate” result at last follow-up. Similarly, Herschorn and colleagues reported a very high degree of patient satisfaction in a series composed of only neuropathic bladder patients with all 59 patients reporting that they were delighted, pleased or mostly satisfied with the surgery [377]. The reasons for apparent superior patient satisfaction in neuropathic patients as compared to non-neuropathic patients are unclear.

d) Auto augmentation

As an alternative to enterocystoplasty especially in children with neuropathic bladder, auto augmentation of the bladder was initially described by Cartwright and Snow [413,414]. Auto augmentation may be performed by incision (detrusor myotomy) or excision (detrusor myomectomy) of a portion of the detrusor muscle. Either technique purportedly creates an iatrogenic bladder mucosal “bulge” or pseudodiverticulum and an increase in the storage capacity of the bladder with a concomitant decrease in storage pressures. The reported advantages of detrusor auto augmentation over enterocystoplasty is the avoidance of complications related to the use of bowel in the urinary tract including malignancy, mucous formation, stones, surgical morbidity related to opening and reanastomosis of the GI tract, and metabolic acidosis [375,415, 403].

Level I evidence: There have been no randomized controlled trials, double blind trials or cohort studies which have examined the effects of enterocystoplasty as a treatment for non-neurogenic detrusor overactivity incontinence.

Other evidence: There are few studies on auto augmentation in the adult non-neurogenic population (See Table 8). One small study of 5 patients with urge incontinence showed promising results in all patients at the initial postoperative visit, but clinical deterioration and failure occurred in 4 of the 5 patients at 3 months follow-up [416] (Level 4 evidence). Mean bladder capacity increased but mean volume to first unstable bladder contraction decreased. 4 of the 5 patients continued to have involuntary bladder contractions on cystometry. One retrospective study compared detrusor myomectomy to enterocystoplasty in 61 patients [412]. The population under study included both men and women with neurogenic and non-neurogenic voiding dysfunction. These authors reported comparable clinical success for the two procedures however there was a 22% incidence of serious complications in the 27 patients undergoing enterocystoplasty, compared to only 3% of the 33 patients undergoing detrusor myomectomy.

Long term follow-up of auto augmentation in children with neurogenic bladder has demonstrated disappointing results [417,418]. This has been attributed to eventual fibrosis of the pseudodiverticulum [415]. In an attempt to improve long-term outcomes with this procedure and create a biological “backing” and blood supply for the pseudodiverticulum, a number of variations of this procedure have been described. These variations have included the use of demucosalized bowel segments, stomach, peritoneum and rectus abdominis muscle [415,419-423]. Long-term follow-up demonstrating favourable clinical results with these variations is lacking.

e) Tissue engineering

Various tissue engineering techniques have been utilized in an attempt to create a suitable alternative to enterocystoplasty or autoaugmentation [424,425]. Many of these techniques rely on the use of native urologic tissues either partially or fully. Techniques have included the use of foetal tissues as well as collagen matrices overgrown with transplanted cells especially autologous cells.

Level I evidence: There have been no randomized controlled trials, double blind trials or cohort studies which have compared tissue engineered bladders in humans to any other technique for the treatment of non-neurogenic detrusor overactivity.

Other evidence: There are no published trials using tissue engineering techniques for bladder reconstruction in humans in the non-neurogenic detrusor overactivity population. One case series of 7 patients with neurogenic bladder due to myelome-ningocele demonstrated modest success with tissue engineered autologous bladder constructs (Atala, 2006) [426] (Level 4).

f) Urinary diversion

Urinary diversion away from the bladder is rarely needed for the treatment of non-neurogenic detrusor overactivity. This is usually reserved for patients who fail other surgical measures or who have intractable detrusor overactivity and desire a simplified method of management such as an abdominal urostomy. An ileovesicostomy (“chimney”) procedure or Bricker bilateral ureteroileostomy may be considered depending on the clinical circumstances including the presence or absence of native vesico-ureteral reflux (Leng, 1999) [412]. There are no studies that have examined these techniques in the treatment of non-neurogenic detrusor overactivity incontinence.

CONCLUSIONS

Prospective, randomized, placebo (or sham) controlled trials of surgical therapy for detrusor overactivity incontinence are lacking. There is a need to critically assess these procedures in an evidenced based manner and compare them to each other as well as non-surgical therapies using a variety of outcome measures including quality of life parameters. (Table 8)
Table 8. Enlargement Cystoplasty for Non-neurogenic Detrusor Overactivity Incontinence in Adult Women*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. patients</th>
<th>mean age</th>
<th>bowel segment/Technique</th>
<th>Follow-up (mean)</th>
<th>success criteria</th>
<th>Cure rate</th>
<th>Success rate</th>
<th>% on CIC</th>
<th>Level of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramble et al</td>
<td>1982</td>
<td>15 (7 female)</td>
<td>n/a</td>
<td>ileum or sigmoid</td>
<td>30 months</td>
<td>patient report: success = dry day and night</td>
<td>n/a</td>
<td>86.7%</td>
<td>13.3%</td>
<td>47.7%</td>
<td>Level 4</td>
</tr>
<tr>
<td>Mundy et al</td>
<td>1985</td>
<td>40 (22 female)</td>
<td>28 ileum</td>
<td>ileum</td>
<td>12 months</td>
<td>patient report: cure = absence of presenting symptoms</td>
<td>90%</td>
<td>n/a</td>
<td>15%</td>
<td>Level 4</td>
<td>8 neuropathic patients included in the series</td>
</tr>
<tr>
<td>Kockelbergh et al</td>
<td>1991</td>
<td>45 (31 female)</td>
<td>ileum/col 45 median</td>
<td>ileum in 40 patients, colon in 5 patients</td>
<td>20.3 months</td>
<td>patient report: cure = improvement of incontinence, improved = reduction in urgency</td>
<td>69%</td>
<td>71%</td>
<td>33%</td>
<td>Level 4</td>
<td>3 neuropathic patients included in the series</td>
</tr>
<tr>
<td>George et al</td>
<td>1991</td>
<td>31 (30 women)</td>
<td>51 ileum</td>
<td>ileum</td>
<td>48 months</td>
<td>patient report: cure = lack of symptomatic urge incontinence</td>
<td>74.20%</td>
<td>n/a</td>
<td>19.3%</td>
<td>Level 4</td>
<td>2 IC and 1 radiation cystitis included</td>
</tr>
<tr>
<td>Hasan et al</td>
<td>1995</td>
<td>48 (31 women)</td>
<td>ileum/col 46 median</td>
<td>ileum in 46, colon in 2</td>
<td>38 months</td>
<td>patient report: cure = dry day, improved = improved grading system</td>
<td>n/a</td>
<td>58%**</td>
<td>85%</td>
<td>Level 4</td>
<td>13 neuropathic patients included</td>
</tr>
<tr>
<td>Kelly et al</td>
<td>1997</td>
<td>27 (12 female)</td>
<td>ileum</td>
<td>ileum</td>
<td>18 months</td>
<td>patient report: cure = patient report of voiding at will with no incontinence using an unvalidated questionnaire, improved = subjective improvement of symptoms</td>
<td>61%</td>
<td>72%</td>
<td>56%</td>
<td>Level 4</td>
<td>8 neuropathic patients included in the series</td>
</tr>
<tr>
<td>Awad et al</td>
<td>1998</td>
<td>51 (all female)</td>
<td>ileum</td>
<td>ileum</td>
<td>75.4 months</td>
<td>patient report: cure = no pads by patient report, improved = occasional &quot;leaks&quot; or a mean of 1 pad per day</td>
<td>53%</td>
<td>78%</td>
<td>44%</td>
<td>Level 4</td>
<td>27 IC patients included in the series</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Detrusor Myectomy/Auto-augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenneth et al 1994 5 (4 women) ileum myectomy 16 weeks</td>
</tr>
<tr>
<td>ter Meulen et al 1997 6 (3 women) ileum myectomy 3 months</td>
</tr>
<tr>
<td>Swami et al 1998 27 (n/a) n/a ileum myectomy 27 months</td>
</tr>
<tr>
<td>Leng et al 1999 37 (n/a) n/a ileum myectomy 3 months</td>
</tr>
</tbody>
</table>

*results reported for the entire cohort (males+females, and neurogenic vs non-neurogenic) unless otherwise noted | 13.3% estimated from patients who would assist voiding | |
*does not include neurogenic patients | n/a not available, not applicable, or not reported |
Recommendations

Augmentation enterocystoplasty should be reserved for patients who fail all forms of conservative therapy and are willing to accept the potential perioperative, and postoperative morbidity associated with the procedure as well as the potential need for permanent intermittent urethral catheterization. Women with non-neurogenic detrusor overactivity incontinence should be advised that, in the long term, only 50% of women are satisfied with the outcome from this procedure. (Grade C)

VI. COMPLICATIONS OF SURGERY FOR DETRUSOR OVERACTIVITY

1. AUGMENTATION CYSTOPLASTY

Complications associated with enterocystoplasty are significant and include those related to factors derived from the bowel segment being in direct contact with the urine as well as other operative and perioperative morbidity. Short and long term complications of enterocystoplasty have been recently reviewed by Greenwell et al and are summarized in Table 9 [402]. Especially clinically relevant is the potential need for long-term clean intermittent catheterization in these patients. This possibility must be discussed with the patient preoperatively as patients should be willing and able to accept permanent clean intermittent catheterization (CIC) as a method of bladder emptying. Inability or unwillingness to perform CIC in those in whom it is necessary can lead to life threatening complications such as pouch perforation, urosepsis and death. Mucous build-up in the augmented bladder may also be troublesome but can be controlled by a number of measures [427]. Malignant transformation is a long-term risk of bladder augmentation and requires ongoing lifetime surveillance [428-430].

Table 9. Complications related to enterocystoplasty *

<table>
<thead>
<tr>
<th>Complication</th>
<th>Reported Range (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Term Complications</strong></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0-1.35</td>
</tr>
<tr>
<td>Infection</td>
<td>0-1.5</td>
</tr>
<tr>
<td>Fistula</td>
<td>0-0.2</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>0-1.8</td>
</tr>
<tr>
<td>PE/DVT</td>
<td>0-1.7</td>
</tr>
<tr>
<td>MI</td>
<td>0-1.1</td>
</tr>
<tr>
<td>Patch necrosis</td>
<td>0-1.7</td>
</tr>
<tr>
<td><strong>Long Term Complications</strong></td>
<td></td>
</tr>
<tr>
<td>GIC</td>
<td>14-100</td>
</tr>
<tr>
<td>Metabolic</td>
<td>0-19</td>
</tr>
<tr>
<td>Renal deterioration</td>
<td>0-16</td>
</tr>
<tr>
<td>Asymptomatic UI</td>
<td>0-50</td>
</tr>
<tr>
<td>Symptomatic UI</td>
<td>0-100</td>
</tr>
<tr>
<td>Stones</td>
<td>0-30</td>
</tr>
<tr>
<td>Pustulation</td>
<td>0-9</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>0-64</td>
</tr>
<tr>
<td>Failure to resolve underlying urinary problem</td>
<td>5-42</td>
</tr>
</tbody>
</table>


VII. NEUROMODULATION

Sacral nerve stimulation (SNS) involves the stimulation of the sacral nerves to modulate the neural reflexes that influence the bladder, sphincter and pelvic floor. The initial experience with sacral nerve stimulation for use in bladder dysfunction was reported by Tanagho and Schmidt (1981) [431]. Since then, SNS using the Interstim (Medtronic, Minneapolis, Minnesota, U.S.A.) has been an invasive therapy that was approved by the FDA in 1997 for treatment of refractory urge incontinence. Use has been extended to include significant urgency, frequency and idiopathic urinary retention. World-wide, the number of implants passed 10,000 in 2003 with more than 70% of the implants in the U.S.

a) Surgical Methods

Implantation of SNS consists of two steps: a) Stage I, or the trial stage – This involves the placement of a stimulation lead next to the dorsal root of S3 for a time period between 1-4 weeks. If the patient’s symptoms under the existing list of indications for SNS improves more than 50 %, then the patient is a candidate to undergo the second step; b) Stage II or Permanent Step – In this step the permanent neurostimulator is implanted in the soft tissue of the buttock of the patient.

b) Reports of RCT on three indications of UI, U/F and UR

The initial report on the efficacy of SNS on treatment of refractory urinary urge incontinence was reported in 1999 (Schmidt 1999) [432](Level 2- as no placebo or sham control was used). This study reported the treatment of 76 patients with refractory urgent urinary incontinence from 16 contributing worldwide centres. The patients were randomized to immediate implantation and a control group with delayed implantation for a six-month period. At six months, the number of daily incontinence episodes, severity of episodes, and absorbent pads or diapers replaced daily due to incontinence were significantly reduced in the stimulation group compared to the delayed group. Of the 34 stimulation group patients, 16 (47 percent) were completely dry, and an additional 10 (29 percent) demonstrated a greater than 50 percent reduction in incontinence episodes. The interesting finding was that during the therapy evaluation, the group returned to the baseline level of incontinence when the stimulation was inactivated. Complications
were site pain of the stimulator implantation in 16 percent, implants infection in 19 percent, and leak migration in 7 percent.

The use of SNS in urgency frequency was reported in 2000 (Hassouna 2000)\(^{433}\). Similar to the previous design, 51 patients from 12 centres were randomized into an immediate stimulation group and a control group (25 and 26 patients respectively) ((Level 2- as no placebo or sham control was used)). Patients were followed for one, three and six months, and afterwards at six-month intervals up to two years. At the six-month evaluation, the stimulation group showed improvement in the number of voiding episodes (16.9 + 9.7 to 9.3 + 5.1) volume per void (118 + 74 to 226 + 124 ml) and degree of urgency (the rank 2.2 + .6 to 1.6 + .9). In addition, significant improvement in quality of life was demonstrated, as measured by SF-36.

Use of SNS for urinary retention was published in 2001 (Jonas 2001)\(^{434}\), and in this study 177 patients with urinary retention refractory to conservative therapy were enrolled from 13 worldwide centres between 1993 and 1998 (Level 2- as no placebo or sham control was used). Thirty-seven patients were assigned to treatment and 31 to the control group. The follow-up was done at one, three, six, twelve and eighteen months. The treatment group showed 69 percent elimination of catheterization at six months and an additional 14 percent with a greater than 50 percent reduction in catheter volume per catheterization. Temporary inactivation of SNS therapy resulted in significant increase in residual volume, but the effectiveness of central nervous stimulation was sustained for 18 months after implantation.

In 2000, a follow-up report of some of these patients was published (Siegl 2000)\(^{435}\) (Level 3). This report showed follow-up results after three years in all the indications. Fifty-nine percent of 41 had urinary urge incontinence. 46 percent of these patients were completely dry. After two years, 56 percent of the urgency frequency patients showed greater than 50 percent reduction in voids per day, and after 1-1/2 years, 70 percent of 42 retention patients showed greater than 50 percent reduction of catheter volume per catheterization.

The results of the use of SNS in the U.S. population were published in 2002 (Pettit 2000)\(^{436}\) (Level 3). This publication showed the data collected from the U.S. patient registry. The report included the use of SNS in 81 patients with all three indications: 27 for urgent continence, 10 with urgency frequency and 10 with urinary retention. In this report, 27 from 43 patients with urgent continence, 10 out of 19 with urgency frequency and 10 out of 19 with urinary retention showed improvement of more than 50 percent.

The results of an Italian registry was published in 2001 (Spinelli 2001)\(^{437}\) (Level 3). This report included the reports of 196 patients – 46 males and 150 females – for idiopathic urinary retention. 50 percent of patients stopped catheterization and another 13 percent catheterized once a day at one year after implantation. At the 12-month follow-up, 50 percent of patients with hyper-reflexia had less than one incontinence episode daily and the problem was completely solved in 66 patients. Of the patients with urgent continence, 39 percent were completely dry and 23 percent had less than one incontinence episode daily.

In Norway, the results of users of this modality were published in 2002 (Hedlund 2002)\(^{438}\) (Level 3). The author reported the first three years of experience with 53 patients: 45 women and 8 men. This study showed similar results to previous studies.

c) Urinary Retention

Aboseif et al 2002 reported on the use of SNS in functional urinary retention (Level 3). 32 patients were evaluated and underwent temporary PNE. Those who had a least a 50% improvement in symptoms during the test period underwent permanent generator placement. All patients who went to permanent generator placement were able to void spontaneously. There was both and increase in voided volume (48 to 198ml) and decrease in post void residual (315ml to 60 ml). 18/20 patients reported a greater than 50% improvement in quality of life.

d) Other Indications

Use of SNS for other off-labelled applications has been reported in the form of abstracts. The off-labelled usage has included use of SNS in neurogenic bladder; interstitial cystitis, and chronic pelvic pain. All these results are limited case series reports. (Level 5)

e) Complications

The reported complications of SNS includes infection, revision of stage I or II, lead migration, and undesirable stimulus. Changes in other visceral functions (sexual function; bowel function) has also been reported.

Stoller in 1987 reported that stimulation of the peripheral tibial nerve in pig-tailed monkeys was able to inhibit bladder overactivity (Gillon 1989)\(^{439}\) (Level 3). This initial work led to its use in patients with refractory overactive bladder.

1. Results

In 2000 Klinger et al performed a prospective trial on 15 patients with urgency-frequency syndrome. They underwent 12 weeks of stimulation with the SANS device (Level 3). Ten patients responded with a reduction in voiding frequency per day (16 to 4) and daily leakage episodes (4 to 2.4). The only complication was one haematoma at the puncture site.
Govier et al (2001) [440° (Level 3) in a multicenter study reported the efficacy of SANS in 53 patients. All patients had refractory OAB and were seen at 5 different sites in the U.S. The patients completed a 12-week stimulation. 71% of the patients had at least a 25% decrease in daytime or night time frequency. No adverse effects were noted.

Level 2-3 evidence suggests that sacral neuromodulation may provide benefit in the treatment of patients with refractory urinary incontinence, urgency/frequency and idiopathic, non-obstructive urinary retention.

The mechanism of action of neuromodulation remains unknown.

The predictors of outcome and patient response to neuromodulation remain unknown.

Longer term and independent observational studies are needed to examine the longevity of the neuromodulation and identification of the most appropriate patient who should undergo this treatment.

2. COMPLICATIONS OF NEUROMODULATION

Several complications related to sacral neuromodulation have been well documented. Overall, the reported surgical revision or removal rate has been reported to be as high as 16-32% [441, 442]. Seigel et al reported on adverse events in 219 patients with pain at the stimulator site being the most common (Table 10) [443]. This is the most frequently reported complication in many series [442, 444]. Generally relocation of the device into another buttock or lower abdominal site will improve the pain.

| Table 10. Adverse events related to Interstim implantation in 219 patients* |
|-----------------|-----------------|
| Pain at the stimulator site | 15.3% |
| New pain | 9.0% |
| Lead migration | 8.4% |
| Infection | 6.1% |
| Transient electric shock | 5.5% |
| Pain at the lead site | 5.4% |
| Changes in bowel function | 3.0% |

*adapted from: [454]

Several recent studies have reported longer-term results of sacral neuro-modulation in a prospective fashion. van Kerrebroeck, et al reported a five-year prospective study using validated tools for urge incontinence, urinary frequency and retention. 17 centres were included, worldwide, with 163 patients of whom 87% were female. Of these patients, 152 eventually underwent permanent implantation of the InterStim device. Of those undergoing implantation, 96 (63.2%) had urge incontinence and 25 (16.4%) had urgency and frequency. Voiding diaries were collected post-insertion, annually, with clinical success being defined as 50% or greater improvement in primary voiding dysfunction variables. At five years, urge incontinence leaking episodes decreased from a mean of 9.6 (plus or minus 6) to 3.9 (plus or minus 4) episodes per day. For those patients with urinary urgency, mean voids decreased from 19.3. (plus or minus 7) per day to 14.8 (plus or minus 7.6) whereas mean voided volume increased from 92.3. (plus or minus 52.8 ) to 165.2 (plus or minus 147.7). All changes were noted to be statistically significant according to the authors’ findings, with no life-threatening or irreversible adverse events being recorded. However, 279 device- or therapy -related adverse events in 102 patients were noted. Overall, 23.7% of patients during the study period required device exchange (36 patients). An additional twelve (7.9%) required re-positioning of the pulse generator, and ten (6.6%) required a lead and pulse generator replacement, and finally, ten (6.6%) required only lead re-positioning. An additional eleven patients (7.2%) required either permanent or temporary explantation, due to a variety of indications. The authors concluded that neuromodulation provided long-term benefit for urge incontinence, urinary frequency and urinary retention. (Level 3 evidence)

A second long-term outcomes report for neuro-modulation was published by van Voskuilen [446]. This was a single institution study and was a retrospective assessment of all patients implanted. There were 149 patients, including 107 subjects with urgency and frequency and/or urge incontinence as indication for implantation. Mean follow-up was 64.2 months (standard deviation 38.5). 194 adverse events were recorded, including six infections, with one explantation for infection. 129 re-operations were performed, with 21 complete explantations. There was a "learning curve" with time such that incidents of re-operations decreased substantially after 1996, correlating with improved experience with the device. This also correlated with a more "proactive" approach toward adverse events, including earlier diagnosis and intervention. Revision rates decreased overall from 4.25 in 1990, the first year of the study, to 0.00 from 2001 through the end of study, in 2003. The most common adverse event encountered in this population was pain with stimulation, followed by undesirable changes in voiding function, 64 and two, respectively, and pain at the IPG site, which was 41. There were also ten cases of lead migration and six cases of device-related failures.

Based upon a stringent review of the literature, a recent NICE guidance stated that sacral nerve stimulation was recommended for patients with detrusor overactivity who had failed conservative treatments. The NICE guideline concluded that approximately two-thirds of the patients achieved continence or at least substantial improvement of...
symptoms over periods ranging from 3-5 years, with approximately one-third of the patients requiring a re-intervention due to device-site or infection related complications.

Barizzelli reported a systematic review of the literature and acknowledged a similar finding [447]

Recommendation

Evidence Level: Sacral neuro-modulation appears to have benefit for patients with urge incontinence, as well as urgency and frequency. (Level 1, 2, and 3)

Recommendation Level A.

4 NICE guidelines reference

VIII. URETHRAL DIVERTICULUM

Search of Medline for urethral diverticulum (UD) and female resulted in 576 published articles from 1952 to 2008. Despite case reports dating to 1786 (Hey), most studies consist of case series and consist of small numbers without control groups or comparison of differing interventions.

Diagnosis of UD was first advanced by Davis and Cian when they introduced the Double Balloon Positive Pressure Urethrography technique in 1956. Recently, longer term follow up studies post intervention and advances in imaging such as magnetic resonance imaging (MRI) has led to increased clinical awareness and diagnosis of this condition. (Daneshgari 1999) [448] (Figure 12).

The important clinical topics concerning UD are:

1. CLASSIFICATION
2. IMAGING MODALITY USED FOR CHARACTERIZATION AND DIAGNOSIS
3. INDICATIONS FOR CONCOMITANT PROCEDURES SUCH AS ANTI-INCONTINENCE PROCEDURES,
4. USE OF INTERPOSITIONING TISSUES.
5. OUTCOME MEASURES AND COMPLICATIONS OF UD REPAIR

1. CLASSIFICATION

Leach (Leach et al. 1993) [449] originated a classification system designed to accurately describe the characteristics of urethral diverticulae. The system utilizes the acronym LNSC3, which represents descriptive parameters for L = Location, N = Number, S = Size, C1 = Configuration, C2 = Communication, and C3 = Continence. In a series of 61 patients, urethral diverticulae were most commonly single in number (90 percent) and shape (62 percent). The location of the diverticulum swelling (62 percent), and ostium (60 percent) was mid-urethra. Fifty-six percent of the patients were incontinent (Leach et al 1993) [449].

Leng and McGuire divided diverticulae based on the integrity of the periurethral fascia, although diverticulae were described generally as primary diverticulae consisting of a mucosal layer only with narrow neck ostia bound by intact periurethral fascia. In contrast, pseudodiverticulae are often multi-layered with wide mouthed ostia on cystoscopic examination in association with a periurethral fascia defect. Rupture or erosion of the periurethral fascia often correlates with a history of prior suspension or a recurrent urethral diverticulae (Leng and McGuire 1998) [450]. These authors introduced the possibility that recurrence rates were influenced by global defects in the periurethral fascia thus potentiating de novo diverticulum formation or recurrence even after successful initial intervention.

2. IMAGING MODALITY USED FOR CHARACTERIZATION AND DIAGNOSIS

Optimal imaging modality for diagnosis of UD continues to be discussed in the literature. However, increasing data supports the definitive role of MRI examination in defining these lesions. The existing modalities include:

a) Voiding Cysto Urethrogram (VCUG) /Double Balloon Retrograde Urethrography
b) Ultrasound
c) MRI

The value of concomitant cystoscopy during the evaluation process lacks any significant evidence although this practice appears to be widely used.

Figure 12: Urethral diverticulum
Similarly, the use of urodynamics (with or without fluoroscopy) while very commonly done in naturalistic settings, has not been adequately studied to assess contribution to the overall assessment of UD.

a) Voiding Cysto Urethrogram (VCUG) /Double Balloon Retrograde Urethrography

In 1928, Norris and Kimbrough were the first to utilize cysto urethrography to define female bladder and urethral anatomy. A variation of this technique was repeated by Davis using a specialized double balloon catheter. Reported sensitivity for these techniques has ranged widely from 44 to 100 percent (Ganabathi 1994; Jacoby 1999; Golomb 2003 Level 3) [451-453]. Other authors have argued for the value of VCUG combined with urodynamics to assist in structural and functional analysis of the entire lower urinary tract. (Rufford, 2005, Level 4)[454]

b) Ultrasound

In 1977, Lee and Keller reported the use of abdominal ultrasound to identify urethral diverticulae (Lee 1977) [455] (Level 3). This modality may be used when a high clinical suspicion exists and when urographic results are negative. Diverticulae appear as anechoic or hypo echoic (to periurethral tissue) cavities with enhanced through transmission. Newer higher frequency ultrasound probes associated with intraluminal probe use may further enhance the utility of this technique. (Yang, 2004, Level 4) [456]. Ultrasound has been shown to have 100% sensitivity as compared to other modalities for the diagnosis of UD. (Gerrard, 2003, Level 3) [457].

c) MRI (Figure 13)

MRI has the advantage of multiplanar capabilities and excellent soft tissue definition. These qualities allow for differentiation between urethral diverticulae and other periurethral masses. Both T1 rated and T2 weighted images have been used or could be used for diagnosis of MRI. The T2 weighted images allow a high signal intensity of the urine, and collections within the urethral diverticulae making it a preferred method of imaging for urethral diverticulae (Level 3). The multiplanar capability of the MRI allows for a) identification of multiple urethral diverticulae; and, b) surgical planning for repair of the urethral diverticulae. Neitlich et al. applied a high-resolution fast stain echo MRI technique using a torso multicoil resulting in an examination time of 15 minutes. This study prospectively compared double balloon urethrography with MRI imaging of the urethra for detection of urethral diverticulae with a resultant sensitivity of 25 and 100 percent respectively. (Neitlich 1998 Level 2) [458] Another study evaluated diverticulae preoperatively with MRI classifying them simple, « U » shaped, or circumferential based upon MRI appearance. Recurrence after resection was significantly higher in « U » shaped (33%) or ring lesions (60%) then in the simple group (0%).(Han, 2007, Level 2)459 MRI has also been shown to alter surgical management in some patients (15% of 27 patients). (Foster 2007, Level 4) [281]. Attempts at refining MRI technique using endo cavity techniques may improve detection and characterisation of these lesions. (Lorenzo, 2003, Level 3) [460].

There is no Level 1 evidence to support the optimal imaging modality. There are differences in the calculated sensitivity of each imaging modality between the various recorded studies. Moreover, the results of the studies are limited by differences in the patient population, study techniques, and interpretive skills of the radiologists.

3. TREATMENT

Surgery for stress incontinence may be successfully performed along with urethral diverticulectomy. Leach (Leach and Bavendam 1987) [461] described simultaneous needle bladder neck suspension in 22 women with stress incontinence (Level 3). At the main follow-up of 20.5 months, 77 percent were totally continent and no significant complications were noted. Four of the five failures were secondary to ISD. Swierzewski (Swierzewski and McGuire 1993) [462] performed simultaneous autologous rectus fascia vaginal sling and urethral diverticulectomy in 14 women (Level 3). All were cured of the stress continence and one developed severe detrusor overactivity. The diverticulae recurred in one patient. More recent reports suggest that when an anti-incontinence procedure is not performed at time of diverticulectomy, rates of symptomatic incontinence are high with 49% of women reporting de novo SUI, and when incontinence was pre-existent, a 73% rate of persistence (Lee, 2008, Level 3) [485].

Use of labial (Martius) fat pad, vaginal wall bipedicled...
flap and autologous fascia in forms of pubovaginal sling has been used as interpositioning techniques for repair of UD. All reported cases are case series (Level 3). In several series, use of perivesical fascia as the interpositioning layer has been reported.

The optimal outcome of repair of UD is a) absence of UD recurrence; b) relief of symptoms; and c) absence of complications. A wide range of measured outcomes is reported in the literature in mostly in form of case series (Level 3). The potential complications of the UD repair are reported as either short term (bleeding, urinary tract infection) or long term (urethrovaginal fistula, urethral pain syndrome, urinary incontinence, recurrent diverticulum). Recurrence of UD has been reported as long as 5 years after surgery. Presence or absence of additional pathologies such as neoplasm (squamous cell carcinoma, clear cell carcinoma, nephrogenic adenoma, vaginal leiomyoma), malakoplakia, and calculi formation within the UD has also been reported as an outcome measure. The incidence of concomitant pathology is reported in less than 5% of large series (Kochakarn 2000) [463].

In 1875, Tait was the first to report complete excision of a urethral diverticulae (Tait 1875) [464]. The following approaches have been reported in the literature for urethral diverticulum.

1. Endoscopic Approach – This technique uses a transurethral marsupialisation. (Davis 1970; Lapides 1979) [465,466].

2. Packing/Obliterative Procedures – The diverticulae cavity is packed with oxidized cellulose followed by closure of the diverticulum and vaginal wall. (Ellik 1957) [467].

3. Open Marsupialisation – The Spence technique, which is essentially a meatotomy, is often performed for distal diverticulum connecting the posterior aspect of the urethral wall. (Spence 1970) [468].

4. Open Diverticulectomy – This technique uses mostly vaginal exposure to a) identify the diverticulum, b) dissect the diverticulum, c) repair the defect in the periurethral fascia. This technique has been the most widely used technique and the most widely reported in the literature. For the majority of the cases, a single closure of the periurethral fascia suffices for repair; however, use of additional inter-positioning tissues such as Martius fat pad has been reported.

5. Retropubic approach for ventrally based proximal diverticulae – This is used for very proximal and ventrally positioned proximal diverticulae, which are not the most common type of presentation for diverticulum.

6. Supra-Urethral meatus Approach to Ventrally Based Diverticulum – In this approach for urethrolysis, a semi-circle incision is made above the urethral meatus thereby gaining an approach to the ventral urethral space.

7. Transvaginal resection with periurethral fascia dissection and layered closure (most common)

8. Urethral transection with circumferential dissection. (Rovner, 2003, Level 3) [469].

All the reported surgical techniques are case series (Level 3), and there is no published report of comparing the techniques or the outcomes in a prospective, randomized manner. One series reports the longest follow up of transvaginal resection. Sixty four women were followed up to twenty years, with recurrence in 11, urinary tract pain in 11, dyspareunia in 14, urinary urgency in 39 (12 with urge incontinence), and 24 with de novo stress incontinence. This report underscores the importance of assessing all functional outcomes of UD interventions. (Ljungqvist, 2007, Level 3) [470]

IX. NON-OBSTETRIC URINARY FISTULAE

I. INTRODUCTION

In developing countries birth trauma remains the aetiology for the majority of fistulae. (Arrowsmith 1996) [471]. In developed countries, modern obstetric care has substantially limited the risk of vesicovaginal fistulae and fistulae are usually the result of complications of gynaecological or other pelvic surgery. Evidence for fistula evaluation, timing of corrective intervention, methods of and adjuncts to correction, and associated management strategies is based on clinical series and / or case studies (Levels 2, 3 and 4) and lacks definitive randomized control analysis.

2. SPECIFIC AETIOLOGIES

In developed countries the most common cause of vesicovaginal fistula is routine abdominal or vaginal hysterectomy. At least 75% of genitourinary fistulae are subsequent to this cause (Jonas 1984, Symmonds 1984, Lee 1988, Tancer 1992) [472-475]. Fistulae occurring after hysterectomy are thought to be due to unrecognized direct bladder trauma, tissue necrosis caused by inadvertent suture placement though the bladder wall (probably most common and arising from suture placement at time of vaginal vault reconstruction), or thermal injury from electrocautery either as an isolated factor or in association with direct surgical injury. Tissue necrosis may also occur following previous surgery and with pelvic abscess or infection. Tissue necrosis results in fibrosis and induration, eventuating in an epithelial or mucosal lining of the fistula tract (Kursh, 1988) [476].

In 1980 Goodwin reported 32 patients with fistulae as a direct result of gynaecological intervention (Goodwin
Tancer (1992) [475] noted a similar group of 151 patients and found that 91% (137) were postsurgical with 125 caused by gynaecological surgery. The most common procedure accounting for fistula was hysterectomy in 73% (110) of cases (99 of which were performed transabdominally). Factors thought to contribute to the risk of fistula formation due to hysterectomy include: prior caesarean section, intrinsic uterine disease (endometriosis) and prior ablative treatment for carcinomas (pelvic radiation therapy). Similar risk factors were identified by Blandy et al. (1991) [478]. The incidence of fistula after hysterectomy is generally accepted to be 0.1 - 0.2%. (Harris, 1995) [479] Recent meta-analysis of the gynaecological literature suggests that the rate of iatrogenic ureteral injury during hysterectomy approaches a crude occurrence rate of 6.2 per 1000 cases, while bladder injury occurs at 10.4 per 1000 cases. (Gilmour, 1999) [480] Additional surgical aetiologies include: general surgical interventions in the pelvis (i.e. low anterior resection), anterior compartment repairs, or stress incontinence interventions. (Armenakas, Pareek, & Fracchia 2004) [481]. In a large series of 207 VVF, 83% were due to abdominal hysterectomy, 8% vaginal hysterectomy, 4% radiation and the remainder miscellaneous causes (Elieber et al. 2003) [482]. Intraoperative cystoscopy appears to lessen the risk of fistula formation by up to 90% for ureteral and 85% for bladder lesions. (Gilmour, Dwyer, & Carey 1999) [480].

Other causes of fistulae include: malignancy (Kottmeier, 1964) [483], radiation (Cushing, 1968, Stockbine 1970, and Villasanta, 1972) [484-486] gastrointestinal surgery (low anterior resection) (Cross, 1993) [487], inflammatory bowel disease and urinary tuberculosis (Ba-Thike et al, 1992) [488]. Symmonds' experience at the Mayo clinic revealed only 5% of 800 vesicovaginal fistulae to be due to obstetric causes (Symmonds, 1984) [473]. Rarely, foreign bodies such as pessaries, diaphragms, and intrauterine devices also may lead to fistula formation (Goldstein et al., 1990) [489]. Iatrogenic CO2 laser therapy for cervical disease has also resulted in bladder fistulae (Colombel, 1995) [490]. Autoimmune diseases such as Behcet's have also been implicated as causative for vesicovaginal fistulae, due to extensive vasculitis related bladder wall necrosis. (Monteiro, 1995) [491]. Cervical, vaginal and endometrial carcinoma account for 3-5% of VVF in the developed world, and are the most common malignancies associated with this phenomenon.

3. EVALUATION

The best preventative strategy for fistulas is early identification at the time of surgery with immediate repair of the bladder / ureteral injury. Physical examination is the most important diagnostic component in the evaluation of a woman with a suspected genitourinary fistula. Vaginal examination should try to identify the fistula tract and the degree of vaginal access.

Aiding physical examination, dyes may be instilled into the bladder and coloured vaginal drainage assessed. This tool is particularly helpful for obscure fistulas (Drutz & Mainprize 1988) [492].

Cystoscopy (Figure 14) is a crucial adjunct to demonstrate the location and size of the fistula as well as proximity to one or both ureteral orifices. Cystoscopy also assesses the bladder mucosa for oedema and persistent necrosis which may complicate planned surgical repair.

Figure 14: Post-hysterectomy cystoscopic appearance of a VVF

Patients may present while in the hospital with prolonged ileus, excessive pain, haematuria or flank pain (if a simultaneous ureteral injury also is present) (Kursh, 1998) [476]. If the fistula tract is large enough a significant amount, if not all, urine drains through the vagina, producing continuous or total incontinence. In other cases, fistula drainage may be minimal and intermittent and may be initially mistaken for stress incontinence occurring postoperatively. Patients with urethrovaginal fistulae arising from urethral catheter trauma may not develop symptoms until catheter removal has occurred. Incontinence arising from a urethrovaginal fistula may be intermittent unless the fistula extends across the bladder neck, in these cases severe and total incontinence is usually encountered. Fistulae may develop up to twenty years post radiation (Graham 1965; Raz 1992) [493,94]. Additionally, persistent clear vaginal discharge after hysterectomy may arise from leakage of peritoneal fluid from a vaginal cuff through a peritoneal sinus tract (posthysterectomy pseudo incontinence) (Ball, 1995) [494]. Ginsberg et al, 1998 [495], reported five patients with this finding, all of whom were cured by vaginal cuff revision.
Intravenous pyelography should be performed in women with any urinary fistula primarily to detect ureteric injury but also for congenital ureteric anomalies. Symmonds (1984) reported a 10% risk of a simultaneous ureteral component with vesicovaginal fistulae. The cystogram phase of the IVP may also suggest the presence of a fistula if early pooling of urine in the vagina occurs or wisps of urinary extravasation are noted. Retrograde pyelography may be employed for diagnosing the site of a ureterovaginal fistula or the possibility of a combined uretero- and vesicovaginal fistula, although no direct studies have evaluated this diagnostic technique against other imaging modalities.

Voiding cystourethrogram (VCUG) may also help determine fistula presence and location. Also, the VCUG may demonstrate other lower urinary tract abnormalities that may impact upon surgical reconstruction (vesicoureteral reflux, cystocele, urethral diverticulum). Occasionally contrast examination of the vagina (vaginography) may help demonstrate an irregular fistulous tract. Zimmern et al. (1994) [496] described the procedure for injecting contrast material through the vagina with a large balloon occluding the vaginal introitus. Level 3 evidence supports the use of this study.

Hilton (1998) [497] argues that urodynamics are necessary in the woman with a lower urinary tract fistula. He noted the following urodynamic abnormalities while evaluating 30 women with fistulae: 47% urodynamic stress incontinence, 44% detrusor overactivity, and 17% with poor bladder compliance. Urodynamics, however, are often difficult to perform due to continuous loss of instilled fluid through the fistula tract and therefore in many cases may not be additive to the overall evaluation of the patient. No evidence exists as to the role of urodynamics in predicting post-operative stress incontinence after fistula repair.

Summary

The evaluation of urinary fistulae is based on evidence of loss of urine on physical evaluation, cystoscopic inspection of the bladder, and assessment of lower ureteral integrity (either IVP of retrograde pyelography).

Mandatory evaluation includes clinical examination with or without the use of dyes (Level 3) Intravenous urogram (Level 3,4), Cystoscopy (Level 3)

Optional testing: Voiding cystourethrography (Level 3,4), Urodynamics (Level 4)

4. TREATMENT

a) Conservative and minimally Invasive treatment

Regardless of the timing of presentation, a trial of conservative therapy may be implemented which uses continuous urethral catheter drainage. Level 4.5 evidence suggests that a variety of conservative techniques may be curative and possibly should be attempted first in patients with single fistula tracts which are less than 1 cm in size, and which are not associated with complicating factors such as prior radiation. Tancer et al (1992) [438] reported 3 of 151 patients with spontaneous closure of fistula using this strategy. Spontaneous closure occurred with 3 fistula tracts identified early in the postoperative period in 45 women managed in this fashion. Often, however, the patient has already undergone a trial of catheter drainage at the time of initial evaluation and therefore further catheter drainage may be helpful. No definitive evidence suggests the optimal time for catheter drainage. (Level 4)

Another possible conservative therapy utilizes electrocoagulation or fulguration of the lining of the fistulous tract (O’Connor 1980, Alonso 1985, Molina 1989, Stovsky, 1994) [498-501]. In Stovsky’s experience 11 of 17 (73%) of patients with small (less than 3mm) fistulae treated with electrofulguration and 2 weeks of catheter drainage resolved. McKay (1997) [502] recently described successful cystoscopically placed suture closure of a vesicovaginal fistula, with no secondary incision.

Recently, the use of tissue adhesives has been described as a sealant for fistula tracts. Evans et al. (2003) [503] reported the use of fibrin sealant for five patients who had complex vesicovaginal fistulae. All five were successfully managed without complication. (Level 4)

Summary

Level 4/5 evidence suggests that conservative management techniques may be utilized in selected patients with small fistulae. More research is needed to better identify the patients who would best be managed in this manner.

b) Surgical Therapy

1. TIMING OF INTERVENTION

Previously, many authors have advocated a waiting period of at least 3 to 6 months before intervening with surgical therapy (O’Connor 1951, Wein 1980, Blandy 1991) [504,505,478]. No specific evidence exists as to the need for this delay in intervention. More recently surgeons have advocated an individualized approach without an observational period. Several authors have reported excellent results with early interventions (Persky, 1979, Goodwin 1980, Wang 1990, Raz 1992, Blaivas 1995, Raz 2000) [506,477,507,94,508,509]. There is Level 3 evidence that fistulae identified within the first 24 to 48 hours postoperatively can be safely repaired immediately. Those identified days to weeks after surgery require careful planning and selection. Wang and Hadley
successfully managed 15 of 16 (94%) high lying (vaginal apical) fistulae through a transvaginal approach, with all 7 patients who were less than three months from initial surgery cured of fistula. (Wang 1990) [507].

Summary
The timing for surgical intervention may depend on presenting factors such as tissue integrity. Intervention immediately following early diagnosis is successful in some series. Additionally, surgical approach (abdominal versus vaginal may also impact this decision). More research is necessary to identify optimal timing of fistula repair.

Evidence for timing of Surgery Level 4,5

2. Preoperative Preparation
No specific evidence supports any preoperative preparation as being crucial for surgical success. Individualization of operative decision will be impacted by the unique needs of each woman undergoing intervention. Local preparation such as vaginal douches with antiseptic agents the evening before and the morning of surgery have been used in the past but no evidence supports this technique. A recent RCT evaluating the use of antibiotic prophylaxis for fistula surgery showed no benefit to use of perioperative antibiotics (Tomlinson AJ & Thornton JG 1998) [510]. Oestrogen replacement therapy has also used in those patients with poor quality of vaginal tissues (Raz 1992) [94]. (Level 4/5)

Summary
No specific preoperative preparation has been shown to alter outcome. Antibiotic prophylaxis does not influence post-operative infective morbidity or outcome. (Level 1 / 2)

3. Surgical Approaches
Surgical approaches used for vesicovaginal fistulae include: combined abdominal vaginal, vaginal, or abdominal approaches. The approach chosen is dependent upon several factors, including location of fistula, quality of the tissues, and surgical experience and training. Vaginal surgery is more rapid and results in less morbidity and more rapid recovery; however, the vaginal route is difficult in patients with a significant degree of fibrosis, pelvic immobility, or with large fistula tracts with possible injury in close proximity to the ureteral orifices. (Carr & Webster 1997) [329] (Dupont & Raz 1996) [511] The abdominal approach may be more appropriate for the poorly visualized tract, the narrow or immobile vagina, and those with close proximity to a ureteral orifice. Laparoscopic repair also provides an alternative approach.

Other considerations for surgical repair include; type of suture, method of urinary drainage, and the use of tissue interposition graft.

There is only level 4 and 5 evidence to support any of the surgical techniques.

5. Vaginal Approach
The vaginal approach utilizes an anterior vaginal wall flap for coverage. Subsequently a tension free closure is performed utilizing a long acting (polyglycolic acid or polydioxanone) suture and non-overlapping multiple closure lines. Interposition tissue may be mobilized from labia, peritoneum, or vagina.

There is only level 4,5 evidence to support these techniques.

A suprapubic catheter should be placed (Zeidman 1988) [512]. Urinary drainage may also be supplemented with a urethral catheter. If the fistula communication occurs in proximity to the ureteral orifices, ureteric catheterization with cystoscopic assistance is generally performed prior to fistula closure. Optimal visualization is dependent on tissue mobility. The use of lateral relaxing incisions may help operative visualization and approach to the fistulous tract (Zimmern 1994) [602]. If the fistula repair is tenuous or there is concern regarding apposition of suture lines a Martius interpositional graft may be utilized. If this is not obtainable, alternative graft sources include a peritoneal flap (Raz 1993) [513] or an interposition graft utilizing gracilis muscle tissue. The peritoneum can be freed from the posterior aspect of the bladder and easily advanced to cover the layers of the closure as well (Raz 1993) [513]. (Level 4)

Level 4,5 evidence suggests that the Martius labial interposition graft provides a satisfactory graft material (Raz 1992, Blaivas 1995, Blaivas 2000, Hoskins, 1984) [94,508,514,515]. Several authors have used this graft as an adjunct to repair associated with complicated incontinence with excellent results. (Ghoniem 1995, Carr 1997) [517,329] Martius flap interposition has been used for both urethrovaginal and vesicovaginal fistulas and seemed to convey an advantage (0 recurrences in 13 women) over repairs which did not use flap interposition (4 recurrences in 21 women) (Rangnekar, Imdad, Kaul, & Pathak 2000) [518].

The vast majority of vesicovaginal fistulae can be closed in one operation using the previously described approach. Raz reported a success rate of 92% (64/69) for vesicovaginal fistulae, 2/3 of which had failed 1 to 3 prior repairs using this technique (Raz 1992) [94]. Many of these repairs used a peritoneal graft interposition.

Other variants for vaginal the approach include the Latzko which essentially produces a partial colpocleisis with risks of vaginal shortening and overlapping suture lines. (Enzelsberger & Gitsch 1991) [519] Additionally, vaginal cuff excision has been advocated as another ablative method for closing fistula tracts. (Iselin, Aslan,
6. **Abdominal Approach**

All bladder fistulae (except those extending into the urethra) may be approached utilizing the abdominal approach, and this is the preferred approach in those patients requiring bladder augmentation or ureteral re-implantation. The earliest experience was reported by O’Conor (1951, 1973) for abdominal transvesical repair of vesicovaginal fistulae. This technique may require placement of ureteral catheters to localize the ureteral orifices. An abdominal incision is then performed (midline or Pfannenstiel), followed by bisection of the bladder to the level of fistula. The bladder and vagina are mobilized and separated from each other by dissecting along the vesicovaginal septum. A complete excision of the fistula tract is completed. If the tract is extensively indurated, a posterior bladder flap may be mobilized to repair the defect. (Gil-Vernet, 1989) [522]. Recently, Nesrallah et al reported a 100% success rate using the O’Conor transabdominal supravaginal technique in 29 patients. (Nesrallah 1999) [523]. Other authors have reported similar results.

Separate closure of the vagina and bladder are performed utilizing absorbable sutures (polydioxanone or polyglycolic) and may be performed intra- or extraperitoneally. The intraperitoneal technique allows for easy harvest of the omentum.

Level 4 evidence supports the use of omentum as an interpositional graft. Wein (1980b) [524] utilizing an omentum graft based on the right gastroepiploic artery noted adequate length and tension free apposition of this tissue between the vaginal and vesical components of the fistula repair. Other authors have found the omentum to be reproducibly present for interpositional uses. (Turner-Warwick, 1976) [525] (Kiricuta, 1972) [526] The omentum is secured between the bladder and vagina with 3-0 polyglycolic acid sutures.

Bladder augmentation can also be performed with the intraperitoneal approach into the already bivalved bladder. Large or small bowel may be utilized. This closure is often reinforced with an omentum pedicle graft. Reported success rates with this approach are approximately 85% - 90% and have been reported by numerous authors. (Marshall 1979, Wein 1980a, Gil-Vernet 1989, Udeh 1985, Demirel 1993, Kristensen 1994, Blaivas 1995, Raz 2000) [527,505,522,528-530,508].

7. **Laparoscopic Approach**

Laparoscopy provides an alternative approach for fistula repair. Level 3,4 evidence suggests that this approach may be successful for some patients. Nehzat et al (1994) [531] reported a successful repair of a laparoscopically caused fistula is a single patient. In a larger series Ou et al (2004) [543] evaluated retrospectively the value of laparoscopic repair as compared to vaginal or abdominal repair in 16 patients. Only two patients actually underwent laparoscopic repair, and both repairs were successful, however one patient had a prolonged hospitalization. (Level 5 Evidence)

8. **Complicated Vesicovaginal Fistulae**

Complicated vesicovaginal fistulae can be defined as those fistulae of large size (3 to 5 centimetres or greater in diameter), fistulae occurring after prior attempt at closure, fistulae associated with prior radiation therapy, fistulae associated with malignancy, fistulae occurring in compromised operative fields due to poor healing or host characteristics, and fistulae that involve the trigone, bladder neck and/or urethra.


Prior radiation therapy may increase the risk of vesicovaginal fistula despite the use of the tissue interposition (Obrink 1978, Raz 1992) [542,94]. Overall results range around 50% successful closure, but Bissada achieved 80% successful closure in his group of 10 post-radiation patients. (Bissada, 1992 Level 5 Evidence) [541]

**Summary**

No specific intra-operative intervention has been shown to influence outcome.

Urethrovaginal fistulae may be very small pinpoint fistulae demonstrated by vaginal voiding or may present as complete urethral and bladder neck loss with total urinary incontinence. This circumstance most commonly results from prior gynaecological surgery, with anterior repair and urethral diverticulectomy comprising the most common inciting procedures (Blaivas 1989, Raz 2000) [555,520] (Level 4 Evidence)
Previously, birth trauma was a cause of majority of urethral defects; however, in developed nations this is now a rare cause of urethrovaginal fistulae. Prolonged obstructive labour, however, remains a major cause of urethral injury in developing nations (Elkins 1994) [544].

Level 4 Evidence suggests that techniques used for urethrovaginal fistula closure are very similar to those utilized for transvaginal vesicovaginal fistula repair (Webster 1984) [545]. A significant difference however is that the urethrovaginal fistula should not be completely excised but rather circumscribed and oversewn. Complete urethral loss is a more daunting surgical challenge and a multiplicity of techniques has been described for this (Blaivas 1989, Blaivas 1996, Hendren 1980 and 1998, Patil 1980) [555,546-548,540]. These techniques usually employ some type of flap utilizing either vaginal, bladder, or alternative tissue in an inlay versus tabularised reconstruction (Blaivas 1989) [555]. Simultaneous stress incontinence procedures should be performed to obviate the risk of postoperative incontinence (Blaivas 1990) [549] (Level 3,4 Evidence)

i) Preoperative Evaluation

The physical examination is important to identify the extent and amount of urethral loss and associated vaginal pathologies such as prolapse and functional problems such as stress incontinence.

ii) Operative Technique

Small to intermediate size fistulae may be managed with a tension-free layered closure. Distal fistulae may be managed with extended meatotomy (Spence 1970) [468]. (Level 5) Complete reconstruction is necessary for large fistulae with extensive loss including those that involve the bladder neck. The optimal continence procedure required in such cases has not been critically studied.

Interpositional tissue should be considered whenever the closure lines or vaginal tissues are of poorer quality (Webster 1984, Leach 1991) [545,550] (Level 4,5 Evidence)

Summary

Although the risk of non-obstetric fistulae after gynaecological surgery approaches 0.1% in developed countries, evidence supporting optimal surgical preparation, approach and technique, and post surgical management is predominantly based on case series (Level 4).

Conservative or minimally invasive management (including catheter drainage, cystoscopic fulguration of fistula tract, and use of occlusive agents) has been reported the overall results for vesicovaginal fistulae with these methods are highly variable. Expert opinion suggests that an attempt at conservative management should be considered during the early management of a newly diagnosed vesicovaginal fistula. (Level 4 / 5)

Although vaginal, abdominal, and laparoscopic techniques have been described no clear advantage exists between these techniques. Very little evidence supports laparoscopic management. Surgeon preference, fistula location, and complicating factors (such as prior pelvic radiation, altered wound healing – i.e. chronic steroid use, proximity to ureteral orifices, and time of diagnosis) may all impact on method of repair. Timing of repair (Level 4) appears not to influence long term success and surgical repair may be performed at time of identification if factors such as wound healing are considered optimal by the operative surgeon.

Evidence supporting surgical adjuncts such as use and type of interpositional tissues and effect on outcome of repair is limited (Level 4).

Rigorous scientific assessment of the outcome of surgery for urinary incontinence is important because it enables comparison to be drawn between procedures. Patients can then make informed decisions in light of the risks and benefits demonstrated. Health care providers can identify cost effective treatments and surgeons can bench mark their practice.

Commonly used outcome measures are urodynamics, pad tests, bladder diaries, symptom questionnaires, symptom-bother questionnaires, quality of life (QoL) instruments, and measures of satisfaction. All of these tools are discussed in more detail by other chapters. The aim of this section is to highlight issues specific to the assessment of surgical outcome.

Any outcome measure must be reliable, valid, and responsive to change. It is also important that the results are interpretable within clinical practice.

Reliability concerns the extent to which an experiment, test or any measurement yields the same results on repeated trials.

Any measurement will have a degree of error associated with it. If this is large the test is not reliable and it is unlikely to be a useful outcome measure.

1. OBJECTIVE TESTS

a) Urodynamics

Several studies have demonstrated that urodynamics have poor test re-test reliability. Homma et al (Homma et al. 2000) [606] demonstrated that on repeating urodynamics after 2-4 weeks the results tend towards
normality. The was a 10-13% increase in bladder volumes (p<0.01), a 10% decrease in the number of subjects with detrusor overactivity and 18% reduction in the amplitude of detrusor contractions.

The test-retest reliability of urodynamics to detect detrusor overactivity was investigated in children by Griffiths et al. Urodynamics were repeated on three occasions, 10% changed from stable to unstable and 14% from unstable to stable (Griffiths et al. 1982) [551].

Cardozo et al. found 15% of women who complained of stress incontinence had no demonstrable loss on videourodynamic but were wet on Urilos pad tests (Cardozo et al. 1980) [552]. Urodynamics appeared not to be sensitive enough to detect this loss.

In 1997, Jensen et al. reviewed 26 studies that compared the urodynamic diagnosis to patients’ symptoms. They found that urodynamic evaluation failed to demonstrate incontinence in up to 25% (mean 9%) of patients who complained of urinary leakage (Jensen et al. 1997) [553].

Studies comparing static to ambulatory urodynamics have shown 25-60% of patients, with symptoms of overactive bladder, have negative stationary tests for detrusor overactivity which can then be identified on ambulatory testing (van Waalwijk van Doorn et al. 1987; Griffiths et al. 1989; Webb et al. 1991) [564, 580,557. However there is no test re-test data for ambulatory studies.

Hilton demonstrated that post operative urodynamics failed to demonstrate leakage in almost 40% of women who on questionnaire responses still had some leakage.

Post-operatively urodynamics have become the gold standard in the ‘objective’ assessment of surgical outcome (Jarvis 1994) [20]. However, there is little evidence of reliability to support this position.

**b) Cough stress test**

This can be a useful test to assess the resolution of stress incontinence following surgery(Yalcin et al. 2004) [558]. It however cannot be used to assess improvement. Before and after surgery the test should be standardised for bladder volume, number and force of coughs, and the position of the subject. There is no agreed standard for these factors and this limits the use of cough test data in meta-analysis of incontinence surgery.

**c) Pad tests**

Pad tests have been used to objectively define cure using a cut-off point at which the test is positive. There is considerable variation in the duration of pad tests are used. Short pad test 1-hour have been demonstrated to be unreliable measures and therefore not suitable outcome measures (Simons et al. 2001) [559]. There is evidence that the 72 hour pad test is most reliable duration for pad testing (Karantaxis et al. 2005) [560].

The number of pads used per 24 hours has been shown not to accurately reflect the amount of urine lost. (Dylewski et al. 2007) [561].

However all of these evaluations have been made in pre treatment samples and therefore may not be valid post-operatively when leakage episodes may be less frequent and severe.

**d) Bladder Diaries**

Bladder diaries, 3- 7 days, have been shown to be reliable measures of incontinence prior to surgery (Wyman et al. 1988) [562] however, their reliability may also be a function of the duration of the test and the frequency of incontinence episodes. Hence following surgery a patient with infrequent but bothersome incontinence episodes may appear cured on a 3 day diary- having no incontinence episodes. There has been no research to establish the clinical significance of improvements in bladder diaries, whether change in incontinence episodes should be reported as a percentage change from baseline or in reduction in the number of episodes.

**2. SYMPTOM QUESTIONNAIRES**

There a several symptom questionnaires available. Committee x has evaluated the psychometric properties of the available symptom questionnaires in detail, using an A,B,C grading system.

The content of a questionnaire is a psychometric property which is important, yet frequently overlooked. In selecting a symptom questionnaire for a surgical study it is important to consider if the instrument covers the recognised complications. For example the Severity of Symptoms Index SSI is a psychometrically valid instrument but it only addresses stress incontinence symptoms (Black et al. 1996) [237]. It does not measure common complications such as voiding difficulty or overactive bladder. Few questionnaires have comprehensive assessment of the impact incontinence on sexual function.

If an instrument is being used to assess a new innovation then one should select an instrument with the capacity to report in free text other symptoms not covered by the questionnaire.

Other factors which should be consider are the incidence of recurrent UTI, any pad use, drugs for OAB, re-operation , clean intermittent self catheterisation rates, and the speed of recovery. These can be used to compare procedures and are useful to counsel patients before surgery.

Another property to consider is does the questionnaire measure the presence of symptoms and the bothersomeness as separate items? Some instru-
ments separate symptoms and bother e.g. BFLUTS however others combine these factors one question e.g. KHQ.

Bother is a complex factor which is probably affected by personality, previous experience, other comorbidities and other factors. It is probably therefore more useful to use separate questions of symptoms and bother.

Symptoms are easily comparable between studies for meta analysis however they cannot be summated into a meaningful primary end point.

New innovations can be associated with new complications. It is important that these are assessed. Although it is difficult to compare the significance of different complications.

3. QUALITY OF LIFE (QoL) INSTRUMENTS

Committee x has provide a comprehensive review of the large number of QoL instruments available and their psychometric properties, reliability, validity, responsiveness.

To be a useful outcome measure in research & clinical practice the output of these instruments must have clinical meaning. Many studies report statistic changes in score but these have no clinical meaning. Further research is required to establish clinical meaning.

The most commonly use method to establish this is Minimally Clinically Important Change (MCID), although even this has limitations. There are several method to calculate MCID and it is probably disease and population dependant (Wyrwich et al. 2005) [563]. To date three QoL instruments have reported MCID but none are for a surgical interventions (Kelleher et al. 2004; Yalcin et al. 2006; Hendriks et al. 2008) [564-566]. MCID is not specific to an instrument and therefore for should currently be calculated for each study.

QoL instruments frequently are divided into domains for example physical, social, emotional & personal. An individual may attribute different importance to each of these domains therefore they should not be combined into a global score unless there is psychometric evidence that this is valid. Instead a global assessment scale should be used.

4. GLOBAL ASSESSMENT SCALES

This is term applied to a health-related index that provides a broad overview of a complex phenomenon. Selection of a response involves a patient implicitly evaluating feelings, perceptions, opinions, expectations, goal achievement, satisfaction, beliefs, and previous health state and then coming to a single judgement.

Global assessments usually consist of a single question. There are two common formats; state evaluation (How are you today?) and transition evaluations (How are you compared to before treatment?). These scales are very simple to use and are clinically intuitively understandable however they lack detail to identify reason for success or failure.

They are often used as anchor questions to determine MCID of QoL instruments.

The fact that a global impression index results in a single score means they can used as primary endpoints.

5. SATISFACTION

Almost 30 years ago, Norton hypothesised that a reduction in the number of leaks by 50% may not mean patients feel 50% better (Norton 1982) [567]. It may be that the fact of being incontinent, regardless of the amount or frequency, is what determines restrictions. This implies that nothing short of total dryness will be accepted by the patient as success. It is this concept which is addressed when assessing satisfaction.

Satisfaction is also a function of patients’ goals and expectations. Robinson et al found that 43% patients wanted “a good improvement so that symptoms no longer interfere with their life” however 17 % expected a complete cure of all symptoms in keeping with the National Institute of Health (NIH) definition of cure. The NIH definition of cure of stress incontinence is the resolution of the symptom of incontinence, the resolution of the sign of stress incontinence (a negative stress test with a full bladder) and the absence of new symptoms or side effects (Weber et al. 2001) [568]. It may be that pre-operative counselling can alter patients’ expectations and thereby ultimately alter the outcome of surgery – if it is assessed through satisfaction.

6. HEALTH-ECONOMIC OUTCOMES

Several incontinence operations appear to have similar efficacy. The trend is to develop less invasive operations for incontinence. Health-economic factors may ultimately be the only significantly different factor between procedures. Generic instruments such as ED-5D from which QALYs can be estimated may not be sensitive enough to detect change however there are currently no condition specific tools available. A preference-based measure of health developed from the King’s Health Questionnaire has been published however this is for use in OAB conditions not stress incontinence.(Brazier et al. 2008) [569]

CONCLUSION

Currently used objective outcome measures may not be sensitive enough to detect surgical failure. The only ‘subjective’ outcome measure which does not involve complex judgemental factors is the assessment of symptoms. These should be administered using a validated symptom questionnaire, by an independent party to avoid bias associated with patient surgeon.
relationship. Symptoms are easily comparable between studies for meta analysis however because they consist of multiple answers they are not suitable as primary outcome measure. The lack clinical meaning of results from QoL instruments restricts their usefulness and requires further research. In view of this a validated global impression scale may be a better primary outcome measure. Until further research establishes a universal outcome tool it is advisable to use multiple outcomes. This is in keeping with the recommendation of several societies and regulatory organisations; the AUA ([Lose et al. 1998] [261], the NIH ([Weber et al. 2001] [568] the IUGA, ([Ghoniem et al. 2008] [570] and ICS ([Mattiasson et al. 1998] [571]).

**Recommendations**

1. Most outcome measures used have been developed in non-surgical areas. Further research is required ensure they are clinically useful surgical outcome measures.
   a. When a QoL instrument is to be used ensure the study includes a calculation of MCID.
   b. A validated global impression index may be a useful primary outcome measure for surgical trials.
2. Until further research establishes a universal outcome tool it is advisable to use multiple outcomes.
   a. Symptoms and separate bother questionnaire
   b. Clinical important outcomes (pad use, re-operation rates, anticholinergics, CISC, recurrent UTI)
   c. Complications
   d. QoL tool with MCID
   e. Global Impression Index
   f. Health- economic outcome

**XI. ARTIFICIAL URINARY SPHINCTER IN WOMEN**

The artificial urinary sphincter has been utilized for the treatment of sphincter dysfunction in women in special circumstances (failed prior procedures) or rarely as a primary intervention. The majority of experience with the artificial urinary sphincter in women has been in neurogenic patients, with comparatively little data for women with non-neurogenic stress incontinence. The procedure may be performed either by a transvaginal [572] or transabdominal approach [573,574] (**Figure 15**).

Appell in 1988 reported results of artificial sphincter implantation in 34 women who experienced complete incontinence, with only three of the 34 requiring revision after transvaginal placement [575]. Subsequently, Hadley in 1991 reported 13 of 14 patients (93%) who attained reasonable urinary control (defined as no or one pad per day for stress incontinence).

Various authors have proposed either the trans-abdominal or the transvaginal approach as being superior due to operative technique-related issues, including operative dissection for cuff placement though no robust evidence is available to support their views. The trans-vaginal approach is considered to be superior for cuff dissection and placement. The transabdominal approach is considered to provide better exposure, especially for bladder neck placement, assuring placement between the urethra and the vaginal wall [573,576,577]. Laparoscopic placement has been described as a method to decrease morbidity associated with the abdominal approach [578].

Overall success rates range between 76% and 89%, with lower success rates and higher revision rates being noted in those patients with neurogenic voiding dysfunction as the primary indication for placement. The most extensive experience with artificial sphincter implantation is that of Costa (2001) who reported 207 patients with a mean of four-year follow-up. An overall success rate of 89% was reported in the non-neurogenic population with an overall vaginal extrusion rate of 6%.

A recent Cochrane Review failed to find sufficient evidence to support use of the artificial urinary sphincter and recommended large scale clinical trials to determine the possible role of these devices in the management of incontinence in women [579].

**Recommendation**

Only Level 3 / 4 evidence is available to support use of the artificial sphincter. This would support a Level B recommendation for use.
REFERENCES


308 (2007) MAUDE database


approach to the study of human detrusor physiology and pathophysiology. Br J Urol, 75 Suppl 1, 18-26


Committee 15

Surgery for Pelvic Organ Prolapse

Chairman
L. BRUBAKER (USA)

Members
C. GLAZENER (U.K),
B. JACQUETIN (France),
C. MAHER (Australia),
A. MELGREM (USA),
P. NORTON (USA),
N. RAJAMAHESWARI (India),
P. VON THEOBALD (France)
## CONTENTS

<table>
<thead>
<tr>
<th>INTRODUCTION</th>
<th>IV. CONCOMITANT SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. OUTCOME ASSESSMENT</td>
<td>1. EFFECT OF COMBINATION PROCEDURES</td>
</tr>
<tr>
<td>1. OUTCOME ASSESSMENT: ANATOMY</td>
<td>2. HYSTERECTOMY - The Role of Hysterectomy in Surgical Treatment of Prolapse</td>
</tr>
<tr>
<td>2. OUTCOME ASSESSMENT: SYMPTOMS</td>
<td>3. CONTINENCE TREATMENT (Treatment and Prophylaxis)</td>
</tr>
<tr>
<td>3. OUTCOME EVALUATION: QUALITY OF LIFE</td>
<td>4. CONCOMITANT PERIOPERATIVE PELVIC PHYSICAL THERAPY</td>
</tr>
<tr>
<td>II. SELECTION OF SURGICAL ROUTE FOR RECONSTRUCTIVE POP PROCEDURES</td>
<td>V. THE ROLE OF AUGMENTING MATERIALS IN POP SURGERY</td>
</tr>
<tr>
<td>1. COMPARISON OF OPEN ABDOMINAL TO VAGINAL</td>
<td>1. AUGMENTATION FOR ANTERIOR WALL SURGERY</td>
</tr>
<tr>
<td>2. SAFETY ISSUES RELATED TO THE CHOICE OF SURGICAL ROUTE</td>
<td>VI. RECTAL PROLAPSE</td>
</tr>
<tr>
<td>3. LAPAROSCOPIC AND ROBOTIC SURGERY</td>
<td>1. PERINEAL PROCEDURES</td>
</tr>
<tr>
<td></td>
<td>2. TRANSABDOMINAL PROCEDURES</td>
</tr>
<tr>
<td>III. EFFICACY OF SPECIFIC PROCEDURES</td>
<td>VII. RECOMMENDATIONS</td>
</tr>
<tr>
<td>1. RECONSTRUCTIVE PROCEDURES</td>
<td>REFERENCES</td>
</tr>
<tr>
<td>2. OBLITERATIVE PROCEDURES: LeFort colpocleisis, Colpectomy and colpocleisis</td>
<td></td>
</tr>
</tbody>
</table>

1274
Surgery for Pelvic Organ Prolapse

L. BRUBAKER,

C. GLAZENER, B. JACQUETIN, C. MAHER, A. MELGREM, P. NORTON,

N. RAJAMAHESWARI, P. VON THEOBALD

INTRODUCTION

Surgery for pelvic organ prolapse (POP) is common with increasing high-quality evidence to guide surgical practice. Yet many important basic questions remain, including the optimal timing for POP surgery, the optimal pre-operative evaluation of urinary tract function and the post-operative outcome assessment. Olsen [1] and Fialkow [2] have separately documented high rates of surgery for POP and/or urinary incontinence (UI) in US women. In Fiakow’s study, 169 women who underwent a primary prolapse surgery (+ concomitant UI procedure) were identified (Table 1).

In addition, there remains uncertainty about the longevity of prolapse repairs, with some experts stating that recurrences may be inevitable in at least a subgroup of women. Olsen’s recurrence rate estimate was based on 384 women in the Kasier Permanente Northwest population who underwent at least one POP/UI procedure. In that study, only 13 sacrocolpopexies were performed, reflecting the surgical practice in 1995. Until women at higher risk for recurrence are reliably identified prior to surgery, re-operation rates of up to 30% may persist.

Despite the need for additional studies to guide many aspects of POP surgical care, this chapter can be used to facilitate evidence-based management of POP. This committee has deliberated, graded evidence and provided recommended areas of high priority for current surgical care as well as further POP research. Readers of this chapter are also encouraged to periodically review continuously updated evidence from reviews including the Cochrane and NICE reports [3, 4]. This chapter also includes scientific contributions with lower levels of evidence than these reviews so that we can highlight the areas for future research.

I. OUTCOME ASSESSMENT

One of the most glaring limitations in recommending evidence-based POP surgery is the lack of an optimal method for determining outcome. While anatomic correction is usually reported, there is good evidence that POP and POP repairs have significant impact on urinary, sexual, and ano-rectal function; these aspects should be taken into account when assessing the outcome of POP surgeries. Therefore, recognizing that pelvic organ prolapse is a multidimensional disorder, outcomes of treatments should be evaluated in multiple domains. Group consensus statements

Table 1. Age-specific incidence of surgically-managed POP and UI (per 1,000 women years)

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>At risk women</th>
<th>POP only</th>
<th>UI only</th>
<th>POP and UI</th>
<th>All cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>23,560</td>
<td>0.17</td>
<td>0.00</td>
<td>0.04</td>
<td>0.21</td>
</tr>
<tr>
<td>30-39</td>
<td>34,893</td>
<td>0.31</td>
<td>0.34</td>
<td>0.11</td>
<td>0.77</td>
</tr>
<tr>
<td>40-49</td>
<td>36,120</td>
<td>0.72</td>
<td>0.72</td>
<td>0.30</td>
<td>1.74</td>
</tr>
<tr>
<td>50-59</td>
<td>18,976</td>
<td>0.94</td>
<td>1.05</td>
<td>0.47</td>
<td>2.48</td>
</tr>
<tr>
<td>60-69</td>
<td>15,368</td>
<td>2.10</td>
<td>0.78</td>
<td>0.26</td>
<td>3.12</td>
</tr>
<tr>
<td>70-79</td>
<td>12,958</td>
<td>2.54</td>
<td>0.85</td>
<td>0.31</td>
<td>3.70</td>
</tr>
<tr>
<td>80+</td>
<td>5,844</td>
<td>1.71</td>
<td>0.17</td>
<td>0.34</td>
<td>2.22</td>
</tr>
<tr>
<td>Total</td>
<td>147,719</td>
<td>0.91</td>
<td>0.56</td>
<td>0.24</td>
<td>1.70</td>
</tr>
</tbody>
</table>

Adapted from Fialkow et al. Int Urogynecol J (2008) 19:437-440 (2)
agree with this philosophy, although there is no evidence-based recommendation for optimal outcome assessment at this time [5]. In addition, it is imperative that future research address the patient’s global perspective as an outcome in order to understand the contributions of various anatomical and functional sub-outcomes on the overall patient experience.

1. OUTCOME ASSESSMENT: ANATOMY

There is no consensus on several critical areas of outcomes. There are significant difficulties in creating dichotomous anatomical outcome criteria for success and failure, especially in the absence of symptoms. This difficulty is exacerbated in the situation where support loss is evident in an unoperated portion of the vagina and there is no consensus regarding coding of “de novo” POP. Finally, it is likely incorrect to strive for “perfect” support of the vagina (Stage 0) as this is inconsistent with the demographic profile of asymptomatic vaginally parous women [6].

In addition, the five-level staging system of the current POP-Q (Stages 0-IV) may be insufficient to discriminate among clinically important groups of women with POP, placing virtually all such women into Stage II or III. While the staging may facilitate comparisons, it may not describe sufficient detail as the individual POP-Q measurements provide. While most surgeons believe that prolapse beyond the hymen following POP surgery is not an optimal anatomic outcome, the required level of support above the hymen is not known and the relationship with symptoms remains poorly understood.

2. OUTCOME ASSESSMENT: SYMPTOMS

It is well recognized that symptoms and anatomy do not necessarily correlate in women with pelvic organ prolapse. Burrows et al reported that while women with more advanced prolapse are less likely to experience stress urinary incontinence, bothersome sexual or ano-rectal symptoms do not correlate with prolapse severity [7]. The symptom of feeling or seeing a bulge is reliably associated with the anatomic finding of prolapse [8]. However, other symptoms may impact the perception or bother of the anatomic finding. FitzGerald et al reported that women planning sacrocolpopexy with Stage II POP and prior pelvic surgery reported more symptoms and quality of life impact than those with more advance prolapse [9]. Symptoms of urinary incontinence, fecal incontinence, sexual dysfunction, voiding dysfunction and defecatory dysfunction are common in women with prolapse, but are not well correlated with anatomic findings [10]. Nonetheless, most patients expect resolution of pelvic symptoms following surgery.

a) Urinary Symptoms

Urinary Incontinence: There is a risk of de novo stress incontinence following POP repair by any route. This risk is approximately 44% following sacrocolpopexy in stress continent women [11] and can be reduced by concomitant Burch colposuspension. It is not known if other continence procedures are protective in this surgical setting. Estimates for de novo stress incontinence following vaginal repair range between 15 to 80% [12]. An ongoing trial (Clinicaltrials.gov NCT 00460434) is assessing the utility of concomitant TVT at the time of vaginal prolapse repair in stress continent women. The risk of urge incontinence is also present, although there is growing evidence that prolapse repair improves this risk [13, 14]. Improvement of urge incontinence may be a welcome side effect of the surgery, but it is not an indication for surgery per se.

Voiding dysfunction: Voiding function is expected to improve after surgical correction of prolapse. Fitzgerald and co-workers found significant improvement in bladder emptying in patients after surgery for advanced POP [15]. Before surgery, the average post-void residual in 35 patients was 226 mL, and this was reduced to less than 100 mL in 89% of the women after surgery for POP.

b) Sexual function

The effect of POP on sexual function is variable, but repair of POP may improve sexual function. In the Colpopexy and Urinary Reduction Efforts (CARE) trial, more women were sexually active one year after abdominal sacrocolpopexy (171, 76.3%) compared to before surgery (148, 66.1%), and significantly fewer women reported sexual interference from pelvic and vaginal symptoms [16]. Pauls and colleagues [17] reported no change in sexual function and sexual frequency using the Female Sexual Function Index (FISI) and other standardized questionnaires in prospectively surveyed women undergoing POP surgery with and without continence procedures. In those women, the most bothersome barrier to sexual activity before repair was vaginal bulging; postoperatively, it was vaginal pain. De novo dyspareunia is a risk of many transvaginal prolapse repairs.

c) Ano-Rectal Symptoms

Ano-rectal symptoms are common in women with POP [18]. Fifteen to 20% of women with POP or SUI also report fecal incontinence [19]. Meschia evaluated 881 women with UI or POP, of whom 178 also had anal incontinence. Two-thirds reported constipation, with other common complaints of incomplete evacuation, and splinting in the vaginal or perineal body to effect evacuation [20].

Although such symptoms are common, they do not correlate well with prolapse stage. Bradley et al [18] described the prevalence of pre-operative bowel symptoms and Colorectal-Anal Distress Inventory symptom scores in 322 women planning sacrocolpopexy. Correlations between symptoms and
prolapse were negative and weak, indicating that bowel symptoms do not increase with increasing prolapse stage [18].

Although there is no level 1 evidence regarding the impact of POP surgery on these symptoms, ano-rectal symptoms were assessed in the CARE trial. Surgeons were allowed to include posterior colporrhaphy (in addition to sacrolcopexy) at their discretion. The sacrocolpopexy with posterior colporrhaphy group (n= 87) had more baseline obstructive colorectal symptoms (higher Colo-Rectal-And Distress Inventory(CRADI) and CRADI-obstructive scores: P =.04 and .01, respectively) than the sacrocolpopexy alone group (n =211). However CRADI total, obstructive, and pain/irritation scores significantly improved in both groups (all P =.01) [21].

3. OUTCOME EVALUATION: QUALITY OF LIFE

It is recommended that investigators describe the impact of POP surgical treatment on quality of life. Maher et al reported significant improvements in condition-specific and generic QOL after SSLF, similar to that after abdominal sacrocolpopexy [22]. The CARE trial also reported significant improvements in quality of life following sacrocolpopexy at three months and two years [11, 14]. In that trial, Nygaard et al reported pre-surgical physical activity levels [23]. Most participants were physically active preoperatively, but reported that prolapse substantially interfered with exercise or recreation (27%), household work or yard work (19%) and work outside the home (8%). The interference was not associated with the stage of prolapse.

In the first study of its kind, Jelovsek et al assessed body image using a modified body image scale [10]. These investigators reported that women seeking treatment for advanced pelvic organ prolapse had measurable decreases in body image and overall quality of life. The idea that distortion of body image is a factor that impacts quality of life is novel and a fruitful area for further research.

II. SELECTION OF SURGICAL ROUTE FOR RECONSTRUCTIVE POP PROCEDURES

The individual woman’s surgical history and goals, as well as her individual risks for surgical complications, prolapse recurrence and de novo symptoms impact surgical planning. In addition, the route and method of access for reconstruction may include laparoscopic and robotic techniques. In the U.S., 80-90% of prolapse surgeries are completed vaginally [24].

1. COMPARISON OF OPEN ABDOMINAL TO VAGINAL

Level one evidence supports a higher anatomic efficacy with abdominal route of surgery. There are three randomized controlled trials designed with the specific aim to compare vaginal and abdominal routes for the surgical correction of POP [22, 25-27] as well as a Cochrane review [27] and the major outcomes are summarized in Table 14. Although these studies had relatively small numbers for comparison (approximately 40 women in each comparison group), the effect sizes were large.

In the first trial designed to compare route of POP repair, Benson et al reported that the abdominal route had better anatomic results 1 to 5.5 years (mean 2.5 years) after surgery compared with the vaginal route, OR for optimal cure (no symptoms of POP, no anatomic defect beyond the hymeneal ring) 3.44, 95%CI 1.24-9.69). The Benson study was stopped when the planned interim analysis revealed the superiority of the abdominal approach. Of the 101 women randomized, ten decided against surgery after randomization, 3 refused their abdominal route randomization assignment, and 8 were not available for long term evaluation, leaving a sample size of 80 women. A significant proportion of participants who were randomized to the abdominal group also had vaginal procedures performed (30% anterior colporrhaphy and 50% posterior colporrhaphy.) Needle urethropexy, a widely used procedure at the time of the trial that has since been abandoned, was used as the primary incontinence procedure in the vaginal repairs. Since that time, the combination of needle urethropexy and sacrospinous ligament suspension has been abandoned because it predisposes to upper vaginal wall prolapse [28]. Given that this was the first such trial, the optimal vaginal approach was not known.

Experts have expressed concern that the specific primary prolapse procedures performed may have been responsible for differences in outcome rather than the surgical route: these include (vaginal route) bilateral sacrospinous suspension, vaginal paravaginal repair, Pereyra needle urethropexy; and (abdominal route) sacrocolpopexy, retropubic paravaginal repair, and Burch colposuspension. In addition, the results for women with concomitant hysterectomy were not reported separately. The abdominal route was associated with higher costs, longer operating times, and increased complications, although the numbers did not reach statistical significance due to small numbers. Of note is that post-operative dyspareunia was seen only in the vaginal group (15/26, 58%).

Lo and Wang (1998) randomized 138 women with Stage III-IV uterine prolapse or vaginal vault prolapse; 20 were excluded after randomization for inability to follow-up. Of the remaining 118, 52 underwent sacrocolpopexy with mersilene mesh and 66 underwent sacrospinous ligament fixation with polypropylene suture. The definition of cure was POP no greater than Stage II (no greater than 1 cm beyond the hymeneal ring), and at a median of 2.1 years after
the index surgery, 49/52 (94%) of women undergoing SC were cured, while 53/66 (80%) of women undergoing SSLF met the definition of cure. Complications were higher in the vaginal group with increased blood loss and longer hospital stays, with some serious complications of rectovaginal fistula and ureteric injury. While there are several methodologic problems with this RCT, there was a higher rate of dyspareunia due to vaginal narrowing in the SSLF group (7/66, 39%, 4 of whom were sexually inactive due to the complication) compared to the SC group (1/52, 9%).

Maher and colleagues (2004) performed an RCT randomizing 95 women to sacrocolpopexy (n=47) and sacrospinous ligament fixation (n=48) with follow up at two years (6-60 months). This study differs from that of Benson in that all subjects had already undergone hysterectomy, no patients in the vaginal group had either a needle urethropexy or vaginal paravaginal repair, and the minimum allowed duration of follow-up was six months (mean 22-24 months) rather than Benson’s 12 months (mean 30 months.) Although this group reported comparable subjective and objective outcomes between the two surgical groups, a subanalysis showed anatomic superiority of the abdominal group (OR18, 95% CI .05, .55) with a significantly higher rate of combined recurrent anterior and apical prolapse. However, the abdominal route had longer operating times, longer hospitalization, more complications, and higher medical costs compared with the vaginal route.

The Cochrane review on the surgical management of prolapse by Maher et al summarizes these studies and concludes that these trials provide level 1 evidence that the overall outcome (including quality of life) is similar between abdominal and vaginal approaches, but that sacrospinous-based vaginal procedures have a higher anterior and apical anatomical recurrence rate and higher rates of dyspareunia than sacrocolpopexy-based abdominal repairs. This is somewhat offset by the higher short term morbidity of open abdominal sacrocolpopexy [22].

2. SAFETY ISSUES RELATED TO THE CHOICE OF SURGICAL ROUTE

In these trials, serious perioperative injuries are more common with abdominal than vaginal surgery. While it is known that the number of complications increases as the number of procedures increases, the number of procedures is less related to the route of surgery and more to the severity and number of pelvic floor defects requiring surgical correction. Safety associated with mesh will be considered separately later in the chapter.

Boyles [24] found that pre-existing comorbidities did not increase the risk of complications in a review of discharge diagnoses after surgery for POP, but this finding seems counter-intuitive and points out the limitation of this kind of review: it is unknown how the route of surgery nor preventative measures in individual cases affects these findings, and a prospective comparison is needed. Boyles examined mortality risk in some detail. Although the mortality rate was low (.53 per 1000 women), women who died were significantly older than those who survived (69.1 versus 52.1). Details on the route of surgery were often incomplete. In summary, what little is known about safety agrees with the commonly held opinion that vaginal surgery for POP is safer than abdominal surgery, and this may be an important consideration when deciding on the route of surgery for individual patients.

3. LAPAROSCOPIC AND ROBOTIC SURGERY

There are multiple reports of the feasibility of various abdominal prolapse repairs being performed using laparoscopic (with or without robotic assistance) surgical techniques, most reporting good short- and intermediate-term results. As of March 2008, no randomized controlled trials have been reported comparing laparoscopic to conventional abdominal POP procedures. There is no reason to believe that the same procedure performed in precisely the same manner using the same materials would have any different outcome using the laparoscopic abdominal technique compared to the open abdominal technique. However, there is likely to be different adverse events depending on the technique of access. In addition, procedures are sometimes modified to allow them to be performed more easily with laparoscopy, and so it is essential to establish independently the effectiveness and safety of the modified procedures in a well-designed RCT. Similarly the learning curves and number of procedures together with the frequency of performing these technically challenging operations have yet to be established for prolapse surgery by all routes and techniques.

III. EFFICACY OF SPECIFIC PROCEDURES

There are a variety of procedures suitable for surgical correction of prolapse. Table 2 briefly summarized the main concepts of the broad surgical categories.

1. RECONSTRUCTIVE PROCEDURES

a) Apical support procedures

The apex is the keystone of pelvic organ support. Support of the apex must be assessed regardless of the presence or absence of the uterus. Without good suspension of the uterus or post-hysterectomy vaginal cuff, the anterior and posterior walls are exposed to intra-abdominal forces that drive these tissues toward the introitus. Because of the significant contribution of the apex to anterior vaginal support, the best surgical
correction of the anterior and posterior walls may fail unless the apex is adequately supported [30, 31].

While recognition of apical defects is one of the biggest problems in the evaluation of pelvic support defects, surgical correction of the apex has several good options with relatively high success rates.

1. SACROCLOPOPExY

Sacrocolpopexy has proven to be a durable technique for apical support with an acceptable risk/benefit ratio (Tables 3 and 4). While level 1 evidence supports the usefulness of this procedure in POP, investigators are just beginning to test the hypothesis that will refine this technique, optimize concomitant procedures and urinary tract function. Because concomitant hysterectomy increases the risk of mesh erosion [32], alternative techniques including sacrohysteropexy or supracervical hysterectomy are being used based on clinical judgment.

Sacrocolpopexy requires an intervening material, typically a synthetic mesh. Level 1 evidence supports the superiority of polypropylene mesh to fascia lata for objective anatomic support following sacrocolpopexy [97]. There is no evidence for the equivalence or superiority of any material other than permanent synthetic mesh for this procedure. Expert opinion strongly warns against simple suturing of the apical skin as this is insufficient fixation and likely to result in recurrent prolapse.

Mesh erosion is a known complication of sacrocolpopexy regardless of performance of concomitant hysterectomy. A recent review [33] noted the rates of erosion to be 2-11% from institution to institution. Visco and colleagues [98] reported on 155 women and found an erosion rate of 3.2% with abdominal sacrocolpopexy, 4.5% when combined with colpoperineopexy, 20% when a combined abdominal/vaginal approach was used (sutures passed vaginally to abdominally) and 40% when mesh was introduced vaginally. Cundiff et al presented suture/mesh complications from the CARE trial [32] The predominant graft used was synthetic mesh; Mersilene (42%) or Polypropylene (48%). Twenty subjects (6%) experienced mesh/suture erosion. Unadjusted risk factors for mesh/suture erosion were expanded polytrfluoroethylene (ePTFE) mesh (ePTFE 4/21 (19%) versus non-ePFTE 16/301 (5%): OR 4.2), concurrent hysterectomy (OR 4.9) and current smoking (OR 5.2). Of those with mesh erosion, most affected women (13/17) underwent at least one surgery for partial or total mesh removal. Two were completely resolved, 6 had persistent problems and 5 were lost to follow-up. No resolution was documented in the 4 women who elected observation. These investigators concluded that expanded PTFE mesh should not be used for sacrocolpopexy and documented that concurrent hysterectomy and smoking are modifiable risks for mesh/suture erosion. These data is corroborated by the majority of other evidence from Level 3 reports [84, 99, 100], although there is conflicting level 2 data from [91]. While uterine preservation (or supracervical hysterectomy) is an alternative, the utility and safety of these techniques are not known. In a level 2 RCT, Roovers et al reported poor outcomes for sacral hysteropexy as compared to vaginal repair [90].

Allograft fascia lata has been described variably as an alternative to mesh: the biologic graft avoids the risk of mesh erosion, but resulted in unexpected failures in which no mesh could be seen during reoperation [101-104].

Similarly, Flynn et al [105] reported on 24 colpopexies using allograft fascia lata in a retrospective design, and found unacceptable rates of anatomic improvement at one year follow-up.

<table>
<thead>
<tr>
<th>Table 2. RCTs comparing abdominal versus vaginal approaches to POP surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Benson 1996 [25]</td>
</tr>
<tr>
<td>Lo 1998 [26]</td>
</tr>
<tr>
<td>Maher 2004 [22]</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*recruitment halted after first interim analysis showed superiority of abdominal route.
**138 randomized, but 20 excluded after randomization for inability to follow-up.

apical cure defined as no prolapse symptoms, no anatomic defect beyond the hymeneal ring
bsubjective cure defined as no symptoms of POP
csubjective cure defined as no symptoms of POP, anatomic defect less than Baden-Walker grade 2 (prolapse to the hymeneal ring.)
Table 3. Table of Main Categories of Operations:

<table>
<thead>
<tr>
<th>Operation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOR APICAL SUPPORT (UTERINE OR VAULT PROLAPSE)</strong></td>
<td></td>
</tr>
<tr>
<td>Sacrocolpopexy</td>
<td>Fixation of vagina through suspension material (preferably anterior and posterior vaginal arms of synthetic mesh to bridge to the anterior longitudinal ligament of sacrum.</td>
</tr>
<tr>
<td>Sacrocolpoperineopexy</td>
<td>Same technique as above, except that the posterior arm of mesh extends to the perineal body.</td>
</tr>
<tr>
<td>Iliococcygeus fascia fixation</td>
<td>An extraperitoneal vaginal procedure that attaches the vaginal apex to the fascial coverings of the iliococcygeus muscles bilaterally, often with a suture-passing device.</td>
</tr>
<tr>
<td>Levator myorrhaphy with apical plication</td>
<td>Wide midline plication of the levator with fixation of the vaginal cuff.</td>
</tr>
<tr>
<td>Mayo culdoplasty</td>
<td>A modification of the McCall’s culdoplasty attaches the apex to plicated uterosacral ligaments.</td>
</tr>
<tr>
<td>Sacrospinous ligament suspension procedures</td>
<td>This procedure suspends the vaginal apex to the sacrospinous ligament either unilaterally or bilaterally, typically using an extraperitoneal approach. The enterocele, anterior and posterior walls are repaired as needed.</td>
</tr>
<tr>
<td></td>
<td>Traditional version: attaches one edge of the apex to the ligament using permanent suture.</td>
</tr>
<tr>
<td></td>
<td>Michigan modification [29] avoids a suture bridge and draws the entire vaginal apex into direct contact with the coccygeus muscle and underlying ligament, using delayed absorbable sutures across the entire vaginal cuff.</td>
</tr>
<tr>
<td>Uterosacral ligament suspension</td>
<td>This intraperitoneal vaginal procedure traditionally uses permanent suture to suspend the vaginal apex to the remnants of the uterosacral ligaments at the level of the ischial spines and cephalad, with incorporation of the (often reconstructed) fibromuscular walls of the anterior and posterior vagina.</td>
</tr>
<tr>
<td><strong>FOR ANTERIOR VAGINAL WALL PROLAPSE</strong></td>
<td></td>
</tr>
<tr>
<td>Anterior colporrhaphy</td>
<td>Midline plication of endopelvic fascia of anterior vagina.</td>
</tr>
<tr>
<td>Paravaginal repair</td>
<td>Attachment of lateral vaginal to arcus tendineous fascia pelvis (either abdominally or vaginally)</td>
</tr>
<tr>
<td><strong>FOR POSTERIOR VAGINAL WALL PROLAPSE</strong></td>
<td></td>
</tr>
<tr>
<td>Posterior colporrhaphy</td>
<td>Midline plication of endopelvic fascia of posterior vagina.</td>
</tr>
<tr>
<td>Posterior site-specific repair</td>
<td>Identification and repair of specific defects in recto-vaginal fascia.</td>
</tr>
<tr>
<td>Trans-anal repair</td>
<td>Rectal mucosa separated and the rectovaginal septum is plicated from rectal side.</td>
</tr>
<tr>
<td><strong>FOR ANY PROLAPSE</strong></td>
<td></td>
</tr>
<tr>
<td>Colpocleisis</td>
<td>Closure of vagina following removal of most (partial) or all (complete) vaginal skin.</td>
</tr>
</tbody>
</table>
Table 4. Sacrocolpopexy outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients, (number lost to follow-up, if known)</th>
<th>Follow–up (months)</th>
<th>Success rate (%)</th>
<th>Criteria for success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthure [34]</td>
<td>1949</td>
<td>50 (2)</td>
<td>NS</td>
<td>90</td>
<td>No recurrence of uterine prolapse or enterocele</td>
<td>Uterus, cervical stump or cuff directly affixed to sacrum</td>
</tr>
<tr>
<td>Falk [35]</td>
<td>1961</td>
<td>3 (0)</td>
<td>≤ 36</td>
<td>100</td>
<td>Cured</td>
<td>Uterus, cervical stump or cuff directly affixed to sacrum</td>
</tr>
<tr>
<td>Lane [36]</td>
<td>1962</td>
<td>24</td>
<td>NS</td>
<td>92</td>
<td>No recurrence of prolapse</td>
<td>20 patients had the synthetic material stapled to the sacrum, 2 of whom had prolapse recurrence due to staples becoming dislodged from the sacrum</td>
</tr>
<tr>
<td>Birnbaum [37]</td>
<td>1973</td>
<td>9 (0)</td>
<td>33</td>
<td>100</td>
<td>Good support</td>
<td></td>
</tr>
<tr>
<td>Rust [38]</td>
<td>1976</td>
<td>12 (0)</td>
<td>24</td>
<td>100</td>
<td>No vaginal vault prolapse</td>
<td></td>
</tr>
<tr>
<td>Feldman [39]</td>
<td>1979</td>
<td>21 (0)</td>
<td>16</td>
<td>95</td>
<td>Adequate vaginal support, sufficient vaginal depth and appropriate vaginal axis</td>
<td>The patient with the failure had apparent detachment of the graft from the apex based upon exam</td>
</tr>
<tr>
<td>Cowan [40]</td>
<td>1980</td>
<td>39</td>
<td>30</td>
<td>97</td>
<td>Good vaginal support, no pelvic complaints</td>
<td>Surgical failure involved distal detachment of mesh from vagina</td>
</tr>
<tr>
<td>Symmonds [41]</td>
<td>1981</td>
<td>17 (1)</td>
<td>NS</td>
<td>94</td>
<td>Good vaginal support and function</td>
<td></td>
</tr>
<tr>
<td>Lansman [42]</td>
<td>1984</td>
<td>8 (0)</td>
<td>5.5</td>
<td>100</td>
<td>No recurrence of an enterocele or vault prolapse</td>
<td></td>
</tr>
<tr>
<td>Grundsell [43]</td>
<td>1984</td>
<td>9 (0)</td>
<td>46.8</td>
<td>100</td>
<td>No recurrences of vault prolapse</td>
<td></td>
</tr>
<tr>
<td>Addison [43]</td>
<td>1985</td>
<td>56 (2)</td>
<td>39</td>
<td>96</td>
<td>Good vaginal vault suspension in a normal axis</td>
<td>Fascia lata was graft material used for patient with early recurrence 1 patient unimproved as a presacral hemorrhage prevented successful completion of the procedure</td>
</tr>
<tr>
<td>Kauppila [45]</td>
<td>1985</td>
<td>14 (0)</td>
<td>30</td>
<td>71</td>
<td>Adequate vaginal support on exam</td>
<td>6 of 14 patients had direct attachment of the vaginal apex to presacral fascia, and 4 of these recurred. None of 8 patients in whom graft was used recurred.</td>
</tr>
<tr>
<td>Kauppila [46]</td>
<td>1986</td>
<td>9 (0)</td>
<td>50</td>
<td>100</td>
<td>Excellent vaginal support on exam</td>
<td>Fascial grafts used to suspend the cuff in all patients</td>
</tr>
<tr>
<td>Drutz [47]</td>
<td>1987</td>
<td>15 (0)</td>
<td>28</td>
<td>93</td>
<td>Well-supported vault</td>
<td>1 patient with recurrent vault prolapse was the only with direct attachment of the vagina to the promontory</td>
</tr>
<tr>
<td>Angulo [48]</td>
<td>1989</td>
<td>18 (0)</td>
<td>13</td>
<td>100</td>
<td>Free of symptoms that caused consultation and no degree of prolapse found on vaginal exam</td>
<td></td>
</tr>
<tr>
<td>Baker [49]</td>
<td>1990</td>
<td>59 (6)</td>
<td>6</td>
<td>100</td>
<td>No complaint of protrusion from the vagina</td>
<td>51/59 patients had postoperative records available, at which time all patients had a well-supported vagina</td>
</tr>
</tbody>
</table>
Table 4. Sacrocolpopexy outcomes (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients, (number lost to follow-up, if known)</th>
<th>Follow-up (months)</th>
<th>Success rate (%)</th>
<th>Criteria for success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maloney [50]</td>
<td>1990</td>
<td>10 (0)</td>
<td>26</td>
<td>90</td>
<td>Complete relief of symptoms</td>
<td></td>
</tr>
<tr>
<td>Creighton [51]</td>
<td>1991</td>
<td>23</td>
<td>17</td>
<td>91</td>
<td>No vault prolapse on exam and no complaints of prolapse</td>
<td></td>
</tr>
<tr>
<td>Snyder [52]</td>
<td>1991</td>
<td>147 (15)</td>
<td>43</td>
<td>93 (108/116)</td>
<td>Lack of major long-term postoperative complications, restoration of functional vagina in the proper axis, and no recurrence of presenting symptoms with at least 6 months of follow-up</td>
<td>Graft attached to the entire length of the vagina in the rectovaginal septum</td>
</tr>
<tr>
<td>Imparato [53]</td>
<td>1992</td>
<td>71 (8)</td>
<td>NS</td>
<td>78</td>
<td>Excellent, well-suspended vault on exam</td>
<td>50 had direct attachment of the vaginal apex to the anterior sacrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good vault suspension, but asymptomatic vaginal “relaxation”</td>
<td>16</td>
</tr>
<tr>
<td>Timmons [54]</td>
<td>1992</td>
<td>163</td>
<td>33</td>
<td>99</td>
<td>Good vaginal vault support</td>
<td></td>
</tr>
<tr>
<td>Traiman [55]</td>
<td>1992</td>
<td>9 (0)</td>
<td>36.5</td>
<td>91</td>
<td>Good results on exam</td>
<td>1/2 patients with direct attachment of the vagina to the sacral promontory failed</td>
</tr>
<tr>
<td>Iosif [56]</td>
<td>1993</td>
<td>40 (0)</td>
<td>36</td>
<td>97</td>
<td>Complete symptom relief, no vault prolapse</td>
<td>Patient with failure had detached graft from apex</td>
</tr>
<tr>
<td>van Lindert [57]</td>
<td>1993</td>
<td>61</td>
<td>32</td>
<td>97</td>
<td>No recurrent vaginal prolapse</td>
<td>8 patients had preservation of the uterus</td>
</tr>
<tr>
<td>Grunberger [58]</td>
<td>1994</td>
<td>62 (14)</td>
<td>75.6</td>
<td>94</td>
<td>No moderate vaginal vault prolapse on exam</td>
<td>42 patients had direct attachment of the vagina to the sacral promontory 8 had lyodura loops</td>
</tr>
<tr>
<td>Lecuru [59]**</td>
<td>1994</td>
<td>203</td>
<td>32.5</td>
<td>86.7-100</td>
<td>Anatomically good results</td>
<td>The range of success is due to 4 different techniques which were compared</td>
</tr>
<tr>
<td>Nezhat [60]</td>
<td>1994</td>
<td>15 (0)</td>
<td>3 – 40</td>
<td>100</td>
<td>Complete relief of symptoms, excellent vaginal vault support</td>
<td>All cases done laparoscopically; 1 converted to laparotomy</td>
</tr>
<tr>
<td>Valatis [61]</td>
<td>1994</td>
<td>41 (2)</td>
<td>21</td>
<td>88</td>
<td>No third degree enterocele on exam, no symptomatic enterocele</td>
<td>One failure had direct attachment of the vagina to the sacrum</td>
</tr>
<tr>
<td>Virtanen [62]</td>
<td>1994</td>
<td>30 (3)</td>
<td>36</td>
<td>85</td>
<td>Good vaginal vault support on exam</td>
<td>2 patients with recurrences had failure at the vaginal apex (absorbable sutures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td>Patient “satisfied” with the procedure</td>
</tr>
</tbody>
</table>
Table 4. Sacrocolpopexy outcomes (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients, (number lost to follow-up, if known)</th>
<th>Follow-up (months)</th>
<th>Success rate (%)</th>
<th>Criteria for success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brubaker [63]</td>
<td>1995</td>
<td>65 (0)</td>
<td>3</td>
<td>71</td>
<td>No anterior or apical prolapse</td>
<td>63/65 patients had abdominal anterior compartment repair at the time of the sacrocolpopexy</td>
</tr>
<tr>
<td>de Vries [64]</td>
<td>1995</td>
<td>101 (29)</td>
<td>48</td>
<td>32</td>
<td>Fully cured (patient satisfaction based upon questionnaire)</td>
<td>Questionnaires sent to patients to evaluate pain, prolapse-related complaints and functional disorders. Patients indicated symptoms before surgery, &gt;1 year after surgery, and &gt;1 year after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>Considerable improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29</td>
<td>No improvement</td>
</tr>
<tr>
<td>Benson [25]</td>
<td>1996</td>
<td>40</td>
<td>60</td>
<td>58</td>
<td>(another 26% of patients had “satisfactory” outcomes)</td>
<td>Patient asymptomatic, vaginal apex supported above the levator plate, no protrusion beyond the hymen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 weeks</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Hardiman [65]</td>
<td>1996</td>
<td>80</td>
<td>47</td>
<td>99</td>
<td>No recurrent vault prolapse</td>
<td>Abdominal sacral colpoperineopexy performed in all patients due to posterior compartment defects and perineal descent associated with vaginal vault prolapse</td>
</tr>
<tr>
<td>Cundiff [66]</td>
<td>1997</td>
<td>19 (0)</td>
<td>11 weeks</td>
<td>100</td>
<td>No prolapse &gt; stage II (63% stage 0, 21% stage I, 16% stage II)</td>
<td>All patients underwent laparoscopic sacral colpopexy, Burch colposuspension and modified culpoplasty, with paravaginal defect repairs and posterior colporrhaphy added as indicated</td>
</tr>
<tr>
<td>Ross [67]</td>
<td>1997</td>
<td>19 (2)</td>
<td>12</td>
<td>100</td>
<td>No recurrent vault prolapse at 6 weeks postoperatively</td>
<td>All patients underwent laparoscopic sacral colpopexy</td>
</tr>
<tr>
<td>Costantini [68]</td>
<td>1998</td>
<td>21 (0)</td>
<td>31.6</td>
<td>90</td>
<td>Overall satisfaction per postoperative questionnaire; in all patients prolapse was reduced on exam postoperatively</td>
<td>7 patients underwent hysterocolpopexy</td>
</tr>
<tr>
<td>Occelli [69]**</td>
<td>1999</td>
<td>271 (54)</td>
<td>66</td>
<td>97.7</td>
<td>Cured for prolapse</td>
<td></td>
</tr>
<tr>
<td>Patsner [70]</td>
<td>1999</td>
<td>175 (0)</td>
<td>≥ 12</td>
<td>97</td>
<td>No “mesh failures”</td>
<td></td>
</tr>
<tr>
<td>Pilsgaard [71]</td>
<td>1999</td>
<td>35 (4)</td>
<td>24</td>
<td>97</td>
<td>No recurrent vault prolapse</td>
<td>The 1 patient with recurrent vault prolapse was noted to have the mesh detached from the promontory</td>
</tr>
<tr>
<td>Schettini [72]</td>
<td>1999</td>
<td>15 (0)</td>
<td>15</td>
<td>100</td>
<td>High position of the vaginal apex</td>
<td></td>
</tr>
<tr>
<td>Sze [73]</td>
<td>1999</td>
<td>56 (9)</td>
<td>23</td>
<td>81</td>
<td>No recurrent prolapse to or beyond the hymen</td>
<td>All 9 patients with recurrent prolapse were symptomatic</td>
</tr>
<tr>
<td>Diana [74]</td>
<td>2000</td>
<td>15</td>
<td>20</td>
<td>100</td>
<td>No relapse of the treated prolapses</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Number of patients, (number lost to follow-up, if known)</td>
<td>Follow-up (months)</td>
<td>Success rate (%)</td>
<td>Criteria for success</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>----------------------------------------------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fox [75]</td>
<td>2000</td>
<td>29</td>
<td>14</td>
<td>100</td>
<td>&gt; Stage I prolapse at any site</td>
<td>Procedure involved sacrocolpopexy and mesh interposition for the correction of both vault prolapse and rectocele</td>
</tr>
<tr>
<td>Nieminen [76]</td>
<td>2000</td>
<td>26 (6)</td>
<td>105</td>
<td>64</td>
<td>Any symptomatic prolapse, or asymptomatic stage II-IV prolapse</td>
<td>Direct attachment of the vagina to the sacrum in 4 patients</td>
</tr>
<tr>
<td>Winters [77]</td>
<td>2000</td>
<td>20 (0)</td>
<td>11</td>
<td>100</td>
<td>No recurrent enterocele or vault prolapse</td>
<td>Attempted to correct rectoceles abdominally with extension of the graft</td>
</tr>
<tr>
<td>Baessler [78]</td>
<td>2001</td>
<td>33 (2)</td>
<td>26</td>
<td>100</td>
<td>No recurrence of vaginal vault prolapse enterocele or anterior rectal wall prolapse</td>
<td></td>
</tr>
<tr>
<td>Geomini [79]</td>
<td>2001</td>
<td>45 (5)</td>
<td>38</td>
<td>93</td>
<td>No vault prolapse</td>
<td>Culdoplasty done only selectively; 2/3 failures were noted to be a result of graft detachment from the vagina (staples and a tacker used for attachment)</td>
</tr>
<tr>
<td>Scarpero [80]</td>
<td>2001</td>
<td>20</td>
<td>11</td>
<td>100</td>
<td>No recurrent enterocele or vault prolapse</td>
<td>All patients underwent sacrocolpopexy, Halban’s culdoplasty and paravaginal repair</td>
</tr>
<tr>
<td>Sullivan [81]</td>
<td>2001</td>
<td>236 (31)</td>
<td>64</td>
<td>100</td>
<td>No recurrence of vaginal or rectal prolapse</td>
<td>Total pelvic mesh repair involved attachment mesh strip between the perineal body and the sacrum, and then attaching two additional strips laterally to the pubis to support the vagina and bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34% Very satisfied</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38% Satisfied</td>
<td></td>
</tr>
<tr>
<td>Collopy [82]</td>
<td>2002</td>
<td>89 (0)</td>
<td>56.7</td>
<td>100</td>
<td>No recurrence of rectal or vaginal vault prolapse</td>
<td>All had concomitant culdoplasty</td>
</tr>
<tr>
<td>Cosson [83]</td>
<td>2002</td>
<td>77 (12)</td>
<td>12</td>
<td>94</td>
<td>No evidence of clinical prolapse</td>
<td>All patients had a laparoscopic sacrocolpexy with other procedures as indicated; 6 other patients had attempted laparoscopic surgery, but required conversion to a laparotomy</td>
</tr>
<tr>
<td>Culligan [84]</td>
<td>2002</td>
<td>245</td>
<td>61.2</td>
<td>85</td>
<td>Any POP-Q point ≥ 2</td>
<td>No apical failures observed</td>
</tr>
<tr>
<td>Lefranc [85]</td>
<td>2002</td>
<td>85 (0)</td>
<td>126 (median)</td>
<td>90.6</td>
<td>No relapse of any prolapse</td>
<td>All patients without preoperative SUI had a prophylactic Burch procedure done</td>
</tr>
<tr>
<td>Leonardo [86]</td>
<td>2002</td>
<td>25 (0)</td>
<td>48</td>
<td>100</td>
<td>No recurrent prolapse</td>
<td></td>
</tr>
<tr>
<td>Lindeque [87]</td>
<td>2002</td>
<td>262 (0)</td>
<td>≥ 16</td>
<td>99</td>
<td>No vaginal vault prolapse</td>
<td>1/3 failures due to graft detachment from vagina</td>
</tr>
<tr>
<td>Medina [88]</td>
<td>2002</td>
<td>97 (1)</td>
<td>19</td>
<td>90</td>
<td>&lt; Grade I prolapse</td>
<td>Etiology of 1 failure was graft detachment from the vagina (etiology of other 4 unknown)</td>
</tr>
</tbody>
</table>
Table 4. Sacrocolpopexy outcomes  (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients, (number lost to follow-up, if known)</th>
<th>Follow–up (months)</th>
<th>Success rate (%)</th>
<th>Criteria for success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culligan [84]</td>
<td>2002</td>
<td>245</td>
<td>61.2</td>
<td>85</td>
<td>Any POP-Q point ≥ 2</td>
<td>No apical failures observed</td>
</tr>
<tr>
<td>Lefranc [85]</td>
<td>2002</td>
<td>85 (0)</td>
<td>126 (median)</td>
<td>90.6</td>
<td>No relapse of any prolapse</td>
<td>All patients without preoperative SUI had a prophylactic Burch procedure done</td>
</tr>
<tr>
<td>Leonardo [86]</td>
<td>2002</td>
<td>25 (0)</td>
<td>48</td>
<td>100</td>
<td>No recurrent prolapse</td>
<td></td>
</tr>
<tr>
<td>Lindeque [87]</td>
<td>2002</td>
<td>262 (0)</td>
<td>≥ 16</td>
<td>99</td>
<td>No vaginal vault prolapse</td>
<td>1/3 failures due to graft detachment from vagina</td>
</tr>
<tr>
<td>Medina [88]</td>
<td>2002</td>
<td>97 (1)</td>
<td>19</td>
<td>90</td>
<td>&lt; Grade I prolapse</td>
<td>Etiology of 1 failure was graft detachment from the vagina (etiology of other 4 unknown)</td>
</tr>
<tr>
<td>Reddy [89]</td>
<td>2002</td>
<td>11 (0)</td>
<td>60</td>
<td>100</td>
<td>No prolapse symptoms or vault prolapse based upon patient questionnaire</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64 Satisfied</td>
<td>Considerable improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Roovers [90]</td>
<td>2002</td>
<td>12</td>
<td>18</td>
<td>92</td>
<td>No symptomatic genital prolapse</td>
<td>All patients had sacrocolpopexy and RPU</td>
</tr>
<tr>
<td>Brizzolara [91]</td>
<td>2003</td>
<td>124</td>
<td>36</td>
<td>98</td>
<td>No recurrent vault prolapse</td>
<td></td>
</tr>
<tr>
<td>Marinovic [92]</td>
<td>2003</td>
<td>12 (0)</td>
<td>39</td>
<td>83</td>
<td>No recurrent prolapse (anterior, posterior, or vault)</td>
<td></td>
</tr>
<tr>
<td>Sanz [93]</td>
<td>2003</td>
<td>11</td>
<td>12-24</td>
<td>100</td>
<td>Excellent vaginal support, no recurrence of prolapse</td>
<td>A suture anchor system was used for placement of the suture in the mesh at the sacrum</td>
</tr>
<tr>
<td>Podratz [94]</td>
<td>1995</td>
<td>50(6)</td>
<td>70</td>
<td>70</td>
<td>Asymptomatic (including no incontinence) and durable repair by exam</td>
<td></td>
</tr>
<tr>
<td>Hilger [95]</td>
<td>2003</td>
<td>69(31)</td>
<td>164</td>
<td>74</td>
<td>Subsequent POP operation or a positive response to question 5 on the PFDI***</td>
<td></td>
</tr>
<tr>
<td>Lo [96]</td>
<td>1998</td>
<td>52 (not clear)</td>
<td>25</td>
<td>94</td>
<td>No prolapse &gt; Stage II</td>
<td>Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension.</td>
</tr>
<tr>
<td>Maher [22]</td>
<td>2004</td>
<td>47 (1)</td>
<td>24</td>
<td>76% objective</td>
<td>Objective: No POP beyond halfway point Subjective: No symptoms of POP</td>
<td>Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension.</td>
</tr>
</tbody>
</table>

NS = not stated  
SUI = stress urinary incontinence  
RPU = retropubic urethropexy  
RCT = randomized clinical trial  
*Some patients also included in Addison’s series  
**Only abstract reviewed (paper not in English)  
***Question 5 on the Pelvic Floor Distress Inventory – “Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?”
Gastrointestinal problems may occur following open sacrocolpopexy. One in 20 women in CARE trial experienced significant gastrointestinal morbidity after sacrocolpopexy. Of 322 women in the study, 19 had symptoms of possible ileus or small bowel obstruction; of these, 4 had reoperation for small bowel obstruction, 11 were readmitted for medical management, and 4 had a prolonged initial hospitalization for gastrointestinal symptoms [106].

Abdominal sacrocolpopexy has greater morbidity, higher cost and less dypareunia than vaginal sacrospinous ligament suspension [22, 25]. These disadvantages have prompted surgeons to seek alternatives that maintain the advantages and reduce procedure-associated morbidity.

Laparoscopic sacrocolpopexy is performed in some centres, with and without robotic assistance. Only case series are available for evaluation. Von Theobald et al reported a series of 100 patients with 8 year followup [107]. Higgs reported on 140 consecutive women undergoing laparoscopic sacrocolpopexy with mesh [108]. At a median follow up of 66 months, 66 women were examined and a further 37 had questionnaire data available only. Subjects lost to follow-up were not included in the analysis, and could be failures or successes. Symptomatic improvement was good with 79% subjects reporting prolapse symptoms as “cured” or “improved”, but 39/103 (38%) had persistent symptoms of POP. Anatomic prolapse was seen on exam in 21/66 women examined.

2. Transvaginal Apical Suspension Techniques

Support of the vaginal cuff following hysterectomy is recommended by most authorities, and may be achieved by sacrospinous ligament suspension or reattachment of the uterosacral ligaments to the vaginal cuff, McCall culdoplasty, and Mayo culdoplasty. A single study compared these three methods of transvaginal apical suspension at the time of hysterectomy to determine th efficacy of prevention of posterior enterocele as a proxy for apical support [109].

- Iliococcygeus fascia fixation

There are no randomized trials that support the use of this procedure. Several case series have provided some information. Shull reported that apical support was optimal in 39/42 (83%) of patients, but eight others had apical or other defects [110]. Meeks and colleagues reported a 96% objective cure in 110 women followed up to 13 years [111]. In a retrospective case-control study, Maher and colleagues reported similar subjective (91% v 94%) and objective (53% v 67%) cure rates with iliococcygeus fixation (n=50) compared to sacrospionous fixation (n=78) [112].

- Levator myorrhaphy with apical plication

Francis and Jeffcoate [113] described their retrospective series using levator myorrhaphy with vaginal vault suspension to the plication. A large sponge pack in the rectum is used to avoid overplication and bowel dysfunction. Five of 35 women responding to the questionnaire had transient ureteral complications, one requiring re-operation. Seventeen women were quite satisfied, while six were dissatisfied.

- Mayo culdoplasty

A large retrospective series from the Mayo clinic described an 82% satisfaction rate on subjective follow-up with few complications [114]. It may achieve its suspension in a mechanism similar to the uterosacral ligament suspension, but no direct comparisons have been reported. A retrospective case series of 411 women undergoing Mayo culdoplasty in two other institutions found that a more dorsal “deep” placement of sutures through the uterosacral ligaments reduced the incidence of ureteral obstruction compared to other published series [115].

- Sacrospinous ligament suspension (SSLS)

The sacrospinous ligament suspension was first described in 1958 [116]. The traditional procedure as described by Nichols has been associated with high rates of anterior wall recurrences in some studies [117].

Table 5 contains outcomes from studies that have included SSLS. Uncontrolled retrospective case series and clinical trials in which SSLS was used in one arm suggest that anterior recurrence is more common (6% to 28.5%) than apical recurrence (2.4% to 19%). Reoperation rates after SSLF range from 1.3% to 37%, with all but two series reporting rates less than 7%.

Case series provide the majority of evidence regarding the SSLS complications which include buttock pain and sacral/pudendal neurovascular injury. Sze et al reviewed 22 studies that included 1229 SSLS procedures and reported that 3 patients (0.2%) had life-threatening hemorrhage from sacral or pudendal vascular injury with a 2% transfusion rate [118], Buttock pain occurred in 3% of patients, with resolution within 6 weeks for most affected women.

- Uterosacral ligament suspension

First described by Miller [126] in 1927 and popularized by Shull [127], this procedure maintains the vaginal axis in the midline and allows adjustment of the vaginal length. A weakness of the procedure is the risk of ureteral injury; therefore intraoperative cystoscopy after the sutures are tied down is an essential part of this procedure. The current evidence supporting the use of ULS is limited to seven uncontrolled retrospective case-series (Table 6). In these studies, ULS is associated with low overall recurrence (4% - 18%), anterior vaginal prolapse recurrence of 3.5% - 11%, and reoperation of less than 7%. These promising results are balanced by ureteral injury with this procedure.
Table 5. Anatomic Outcomes from CARE cohort at 3 and 24 months.

<table>
<thead>
<tr>
<th>POP-Q (mean± SD or N(%))</th>
<th>3 mo</th>
<th>Test</th>
<th>24 mo</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Burch N=149</td>
<td>No Burch N=164</td>
<td></td>
<td>Burch N=117</td>
</tr>
<tr>
<td>Point C</td>
<td>-8.3±1.8</td>
<td>-8.5±1.6</td>
<td>0.07</td>
<td>-8.0±1.5</td>
</tr>
<tr>
<td>Point Ba</td>
<td>-2.6±0.7</td>
<td>-2.0±0.9</td>
<td>&lt;0.001</td>
<td>-2.2±0.9</td>
</tr>
<tr>
<td>Point Bp</td>
<td>-2.4±0.9</td>
<td>-2.4±0.9</td>
<td>0.70</td>
<td>-2.0±1.3</td>
</tr>
</tbody>
</table>

Stage

| | | | |
| 0 | 55 (37.7%) | 29 (17.8%) | |
| 1 | 70 (47.9%) | 80 (49.1%) | |
| 2 | 19 (13.0%) | 53 (32.5%) | |
| 3 | 2 (1.4%) | 1 (0.6%) | |

Table 6. Sacrospinous Ligament Suspension Procedures

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>No. of Pts.</th>
<th>Mean Follow-up Months (range)</th>
<th>Definition of anatomic success*</th>
<th>Anatomic success – all segments</th>
<th>Anatomic recurrence by segment</th>
<th>Reoperation for prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morley [29]</td>
<td>1988</td>
<td>92</td>
<td>51.6 (1-132)</td>
<td>Not defined</td>
<td>90%</td>
<td>Apex 4% Anterior 6%</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Imparato [53]</td>
<td>1992</td>
<td>155</td>
<td>Not stated</td>
<td>Not defined</td>
<td>90.3%</td>
<td>Not reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Shull [119]</td>
<td>1992</td>
<td>81</td>
<td>(24 – 60)</td>
<td>Grade 0-1</td>
<td>82%</td>
<td>Apex 4% Anterior 12% Posterior 1%</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Pasley [120]</td>
<td>1995</td>
<td>144</td>
<td>35 (6-83)</td>
<td>Asymptom-atic and above hymen</td>
<td>85.4%</td>
<td>Apex 5.6% Anterior 7.6% Posterior 1.4%</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Benson [25]</td>
<td>1996</td>
<td>42</td>
<td>30 (12-66)</td>
<td>Vaginal walls above hymen or apical descent less than 50% length#</td>
<td>67%</td>
<td>Apex 12% Anterior 28.5% Posterior 2.3%</td>
<td>14 (37%)</td>
</tr>
<tr>
<td>Paraiso [121]</td>
<td>1996</td>
<td>243</td>
<td>76. (1-190)</td>
<td>Grade 0 or asymptomatic grade 1</td>
<td>79.7% at 5 years</td>
<td>Apex 4.9% Anterior 15.9% Posterior 4.9%</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Penalver [122]</td>
<td>1998</td>
<td>160</td>
<td>40 (18-78)</td>
<td>‘any symptomatic descent’</td>
<td>85%</td>
<td>Apex 6% Anterior 8% Posterior 2.5%</td>
<td>11 (6.8%)</td>
</tr>
<tr>
<td>Colombo [123]</td>
<td>1998</td>
<td>62</td>
<td>83 (48-108)</td>
<td>Grade 0-1</td>
<td>74%</td>
<td>Apex 8% Anterior 14% Posterior 3%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Meschia [124]</td>
<td>1999</td>
<td>91</td>
<td>43 (12-86)</td>
<td>Grade 0-1</td>
<td>85%</td>
<td>Apex 4% Anterior 13% Posterior 9%</td>
<td>None reported</td>
</tr>
<tr>
<td>Sze [73]</td>
<td>1997</td>
<td>75</td>
<td>24 (3-72)</td>
<td>above hymen</td>
<td>71%</td>
<td>Anterior 21% Other 8%</td>
<td>7 (12.9%)</td>
</tr>
<tr>
<td>Lantzsch [125]</td>
<td>2001</td>
<td>123</td>
<td>58 (6 – 108)</td>
<td>Not defined</td>
<td>87%</td>
<td>Apex 3.5% Anterior 8% Posterior 1.6%</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Maher [22]</td>
<td>2004</td>
<td>48</td>
<td>22 (6-58)</td>
<td>Grade 0-1</td>
<td>69%</td>
<td>Apex 19% Anterior 14% Posterior 7%</td>
<td>3 (6.3%)</td>
</tr>
</tbody>
</table>
b) Anterior vaginal wall prolapse

1. ANTERIOR COLPORRHAPHY

Since the first description in 1913 by Kelly [134], the success rates of anterior colporrhaphy in the management of cystoceles ranges from 80-100% in retrospective series [135-138] (Table 7). Experts agree that there is a great deal of variation in the clinical performance of anterior colporrhaphy. In two separate randomized control trials, Weber et al [139] and Sand et al [140] reported less favorable outcomes with the anterior colporrhaphy, 42% and 57% respectively. Although colposuspension is not used as a treatment for anterior vaginal support defects, Colombo et al reported long-term follow-up randomized trial results suggesting that the anterior colporrhaphy (97% success rate) was superior to the colposuspension (66%) in the management of the cystocele in women with cystocele and stress urinary incontinence [141].

2. PARAVAGINAL REPAIR

In 1976, Richardson [149] popularized the paravaginal repair originally described by White [142] as early as 1912. Several case series have reported that the range of success rate for the abdominal paravaginal repair is 75-97% [149-153] (Table 8). While this technique can be duplicated laparoscopically, no efficacy information is available.

Since Shull’s [143] initial report on the safety and efficacy of the vaginal paravaginal repair in 1994, several case series have reported success rates between 67 –100% [142-147]. The high success rates have been tempered by complications such as those reported by Mallipeddi [146] in her case series of 45 patients including: 1 bilateral ureteric obstruction, one retropubic haematoma requiring surgery, two vaginal abscesses; two transfusions. In a series of 100 women Young [147] reported 21 major complications and a 18% transfusion rate.

3. OPTIMAL ROUTE OF SURGERY

Surgical correction of pelvic organ prolapse can be divided into two main categories: reconstructive procedures to correct anterior and posterior wall defects and resuspend the vaginal apex or obliterate procedures to close off the vagina. Reconstructive surgery may use the vaginal route or the abdominal route. In planning surgery, the individual patient’s risk for surgery, risk of recurrence, previous treatments, and surgical goals are all considered in deciding on obliterator versus reconstructive procedures, and in deciding whether the vaginal or the abdominal approach will be used for reconstructive repairs. The goal of this section is to examine the evidence for selecting the surgical route in prolapse repairs.

- Selection of Paravaginal Defect Repair Route (vaginal vs abdominal):

No randomized control studies have evaluated the abdominal or vaginal paravaginal repair in isolation. As discussed in the apical section of this chapter, Benson et al [25] and Maher et al [22] have reported RCT’s on upper vaginal prolapse comparing abdominal sacral colpopexy and vaginal sacrospinous colpopexy. Abdominal paravaginal repair was performed in the abdominal group if required and an anterior colporrhaphy without or without vaginal paravaginal laterally. Both authors reported the abdominal group to have a statistically lower rate of postoperative anterior vaginal prolapse than the vaginal group.

Raz et al [154] popularized the needle suspension type procedure for cystoceles and success rates in case series vary from 90-98% [154, 155, 156]. The addition of polyglactin mesh to the repair appears to

---

Table 7. Uterosacral Vault Suspension Procedures

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>No. of Pts.</th>
<th>Mean Follow-up Months (range)</th>
<th>Definition of anatomic success*</th>
<th>Anatomic success –all segments</th>
<th>Anatomic recurrence by segment</th>
<th>Reoperation for prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenkins [128]</td>
<td>1997</td>
<td>50</td>
<td>(6-48)</td>
<td>Not defined</td>
<td>96%</td>
<td>Anterior 4%</td>
<td>None reported</td>
</tr>
<tr>
<td>Comiter [129]</td>
<td>1999</td>
<td>100</td>
<td>17 (6.5-35)</td>
<td>Grade 0-1</td>
<td>96%</td>
<td>Apex 4%</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Barber [130]</td>
<td>2001</td>
<td>46</td>
<td>15.5 (3.5-40)</td>
<td>Stage 0/1 or Stage 2 without symptoms</td>
<td>90%</td>
<td>Apex 5% Anterior 5% Posterior 5%</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Karram [131]</td>
<td>2001</td>
<td>168</td>
<td>21.6 (6-36)</td>
<td>Grade 0-1</td>
<td>88%</td>
<td>Apex 1% Anterior or posterior 11%</td>
<td>11 (5.5%)</td>
</tr>
<tr>
<td>Shull [127]</td>
<td>2001</td>
<td>289</td>
<td>Not stated</td>
<td>Grade 0-1</td>
<td>95%</td>
<td>Apex 1% Anterior 3.5% Posterior 1.4%</td>
<td>None reported</td>
</tr>
<tr>
<td>Amundsen [132]</td>
<td>2003</td>
<td>33</td>
<td>28 (6-43)</td>
<td>Stage 0 or 1</td>
<td>82%</td>
<td>Apex 6% Posterior 12%</td>
<td>None reported</td>
</tr>
<tr>
<td>Silva [133]</td>
<td>2006</td>
<td>72</td>
<td>61.2 (42-90)</td>
<td>Symptomatic Stage 2 or greater</td>
<td>85%</td>
<td>Apex 3% Anterior 7% Posterior 14%</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No.</td>
<td>Follow-up</td>
<td>Success Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>------</td>
<td>-------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anterior Colporrhaphy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanton [137]</td>
<td>1982</td>
<td>54</td>
<td>up to 2 yrs</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macer [135]</td>
<td>1978</td>
<td>109</td>
<td>5-20yrs</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walter [138]</td>
<td>1982</td>
<td>76</td>
<td>1.2yrs</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porges [136]</td>
<td>1994</td>
<td>388</td>
<td>2.6yrs</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombo [141]</td>
<td>2000</td>
<td>33 AC</td>
<td>8-17yrs</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 colposuspension</td>
<td>8-17 yrs</td>
<td>66%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sand [140]</td>
<td>2001</td>
<td>70 AC</td>
<td>1yr</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 AC&amp; mesh</td>
<td>1yr</td>
<td>75% No mesh complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weber [139]</td>
<td>2001</td>
<td>57 AC</td>
<td>23 month</td>
<td>37%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 AC+mesh</td>
<td>23 month</td>
<td>42% No mesh complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal Paravaginal Repair</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White [142]</td>
<td>1912</td>
<td>19</td>
<td>up to 3 yrs</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shull [143]</td>
<td>1994</td>
<td>62</td>
<td>.6 yrs</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grody [144]</td>
<td>1995</td>
<td>72</td>
<td>0.5-3yrs</td>
<td>99%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elkins [145]</td>
<td>2000</td>
<td>25</td>
<td>0.5-3yrs</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallipeddi [146]</td>
<td>2001</td>
<td>45</td>
<td>.6yrs</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young [147]</td>
<td>2001</td>
<td>100</td>
<td>11 months</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morse [148]</td>
<td>2007</td>
<td>27 VPVR</td>
<td>13</td>
<td>54%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>86 AC</td>
<td>24</td>
<td>45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal Paravaginal Repair</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richardson [149]</td>
<td>1976</td>
<td>60</td>
<td>1.7yrs</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richardson [150]</td>
<td>1981</td>
<td>213</td>
<td>0.5-6yrs</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shull [151]</td>
<td>1989</td>
<td>149</td>
<td>0.5-4yrs</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruce [152]</td>
<td>1999</td>
<td>27 APR&amp; sling</td>
<td>17 months</td>
<td>93%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 APR</td>
<td>17 months</td>
<td>76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotti [153]</td>
<td>1998</td>
<td>40</td>
<td>39 months</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sling type support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raz [154]</td>
<td>1989</td>
<td>107 AC &amp; needle</td>
<td>2yrs</td>
<td>98%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raz [155]</td>
<td>1991</td>
<td>50</td>
<td>2.8yrs</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardy [156]</td>
<td>1991</td>
<td>58 AC &amp; needle</td>
<td>2yrs</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benirzi [157]</td>
<td>1996</td>
<td>36 AC &amp; vaginal wall sling</td>
<td>17months</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dmochowski [158]</td>
<td>1997</td>
<td>47 Raz type</td>
<td>47months</td>
<td>43%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross [159]</td>
<td>1997</td>
<td>36 AC &amp; sling</td>
<td>20months</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safir [160]</td>
<td>1999</td>
<td>112 Raz + polyglactin mesh</td>
<td>21months</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldberg [161]</td>
<td>2001</td>
<td>53 AC &amp; sling</td>
<td>1 yr</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 AC</td>
<td>1yr</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APR Abdominal paravaginal repair
AC Anterior colporrhaphy
Definition varies between authors
have little impact on the success [160]. Dmochowski et al [158] reported a lower success rate using a stricter outcome definition of success.

Goldberg et al [161] reported results from a case control study of women with cystocele and stress urinary incontinence. He suggests that the addition of the pubovaginal sling to the anterior colporrhaphy significantly reduced the recurrence rate of cystocele from 42% in the control group to 19% in the anterior colporrhaphy and sling group (P<0.05).

The surgical management of anterior vaginal prolapse remains controversial. In reconstructive gynaecology surgery Level 1 [22, 25] evidence suggest the combined use of abdominal sacral colpopexy with or without retropubic colposuspension or paravaginal repair is superior to the vaginal approach including sacrospinous colpopexy and anterior colporrhaphy with or without vaginal paravaginal repair in the management of anterior vaginal prolapse (Grade B recommendation).

Level 2 evidence suggests that in women with stress urinary incontinence and anterior vaginal support defects, the addition of a sling at the time of anterior colporrhaphy enhances anatomical outcome as compared to anterior colporrhaphy alone or in combination with other continent surgery [140, 161]. This evidence arises from one institution and one sample of women is reported twice.

c) Posterior vaginal wall prolapse

In standard posterior colporrhaphy, the posterior vaginal wall is incised in the midline and rectovaginal fascia identified. The fascia is then approximated in the midline either with continuous or interrupted absorbable suture. In the traditional technique described by Jeffcote [113], this was supplemented with levator ani muscle approximation in the midline.

With the site specific defect repair, following posterior vaginotomy, the defects in the rectovaginal fascia are identified with a rectal finger bringing the rectal wall forward. The connective tissues are pulled across over the defects and sutured with absorbable sutures to close the defect.

1. Midline Plication (traditional posterior colporrhaphy)

In five studies, where traditional posterior colporrhaphy was evaluated, the success rate ranged from 76% to 97% (Table 8), while postoperative dyspareunia rates range from 11 to 27% (Table 8) with denovo dyspareunia rates of 4% to 16% [137, 162-164]. This has been attributed to levator ani plication forming a rigid band across the vagina. Midline fascial plication of rectovaginal fascia without levator plication is believed to reduce this high rate of dyspareunia.

2. Site specific defect repair

Richardson identified discrete defects in rectovaginal fascia and directed repair at the specific sites of defect to produce a more anatomical repair [169]. Both prospective and retrospective case series on the site specific defect repair, have reported success rates in the range of 67-92% with good functional outcomes (Table 9) [167, 170-172]. Table 9 contains a summary of reports using site specific defect repair for posterior vaginal support defects. One uncontrolled comparison of posterior colporrhaphy with site-specific defect repair [173] reported that the recurrence risk was higher in the site specific group at the end of 1 year follow-up (33% vs. 14%) and the postoperative Bp point was (-2.2 SSDR vs. - 2.7 PCR) P=0.001. The functional outcomes of difficult evacuation, fecal incontinence and post-operative dyspareunia were similar in both groups.

Posterior vaginal wall prolapse repair has traditionally used the vaginal approach, although several studies

**Table 9. Midline Fascial Plication (traditional posterior colporrhaphy)**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-up</th>
<th>Success</th>
<th>Dyspareunia Pre-op</th>
<th>Dyspareunia Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn M (164)</td>
<td>171</td>
<td>43 months</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez A* (163)</td>
<td>24</td>
<td>5 years</td>
<td>91%</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td>Arnold W (162)</td>
<td>29</td>
<td>4 years</td>
<td>77%</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>Mellgren A* (165)</td>
<td>25</td>
<td>12 months</td>
<td>96%</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>Maher C** (166)</td>
<td>38</td>
<td>12 months</td>
<td>97%</td>
<td>52%</td>
<td>11%</td>
</tr>
<tr>
<td>Singh (167)</td>
<td>42</td>
<td>18 month</td>
<td>92%</td>
<td>31%</td>
<td>12%</td>
</tr>
<tr>
<td>Robinson (168)</td>
<td>34</td>
<td>41 mos (mean)</td>
<td>NR</td>
<td>33%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*includes levatorplasty

**without levatorplasty
address the transanal / transperineal approaches. The threshold for surgical intervention in the posterior wall has been poorly studied and the relationship between symptoms and anatomy is particularly poorly understood. There is insufficient evidence to recommend a surgical threshold based on anatomical support loss. Symptoms that have been associated with posterior wall prolapse include difficult defecation and splinting. Constipation is recognized as a colonic motility disorder that is not treated by posterior vaginal surgery.

The transvaginal approach appears to be superior to the transanal approach for repair of posterior wall prolapse. Two prospective randomized controlled trials compared the transvaginal and transanal techniques. Nieminen et al reported one-year outcomes for 30 women with symptomatic rectocele who were randomly assigned to vaginal vs. transanal surgery [175]. Despite the small sample size of this group, they reported superiority of the transvaginal route with significant differences in recurrence rate (7% vs. 40%, p=0.04) and symptom improvement (93% vs. 73%, p=0.08) in the transvaginal and transanal groups respectively. No differences were reported in post-operative splinting or sexual function, perhaps due to the small sample size. Improved posterior support was reported with the transvaginal point (POP-Q Ap point -2.8 vs. -1.36). Kahn et al reported the superiority of the 2 year anatomic outcomes transvaginal route in 57 women randomly allocated to transvaginal (N=24) vs. transanal repair (N=33) with 13 % vs. 30%, (p=0.01) respectively [164].

Puigdollers et al reported results from a prospective cohort of women with rectocele and constipation who underwent surgery via endorectal or transperineal route, according to preference of the surgeon). At the end of one year the subjective improvement in constipation was reported in 43% (p < 0.001) and the need to splint decreased in 52%.(p=0.001) [176].

A single non-randomized study reports outcomes for a cohort of women with symptomatic rectocele who were treated laparoscopically (N=40) vs. transanally (n=40). Level 2B evidence from this study supports the superiority of the transanal approach for symptomatic relief (55% vs. 28%, p < 0.02), but lower post-operative dyspareunia rates (22% vs. 36%) with laparoscopic approach [177].

Paraiso et al compared three techniques of vaginal repair – posterior colorrhaphy (PCR), site specific repair (SSDR) and graft augmentation with site specific repair by prospective RCT [174]. Women randomly assigned to the posterior colorrhaphy (n= 37) and the site-specific repair group (n= 37) were reviewed at 17 months. The anatomical success rates were 86% and 78% respectively in the PCR vs. SSDR group. The functional outcomes of difficult evacuation and vaginal digitations were similar in both groups, and there was improvement in the PISQ –12 scores in all the treatment groups. The dyspareunia rates were 20% in the PCR compared to 14% in the SSDR. The anatomical and functional outcomes between SSDR and PCR were similar in this study. These studies do not provide evidence to support use of augmenting materials for posterior prolapse repair.

3. Modifications to traditional repairs

In the case series by Van Dam J H et al combined transvaginal and transanal repair was done in 89 women and evaluated at a follow-up of 52 months. The anatohical success rate was 71% with no persistent or recurrent rectocele on defecography at 6 months. However, denovo dyspareunia was reported in 41% of women and there was deterioration of fecal incontinence in 7 patients [178].

The abdominal route has been employed in the correction of posterior vaginal wall prolapse when a co-existing apical defect required surgery. The technique is a modification of sacrocolpopexy with extension of the posterior mesh to the rectovaginal septum or upto the perineal body. The procedure has been performed completely abdominally or as a combined abdominal and vaginal approach. Table 10 summarizes a series of studies using extended posterior fixation of sacrocolpopexy mesh.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-up</th>
<th>Success</th>
<th>Dyspareunia Pre-op</th>
<th>Dyspareunia Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramov Y [173]</td>
<td>124 (SSDR)</td>
<td>14 months</td>
<td>67%</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>183 (PCR)</td>
<td></td>
<td>86%</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Cundiff G [170]</td>
<td>69</td>
<td>12 months</td>
<td>82%</td>
<td>29%</td>
<td>19%</td>
</tr>
<tr>
<td>Kenton K [171]</td>
<td>66</td>
<td>12 months</td>
<td>77%</td>
<td>26%</td>
<td>8%</td>
</tr>
<tr>
<td>Porter [172]</td>
<td>89</td>
<td>18 months</td>
<td>82%</td>
<td>67%</td>
<td>46%</td>
</tr>
<tr>
<td>Paraiso [174]</td>
<td>37 (SSDR)</td>
<td>17 months</td>
<td>78%</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>27 (PCR)</td>
<td></td>
<td>86%</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>
2. OBLITERATIVE PROCEDURES: LeFort colpocleisis, Colpectomy and colpocleisis

These procedures are offered to women with Stage II-IV POP seeking a relatively non-invasive surgical procedure with cure rates as high as 100% [181] and who no longer wish to preserve coital function per vaginam (Table 11). With partial colpocleisis (for vaginal vault prolapse) or LeFort colpocleisis (for uterine prolapse), rectangles of vaginal epithelium are excised from the dorsal and ventral surfaces of the prolapsed vagina. The vagina is inverted and closed with the two raw surfaces in direct contact and reinforced with sutured skin edges. A small amount of skin is usually preserved on each side of the vagina, speeding the excision and allowing drainage of any secretions. The enterocele need not be addressed because there is no longer room in the vagina to permit descent, and the uterus can be left in situ unless there is separate pathology. In total colpectomy, all vaginal skin is removed, often including a high levator myorrhaphy.

In the U.S., the number of colpocleises has declined from a high of 17,200 procedures in 1992 to a low of 900 procedures in 1997 [24], while the number of total colpectomies decreased from a high of 3229 in 1989 to a low of 32 procedures in 1995. Nevertheless, obliterative procedures have an important role to play in the management of POP: in many women, the loss of coital function is offset by the positive impact on their daily activities. These procedures are performed on an outpatient basis with an immediate return to normal activities, and success rates have been described as high as 100%. High rates of patient satisfaction have been reported [182, 183] with low rates of regret for loss of sexual function. Barber et al reported results from a multicenter study followed by a prospective cohort design with a concurrent control group (184). Despite permanent alterations in sexual function and potential alterations in self-image, improvements in quality of life for the thirty women aged 65 or older who selected obliterative prolapse surgery were similar to the concurrent cohort of forth women who selected reconstructive surgery.

The Pelvic Floor Disorders Network recently completed a large series of women undergoing colpocleisis with one year follow-up [185]. All pelvic symptom scores and related bother significantly improved at 3 and 12 months, and 125 (95%) patients said they were either ‘very satisfied’ or ‘satisfied’ with the outcome of their surgery. These investigators concluded that colpocleisis was associated with high patient satisfaction and was effective in resolving prolapse and pelvic symptoms.

<p>| Table 11. Abdominal Repair (Posterior Extension of Colpofix Mesh) |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-up</th>
<th>Success</th>
<th>Dyspareunia Pre-op</th>
<th>Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baessler K</td>
<td>33</td>
<td>26 months</td>
<td>45%</td>
<td>39%</td>
<td>13%</td>
</tr>
<tr>
<td>Fox S</td>
<td>29</td>
<td>14 months</td>
<td>90%</td>
<td>38%</td>
<td>17%</td>
</tr>
<tr>
<td>Su K</td>
<td>122</td>
<td>12 months</td>
<td>90%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lyons [180]</td>
<td>20</td>
<td>12 months</td>
<td>80%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marinkovic [92]</td>
<td>12</td>
<td>39 months</td>
<td>91%</td>
<td>29%</td>
<td>none</td>
</tr>
</tbody>
</table>

*Laparoscopic approach

<p>| Table 12. Post-Colpocleisis Anatomic Measures. (Data available for 146 patients at baseline, 110 at 3 months and 103 12 months after surgery) |</p>
<table>
<thead>
<tr>
<th>Baseline</th>
<th>3 Mos Post-op</th>
<th>12 Mos Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most distal vaginal point (leading edge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1cm inside hymen</td>
<td>0 (0%)</td>
<td>90/110 (82%)</td>
</tr>
<tr>
<td>≤ 1cm beyond hymen</td>
<td>0 (0%)</td>
<td>107/110 (97%)</td>
</tr>
<tr>
<td>&gt; 1cm beyond hymen</td>
<td>146/146 (100%)</td>
<td>3/110 (3%)</td>
</tr>
</tbody>
</table>
IV. CONCOMITANT SURGERY

1. EFFECT OF COMBINATION PROCEDURES

With apical suspensions: The success of anterior wall support procedures seems to interact with concomitant vaginal apical suspension procedures. Paraiso et al [121] reported a 37% cystocele rate after 243 women had undergone sacrospinous colpopexy and suggested the rate of cystocele may decrease with the iliococcygeous fixation as there was less posterior displacement of the vault. Subsequently, Maher et al [112] reported high rates of cystocele after both sacrospinous and iliococcygeous fixation.

With bladder neck suspension, Kohli et al [186] found the concomitant use of transvaginal bladder neck suspension used in conjunction with the anterior colporrhaphy was also problematic. Women undergoing anterior colporrhaphy alone had a 7% recurrence rate as compared to a 33% recurrence rate after combined anterior colporrhaphy.

2. Hysterectomy - The Role of Hysterectomy in Surgical Treatment of Prolapse

Hysterectomy at the time of POP repairs is the standard practice in most parts of the world despite the fact that descent of the uterus may be a consequence, not a cause of POP. Surprisingly, given its widespread use, concomitant hysterectomy is not an evidence-based practice. Increasingly, women may wish to avoid hysterectomy at the time of POP repairs because of factors such as desire for further childbearing, the belief that the uterus is important for sexual satisfaction, and the success of recent conservative procedures for uterine bleeding and fibroids. While there are no prospective comparative trials, a few smaller studies suggest that there may be no disadvantage in outcome with conservation of the uterus, and operating time is shorter. Well-designed RCT studies comparing the repair of POP with and without hysterectomy should be prioritized.

Several studies report results of preservation of the uterus with sacrohysterectomy. Banu 1997 [187] reported 100% success in a case series of 19 women with following sacrohysterectomy using mersilene mesh at 3-5 year follow-up. Lerón 2001 [188] reported 92% success with the same procedure using teflon mesh in 13 subjects at a mean 15.6 months. Maher 2001 used a laparoscopic-assisted high McCall procedure for hysterectomy in 43 patients, with a reported 79% success rate at a mean 12 months follow-up [189]. Jeon, et al [190] reported outcomes after a median follow-up of 36 months in their retrospective comparison of 168 patients in 3 groups: sacrocolpopexy with synthetic mesh and hysterectomy (N=63); abdominosacral uteropexy with mesh (N=35), and abdominal uterosacrococinal colpopexy and hysterectomy (N=70). Recurrence in the latter group was 6.2 times higher than in the sacrocolpopexy/hysterectomy group, however due to the design and group size, specific hypothesis testing was not possible.

Dietz [191] and co-workers observed 133 Dutch women undergoing a sacrospinous hysteropexy, and examined 60 of these women with mean follow-up of 22.5 months. Eight-four percent of women were highly satisfied about the outcome of the procedure, and the rate of reoperation for uterine descent was 2.3%. The recurrence of anterior wall defects in this study was 35%.

Three studies describe uterine preservation at the time of vaginal reconstruction. Uterine preservation or removal did not appear to affect the risk of POP recurrence, although these studies are significantly underpowered.

Maher et al [189] reported a retrospective comparison of 34 sacrospinous hysteropexies and 36 vaginal hysterectomies with sacrospinous fixation. Uterine conservation was associated with significantly less blood loss (198 vs 402 ml) and decreased operating time (59 vs. 91 minutes). At a 36 month mean follow-up in the hysterectomy group and a slightly shorter follow-up of 26 months in the hysteropexy group, the investigators did not detect differences in subjective success (86% vs. 78%, p=0.70), objective success 72% vs. 74%, p=1.00) or patient-determined satisfaction (86% vs. 85%, p=0.10).

Hefni [192] et al reported a nonrandomized prospective controlled study of 109 women who underwent sacrospinous cervicocolpopexy with uterine conservation [61 (56%)] and sacrospinous colpopexy + vaginal hysterectomy [48 (44%)]. Uterine conservation was associated with significantly less blood loss, decreased operating time and complication rate. At approximately 34 months, anatomic success was similar for the upper vaginal support (93.5% vs. 95%), anterior wall (11.4% vs. 10.4%, p=0.9) and re-operation (5% vs. 4.2%) for the uterine conserving vs. hysterectomy groups respectively.

Van Brummen [193] performed a retrospective comparison of the same two procedures (n=30 with hyst, 44 with hysteropexy) and recurrence of prolapse defined as ≥ grade 2 was similar in hysterectomy (2/30, 6.7%) and women with uterine preservation (5/44, 11.4%).

Neuman et al [194] reported their prospective non-randomised series in an abstract comparing 44 patients undergoing Posterior Intravaginal Sling (PIVS) with (N=44) and without (N=35) hysterectomy according to the patient’s preference. The women who selected uterine conservation were younger (51 vs. 63 yrs). With mean follow-up of 30 months, the
investigators did not detect a significant difference in anatomical results (98.7), patient satisfaction (89.9%), or perioperative morbidity.

**Risks of concomitant hysterectomy**

There is growing evidence that concomitant hysterectomy increases the risk of suture or mesh erosion at the time of sacrocolpopexy. Cundiff et al, [32] in a prospectively planned analysis of the randomized CARE trial, reported that hysterectomy increases the risk of suture/mesh erosion. There are no comparative studies of complete vs. supracervical hysterectomy at the time of sacrocolpopexy to address the appropriate clinical treatment, given this finding.

Several case series have addressed specific risks that concomitant hysterectomy may confer at the time of prolapse repair, especially with regard to concomitant synthetic mesh use. Federow [195] did not detect significant differences in short-term post-op febrile morbidity, haemoglobin change or duration of hospital stay in a series of 235 sacrocolpopexy patients, 36.6% of whom had concomitant total abdominal hysterectomy. Belot et al reported that an inverted T-colpopotomy and concomitant hysterectomy increased the risk of mesh erosions fourfold [198]. Gauruden-Burmeister reported on 120 women, 12 months following armed monofilament polypropylene mesh with a mesh erosion rate of 3% which was not affected by performance of inverted T-colpopotomy in over 50% (197). Collinet et al (198) reported that concomitant hysterectomy at the time of mesh-augmented vaginal reconstructive surgery increases the risk of mesh erosion [OR = 5.17 (p = 0.003] in his retrospective series of 277 patients.

One non-randomized comparative study of 124 women reported by Brizzolara et al suggests that concomitant hysterectomy (n=60) is not a risk factor for mesh erosion [91].

Concomitant culdoplasty. There is insufficient evidence to comment on the utility of concomitant culdoplasty at the time of prolapse repair by any method.

**3. CONTINENCE TREATMENT**

**(Treatment and Prophylaxis)**

Although many women with anterior vaginal wall prolapse also experience stress urinary incontinence, women with advanced prolapse may not have incontinence symptoms. There is no standardized nomenclature to describe clinical or urodynamic findings for stress continent women who exhibit urine loss during prolapse reduction testing. In published papers, the terms "occult", "potential", "masked", "latent", "hidden" and "iatrogenic" are used interchangeably to describe SUI, which occurs following POP surgery in symptom-free patients before surgery. Conventionally, occult stress incontinence is diagnosed when leaking occurs with Valsalva maneuvers after reduction of the prolapse in the absence of detrusor contractions. Using these criteria, incidence of occult stress incontinence has been shown to range between 36% and 80% [12].

Many case series have documented the risk of de novo SUI following POP repair with the incidence of de novo postoperative stress incontinence in patients with a negative preoperative reduction cough stress test has been showed to be 1.9% [199] in a recent retrospective chart review study. Concomitantly, a 67.9% prevalence of occult SUI has been reported in a population of 78 women with POP[200].

The pre-operative lack of symptoms in some women who experience de novo SUI following POP surgery is due to anatomic obstruction of the kinked urethra [201], and may have voiding difficulties due to similar urethral mechanics [202]. Techniques for prolapse reduction to optimally predict the risk of post-operative SUI has not been evidence-based. Visco et al (203) reported that certain techniques have poor predictive values for predicting de novo SUI following sacrocolpopexy.

Level 1 evidence exists from the CARE study which randomized 322 stress-continent women with Stage II-IV POP to a Burch colposuspension or no continence procedure at the time of concomitant open abdominal sacrocolpopexy [11]. The trial ended when the first planned interim analysis demonstrated the significant reduction of de novo SUI three months after surgery in women who were assigned to the Burch colposuspension compared to the group without a continence procedure. This benefit was not offset by any untoward intra-operative or post-operative side effects such as worsening urge incontinence or voiding dysfunction. These benefits were maintained at one year [13] and two years [14].

In the trial reported by Costantini, et al, [204] 66 patients with a negative stress test before and after prolapse reduction and no preoperative history of SUI symptoms were randomized to colposuspension or no colposuspension with a mean follow-up of 39.5 months. The pre- and post-operative definitions are not consistently defined or standardized. Although this paper does not support the routine use of colposuspension at the time of sacrocolpopexy in patients with negative preoperative stress test, the study was significantly underpowered and concluded the concomitant colposuspension increases the rate of post-operative stress incontinence.

The contradictory results between these two studies may be due to different inclusion criteria or differences in sacrocolpopexy technique. Participants in the CARE study were randomized without regard to results of urodynamic testing with prolapse reduction, in order to determine the pre-operative utility of such testing.
Recent prospective randomized trial has shown that women who are continent with prolapse reduction prophylactic TVT® (or other prophylaxis) among bother, was used as an endpoint. Thus, the use of included and any de novo incontinence, regardless of who were incontinent with prolapse reduction were [205]. Although this was a positive trial, only women addressed the surgical stress incontinence prophylaxis from their single small randomized clinical trial that ligament plication [141]. Meschia et al reported results incontinence to cystopexy with or without pubourethral anatomic changes that improve anterior support and decrease posterior vaginal wall support (Table III-IV prolapse but without stress incontinence to either a needle suspension or endopelvic fascial placation without detecting a difference in urinary continence [28]. Similarly Colombo et al. did not find differences in continence outcomes following randomization of 102 women with stage 2-4 prolapse without stress incontinence to cystopexy with or without pubourethral ligament plication [141]. Meschia et al reported results from their single small randomized clinical trial that addressed the surgical stress incontinence prophylaxis with TVT® at the time of vaginal prolapse surgery [205]. Although this was a positive trial, only women who were incontinent with prolapse reduction were included and any de novo incontinence, regardless of bother, was used as an endpoint. Thus, the use of prophylactic TVT® (or other prophylaxis) among women who are continent with prolapse reduction remains an unanswered but important clinical question.

A recent prospective randomized trial has shown that anterior mesh repairs are more likely to lead to postoperative SUI than colporrhaphy alone (23% to 10% respectively) [206] (Tables 12, 13). The Effect of Concomitant Continence Surgery on Prolapse Outcome:

a) Concomitant Sling

Goldberg et al reported that a suburethral sling is protective in the anterior wall [161]. In a randomized trial designed to evaluate the efficacy of cadaveric fascia patch for augmentation of anterior colporrhaphy, Gandhi et al reported that concomitant sling placement reduces anterior wall recurrence [221].

b) Concomitant Colposuspension

In a secondary analysis of a randomized controlled trial of the utility of Burch colposuspension for prevention of post-operative stress incontinence, Brubaker et al reported that Burch colposuspension at the time of open sacrocolpopexy results in anatomic changes that improve anterior support and decrease posterior vaginal wall support (Table 4) [14].

4. CONCOMITANT PERIOPERATIVE PELVIC PHYSICAL THERAPY

Jarvis et al reported the only study to date that has evaluated perioperative pelvic muscle training in women undergoing prolapse surgery [222]. Three months after surgery, subjects in the intervention group had significantly greater reduction in urinary symptoms, including reduction in daytime urinary frequency, and greater improvement in quality of life compared to the control group. Subjects were not followed beyond 3 months postoperatively, however, and only urinary symptoms were assessed. The role of perioperative pelvic muscle training for reducing the recurrence of prolapse or its symptoms in the long-term is unknown.

a) Risk factors for POP and their relationship to the choice of surgical route

Experts believe that it is important to understand the specific risk factors for an individual patient in planning her surgical correction POP results from a continuum of predisposing, inciting, promoting, and decompensating factors [223]. There are limited data regarding risk factors for POP recurrence after surgery, but expert opinion supports the concept that there are certain women who are at high risk for primary and/or recurrent POP. Some established risk factors for primary POP include vaginal delivery, age, obesity, and family history. Most experts recommend that, whenever feasible, POP repair be delayed until after childbearing is complete. As older women may have increased surgical risks compared to younger women [224] some surgeons may advocate the vaginal approach avoiding an incision. Obesity may be viewed as a separate risk for abdominal surgery, with the vaginal approach avoiding the risk associated with an abdominal wall incision [225].

There is no evidence to guide clinical decision making for the woman who develops POP without evident risk factors, such as the young woman or the nulliparous woman. In fact, one study of nulliparous nuns and their multiparous sisters reveals similar rates of POP in siblings after menopause, regardless of parity [226]. Younger women needing repair of POP often choose the most durable procedure allowing coital function.

Expert opinion is supported by level 2 evidence that there are certain women who are at high risk for primary and/or recurrent POP. Dietz-Itza and co-workers [191] found that women with increased body weight (>65 kg) and women under 60 years of age had increase in both anatomical and functional recurrence of prolapse. Women with more severe prolapse are more likely to recur than those with milder support abnormalities.

Other factors are not considered to be risk factors for POP but influence surgery itself. Obviously
<table>
<thead>
<tr>
<th>Author / year type of trial level of evidence</th>
<th>Year</th>
<th>SUI type</th>
<th>Surgery + Follow up</th>
<th>Follow-up</th>
<th>SUI outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bump [28] prospective randomized Level 2</td>
<td>1996</td>
<td>Occult USI (Pressure transmission ratio &lt; 90% or positive stress test during barrier testing) n = 20</td>
<td>Needle urethropexy (Muzsaia) n = 10 Fascia plication n = 10 Without occult SUI n = 9 Needle colposusp. n = 4 fascia plication n = 5</td>
<td>6 weeks and 6 months Needle urethropexy group: SUI = 7% at 6 weeks 14 % at 6 mos. Fascia plication group SUI 21% at 6 weeks 7% at 6 mos.</td>
<td>Needle urethropexy group: urge incontinence 58% at 6 weeks - (36% de novo) 14% at 6 mos. Plication group: Urge incontinence 0% at 6 weeks 7% at 6 mos.</td>
<td></td>
</tr>
<tr>
<td>Colombo [207] randomized Level 1</td>
<td>1996</td>
<td>Negative stress test with prolapse reduction</td>
<td>Cystopecy n = 52 Cystopecy + pubourethral ligaments plication n = 50</td>
<td>2.6 +/- 1.7 y. 2.9 +/- 1.8 y.</td>
<td>SUI : 8% SUI : 8%</td>
<td>1 reoperation 0 long term micturition disorders 2% symptomatic OAB 1 reoperation 10% long term micturition disorders 2% symptomatic OAB</td>
</tr>
<tr>
<td>Colombo [208] randomized Level 1</td>
<td>1997</td>
<td>Overt SUI</td>
<td>post pubourethral ligt plication n = 15 Pereyra procedure n = 21 occult SUI post pubourethral ligt plication n = 40 Pereyra procedure n = 33</td>
<td>&gt; 5 y.</td>
<td>SUI : 40% SUI : 29% SUI : 15%</td>
<td>4% symptomatic OAB after pubourethral plication 2% symptomatic OAB after Pereyra</td>
</tr>
<tr>
<td>Gordon [209] prospective case series Level 3</td>
<td>1999</td>
<td>Occult SUI n = 30</td>
<td>Kelly plication</td>
<td>25,5 m.</td>
<td>Subjective and objective SUI: 50% objective SUI with no subjective complaints: 37%</td>
<td>procedure non effective to prevent postoperative SUI in patients undergoing POP repair</td>
</tr>
<tr>
<td>Chaikin [210] prospective cohort study Level 2</td>
<td>2000</td>
<td>Occult SUI n = 14</td>
<td>Pubovaginal sling</td>
<td>47 mos. (12-108) SUI : 14%</td>
<td>1 (7%) de novo urge incontinence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative stress test reduction n = 10</td>
<td>No additional procedure</td>
<td>44 mos. (12-96)</td>
<td>SUI : 0%</td>
<td>0 de novo urge incontinence</td>
</tr>
<tr>
<td>Klutke [211] retrospective. (charts review) Level 4</td>
<td>2000</td>
<td>Occult SUI n = 55</td>
<td>Burch n = 52 Needle colposusp. N = 3 negative stress test with reduction N = 70</td>
<td>3.5 y (1-7)</td>
<td>SUI : 4%</td>
<td>30% de novo detrusor instability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% de novo detrusor instability</td>
</tr>
</tbody>
</table>

Table 13. SUI prevention at the time of vaginal surgery biologic grafts (continued)
<table>
<thead>
<tr>
<th>Author / year</th>
<th>Year</th>
<th>SUI type</th>
<th>Surgery + Follow up</th>
<th>Follow-up</th>
<th>SUI outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groutz [212] Prospective Level 3</td>
<td>2000</td>
<td>occult SUI n = 30</td>
<td>Stamey</td>
<td>8 mos. (3-19)</td>
<td>Symptomatic urodynamically confirmed SUI 23.3% asymptomatic patients with positive postop stress test 36.7%</td>
<td></td>
</tr>
<tr>
<td>Yamada [213] Retrospective case control Level 4</td>
<td>2001</td>
<td>occult SUI n = 10</td>
<td>suburethral sling</td>
<td>51.2 (24-72)</td>
<td>subjective SUI: 10%</td>
<td>De novo urge symptom: 10%</td>
</tr>
<tr>
<td>Gordon [214] Prospective Level 3</td>
<td>2001</td>
<td>occult SUI</td>
<td>TVT</td>
<td>14.25 +/- 3.08 m. (12-24)</td>
<td>Subjective SUI: 0% objective SUI: 10%</td>
<td>De novo detrusor instability (without obstruction): 13.33%</td>
</tr>
<tr>
<td>Barnes [215] retrospect. (charts review) Level 4</td>
<td>2002</td>
<td>occult SUI n = 38</td>
<td>Pubovaginal sling</td>
<td>15 m. (6-39)</td>
<td>SUI: 5%</td>
<td>De novo urge incontinence: 9.5% 0 permanent retention</td>
</tr>
<tr>
<td>De Tayrac [216] retrospective case control Level 4</td>
<td>2004</td>
<td>Overt SUI n = 29</td>
<td>TVT n = 15</td>
<td>17.3 +/- 1.4 (7-36)</td>
<td>SUI: 6.7%</td>
<td>NB: POP repair included ant mesh repair in all patients</td>
</tr>
<tr>
<td>Groutz [217] Prospective cohorte study Level 3</td>
<td>2004</td>
<td>occult SUI n = 100</td>
<td>TVT</td>
<td>27 m. (12-52)</td>
<td>Symptomatic SUI urodynamically confirmed 1 year follow-up: 2%</td>
<td>De novo urge incontinence: 8%</td>
</tr>
<tr>
<td>Meschia [205] prospective randomized Level 1</td>
<td>2004</td>
<td>Occult SUI</td>
<td>TVT</td>
<td>26 m.</td>
<td>Subjective SUI: 4% objective SUI: 8%</td>
<td>De novo urge incontinence: 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 m</td>
<td>subjective SUI: 36% objective SUI: 44%</td>
<td>De novo urge incontinence: 4%</td>
</tr>
</tbody>
</table>
Table 13. SUI prevention at the time of vaginal surgery biologic grafts (continued)

<table>
<thead>
<tr>
<th>Author / year type of trial level of evidence</th>
<th>Year</th>
<th>SUI type</th>
<th>Surgery + Follow up</th>
<th>Follow-up</th>
<th>SUI outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liang [218] Prospective case_control Level 2</td>
<td>2004</td>
<td>occult SUI (positive pessary test) n = 49</td>
<td>TVT n = 32</td>
<td>objective SUI : 0% subjective SUI: 9,4%</td>
<td>Idiopathic detrusor overactivity 16%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No TVT n = 17</td>
<td>objective SUI : 52,9% subjective SUI: 64,7%</td>
<td>Idiopathic detrusor overactivity 5,9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No masked SUI (negative pessary test n = 30)</td>
<td>no post-op SUI</td>
<td>Idiopathic detrusor overactivity 0%</td>
<td></td>
</tr>
<tr>
<td>Clemons [219] retrospective Level 4</td>
<td>2005</td>
<td>occult SUI n = 64</td>
<td>Suburethral sling grade 3-4 anterior prolapse n = 39</td>
<td>SUI: 13%*</td>
<td>De novo or worsening urge incontinence: 8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suburethral sling grade 3-4 posterior/apical prolapse n = 25</td>
<td>SUI: 0%*</td>
<td>De novo or worsening urge incontinence: 4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No procedure</td>
<td>Objective SUI: 34 (64.2%)</td>
<td>19 patients remained continent after surgery</td>
<td></td>
</tr>
<tr>
<td>Reena [200] prospective cohorte study Level 3</td>
<td>2007</td>
<td>occult SUI (pessary during provocative exercises) n = 53</td>
<td>Burch group N = 157</td>
<td>Symptoms SUI: 19.7% (30) Positive stress test without reduction: 2% (3) with POP reduction: 35.7% (55) Detrusor overactivity: 12.1% (19)</td>
<td>Composite SUI outcome: 32.0% (Symptoms: 25.9% Stress test: 9.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control group N = 165</td>
<td>Subjective SUI: 18.8% (30) Positive stress test without reduction: 5.7% (9) With reduction: 35.8% (58) Detrusor overactivity: 10.4% (17)</td>
<td>2 years</td>
<td>Composite SUI outcome: 45.2% (Symptoms: 40.6% Stress test: 6.7%)</td>
</tr>
</tbody>
</table>
Table 13. SUI prevention at the time of vaginal surgery biologic grafts (continued)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of trial</th>
<th>Year</th>
<th>SUI type</th>
<th>Surgery + Follow-up</th>
<th>Follow-up</th>
<th>SUI outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costantini [204]</td>
<td>Single site, prospective randomized Level 2</td>
<td>2007</td>
<td>Burch group N = 34</td>
<td>Negative stress test before and after reduction No symptoms of UI (history, questionnaire) No leakage during UDS</td>
<td>42 +/- 18 mos (12-74)</td>
<td>De novo SUI: 26.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control group N = 32</td>
<td></td>
<td>38 +/- 19 mos (15-71)</td>
<td>De novo SUI: 3.1%</td>
<td></td>
</tr>
<tr>
<td>Misraï [220]</td>
<td>Laparoscopic sacral colpopexy</td>
<td>2008</td>
<td>No SUI procedure</td>
<td>Negative stress test</td>
<td>20.4 mos.</td>
<td>De novo SUI: 13%</td>
<td></td>
</tr>
</tbody>
</table>

w = week m = month y = year SUI= stress urinary incontinence colposusp= colposuspension TVT= tension free vaginal tape ranscut= transcutaneous

Table 14. Concomitant Continence Procedure at Time of Colpocleisis

<table>
<thead>
<tr>
<th>Underwent concomitant incontinence surgery</th>
<th>Bothersome SUI three months after surgery (n=68)</th>
<th>Bothersome SUI 1 year after surgery (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8 (21%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>No</td>
<td>31 (79%)</td>
<td>30 (83%)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (72%)</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>No</td>
<td>6 (21%)</td>
<td>6 (21%)</td>
</tr>
</tbody>
</table>
concomitant clinical consideration, such as a pelvic mass or extensive abdominal mesh from prior hernia repair alters the risk/benefit for certain surgical routes. There is insufficient evidence to guide the route of prolapse surgery for women with known intra-abdominal adhesions. Some surgeons may seek to avoid adhesions using an extraperitoneal approach from the vagina, while others may prefer to manage the adhesions through an incision. A shortened vagina with dyspareunia may dictate procedures that have the potential to improve vaginal depth. In an retrospective cohort study, Hilger found that almost 50% of elderly women who underwent successful abdominal repair of POP did not resume sexual activities, despite the fact that the abdominal repair was selected to preserve coital function [95].

In summary, individual risks factors should be weighed against the perceived risk of recurrence in any one individual woman in order to select the most favorable risk/benefit ratio for their specific support defects.

V. THE ROLE OF AUGMENTING MATERIALS IN POP SURGERY

The use of material is inherent in the performance of abdominal sacrocolpopexy. However, there is increasing interest in the potential role of augmenting materials to enhance POP surgery outcomes with other POP procedures, including vaginal surgery. The Cochrane review of surgically managed POP in 2007 concluded that there were insufficient data about mesh and biological graft augmentation of vaginal repairs, and stressed the need for adequately powered randomized controlled clinical trials [27]. Despite recent results from three recent RCTs [227] addressing the anterior wall and demonstrating the utility of mesh augmentation for that indication, the committee considered the current levels of uncertainty about clinical care scenarios, especially in primary prolapse repairs completed with mesh. Although a prolapse persistence or recurrence is an undesirable outcome, a secondary prolapse procedure has a good likelihood of success, especially when sacrocolpopexy is used. The clinical scenarios for subsequent procedures following failed mesh procedures are highly anecdotal. There is insufficient information about risks and efficacy of secondary procedures following primary mesh repairs.

1. AUGMENTATION FOR ANTERIOR WALL SURGERY

- Synthetic material

In line with our surgical colleagues there has been a move towards the use of prosthesis to augment the native tissue repair in reconstructive gynaecology. Given the relatively high failure rate of the anterior vaginal compartment at prolapse surgery it is likely that anterior vaginal wall repair would benefit most from the use of prosthesis.

The majority of Level 1 and 2 evidence [140, 228] suggest that the use of absorbable synthetic mesh overlay offers a superior anatomical outcome for anterior wall prolapse as compared to anterior colporrhaphy alone, although the evidence is divided based on relatively few women [139].

Synthetic mesh was used by Julian et al who described his prospective case control study in women who had undergone at least 2 previous vaginal repair [228]. These women had an overlay of Marlex mesh to the anterior colporrhaphy reduced the recurrence rate of cystocele from 33% to 0%, but the mesh erosion rate was 25%. Flood et al in a retrospective review of 142 women with Marlex mesh augmentation of anterior colporrhaphy demonstrated a 100 % success rate for cystoceles at 3.2 years and a mesh erosion rate of 2% [229].

Weber et al [139] in a randomized control trial compared the anterior colporrhaphy [33], ultra-wide anterior colporrhaphy [24] or anterior colporrhaphy with absorbable polyglactin (Vicryl) 910 mesh [26] in the management of cystoceles. The study size was too small to detect small differences (or no differences) in efficacy or adverse events. However, at a mean follow-up of nearly 2 years the groups had similar proportions of women experiencing satisfactory or optimal anatomic results, 30%, 48% and 42% respectively.

Sand et al [140] in a larger RCT randomly allocated cystoceles to anterior colporrhaphy alone (n=70) and to anterior colporrhaphy plus polyglactin mesh overlay (n=73). At I year the success rate in the mesh group was 75% and significantly greater than the 57% success rate in the anterior repair group alone (P=0.02). Concurrent paravaginal defect were present in 11 women and concomitant paravaginal repair was significantly associated with a lower recurrence of cystocele overall (P=0.02). In a separate study multivariate logistic regression demonstrated concurrent pubovaginal slings for stress urinary incontinence, to be associated with significantly fewer recurrent cystoceles (odds ratio, 0.32; p=0.005) [221].

A variety of polypropylene mesh overlays have been evaluated in case series for the management of anterior wall prolapse. The anatomical success rate varies from 76 to 100% [230-235]. Salvatore et al reported worrying functional outcomes after a prolene mesh overlay including a mesh erosion rate of 13%, overactive bladder increasing from 28 to 56% and dyspareunia increasing from 18 to 38% postoperatively [236]. Visco et al suggested that the mesh erosion or infection rate was increased four-fold when mesh was
Two randomised control trials have been published comparing overlaying polypropylene mesh and traditional anterior colporrhaphy. Hiltunen et al compared 104 women undergoing anterior compartment prolapse repair with 6x11cm low weight monofilament polypropylene (Parietene light, Sofradim Co, Trevoux, France) with 97 undergoing traditional anterior colporrhaphy [206]. At 12 months the objective success (stage 0 or 1 Aa and Ba) rate was 93 in the mesh group and 61% in no mesh group (P<.001). Symptomatic anterior compartment prolapse was significantly lower at 4% in the mesh group as compared to 15% in the no mesh group (p<0.05). Mesh erosions were seen in 17.3%. Sivaslioglu et al reported on 43 undergoing low weight polypropylene mesh as compared to 42 undergoing site-specific vicryl repair and at 12 months found the objective success rate (leading edge of cystocoele was <71 cm in relation to hymen (stage 1) was significantly higher at 91% in the mesh group and 72% in the non-mesh group [239]. The mesh erosion rate was 6.9% and de novo dyspareunia was reported in 4.6% in the mesh group and none in the non-mesh group. Quality of life assessment demonstrated no difference in outcomes between the groups and no patient in either group underwent further surgery for anterior compartment prolapse. Since 2004, a variety of kit transobturator armed polypropylene meshes have been available. A recent RCT compared anterior polypropylene mesh (n=38) with anterior colporrhaphy. At 1 year the objective success rate (defined as less than POP-q stage II anterior vaginal prolapse) was higher in the mesh group (89% vs. 55%). Functional outcomes including quality of life, sexual activity and dyspareunia were similar in both groups with a 5% mesh erosion and 2% unilateral leg pain that settled by 8 weeks after the surgery in the mesh group [240].

Fatton et al reported on 106 women three months following vaginal mesh polypropylene mesh (anterior, posterior or total) with a 95% success rate and 4.7% mesh erosion rate in short term followup [241]. Concomitant hysterectomy was not performed and the authors felt surgeon experience was important in minimizing mesh erosion, a view that was supported by Dwyer and Orielly who reported a decreasing rate of mesh complications with increasing surgeon experience [242].

Gauruden–Burmester reported on mesh contracture rate by performing postoperative introital ultrasound measurements and revealed the vaginal polypropylene anterior mesh contracted from 7.5cm to 3.5cm (54%) and 11.5cm to 6.4cm (46%). While the mesh contracture was significant the authors found the mesh contraction was not associated with postoperative vaginal length measurements [197]. Majority Level 1 evidence suggests that polypropylene mesh overlay has a superior anatomical outcome as compared to traditional anterior colporrhaphy. These findings need to be tempered with Level 2 and 3 evidence suggesting that significant functional complications are associated with the employment of non-absorbable meshes at the time vaginal reconstructive surgery [98, 228, 236].

The consequences of these complications are not insignificant and may result in multiple subsequent surgical procedures and residual symptoms. There is a lack of evidence on the optimal management of such mesh-provoked complications. A single RCT demonstrated an armed polypropylene mesh kit had a superior anatomical outcome at one year compared to anterior colporrhaphy. This study is significantly underpowered to adequately assess functional outcomes [240]. There remains a significant paucity of data available on efficacy of the commercially available kit armed polypropylene meshes for anterior compartment prolapse. A single well designed RCT and level 2 evidence suggest the porcine dermis graft overlay to be more effective than Anterior colporrhaphy alone. A significant body of Level 2 and 3 evidence has not been able to reproduce these results. A single RCT and level 3 evidence suggest little benefit is be derived from cadaveric fascia lata or dermis as a graft material.

2. BIOLOGIC GRAFTS

Alternatively to synthetic prosthetic grafts autologous material may have a lower risk of host rejection or infection. Cosson [243] described an autologous 6-8cm long and 4 cm wide vaginal patch suspended from the tendinous archs of the pelvic fascia and tucked under the anterior repair. The success rate (~grade 1 POP) was 93% at a mean follow-up of 16 months. Allografts from postmortem tissue banks have been used for many years in orthopedic surgery and decrease the risk associated with harvesting autologous rectus sheath or fascia lata. Cadaveric fascia lata with or without pubovaginal sling has been utilised to correct anterior compartment prolapse with a success rate varying from 81-100% with acceptable
complication rates [244-247]. Gandhi et al have reported preliminary results of a randomized control trial comparing anterior colporrhaphy alone and augmented with fascia lata graft for cystoceles [221]. At 1 year they were not able to demonstrate that the addition of the fascia lata graft improved outcomes with the success rate after anterior colporrhaphy alone being 71% as compared to 82% in those augmented with the fascia lata graft (P=0.07). No complications were reported. Cadaveric dermis has been employed as a graft material in the anterior compartment with success rates varying from 42-84% at 2 years [248-250]. Concerns regarding prion transmission causing infectious diseases [251] or residual antigenicity [252] that may cause host graft reactions have encouraged the use of porcine or bovine xenografts.

Leboeuf et al retrospectively reviewed 24 women with native tissue four corner defect repair (FDR) and 19 FDR [253]. At 15 months the success rate was 100% in the FDR group and reduced to 84% if Pelvicol overlay was utilized. Wheeler et al reported on 36 women who all underwent high uterosacral vault suspension with anterior repair augmented with porcine dermis and at 17 months found a 50% recurrence rate [254]. The authors highlighted that despite the high objective failure rate greater that 90% of the women were satisfied or somewhat satisfied with the repair and 83% would undergo the surgery again. Handel et al retrospectively compared anterior colporrhaphy (n=18), porcine dermis (n=56) and polypropylene graft (n=24) in those with cystocele [255]. The success rate at 13 months was 94%, 64% and 96% respectively with a 21% rate of vaginal extrusion of the porcine dermis graft. Alternatively to these relatively disappointing results, a number of groups have reported satisfactory objective results utilizing the porcine dermis. Goemelsky et al found in 70 women after 2 years, an 87% success rate with no complications [256]. Simmsman et al also after 2-year review of 89 women reported a 78% success rate with a 17% rate of graft erosions [257]. Meschia et al in a multicentre randomised clinical trial compared the anterior colporrhaphy (n=103) and anterior colporrhaphy-augmented with 4x7cm piece of porcine dermis [258]. The success rate at 1 year was 93% in the anterior colporrhaphy with porcine graft overlay group as compared to 81% in anterior colporrhaphy alone group (P<0.001) with a 1% rate of graft erosion.

Tables 15, 16 and 17 summarize studies using augmenting materials for various transvaginal procedures. Biological grafts do not appear to enhance to results of traditional posterior colporrhaphy. Pariso, et al reported the results of a randomized trial in which 3 groups of women were allocated to posterior colporrhaphy, site-specific defect repair or biograft augmentation with xenograft and followed over 17 months [174]. Women with graft augmentation had the highest anatomic failure rate (46%) compared to PCR and SSDR group (14% and 22% respectively). The functional outcomes in all the 3 groups were similar. Similarly, in the prospective cohort study by Altman, et al, augmentation with the porcine collagen in 23 patients resulted in a recurrence rate of 41% at 38 months [271] without major materials-related complications.

Several case series demonstrate that the surgical therapeutic ratio of augmentation with synthetic material is not favourable. Case series report that synthetic grafts are associated with high anatomical success rates at the cost of complications and sequelae. De Tayrac and colleagues reported an anatomical cure rate of 92% at two-years following a combined sacrospinous suspension with polypropylene mesh posterior repair. In this case series of 26 women, one patient developed denovo dyspareunia and 3 developed vaginal erosion [237]. In the French multicenter case series reported by de Tayrac et al, investigators evaluated 76 women who underwent posterior repair using low-weight polypropylene mesh coated with absorbable hydrophilic film [238]. At a median follow-up of 10 months, they reported a 2.6% recurrence rate, 12% denovo dyspareunia rate and 6.3% vaginal mesh erosion rate.

A retrospective case series of 50 women with mesh placement in the posterior compartment (with or without anterior placement) was reported by Dwyer et al. [242]. Despite no recurrences, at a mean follow-up of 29 months, he reported 6 mesh erosions (12%), 1 denovo dyspareunia and one rectovaginal fistula. Similarly, Lim et al reported a 30% rate of vaginal erosion, 27% denovo dyspareunia rate as well as a 22% recurrence rate 35 months after posterior repair augmented with composite polyglactin 910-polypropylene mesh [268]. Milani et al augmented the midline fascial plication for rectoceles repair with polypropylene mesh in 31 women. After the median follow-up of 17 months the anatomical success rate was 94% but the rate of dyspareunia in this group increased from 6% to 69% (p= <0.05) and the mesh erosion rate was 6.5% with one pelvic abscess [269].

Gauruder-Burmester et al evaluated 48 subjects with posterior wall defects in their study with a polypropylene mesh kit. At the end of one year follow-up reported good outcomes with an anatomical success at posterior vaginal wall as 100%, cure of dyspareunia postoperatively and no mesh erosions in the posterior compartment [197]. In the case series by Fatton et al, evaluating a polypropylene mesh kit,
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type</th>
<th>No</th>
<th>Review Months</th>
<th>Success Rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julian (228)</td>
<td>1996</td>
<td>Marlex Control</td>
<td>12</td>
<td>24</td>
<td>100%</td>
<td>25% mesh erosion, infection</td>
</tr>
<tr>
<td>Nicita (234)</td>
<td>1998</td>
<td>Prolene</td>
<td>44</td>
<td>14</td>
<td>100%</td>
<td>3 uterine prolapse</td>
</tr>
<tr>
<td>Flood (229)</td>
<td>1998</td>
<td>Marlex</td>
<td>142</td>
<td>38</td>
<td>100%</td>
<td>3 mesh erosions</td>
</tr>
<tr>
<td>Migliari (232)</td>
<td>1999</td>
<td>Mixed fiber</td>
<td>15</td>
<td>23</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Migliari (231)</td>
<td>2000</td>
<td>Polypropylene</td>
<td>12</td>
<td>20</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Natale (233)</td>
<td>2000</td>
<td>Polypropylene</td>
<td>138</td>
<td>19</td>
<td>97%</td>
<td>13 mesh erosions, 9 dyspareunia, 1 haematoma</td>
</tr>
<tr>
<td>Sand (140)</td>
<td>2001</td>
<td>Polyglactin</td>
<td>73</td>
<td>12</td>
<td>75%</td>
<td>no mesh complications</td>
</tr>
<tr>
<td>Weber (139)</td>
<td>2001</td>
<td>Polyglactin</td>
<td>26</td>
<td>23</td>
<td>42%</td>
<td>no mesh complications</td>
</tr>
<tr>
<td>Salvatore (236)</td>
<td>2002</td>
<td>Prolene</td>
<td>32</td>
<td>17</td>
<td>87%</td>
<td>13% mesh erosions</td>
</tr>
<tr>
<td>O’Reilly (235)</td>
<td>2003</td>
<td>Polypropylene</td>
<td>81</td>
<td>28</td>
<td>88%</td>
<td>no mesh erosions</td>
</tr>
<tr>
<td>Cervigini (230)</td>
<td>2007</td>
<td>Polypropylene</td>
<td>218</td>
<td>38</td>
<td>76%</td>
<td>12.3% erosions 7% Vaginal stenosis</td>
</tr>
<tr>
<td>Jo(259)</td>
<td>2007</td>
<td>Polypropylene</td>
<td>38</td>
<td>18</td>
<td>94%</td>
<td>0 erosions</td>
</tr>
<tr>
<td>Rodríguez (260)</td>
<td>2005</td>
<td>Polypropylene</td>
<td>98</td>
<td></td>
<td>85%</td>
<td>0 erosions</td>
</tr>
<tr>
<td>Amrute (261)</td>
<td>2007</td>
<td>Polypropylene</td>
<td>76</td>
<td>30</td>
<td>95%</td>
<td>3% erosions</td>
</tr>
<tr>
<td>de Tayrac(262)</td>
<td>2005</td>
<td>Polypropylene</td>
<td>84</td>
<td>24</td>
<td>92%</td>
<td>8.3%</td>
</tr>
<tr>
<td>de Tayrac(263)</td>
<td>2006</td>
<td>Polypropylene</td>
<td>55</td>
<td>37</td>
<td>89.1%</td>
<td>9.1% mesh erosion 5.5% mesh shrinkage 16.7% dyspareunia 10% dyspareunia</td>
</tr>
<tr>
<td>de Tayrac(237)</td>
<td>2006</td>
<td>Polypropylene</td>
<td>48</td>
<td>18</td>
<td>98%</td>
<td>8.3% erosions</td>
</tr>
<tr>
<td>de Tayrac(238)</td>
<td>2007</td>
<td>low weight Polypropylene coated</td>
<td>32</td>
<td>13</td>
<td>93%</td>
<td>6.3% erosion 12.8% de novo dyspareunia</td>
</tr>
<tr>
<td>Hiltunen (206)</td>
<td>2007</td>
<td>RCT low weight Polypropylene</td>
<td>104</td>
<td>12</td>
<td>93%</td>
<td>17.3% erosions 4 TVT 1 vault prolapse 5 TVT 1 ant mesh</td>
</tr>
<tr>
<td>Sivaslioglu (239)</td>
<td>2007</td>
<td>RCT low weight Polypropylene Site specific vicryl AC</td>
<td>43</td>
<td>12</td>
<td>91%</td>
<td>6.9% mesh erosions 4.6% de novo dyspareunia dyspareunia</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Type</td>
<td>No</td>
<td>Review Months</td>
<td>Success Rate</td>
<td>Complications</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>-----</td>
<td>---------------</td>
<td>--------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Nguyen (240)</td>
<td>2008</td>
<td>RCT Armed Polypropylene</td>
<td>38</td>
<td>12</td>
<td>89%</td>
<td>5% Erosion 9% dyspareunia 16% dysparuenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perigee AC</td>
<td>38</td>
<td></td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Altman (264)</td>
<td>2007</td>
<td>Polypropylene Prolift</td>
<td>123</td>
<td>2</td>
<td>87%</td>
<td>1.5% mesh erosions 3.2% organ perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biological Grafts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosson (243)</td>
<td>2001</td>
<td>Autologous Vaginal patch</td>
<td>47</td>
<td>16 months</td>
<td>93%</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groutz (245)</td>
<td>2001</td>
<td>cadaveric &amp; pubovaginal sling</td>
<td>19</td>
<td>20</td>
<td>100%</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobashi (265)</td>
<td>2002</td>
<td>cadaveric fascia lata &amp; sling</td>
<td>132</td>
<td>12</td>
<td>87%</td>
<td>1 osteitis pubis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung (248)</td>
<td>2002</td>
<td>cadaveric dermis</td>
<td>19</td>
<td>24</td>
<td>84%</td>
<td>1 infection removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clemons (249)</td>
<td>2003</td>
<td>cadaveric dermis</td>
<td>33</td>
<td>18</td>
<td>59%</td>
<td>1 incision breakdown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powell (247)</td>
<td>2004</td>
<td>cadaveric fascia lata</td>
<td>58</td>
<td>24</td>
<td>81%</td>
<td>10% graft erosion 2 transfusions 1 cystotomy 3 ureteral kinking</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frederick (244)</td>
<td>2005</td>
<td>cadaveric fascia lata &amp; sling</td>
<td>251</td>
<td>6</td>
<td>93%</td>
<td>1 osteitis pubis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gandhi (221)</td>
<td>2005</td>
<td>RCT AC &amp; fascia lata (Tutoplasta)</td>
<td>76</td>
<td>13</td>
<td>82%</td>
<td>no graft complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC no graft</td>
<td>78</td>
<td>13</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Ward (250)</td>
<td>2007</td>
<td>cadaveric dermis</td>
<td>39</td>
<td>24</td>
<td>42%</td>
<td>1 de novo dyspareunia No graft erosions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Xenographs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebouf (253)</td>
<td>2004</td>
<td>FDR &amp; Pelvicol PDR</td>
<td>9</td>
<td>15</td>
<td>84%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>15</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salomon (266)</td>
<td>2004</td>
<td>porcine dermis transoburator</td>
<td>27</td>
<td>14</td>
<td>81%</td>
<td>1 graft r/o vaginal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gomelsky (256)</td>
<td>2004</td>
<td>porcine dermis</td>
<td>70</td>
<td>24</td>
<td>87%</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeler (254)</td>
<td>2006</td>
<td>porcine dermis Ulerosacral repair</td>
<td>28</td>
<td>18</td>
<td>50%</td>
<td>2% granulation tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meschia (258)</td>
<td>2007</td>
<td>Porcine AC</td>
<td>98</td>
<td>12</td>
<td>93%</td>
<td>1% vaginal extrusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>103</td>
<td>12</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handel (255)</td>
<td>2007</td>
<td>Porcine dermis Polypropylene AC</td>
<td>56</td>
<td>13</td>
<td>64%</td>
<td>21% vaginal extrusions 4% mesh erosion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>13</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>13</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Simsiman (256)</td>
<td>2006</td>
<td>Porcine graft</td>
<td>89</td>
<td>24</td>
<td>78%</td>
<td>17% erosions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robles (267)</td>
<td>2007</td>
<td>Porcine dermis Polypropylene arm</td>
<td>90</td>
<td>8</td>
<td>85%</td>
<td>no complications</td>
</tr>
</tbody>
</table>

Variable definitions of success used.
**Table 16. Augmenting Materials for the Posterior Vagina**

### SYNTHETIC MESH

<table>
<thead>
<tr>
<th>Author</th>
<th>Graft</th>
<th>N</th>
<th>Follow-up</th>
<th>Succes %</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permanent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altman D [264]</td>
<td>Polypropylene</td>
<td>91</td>
<td>6 months</td>
<td>91%</td>
<td>Rectal perforation N=4, Wound infection N=1</td>
</tr>
<tr>
<td>De Tayrac [237]</td>
<td>Polypropylene</td>
<td>26</td>
<td>22 months</td>
<td>92%</td>
<td>Vaginal erosion N=3</td>
</tr>
<tr>
<td>De Tayrac [238]</td>
<td>Polypropylene</td>
<td>76</td>
<td>10 months</td>
<td>72%</td>
<td>Vaginal erosion 6.3%, De novo dyspareunia 13%</td>
</tr>
<tr>
<td>Dwyer P [242]</td>
<td>Polypropylene</td>
<td>50</td>
<td>29 months</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Fatton B [241]</td>
<td>Polypropylene</td>
<td>28 (isolated)</td>
<td>25 weeks</td>
<td>86.2%</td>
<td>Rectovaginal fistula N=1</td>
</tr>
<tr>
<td>Gauruder-Burmester A [197]</td>
<td>Polypropylene</td>
<td>48</td>
<td>12 months</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Lim Y [268]</td>
<td>Prolene-vicryl</td>
<td>37</td>
<td>35 months</td>
<td>78%</td>
<td>Mesh erosion N=11</td>
</tr>
<tr>
<td>Milani [269]</td>
<td>Polypropylene</td>
<td>31</td>
<td>17 months</td>
<td>94%</td>
<td>Mesh erosion 6.5%</td>
</tr>
<tr>
<td>Parker MC [270]</td>
<td>Polypropylene</td>
<td>4</td>
<td>14 months</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

### Absorbable

<table>
<thead>
<tr>
<th>Author</th>
<th>Graft</th>
<th>N</th>
<th>Follow-up</th>
<th>Succes %</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altman D [271]</td>
<td>Porcine Dermis</td>
<td>23</td>
<td>3 years</td>
<td>69%</td>
<td>None</td>
</tr>
<tr>
<td>Ghoniem G [272]</td>
<td>Allograft</td>
<td>91</td>
<td>2.6 years</td>
<td>97.6%</td>
<td>Vaginal hematoma N=1</td>
</tr>
<tr>
<td>Kobashi K [246]</td>
<td>Cadaveric Fascia</td>
<td>73</td>
<td>13 months</td>
<td>90%</td>
<td>Dyspareunia 23%, Granulation tissue 11%</td>
</tr>
<tr>
<td>Kohli N [273]</td>
<td>Porcine Dermis</td>
<td>30</td>
<td>12 months</td>
<td>93%</td>
<td>None</td>
</tr>
<tr>
<td>Paraiso M [174]</td>
<td>Porcine Dermis</td>
<td>31</td>
<td>17 months</td>
<td>54%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Site Specific</td>
<td>37</td>
<td></td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior Colpo.</td>
<td></td>
<td></td>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

### BIOLOGIC GRAFTS

<table>
<thead>
<tr>
<th>Author</th>
<th>Graft</th>
<th>N</th>
<th>Follow-up</th>
<th>Succes %</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sand P [140]</td>
<td>Polyglycolic acid</td>
<td>67</td>
<td>?One yr.</td>
<td>90%</td>
<td>No mesh erosion</td>
</tr>
<tr>
<td></td>
<td>No mesh</td>
<td>65</td>
<td></td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Altman D [271]</td>
<td>Porcine Dermis</td>
<td>23</td>
<td>3 years</td>
<td>69%</td>
<td>None</td>
</tr>
<tr>
<td>Ghoniem G [272]</td>
<td>Allograft</td>
<td>91</td>
<td>2.6 years</td>
<td>97.6%</td>
<td>Vaginal hematoma N=1</td>
</tr>
<tr>
<td>Kobashi K [246]</td>
<td>Cadaveric Fascia</td>
<td>73</td>
<td>13 months</td>
<td>90%</td>
<td>Dyspareunia 23%, Granulation tissue 11%</td>
</tr>
<tr>
<td>Kohli N [273]</td>
<td>Porcine Dermis</td>
<td>30</td>
<td>12 months</td>
<td>93%</td>
<td>None</td>
</tr>
<tr>
<td>Paraiso M [174]</td>
<td>Porcine Dermis</td>
<td>31</td>
<td>17 months</td>
<td>54%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Site Specific</td>
<td>37</td>
<td></td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior Colpo.</td>
<td></td>
<td></td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Type</td>
<td>No.</td>
<td>Followup weeks</td>
<td>Success rate</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>-----</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Abdel Fattah [275]</td>
<td>2008</td>
<td>Apogee</td>
<td>38</td>
<td>12</td>
<td>95% (36/38)</td>
</tr>
<tr>
<td>Gaurder-Burmester [197]</td>
<td>2007</td>
<td>Apogee American Medical Systems</td>
<td>48</td>
<td>52</td>
<td>100%</td>
</tr>
<tr>
<td>Belot F [196]</td>
<td>2005</td>
<td>Prolift, Johnson &amp; Johnson, Ethicon</td>
<td>277</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Abdel Fattah [275]</td>
<td>2008</td>
<td>Prolift, Johnson &amp; Johnson, Ethicon</td>
<td>143</td>
<td>12</td>
<td>94%</td>
</tr>
<tr>
<td>Biertho [276]</td>
<td>2007</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>34</td>
<td>12</td>
<td>91</td>
</tr>
<tr>
<td>Foote [277]</td>
<td>2007</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>52</td>
<td>20</td>
<td>83%</td>
</tr>
<tr>
<td>Matox [278]</td>
<td>2006</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>21</td>
<td>7</td>
<td>37%</td>
</tr>
<tr>
<td>Vardy [279] [280]</td>
<td>2005</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>98</td>
<td>3</td>
<td>99%</td>
</tr>
<tr>
<td>Neuman [194]</td>
<td>2007</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>140</td>
<td>120</td>
<td>99%</td>
</tr>
<tr>
<td>de Tayrac [238]</td>
<td>2007</td>
<td>PIVS Tyco Helathcare, USA</td>
<td>21</td>
<td>42</td>
<td>95%</td>
</tr>
<tr>
<td>Amrute [261]</td>
<td>2007</td>
<td>Polypropelene H shaped</td>
<td>76</td>
<td>123</td>
<td>95%</td>
</tr>
</tbody>
</table>
58 women with rectocele underwent posterior mesh repair. At the short-term follow-up at 3 months, there were two cases of Stage 2 prolapse of the posterior vaginal wall and there were five patients with mesh exposure [241].

Altman, et al, reported a 91% posterior anatomical cure rate in their interim analysis at 2 months following polypropylene mesh repair. The same authors evaluating the perioperative morbidity with this technique at the 6-month follow-up reported four cases of rectal perforation and one wound infection [264].

A variety of kits have been proposed for repair of prolapse that includes apical support loss. Routine use of these kits should be regarded cautiously based on the complications reported in the series in Table 17.

VI. RECTAL PROLAPSE

External rectal prolapse is a circumferential, full-thickness protrusion of the rectum through the anus. This section is limited to a discussion of surgically treatment for external rectal prolapse and does not discuss internal rectal prolapse or various forms of intrasuccesception. More than 90% of patients with rectal prolapse are women [281] and the incidence peaks in women older than 70 years old [282] Pelvic organ prolapse and rectal prolapse may occur concurrently. In a recent study, 48% of patients treated for rectal prolapse developed genital prolapse at some point of time [283]. Patients with rectal prolapse have debilitating symptoms and they usually therefore require surgical intervention. There are some 100 different surgical methods described for surgical correction of rectal prolapse, but there are no randomized, well powered, studies to base clinical decision making on. Available randomized studies have major methodological limitations.

Surgical treatment of complete rectal prolapse includes traditionally been divided into perineal and transabdominal approaches. Perineal procedures include complete (the “Altemeier procedure”), or partial resection (the “Delorme procedure”) of the prolapse. Transabdominal procedures can be performed either with open or laparoscopic techniques and include different types of suspension and sometimes concomitant bowel resection. Mobilization of the rectum down is an integral part of correction of the prolapse. The extent of mobilization varies and there are some data suggesting that the lateral ligaments should be preserved. A recently introduced surgical technique, laparoscopic ventral rectopexy, avoids posterior rectal mobilization and has been found to have low rate of postoperative constipation in initial studies. These results need to be confirmed in larger trials, with longer follow-up, at other institutions.

Concomitant sigmoid resection is frequently used in patients with preoperative constipation symptoms and there are some data that this addition may slightly decrease the risk for postoperative constipation.

There are few randomized studies evaluating surgical treatment for rectal prolapse. In 2000, Bachoo et al. performed a review for the Cochrane collaboration evaluating all randomized or quasi-randomized trials of surgery for rectal prolapse [284]. Ten trials were included with a total of 324 participants and the studies had varying aims. The small sample size of included trials, together with methodological weaknesses, limited the review and the authors suggested larger and better designed trials to define the optimal treatment for rectal prolapse.

The Association of Coloproctology of Great Britain and Ireland initiated a randomized multicenter trial, the PROSPER (Prolapse Surgery: Perineal or Rectopexy) trial, in 2000 which is currently recruiting.

1. PERINEAL PROCEDURES

Perineal procedures offer less surgical trauma, but are associated with higher recurrence rates and therefore usually reserved to old or frail patients. The two most common perineal procedures for rectal prolapse are the Delorme procedure and the Altemeir procedure. In several studies the recurrence rate is stated to be approximately 20% for both these procedures. However, recurrence rates tend to increase with the follow-up time in the studies and it is conceivable that the recurrence rate is significantly higher in fit patients. There are no prospective randomized studies comparing the recurrence rates between these procedures. The Delorme procedure has been the more popular in Western Europe, while the Altemeir procedure has been the dominating perineal procedure in North America.

Agachan et al. compared the outcome after the Delorme procedure and the Altemeir procedure with or without concomitant levatorplasty [285]. The recurrence rate was highest after the Delorme procedure (38%) and lowest after the Altemeir procedure including a concomitant levatorplasty (5%).

a) The Delorme procedure

The Delorme procedure was first described in 1900 by the French military surgeon Edmond Delorme [286]. The procedure includes stripping of the mucosa of the prolapsed rectum and suture plication of the remnant rectal wall. There are several studies on the outcome after the Delorme procedure and results vary between studies [287-291]. The vast majority of studies are retrospective and there are no prospective randomized studies published comparing the results with other surgical techniques. In a recent retrospective study, Marchal et al. [288] reported a complication rate of 15%
and a recurrence rate of 23% in 60 patients undergoing the Delorme procedure. The authors compared the Delorme group of patients with a group of patients undergoing the Orr-Loygue rectopexy and found that the Delorme procedure had a higher recurrence rate. After the Delorme procedure, patients with preoperative constipation had this symptom improved or completely resolved in 54% and worsened in 12% postoperatively. 42% of patients with preoperative incontinence were continent or had continence improvement postoperatively.

b) The Altemeier procedure

Perineal rectosigmoidectomy for rectal prolapse was tried in a few patients in the late 19th century, but it was not until 1952 the procedure was popularized by Altemeier [292]. The prolapsed bowel is transected 2-4 cm proximal to the dentate line and the level should not include the internal or external anal sphincters. The inner tube of the rectum is then mobilized until there is some resistance to achieve more mobilization. The vessels to the rectal mesentery are ligated or transected using the ultrascision equipment. The inner tube of the rectum is transected and sutured to the outer tube with an anastomosis. Some surgeons add a levatorplasty, to decrease the size of the levator hiatus, before suturing the anastomosis. Some surgeons use a stapled technique to achieve the anastomosis.

There are several studies on the outcome after the Delorme procedure and results vary between studies [282, 293-296]. The vast majority of studies are retrospective. There is one randomized study comparing perineal rectosigmoidectomy with pelvic floor repair with abdominal resection rectopexy and pelvic floor repair [297]. The study included ten patients in each group and only one patient had a recurrence. There were no significant differences in functional outcomes.

In a recent retrospective study, Kim et al. reported a complication rate of 14% and a recurrence rate of 16% in 60 patients undergoing the Delorme procedure [294]. Functional improvement was not significantly different, and most patients were satisfied with treatment and outcome.

2. TRANSABDOMINAL PROCEDURES

Transabdominal procedures can be performed either with open or laparoscopic techniques and they include different types of suspension and sometimes concomitant bowel resection. Laparoscopic rectopexy is reported to offer the same or better outcome as after open rectopexy [298-305]. There are two small (21 and 40 patients respectively) randomized studies, with 21 and 40 patients respectively in the literature comparing laparoscopic mesh rectopexy with open mesh rectopexy [299, 306]. Recurrence rates were quite small after both types of procedures and there were no significant differences in functional outcome.

Transabdominal procedures result in general in low recurrence rates [307-309] and the discussion regarding outcomes is therefore focused on functional outcome. As discussed above, some patients may develop worsened constipation postoperatively and not all patients regain normal continence. The mobilization of the rectum at transabdominal procedures can be of varying degrees. The effect of lateral ligament division was assessed in one small randomized study involving 26 patients [310]. The study demonstrated a trend for higher recurrence rate after preservation of the lateral ligaments, while this preservation seemed to decrease the risk for postoperative constipation. A recently introduced technique (laparoscopic ventral rectopexy) provides rectal prolapse repair without any significant rectal mobilization [311]. In the first initial reports, the authors have reported excellent postoperative outcome [311, 312]; however there is no high-quality evidence to recommend this procedure.

a) Rectopexy

The dominating transabdominal technique for the treatment of rectal prolapse in recent decades has been rectopexy. The surgical procedure, open or laparoscopic, begins with mobilization of the rectum. The extent of dissection varies in different series, but most surgeons tend to mobilize the rectum down to the coccyx posteriorly, preserve the lateral ligaments laterally. The extent of anterior dissection varies, from none to mobilization of 2-4 centimeters of the rectovaginal septum.

The choice of fixation method varies in different reports [172, 294, 309, 313, 314]. The fixation can be achieved with different mesh materials fixated usually posteriorly, but sometimes laterally or anteriorly. Suture rectopexy is frequently used and the mesorectum is then fixated to the sacrum with a few sutures. There are few studies comparing different fixation methods or materials in the same report. Novell et al compared the use of Ivalon sponge with suture rectopexy in one randomized trial involving 83 patients [315]. The recurrence rates were the same (one in each group) and functional outcome was not significantly different. Two other randomized trials compared the outcome after different types of mesh. Galili et al. [316] compared polyglycolic acid mesh with polypropylene mesh and Winde et al [317] compared polyglycolic acid mesh with polyglactin mesh. Sample sizes were limited (37 and 49 patients respectively) and no significant differences in recurrence rates or functional outcome were detected. As there has not been possible to detect any difference in outcomes between different fixations methods, some authors argue that suture rectopexy may be preferable as this method does not carry an associated risk for mesh complications [309]. The combination of rectopexy and concomitant sigmoid resection (the “Frykman-Goldberg operation”) is frequently used to decrease the risk for postoperative complications.
constipation problems. Several studies have evaluated postoperative constipation symptoms after resection rectopexy [318, 319]. Benoist et al. compared results after laparoscopic suture rectopexy with (n = 18) or without sigmoid resection (n = 16) [298]. Postoperative constipation was observed in 2 patients (11%) after resection rectopexy and in 10 (62%) after suture rectopexy (P < 0.01). Two small randomized studies have evaluated the effect of concomitant sigmoid resection on constipation after rectopexy. McKee et al. prospectively randomized 18 patients to rectopexy alone or rectopexy combined with concomitant sigmoid resection [320]. Three months postoperatively, 7 patients after rectopexy alone and 2 patients after concomitant sigmoid resection complained of severe constipation. Luukkonen et al. prospectively randomized 15 patients to rectopexy and sigmoid resection or rectopexy without resection [321]. The authors found a lower risk for postoperative constipation in the patients who underwent concomitant sigmoid resection.

Orr-Loygue rectopexy includes mobilization of the rectum and fixing the rectum with two strips of synthetic mesh from the anterolateral sides of the distal rectum to the sacral promontory [322]. In a recent prospective study, Douard et al. evaluated 31 consecutive patients operated with this technique [323]. They reported no recurrences after a mean follow-up of 28 months. Patients with incontinence decreased from 81% preoperatively to 55% postoperatively and continence improved in 96% of patients. Evacuation difficulties increased significantly after surgery, from 23% to 61% of patients. In another recent study, Marchal et al. [288] reported similar results, with a recurrence rate of 4% in 49 patients with a mean follow-up time of 88 months (Marchal, 2005). In patients with preoperative constipation, this symptom was improved or completely resolved in 33% and worsened in 58% postoperatively. In patients with preoperative incontinence, 73% were continent or had continence improvement postoperatively.

b) Laparoscopic ventral rectopexy

Laparoscopic ventral rectopexy provides rectal prolapse repair without any significant posterior rectal mobilization, which therefore decreases the risk for autonomic nerve damage [311]. The rectovaginal septum is opened and dissected. A Marlex mesh is thereafter sutured to the anterior aspect of the distal rectum and fixed proximally to the sacral promontory. No posterior mobilization of the rectum is performed.

The authors have reported recurrence rate of less than 5% after a mean follow-up of 61 months and constipation resolved in 16 of 19 patients with preoperative constipation [311].

VII. RECOMMENDATIONS

The committee makes the following graded recommendations:

- **GRADE A** (usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway.

  Sacrocolpopexy is a highly recommended apical prolapse procedure.

  Synthetic material is superior to biological material for sacrocolpopexy.

  The use of polypropylene mesh for trans-vaginal anterior wall repair improves 1 year anatomic outcomes; this advantage should be weighed against the risk of mesh-related complications and uncertainty regarding long-term functional outcomes.

  Transvaginal route is preferable to transanal route for posterior vaginal prolapse repair.

- **GRADE B** (usually depends on consistent level 2 and/or 3 studies, or “majority evidence from RCTs”)

  A single RCT provides level 1 evidence that concomitant Burch colposuspension is recommended in women without symptoms of stress incontinence at the time of open sacrocolpopexy. There is conflicting Level 2 evidence.

  Concomitant total hysterectomy at the time of mesh-augmented repairs increases mesh erosion; therefore, alternative surgical plans with reduced risks should be considered.

  When hysterectomy is indicated, concomitant anterior repair without augmenting materials is reasonable.

  There is no evidence to support the use of synthetic mesh for trans-vaginal repair (or augmentation of repair) in the posterior wall.

  Levator ani plication during posterior colporrhaphy should rarely be used in sexually active women because of the increased risk of dyspareunia.

  A single RCT provides level 1 evidence that porcine dermis without fascial repair is inferior to posterior vaginal fascial plication or site specific defect repair. This is consistent with a Level 2 cohort study.

- **GRADE C** (usually depends on level 4 studies or “majority evidence” from level 2/3 studies or Dephi processed expert opinion.

  Suspension of the apex by an appropriate method should be considered at the time of each vaginal prolapse repair.
There is no evidence for the superiority of any specific technique for transvaginal apical suspension using native tissue.

Traditional fascial plication of the posterior vaginal wall has a lower anatomic failure rate than site-specific fascial defect repair.

A single level 1 study provides evidence that the use of porcine dermis as an overlay for anterior vaginal repair is superior to traditional vaginal fascial plication, although there is conflicting Level 2 and 3 data.

Trans-vaginal placement of mesh after intraoperative procotomy is discouraged.

Trialists should report sufficient detail regarding anatomic and symptomatic outcomes so that subsequent outcome definitions can be tested in a wide variety of datasets. Primary and recurrent cases should be reported separately. Outcomes of treatments should be evaluated in multiple domains.

Laparoscopic sacrocolpopexy is used as an alternative to open sacrocolpopexy, although no comparative studies report outcomes.

Anatomic support defects without accompanying, relevant symptoms are rarely an indication for prolapse surgery.

Evidence-based surgical alternatives should be offered to all women planning prolapse surgery.

The safety and feasibility of reoperation in the event of recurrent prolapse should be considered when performing the primary repair.

GRADE D = “no recommendation possible” to be used where the evidence is inadequate or conflicting and where expert opinion is delivered without a formal analytical process, such as by Delphi.

There is insufficient information to provide evidence-based recommendations for the route of primary prolapse repair. There is level I evidence that sacrocolpopexy is more effective and durable in correcting anatomical defects, while the native tissue vaginal route is faster and less expensive to perform with a quicker return to activities of daily living. In addition, the vaginal route has fewer serious perioperative complications.

There is insufficient information to provide evidence-based recommendations for the optimal vaginal repair approach, including technique and materials.

There is insufficient information to provide an evidence-based recommendation for trans-vaginal mesh placement following intraoperative cystotomy.

The committee recommends that the following areas be prioritized for future research:

- It is essential to standardized mal method for determining outcome for POP surgery. The lack of consensus significantly impacts the ability to conduct, compare and contrast clinical research in this area.
  - Patient-reported and functional status before and after prolapse surgery.
  - Anatomic resolution (in operated and unoperated compartments) and relationship with symptoms.

- Well-designed RCT studies are needed to:
  - determine the role of hysterectomy (total or subtotal) during repair of POP with in situ uterus,
  - determine the optimal procedure for repair of post-hysterectomy POP,
  - compare native tissue vs. mesh-based apical repair techniques,
  - compare various trans-vaginal techniques for apical support,
  - compare the role of peri-operative physical therapy,
  - compare native tissue vs. mesh-based apical repair techniques,
  - determine the optimal management of stress continent women at the time of prolapse repair, by any technique, and
  - determine the optimal technique for repair of recurrence after primary mesh repair in any compartment.

- Well-designed comparative studies are needed to study
  - the utility of self-prepared mesh vs. kit-prepared mesh for apical and/or anterior prolapse repairs,
  - the safety and efficacy of prolapse-repair meshes that include arms that traverse non-vaginal spaces,
  - management of mesh complications especially mesh contracture and complications associated with armed meshes, and
  - management of recurrent anterior compartment prolapse following unsuccessful permanent mesh.

- Registeries are strongly recommended with the introduction of new devices to ensure safety and inform clinical trial planning.
There is sufficient evidence to support recommendations for some, but not all, decisions regarding the route of POP surgery. Textbooks of pelvic surgery often describe both abdominal and vaginal routes for POP procedures without commenting on the basis for selection of the route of surgery. When mentioned, most authorities state that pelvic surgeons should be proficient at procedures using both routes, and should tailor the procedure to the patient and her specific defects, decrying the “one procedure fits all” concept. However, some procedures for POP require special skills or experience, and not all surgeons will feel comfortable with all procedures. Relative indications cited for abdominal surgery include other reasons that mandate an abdominal approach, such as pelvic masses, the likelihood of dense pelvic adhesions, or the need for other extrapelvic abdominal procedures. Additional factors must include risk factors for failure, medical condition of the patient, risk of abdominal surgery in obesity or the frail elderly, and prior failed procedures for POP.

The emergence of mesh-based procedures poses a dilemma as there is significant uncertainty about the safety and efficacy of secondary prolapse procedures for prolapse recurrence following a primary mesh procedure. There are surgical concerns regarding the status of normal dissection planes, especially following a uterine-conserving mesh-based procedure. Given the high success rates of sacrocolpopexy in women with recurrent prolapse, the risk/benefit ratio of routine mesh placement for primary prolapse procedures needs further evaluation. Appropriate counseling of patient must include the known serious risks of mesh placement and the uncertainty of long-term functional outcomes.

REFERENCES


prolapsed of the vaginal vault with abdominal sacral colpopexy. JACS. 1994;178:283-7.


Committee 16

Conservative and Pharmacological Management of Faecal Incontinence in Adults

Co-Chair

C. Norton (U.K),
W. Whitehead (USA)

Members

D. Z Bliss (USA),
D. Harari (U.K),
J. Lang (U.K)
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
</tr>
<tr>
<td>II. PREVALENCE OF FI AND RISK FACTORS</td>
</tr>
<tr>
<td>III. EDUCATION &amp; “LIFESTYLE” INTERVENTIONS</td>
</tr>
<tr>
<td>IV. DIET AND FLUID INTAKE</td>
</tr>
<tr>
<td>V. BOWEL MANAGEMENT AND RETRAINING PROGRAMMES</td>
</tr>
<tr>
<td>VI. DRUG TREATMENT OF FI</td>
</tr>
<tr>
<td>VII. BIOFEEDBACK AND/OR ANAL SPHINCTER / PELVIC FLOOR MUSCLE TRAINING</td>
</tr>
<tr>
<td>VIII. EXTERNAL ELECTRICAL STIMULATION FOR FI</td>
</tr>
<tr>
<td>IX. FAecal INCONTINENCE IN FRail OLDER PEOPLE</td>
</tr>
<tr>
<td>X. CONCLUSIONS, RECOMMENDATIONS AND ALGORITHM</td>
</tr>
<tr>
<td>REFERENCES</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

At present there is no accepted international consensus on terminology for faecal and anal incontinence. A working definition of anal Incontinence (AI) was adopted at the last consultation [1] as:

“Anal incontinence is the involuntary loss of flatus, liquid or solid stool that is a social or hygienic problem”.

It is proposed by this committee that the consultation adopt this definition, with the additional definition of “faecal incontinence” (FI) as:

“Faecal incontinence is the involuntary loss of liquid or solid stool that is a social or hygienic problem”.

The committee did not recommend that it is essential to choose one or other term to use exclusively, but rather recommends that either AI or FI can be used depending on context, as long as the definition is made clear. As the majority of intervention studies have focused on FI rather than AI as an outcome measure, FI is covered in this chapter, except where AI is specified.

This chapter covers conservative management of FI in adults. There is a specific section on issues of particular relevance to frail older adults (section 9). Covered elsewhere in the volume are surgical management of FI (Committee 17), and people with neurological disease or injury (Committee 10). Risk factors and prevention are covered for all groups. Some techniques developed and evaluated in these specific groups may have applications to an adult population, but most have not yet been evaluated. There is at present a very limited evidence base of high quality trials in FI and it remains challenging to provide strong evidence for most interventions. However, expert consensus in this committee and the world literature is unanimous in recommending conservative interventions, singly or in combination, for the majority of patients with FI as first-line management.

It was noted that outcome measures for FI and AI remain in the development stage and there is no consensus on the best measure to use in treatment trials (see Committee 5); this impacts evaluation of study findings because different criteria for successful outcome have been employed.

Conservative management is defined as any non-operative intervention designed to improve FI incontinence or prevent deterioration. No studies were found exploring how to select patients for operative versus conservative or drug management, and only one study [2] compared these approaches in comparable patient groups, and one study investigated the adjunctive benefits of conservative with surgical management [3], so patient selection remains empirical. The committee recommends a trial of conservative and drug management in the vast majority of patients before considering surgical options because these conservative options are comparatively inexpensive and involve no significant morbidity (see Figure 1). Exceptions would be patients with acute traumatic anal sphincter rupture or an endosonographically confirmed major defect in the external anal sphincter in the presence of gross FI: these patients would be referred for surgical evaluation as first line treatment.

II. PREVALENCE OF FI AND RISK FACTORS

1. SEARCH

For the previous ICI report [4], the literature review covered the period 1966 to 2003, and 11 population based studies were identified. Since then new population-based studies have been published (Table 1), and additional population based surveys have been identified that were missed in our earlier review. We have updated Table 1 to include all studies published through February, 2008, which met the
Active screening in high risk groups

Patient presents with AI

Basic assessment (history, examination, medication and diet review)

- Take out of pathway:
  - Alarm signals: referral for investigation
  - Impaction: treat then evaluate
  - Surgical evaluation needed: e.g. rectal prolapse, recent sphincter injury, recto-vaginal fistula, chloacal deformity

- Address reversible risk factor
  - e.g. Medication; toilet access; loose stools

  - Patient and / or carer education
    - Bowel habit and training
    - Manage constipation
    - Diet (e.g. soluble fibre for loose stool)
    - Medication (e.g. loperamide for loose stool)
    - PFMT / anal sphincter exercises
    - Adequate containment (e.g. pads or plugs) and practical management advice (Committee 20)

If initial management fails to achieve adequate symptom relief consider:
- Diagnostic testing; Biofeedback; Irrigation

Surgical evaluation or symptom management if adequate relief not obtained from conservative management, depending on symptom severity and patient preference
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Risk Factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al (1984)</td>
<td>Postal survey to all patients in 12 GP practices in London. Patient in nursing homes were included. FI was defined as involuntary leakage of feces at least twice in previous mo.89% response rate.</td>
<td>Age, Sex, Self-reported FI, Confirmed by physical interview.</td>
<td>Strong association. No association. 2.10% 0.40%</td>
</tr>
<tr>
<td>Kok et al (1992)</td>
<td>Postal survey of women aged 60+ in Amstelveen, Netherlands. 719 (68.5%) participated. Risk factors for FI not assessed (only for UI). FI defined as occasional involuntary loss of feces.</td>
<td>Age, Overall prevalence</td>
<td>Significant association. 16.90%</td>
</tr>
<tr>
<td>Nelson et al (1995)</td>
<td>Random digit dialing telephone survey in 6,959 community dwelling adults, all ages. FI definition includes flatus.</td>
<td>Age, Female sex, Physical limitations, Poor general health</td>
<td>Adjusted OR=1.01 (CI, 1.01-1.02) OR=1.51 (CI, 1.10-2.11) OR=1.82 (CI, 1.20-2.74) OR=1.64 (CI, 1.48-1.91) Overall prevalence 2.2%</td>
</tr>
<tr>
<td>Nakanishi et al (1997)</td>
<td>Interviews in home of 1,405 men &amp; women &gt;65 yrs. FI was ascertained by asking, &quot;Do you ... soil yourself.&quot;</td>
<td>Age, Female sex, Physical disability, Stroke, Dementia</td>
<td>Significant association No association Significant association Significant association Significant association Prevalence 8.7% men, 6.6% women</td>
</tr>
<tr>
<td>Roberts et al (1999)</td>
<td>Postal questionnaire in age-stratified population sample of 778 men and 762 women aged &gt;50 yrs. FI definition did not include uncontrolled flatus.</td>
<td>Urinary incontinence, Age</td>
<td>&gt; half of FI men and women had urinary incontinence Significant for men but not women Prevalence 17.0% for men and 24.6% for women</td>
</tr>
<tr>
<td>Verhagen et al (2001)</td>
<td>Postal survey of everyone aged 60+ in 7 general practices in Nijmegen, Netherlands. Supplemented by interview by family MD. n=3345 (86.1%) participated. FI was defined as loss of feces with social and hygienic consequences.</td>
<td>Age, Sex, Overall prevalence</td>
<td>Significant for men and women No association. 6%</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bytzer et al (2001)</td>
<td>Postal survey of 8657 randomly selected Australian adults (60% response rate), including 423 w/ self-reported DM. FI was defined as involuntary loss of stool.</td>
<td>Diabetes mellitus</td>
<td>FI &quot;Sometimes&quot;: 12.8% for DM, 3.8% for controls (p&lt;.001). FI &quot;Often&quot;: 2.6% vs. 0.8%, OR=2.74 (CI, 1.40-5.37).</td>
</tr>
<tr>
<td>Perry et al (2002)</td>
<td>Postal survey in 15,904 randomly selected community dwelling adults aged &gt;40 years. FI definition not include flatus but required frequency of &quot;several times a month.&quot;</td>
<td>Age, Sex</td>
<td>Significant association No difference Overall prevalence 3.0% age &gt;40</td>
</tr>
<tr>
<td>Kalantar et al (2002)</td>
<td>Postal survey of 477 randomly selected community dwelling Australian adults, all ages. FI definition excluded flatus and acute diarrhea.</td>
<td>Age, Female sex, Perianal injury/surgery, Loose BMs, Stool urgency, Poor general health, Straining, hard stools</td>
<td>Significant association No difference Significant association Significant association Significant association Significant association No association Prevalence 2% solid, 9% liquid</td>
</tr>
<tr>
<td>Walter et al (2002)</td>
<td>Postal survey of 2000 randomly selected Swedish community dwelling adults aged 31-76. Distinguished flatus and soiling underwear from loss of solid or liquid. Threshold was at least monthly.</td>
<td>Age, Female sex, Loose stools</td>
<td>Significant association in women Significant association for solid or liquid stool. Men reported more soiling of underwear. Significant association Overall prevalence not given</td>
</tr>
<tr>
<td>Edwards, Jones (2001)</td>
<td>Interviews in home of 2,818 men and women &gt;65 yrs. FI defined by the question,&quot;Do you have any difficulty in controlling your bowels?&quot;</td>
<td>Age, Female sex, Anxiety &amp; depression, Physical disability, Urinary incontinence</td>
<td>Significant association Significant association Significant association Significant association Significant association Overall prevalence 3% age &gt;65</td>
</tr>
<tr>
<td>Chen et al (2003)</td>
<td>Door-to-door survey of 1,253 Taiwanese women representative of the population. FI definition included flatus.</td>
<td>POP, Parity &gt;1, Prior GYN surgery, Hypertension, Overactive bladder</td>
<td>OR=3.2 (CI, 1.1-8.9) OR=3.4 (CI, 1.2-9.5) OR=1.8 (CI, 1.1-2.9) OR=2.4 (CI, 1.2-4.9) OR=3.2 (CI, 1.6-6.7) Prevalence 2.8% FI, 8.6% flatus</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MacLennan et al (2000)</td>
<td>Interviews in homes of 3,010 men &amp; women &gt;15 yrs. Distinguished incontinence for flatus from incontinence for stool.</td>
<td>Age, Female sex, Parity &gt;1, Sphincter repair, Vaginal vs. C-section, Vaginal vs. Instrumental</td>
<td>Significant association OR=1.7 (CI, 1.3-2.2) for flatus; OR=1.6 (CI, 1.0-2.5) for stool Significant association No association No association Prevalence 2.3% for FI &amp; 6.8% for flatus in men; 3.5% for FI &amp; 10.9% for flatus in women</td>
</tr>
<tr>
<td>Fornell et al (2004)</td>
<td>Postal survey of 1000 randomly selected 40 year-old and 1000 randomly selected 60 year-old Swedist women. FI defined as leakage &gt;1/month; UI defined as leakage weekly or more often. Reported flatal incontinence separately from stool incontinence.</td>
<td>3rd or 4th degree tear, Parity, Vacuum extraction, Urinary Incontinence, Pelvic Heaviness, Obesity</td>
<td>OR=9.1 (CI, 3.0-27.3) for solid stool No significant association No significant association OR=5.9 (CI, 2.4-14.6) for solid stool OR=3.3 (CI, 1.6-7.0) for solid stool OR=2.5 (1.4-4.2) for liquid FI Prevalence 8.9% FI, 11.4% flatus</td>
</tr>
<tr>
<td>Stenzelius et al (2004)</td>
<td>Postal survey of 8500 men and women 75+ years. About 15% in &quot;special accommodations&quot;. 52.5% response rate. &quot;Have you had problems controlling stools in the last 3 months?&quot; (Flatus was excluded.)</td>
<td>Diarrhea, Urinary Sx other than UI, Memory problems, Difficulty talking, Stomach pain, Female gender, Overall prevalence</td>
<td>OR=6.77 (4.20-10.90) FI, 7.72 (5.80-10.29) DI; OR=2.29 (1.69-3.12) DI; OR=2.26 (1.48-3.46) DI; OR=2.13 (1.56-2.93) DI; OR=1.86 (1.15-3.01) FI; OR=0.70 (0.53-0.93) DI 16.9% FI, 14.5% DI</td>
</tr>
<tr>
<td>Teunissen et al (2004)</td>
<td>Postal survey of population-based sample in the Netherlands. Subjects were aged 60+. Excluded were institutionalized people, dementia, too ill to participate, and those with a catheter. Response rate 88% (5748). FI defined as &quot;Involuntary loss of solid, liquid or mucus feces&quot; at least 2/month.</td>
<td>Age, Sex, FI overall prevalence</td>
<td>No effect No effect 9% (includes 3% with double incontinence).</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Goode et al (2005)</td>
<td>1000 Medicare beneficiaries aged 65+ in 3 counties of Alabama, interviewed in person. Sex and race stratified. Response rate not listed. FI excluded flatus.</td>
<td>Diarrhea</td>
<td>OR=4.55 (2.03-10.20) in women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hysterectomy</td>
<td>OR=6.08 (2.29-16.16) in men;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor health status</td>
<td>OR=1.93 (1.06-3.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR=1.88 (1.01-3.50) in women,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR=2.18 (1.13-4.20) in men.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UI</td>
<td>OR=2.65 (1.34-5.25) in women.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIA or stroke</td>
<td>OR=3.11 (1.30-7.41) in men.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate disease</td>
<td>OR=2.29 (1.04-5.02) in men.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swollen feet &amp; legs</td>
<td>OR=3.49 (1.80-6.76) in men.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall prevalence</td>
<td>4.6% in women, 5.8% in men.</td>
</tr>
<tr>
<td>Quander et al (2005)</td>
<td>In-person interviews with 6,099 Chicago residents aged 65+. Response rate 78.8%. Institutionalized people were eligible. &quot;Have you ever lost control of your bowels when you didn’t want to?”</td>
<td>Age</td>
<td>Strong association.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race</td>
<td>No significant difference.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Income and education</td>
<td>Lower SES strongly associated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
<td>OR=1.7 (1.4-2.1) adjusted.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td>OR=2.8 (2.2-3.5) adjusted.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychotropic meds</td>
<td>All significant associations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall prevalence</td>
<td>9.60%</td>
</tr>
<tr>
<td>Melville et al (2005)</td>
<td>Postal survey of 6000 women aged 30-90 enrolled in an HMO. Response rate 64%. FI meant loss of liquid or solid stool at least monthly.</td>
<td>Age</td>
<td>OR=2.11 (1.47-3.03) for age 50-60 vs. age 30-49.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major depression</td>
<td>2.73 (1.67-4.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UI</td>
<td>2.32 (1.70-3.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical comorbidity</td>
<td>2.58 (1.66-4.01) (high vs. low)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall prevalence</td>
<td>7.20%</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bharucha et al (2006)</td>
<td>2,109 randomly selected females aged 40-69 years from Kaiser HMO. FI defined as any leakage of stool in last 12 months.</td>
<td>BMI (per 5 units) COPD IBS Colectomy UI Overall prevalence</td>
<td>OR=1.2 (1.1-1.3) OR=1.9 (1.3-2.9) OR=2.4 (1.7-3.4) OR=1.9 (1.1-3.1) OR=2.1 (1.7-2.6) 24% at least once; 3.4% monthly</td>
</tr>
<tr>
<td></td>
<td>2,800 adult women responded to postal survey sent to age stratified random sample of adult women in Olmstead County, MN. Response rate 53%. Index question: “In the past 12 months have you experienced accidental leakage of liquid or solid stool?”</td>
<td>Age (per decade) Urgency Diarrhea IBS Anal injury (not obst) Anal fistula Cholecystectomy Obstet injury Overall prevalence</td>
<td>OR=1.3 (1.2-1.4) OR=5.1 (3.7-7.1) OR=2.4 (1.6-3.6) OR=1.9 (1.3-2.7) OR=2.4 (1.3-4.5) 2.5 (1.2-5.2) 1.4 (1.02-1.9) Not significant 12.1% (11.0-13.1)</td>
</tr>
<tr>
<td>Damon et al (2006)</td>
<td>Postal survey of 706 adults in France (30% response rate). AI was defined as &gt;5 of 20 on the Wexner scale.</td>
<td>Age (increase limited to age 80+) Female sex Difficult defecation Incomplete evacuation Overall prevalence</td>
<td>Significant association Significant association Significant association Significant association 7.5% (5.0-10.7%) of women and 2.4% (1.1-4.7%) of men.</td>
</tr>
<tr>
<td>Whitehead et al (2008)</td>
<td>CATI assisted interviews with representative sample of 2229 females and 2079 males in U.S. aged 29+. FI assessed by validated interview version of FISI. FI defined as any involuntary loss of mucus, liquid, or solid stool in last mo.</td>
<td>Age Sex Ethnicity Marital status Education Family income Prevalence in females Prevalence in males</td>
<td>Significant association No significant association Lower rate in Hispanics. No significant association No significant association No significant association 8.8% (7.1-10.4%) 7.7% (6.0-9.4%)</td>
</tr>
</tbody>
</table>
following criteria: [1] Sample is representative of the general population (not a convenience sample or sample recruited from a medical clinic or other setting in which there is a probable selection bias) [2]. At least 500 subjects provided data.

In 2006, Pretlove and colleagues [5] published a systematic review and meta-analysis of 29 studies of AI published prior to September 2004. However, many of the studies included in their analysis were drawn from medical or surgical clinics or were convenience samples. In 2007, the Center for Disease Control commissioned the University of Minnesota to prepare a systematic review of the prevalence and risk factors associated with FI for the State of the Science Conference on the Prevention of Fecal and Urinary Incontinence [6]. Their inclusion criteria differed from ours. The studies identified in both of these publications were reviewed for this report.

2. REVIEW OF EVIDENCE

Prevalence estimates for faecal or anal incontinence vary widely, from 2.2% to 25%. This variability is related to the following differences among studies: a.) Case definition – some studies focus on AI and include subjects with accidental loss of flatus as well as solid stool [7,8], while other studies report the prevalence of FI, defined as the loss of solid or liquid stool or mucus. A few studies have also defined a category of soiling of underwear only and suggest that this occurs frequently [9;10]. In this review, the case definitions used by authors are listed in the literature tables. In the text, FI refers to the loss of solid or liquid stool or mucus, and when studies are referenced that used other definitions such as AI or soiling, these are specified. b.) Age range – FI is strongly associated with aging (Table 1), and studies that limit their subject selection to older individuals yield higher prevalence estimates [11]. Few studies have adjusted their estimates to the demographics of the population. c.) Inclusion of subjects from skilled nursing facilities – Most studies of community prevalence exclude the institutionalized population where prevalence is known to be higher than in the community [12;13], while other studies include a representative mixture of community dwelling and institutionalized subjects [14].

The National Health and Nutrition Examination Survey (NHANES) in the United States (US) provides the a.) best estimate of FI prevalence to date because it surveyed both sexes, all major races represented in the US, and the full range of adult ages, and the authors extrapolated an age-adjusted prevalence estimate for the US; and b.) it provided separate estimates for different types (e.g., solid, liquid, mucus, and flatus) and frequencies of stool loss [15;16]. However, institutionalized individuals and those too ill to travel to examination sites were excluded.

Prevalence estimates. The age-adjusted prevalence of FI (defined as accidental loss of solid, liquid, or mucus incontinence in the month preceding the interview) in the non-institutionalized population of the United States is 8.9% of women and 7.7% of men [16]. When the data are broken down by type of incontinence, liquid incontinence is 2-3 times more common than solid stool incontinence, and incontinence for flatus is 2-3 times more common than the combination of liquid and solid [7;17-19]. In the NHANES study, liquid stool incontinence was reported by 6.2%, solid stool incontinence by 1.6%, and incontinence for mucus by 3.1%; 26% of subjects with any FI reported two or more types of FI consistency. Accidental loss of flatus, which was not included in the definition of FI in the NHANES study, was reported to have occurred at least once in the past month by 46% of men and 51% of women surveyed by NHANES. Table 1 gives prevalence estimates for several countries, but differences in survey methodology make it difficult to interpret observed differences between countries. There are no published data on the incidence (i.e., rate of new onset) of FI or AI in non-institutionalized populations.

Under-reporting of FI. In population based surveys, when people with FI or AI are asked whether they have discussed this problem with their health care providers, only a third have done so: the reported proportion are 36% in the United States [8], 32.6% in France [20], 40.8% in Sweden [21], 27% in Australia [19], and a third in The Netherlands [22]. This is found even in acute care hospitals [23] and nursing homes [24]. In a 1986 study of UK nursing home residents, only 4% of patients with long-standing FI had been referred to their general practitioner for further assessment of this problem [25]. A 1982 study of US nursing home patients found that only 15% of those with incontinence had a physician mention of it in the nursing home records [26]. A possible reason for the failure to recognize and report FI in acute care hospitals and nursing homes is the belief of many health care providers that FI is a normal part of aging: a UK nursing home survey found that the trained staff cited advanced age as the main cause of incontinence [27].

a) Patient characteristics associated with increased risk of FI

1. Age

Most surveys that include young as well as older adults find age to be strongly associated with FI (Table 1). This age-related increase in prevalence of FI is likely attributable to age-related declines in general health, muscle strength, mobility, and cognitive functioning, and the increased prevalence of other diseases that may contribute to FI (see below).

2. Admission to an acute care hospital

Admission to an acute care hospital is frequently
associated with a new onset or exacerbation of FI. A British survey of 627 hospitalised patients aged 65 and over (FI defined as at least one episode weekly) found a prevalence of 14% [28], and this is significantly higher than the community prevalence of FI. An Australian survey of 247 consecutive admissions to an acute care hospital (all ages) found that 22% self-reported FI [29]. Bliss et al. [30] reported that FI was present in 33% of hospitalized patients.

Risk factors for the development of FI subsequent to hospital admission include the following: having loose/liquid stool consistency (RR=11.1; 95% CI=2.2-56.7), greater severity of illness (5.7, 2.6-12.3) and older age (1.1, 1.02-1.1) as independent risk factors in a multivariate analysis [30]. A UK descriptive study found contributing factors to FI in acute hospital inpatients aged 65+ to be faecal loading (57%), functional disability (83%), loose stools (67%), and cognitive impairment (43%) [31]. When compared with 3 other settings (home, care homes and rehabilitation wards), acute hospital inpatients with FI were significantly more likely to have faecal loading, functional disability, and loose stools. Patients with loose stools and less comorbidity were more likely to have resolution of FI after 3 months follow-up.

3. RESIDENCE IN A SKILLED NURSING FACILITY (Table 2)

FI in nursing homes is often discussed separately from FI in community dwelling individuals because a.) risk factors differ and may include a significant iatrogenic contribution, and b.) treatment/management strategies differ. In nursing homes the prevalence of FI ranges from 43% [12] to 54% [32], which is approximately 5 times the rate seen in community dwelling individuals. The incidence (onset rate) of FI in nursing homes was reported to be 20% [32] in France and 27% [33] in the U.S. An estimated 97% of nursing home residents with FI also have UI [13], which is significantly higher than is reported for community dwelling individuals of comparable age; this suggests a different spectrum of aetiologies.

There is a wide variation in the reported prevalence of FI among nursing homes in the UK, ranging from 17% to 95% between individual nursing homes [25;28;34]. As the case-mix within British nursing homes is likely to be comparable, the variations may well be more reflective of different standards of care, rather than of different patient characteristics. A recent nation-wide UK audit of FI in older people found that patients admitted to care homes with pre-existing FI tended to simply be placed on a containment management plan rather than being assessed for causes and possible treatment, and this was despite having good access to continence specialist care [35].

The strongest univariate associations with FI in long-term care studies are physical dependency and impaired mobility, particularly where help is needed to transfer from bed to chair [28;34]. However, faecal loading is also believed to be a significant and treatable cause of FI in this population: A UK study found faecal loading in 70% of residents with FI [31], which suggests that treatable overflow FI is being overlooked in this setting.

4. SEX

Among 15 population-based studies that surveyed both men and women (Table 1), six surveys [8;9;17;36-38] found a significantly higher prevalence in women, eight [10;19;39-43] found no difference, and one study that was limited to people 75 years of age and older found a higher rate in men [11]. Thus, sex is a weak predictor of who will develop FI. However, young women are vulnerable to a unique set of risk factors associated with childbirth (see below). In older people men and women are found to have equal prevalence and men may predominate in advanced old age.

5. RACE

In population based studies, race has not been found to be significantly associated with FI or AI [23;42;44]. However, there is evidence that obstetrical tears are more common in Hispanic, Filipino, and Chinese women compared to Caucasian women [45;46]. In addition to sphincter lacerations, there appears to be a higher incidence of post-partum FI in Asian women compared to Caucasians (OR=3.2) [47] and a lower incidence of post-partum FI in African Americans compared to Caucasian Americans [48;49]. These results may be confounded by a tendency to different parity rates in different groups and possibly by differing birthing practices.

6. OBESITY

Having a body mass index (BMI) >30, which defines obesity, was associated with an increased risk of FI for women in two studies [18;48]. However, other surveys failed to find a significant association [50;51].

7. POOR GENERAL HEALTH

In population-based surveys, poor general health is an independent predictor of FI [8;19;24;42]. FI is associated with increased mortality both in community dwelling older subjects [40] and in nursing home patients [32].

8. PHYSICAL LIMITATIONS

Three population-based surveys assessed physical limitations and found them to be risk factors for FI [8;37;40]. In nursing home patients, mobility impairment is consistently found to be a predictor of FI [12;32;33;52;53].

9. PHYSICAL EXERCISE

Endurance running is associated with diarrhoea and FI in over 10% of individuals [54]. Regular exercise did not predict prevalent FI or incident FI at a five and
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Risk Factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrie et al (1992)</td>
<td>Surveyed 457 residents of a single long-term care hospital in Ontario, Canada Also estimated costs attributable to UI and FI combined. Defined FI as involuntary loss of feces that is a social or hygienic problem.</td>
<td>Dementia</td>
<td>Significant association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mobility impairment</td>
<td>Significant association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis &amp; meds</td>
<td>Significant association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall prevalence</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual cost/patient</td>
<td>$9771 (1992 Canadian $)</td>
</tr>
<tr>
<td>Johanson et al (1997)</td>
<td>All 388 residents of 5 nursing homes, both skilled &amp; unskilled. Questionnaire was completed by patient if possible, otherwise by investigator or nursing staff. FI defined as any involuntary leakage or soiling.</td>
<td>Diarrhea</td>
<td>OR=8.0 (CI, 3.0-21.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheelchair dependent</td>
<td>OR=2.7 (CI, 1.4-4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dementia</td>
<td>OR=4.3 (CI, 2.8-6.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male sex</td>
<td>OR=2.5 (CI, 1.5-4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age &lt;65 yrs</td>
<td>OR=2.6 (CI, 1.0-6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily exercise (-)</td>
<td>OR=0.5 (CI, 0.3-0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hard stools (-)</td>
<td>OR=0.2 (CI, 0.1-0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tube feeding</td>
<td>OR=7.6 (CI, 5.6-10.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of ADLs</td>
<td>OR=6.0 (CI, 4.7-7.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>OR=3.3 (CI, 2.7-4.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Truncal restraints</td>
<td>OR=3.2 (CI, 1.4-7.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pressure ulcers</td>
<td>OR=2.6 (CI, 2.2-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dementia</td>
<td>OR=1.5 (CI, 1.4-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impaired vision</td>
<td>OR=1.5 (CI, 1.4-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fecal impaction</td>
<td>OR=1.5 (CI, 1.1-2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
<td>OR=1.4 (CI, 1.3-1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td>OR=1.3 (CI, 1.2-1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male sex</td>
<td>OR=1.2 (CI, 1.1-1.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall prevalence</td>
<td>43% in 1991; 51% in 1993</td>
</tr>
<tr>
<td>Chassagne et al (1999)</td>
<td>Incidence of new-onset FI in 1,186 residents of nursing homes or long-term care facilities. 234 (20%) developed FI within 296 days. Risk of long-lasting FI reported. France. FI was defined as involuntary loss of feces.</td>
<td>Hx urinary incontinence</td>
<td>OR=2.9 (CI, 1.8-2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased mobility</td>
<td>OR=1.8 (CI, 1.1-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hx dementia</td>
<td>OR=2.1 (CI, 1.2-3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMSE score &lt;15</td>
<td>OR=2.5 (CI, 1.4-4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated mortality</td>
<td>16% vs. 6.7% (p&lt;.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall FI prevalence</td>
<td>54.40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall incidence</td>
<td>20.00%</td>
</tr>
</tbody>
</table>
In community-based surveys, FI is strongly associated with urinary incontinence [18;38] and overactive bladder [7] in both men and women. Among nursing home patients, the association between urinary incontinence and FI is even stronger [12;13;32]. Pelvic organ prolapse is also significantly associated with FI [7;18].

Urinary incontinence and pelvic organ prolapse are unlikely to be causally related to FI but may serve as marker variables to identify patients who are at risk for the development of FI.

Some patient characteristics found to be associated with FI or AI in epidemiological surveys suggest pathophysiological mechanisms that may cause incontinence, and the modification of these risk factors might reduce the risk of developing FI or AI; examples are diarrhoea, obesity, mobility impairment, and endurance running. For other variables found to be associated with FI or AI, no plausible pathophysiological mechanisms that may cause incontinence are identified. For the last group of variables, e.g., age, poor general health, and the development of FI, it may be useful to identify patients at risk for screening and early treatment.

Table 2. Nursing Home Surveys (Continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Risk Factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glabril (2000)</td>
<td>Incidence of FI in National Nursing Home Survey of 1997. Definition of FI not listed. Includes data on 1.465 million residents. Risk factors and cross tabs with other variables not provided in this report. U.S.</td>
<td>Double incontinence, FI only, Overall FI prevalence</td>
<td>44.20% 1.30% 45.50%</td>
</tr>
<tr>
<td>Nelson, Furner (2005)</td>
<td>Used MDS data from all Wisconsin Nursing Homes for 1992 and 1993 to estimate FI incidence and identify risk factors. FI defined as solid or liquid stool loss.</td>
<td>Trunk restraints, Dementia, Race (non-Caucasian) Loss of ADLs Incidence</td>
<td>OR=2.9 (2.0-4.3) for DI   OR=1.8 (1.4-2.2) for DI   OR=2.0 (1.2-3.4) Significant associations 27.10%</td>
</tr>
</tbody>
</table>
have been reported to cause diarrhoea include lactose (in lactase deficient individuals); fructose, sorbitol, aspartame, and other artificial sweeteners that are poorly absorbed; and fat substitutes such as olestra. Some natural foods such as prunes and figs may also cause diarrhoea. The research literature has not established that these foods, food additives, and drugs cause FI, but it has established a link to diarrhoea.

2. Urgency to defecate

Bharucha and colleagues [14] reported that the symptom of urgency (having to rush to the toilet) is a strong risk factor for FI which is independent of diarrhoea and constipation. This is supported by an independent survey in Australia [19] and a survey of elderly health maintenance organization patients in the U.S [24].

3. Constipation

Constipation was found to be a significant positive risk factor for FI in one nursing home survey [12], but in another study, hard stools appeared to be protective [53]. A UK survey of nursing home residents with FI found that faecal loading was present in 70% of individuals [31]. Constipation is considered to be the most common aetiology for FI in children (often referred to in the paediatric literature as encopresis when there is no recognized structural anomaly to explain the incontinence) [62;63]. The mechanism that is presumed to explain constipation-related FI is overflow: a mass of hard stool in the rectum or sigmoid blunts sensitivity for perceiving the movement of new stool into the area and also reflexly dilates the internal anal sphincter allowing liquid stool to seep out [62].

4. Irritable bowel syndrome

Three population based [48;64;65] and several studies of clinic samples have shown an excess incidence of FI in patients with IBS with estimates of odds ratios ranging from 2 to 8. When research criteria are used to diagnose IBS in population based samples [64;65], the proportion of IBS patients with FI is 12.0% to 22.7%. However, Varma et al [48] estimated that 44.6% of patients with a self-reported diagnosis of IBS had FI.

5. Inflammatory bowel disease

FI is more common in patients with inflammatory bowel disease, although the precise prevalence has not been the focus of study and is not known. Estimates range from 22% [66] to 41% [48]. Two mechanisms are recognized for this association: both ulcerative colitis and Crohn’s disease are associated with diarrhoea, which is a risk factor for FI. Crohn’s disease is also associated with the development of anal fistulae that may drain liquid stool to the skin surface and abscesses that may create anatomical defects in the anal sphincters.

6. Haemorrhoids

A significant number of patients with prolapsing haemorrhoids (Grade 3 and 4) experience faecal soiling, although this has not been the specific focus of any study. Johansson and colleagues [67] reported that 21% of 507 patients treated for haemorrhoids listed hygiene or soiling as an indication for seeking treatment. Following treatment with the Milligan-Morgan procedure, 24% of patients who had not listed soiling or hygiene as an indication for surgery developed new onset FI. Bliss and colleagues [24], in a survey of 1,352 subjects older than 65 years who were attending health maintenance organization clinics, found that self-reports of haemorrhoids predicted the frequency and severity of FI.

7. Imperforate anus

High anal atresia is associated with FI 85% of the time and low anal atresia about 57% of the time [68]. The surgical correction of high anal atresia involves identifying the striated external anal sphincter and pulling the healthy portion of the bowel down through this sphincter to create an anus; contributing causes of incontinence are absence of an internal anal sphincter (passive barrier to soiling), weak contraction of the external anal sphincter, and decreased compliance of the neorectum [69-72]. The outcome of surgical repair is improving with improved surgical techniques and the use of the Malone antegrade colonic enema technique, but 10-30% of these patients remain totally incontinent for faeces [73].

c) Obstetric and other injuries to the pelvic floor

Obstetric injuries are the most thoroughly investigated category of risk factors for FI or AI. Table 3 shows studies that were enriched by recruitment from obstetrical hospitals or urogynaecology clinics and that included at least 500 subjects. The table shows that studies which assessed the impact of obstetrical injury soon after childbirth found strong associations to FI while studies that assessed the impact of obstetrical injury retrospectively in middle aged and older women found weaker associations or no associations [18;74-76].

1. Parity

Most surveys investigating parity find it to be a risk factor for FI. The first vaginal delivery carries the greatest risk of new onset FI [77], and each subsequent delivery adds to that risk [7;17;74;75]. A French study [78] found a higher prevalence of AI in women who delivered at home compared to those who delivered in the hospital.

2. Sphincter laceration

A prospective cohort study demonstrated that primiparous women with a 3rd or 4th degree sphincter
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Risk Factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zetterstrom (1999)</td>
<td>For dependent measure of sphincter tears, hospital records of 845 women evaluated. FI was assessed by postal questionnaire at 0, 5, &amp; 9 months postpartum, but data on relative risk were not presented. Reported incontinence of flatus separately from stool.</td>
<td>First delivery, Gesta age &gt;294 days, Fundal pressure, Midline episiotomy, Increasing fetal wt</td>
<td>OR=9.8 (CI, 3.6-26.2), OR=2.5 (CI, 1.0-6.2), OR=4.6 (CI, 2.3-7.9), OR=5.5 (CI, 1.4-18.7), OR=1.3 (CI, 1.1-1.6)</td>
</tr>
<tr>
<td>MacArthur et al (2001)</td>
<td>Postal questionnaires sent to all women delivered during 1 year at 3 hospitals: one in Scotland, one in England, and one in New Zealand. Questionnaires completed 3 mos post-partum. N=7879 (71% response). Reported incontinence for flatus and stool separately.</td>
<td>Forceps delivery, C-section, Age &gt;35 yrs, Asian origin, Vacuum extraction, Episiotomy, Body mass index</td>
<td>OR=1.94 (CI, 1.30-2.89), OR=0.58 (CI, 0.35-0.97), OR=1.75 (CI, 1.04-2.94), OR=3.21 (CI, 2.04-5.05), No association, No association, No association</td>
</tr>
<tr>
<td>Faltin et al (2001)</td>
<td>Questionnaire study in 666 women from general outpatient clinic, 298 from antenatal clinic, 264 from urogynecology, and 984 from a population sample. FI definition was solid, liquid, or flatus at least monthly.</td>
<td>Parity, Anal sphincter tear, Baby over 4 Kg, Operative delivery</td>
<td>OR=3.1 (CI, 1.6-6.0), OR=4.4 (CI, 2.0-9.1), No association, Univariate but not multivariate association</td>
</tr>
<tr>
<td>Wagenius et al (2003)</td>
<td>Postal survey comparing 186 with sphincter laceration to 348 matched controls (82% response rate) approx 4 years after delivery. Obstetric data taken from medical record. Definition of AI included loss of flatus.</td>
<td>Flatus &gt;1/wk, Liquid FI, Solid FI, Dyspareunia</td>
<td>OR=2.71 (1.78-4.15), OR=3.29 (1.93-5.60), OR=1.91 (0.71-5.17), OR=2.67 (1.44-4.92)</td>
</tr>
<tr>
<td>Roman et al (2004)</td>
<td>525 consecutive vaginal deliveries were interviewed 6 wks post-partum. France. Definition of FI unknown.</td>
<td>Forceps delivery, Unassisted delivery at home, Fetal head &gt;93 mm, Maternal age &gt;30 yrs</td>
<td>OR=10.8 (2.82-41.3), OR=50.0 (3.09-802), OR=4.56 (1.46-14.1), OR=4.60 (1.11-19.1)</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
</tbody>
</table>
| Casey et al (2005)             | Interviews completed prior to delivery and again 6 months later at return for advice on contraceptives. 3601 women (93% response rate; 88% Hispanic) competed both surveys. Definition: "Do you have problems controlling you 'gas' or bowel movement until you get to the bathroom? For example, do you stain your panties?" | Oxytocin augment  
2nd stage >2 hrs  
Episiotomy  
3rd or 4th degree tear  
Forceps delivery  
Cesarean delivery  
Fetal weight >4000 g.  
Overall AI prevalence | OR=1.9 (1.2-3.0) univariate only  
No association  
OR=1.7 (1.1-2.6) univariate only  
No association  
No association  
No association  
2.4 (1.3-4.4) adjusted  
2.30% |
| McKinnie et al (2005)          | Survey of 1004 urogynecology clinic patients from 6 sites. Average age 43 years. AI was defined as uncontrollable loss of stool or gas that was bothersome. | Any vaginal delivery vs. nuliparous  
Maternal age  
BMI  
Overall prevalence | OR=2.41 (1.30-4.49)  
OR=1.05 (1.03-1.07) univariate only  
No significant association  
13.10% |
| Faltin et al (2006)            | Postal survey 18 years after delivery in 259 women with sphincter tear vs 281 matched controls without sphincter injury. AI defined as Wexner score of 4 or greater (0-20 scale). | Sphincter laceration  
Age >35 at delivery  
3rd or 4th degree tear  
2nd stage of labor >1hr  
Baby >4 kg  
Forceps or vacuum  
AI prevalence | OR=1.68 (1.01-2.79)  
OR=1.79 (1.01-3.43)  
OR=4.30 (2.62-7.03)  
OR=1.89 (1.29-2.77)  
OR=1.99 (1.05-3.74)  
OR=2.16 (1.37-3.42)  
20.60% |
| Hatem et al (2006)             | Postal survey of all primips delivering in Quebec hospitals during 6 mo period. Survey mailed at 6 mo postpartum. 1291 (52%) completed survey. Definition: "Have you ever lost control of your intestines, resulting in involuntary gas or fecal loss… after childbirth?" | Age >35 at delivery  
3rd or 4th degree tear  
2nd stage of labor >1hr  
Baby >4 kg  
Forceps or vacuum  
AI prevalence | OR=1.79 (1.01-3.43)  
OR=4.30 (2.62-7.03)  
OR=1.89 (1.29-2.77)  
OR=1.99 (1.05-3.74)  
OR=2.16 (1.37-3.42)  
20.60% |
| Borello-France et al (2006);    | Prospective study comparing FI at 6 wks and 6 mo after delivery in 407 with 3rd or 4th degree sphincter lacerations, 390 without sphincter lacerations, and 124 delivered by cesarean section. FI defined as solid, liquid, or mucus leakage in prior month. Risk factors assessed at 6 mo. | Sphincter laceration  
White race  
Antenatal UI  
Severity of laceration  
Maternal age  
BMI (per 5 kg/m2) | OR=2.8 (1.8-4.3) at 6 wks;  
OR=1.9 (1.2-3.2) at 6 mo.  
OR=6.1 (1.3-29.4) in tear group  
OR=2.2 (1.1-4.3)  
OR=2.0 (1.0-4.0)  
OR=1.6 (1.2-2.1)  
OR=1.3 (1.0-1.7) |
laceration recognized at delivery have a substantially increased risk of FI even though sphincteroplasty is routinely performed when a sphincter laceration is detected [79]. Other studies [18;19;74;80-82] support this association, although two studies [14;80] did not.

3. INSTRUMENTED DELIVERY

Forceps delivery was found to be a risk factor for sphincter laceration [83] and FI [47;78;81;82], although two studies did not find this association [14;80]. The evidence that vacuum extraction is a risk factor for FI is more equivocal; two studies reported a significant association [81;84], and one study showed that vacuum extraction increases the risk of sphincter tear [83]. However, other studies failed to find an association of FI with vacuum extraction [18;47]. The evidence for a protective effect of caesarean section is inconclusive.

4. EPISIOTOMY

Midline episiotomy, which was formerly advocated for the prevention of uncontrolled sphincter lacerations and associated FI, has been found to increase the risk of sphincter laceration [77;83]. The risk of AI was reported to be increased in two studies [80;85] and unchanged in a third study [47]. No studies have found episiotomy to be associated with a reduced risk of sphincter laceration or FI/AI.

5. LARGE BABY, PROLONGED SECOND STAGE OF LABOUR

Two studies [77;83] showed a significant association between sphincter laceration and foetal weight greater than 4000 grams. Other studies showed an association between AI and foetal weight greater than 4000 grams [80;81] or foetal head diameter greater than 93 mm [78]. However, a fourth study did not confirm this association [82]. A prolonged second stage of labour was associated with a greater risk of AI in one study [81] but not in a second study [80].

6. MATERNAL CHARACTERISTICS

Age of the mother at the time of vaginal delivery was positively correlated with the risk of FI or AI in 5 studies [47;75;78;79;81], but was reported to be protective in one study [82]. Maternal depression and stress were also reported to be associated with an increased risk of AI [76]. A French study also found AI to be more common in women who had a history of anal or UI surgery and in those who completed high school [76].

d) Sequelae of surgical procedures

1. COLECTOMY AND ILEOANAL ANASTOMOSIS

Because ulcerative colitis and familial polyposis both convey a high risk of colon cancer, the colon is often removed prophylactically. While a number of variations in surgical technique have been described, the commonest procedure is to create a neorectum from loops of ileum sewn together to create a pouch and to connect this to the anal canal. A temporary ileostomy
is usually performed to give the pouch time to heal. Post-operatively, 25-35% of these patients have daytime FI [86-89] and 32-52% have nocturnal FI [86;86;87]. Fazio and colleagues [89] reported that the preoperative frequency of FI was as great in their series of patients as was post-operative FI. The mechanisms that lead to FI in this population include frequent bowel movements (8 or more per day), high pouch pressures that exceed anal canal pressures, and high amplitude contractions of the pouch [90]. Such pouch contractions are recorded in continent as well as incontinent patients with an ileal pouch because the pouch is constructed from innervated bowel; however, the contractions produce higher pouch pressures in the incontinent patients.

When it is possible to preserve the rectum, the ileum can be sutured directly to the rectum, substantially reducing the risk of FI [91]. When bowel resection is performed for the treatment of colon or rectal cancer, some or the entire colon may be preserved, and the remaining colon may be sutured directly to the anal canal or it may be used to create a pouch that is connected to the anal canal. This is associated with a lower incidence of FI (estimated at 18%) according to some authors [92;93], but others [94] reported a rate of 49% FI following colo-anal anastomosis.

One randomised controlled study has investigated the use of daily irrigation of a colonic J-pouch prior to ileostomy closure. Irrigation was not found to improve post-closure nocturnal continence or defaecation frequency [95].

2. INTERNAL ANAL SPHINCTEROTOMY

Patients with chronic anal fissure or haemorrhoids may be offered internal anal sphincterotomy (silt in the internal anal sphincter for 50-60% of its length to reduce anal canal pressures). In a large series of 585 patients with a chronic anal fissure treated in this fashion at the Mayo Clinic, 45% developed FI at some point in their recovery. However, this tended to improve with time from surgery, and at follow-up an average of 72 months after surgery, 11% reported FI [96].

3. RADICAL PROSTATECTOMY FOR PROSTATE CANCER

Published prevalence rates of FI following radical prostatectomy alone range from 9% [97] to 15% [98]. In the largest survey, Bishoff and colleagues [99] reported that prostatectomy by the retropubic approach was associated with FI in 17% of cases whereas prostatectomy by the perineal approach was associated with FI in 32% of cases; the loss of moderate to large amounts of stool was reported by 4% and 10% respectively. Rates of FI are higher when prostate cancer is treated by radiation therapy [47]. These differences may be confounded by differences in severity of disease before treatment, extent of resection, and dose of radiotherapy.

4. HAEMORRHOIDECTOMY

A large series of 507 patients who received the Milligan-Morgan surgical treatment for haemorrhoids were followed up by postal questionnaire 2-11 years after surgery (average of 6 years). A total of 33% (139/507) reported AI including 72 who were incontinent of gas only, 56 who were incontinent to liquid faeces, and 11 who were incontinent to solid faeces [67]. Other reports of surgical treatment for haemorrhoids list a lower incidence of FI [100], but only cases with loss of liquid or solid stool are usually reported. In a community based survey of people over age 65, Bliss [24] found self-reported haemorrhoid surgery was significantly associated with FI.

e) Sequelae of radiotherapy for cancer

The prevalence of FI following external beam radiation therapy for prostate cancer ranges from 14% [97] to 21% [67]. One group estimated the prevalence at up to 46% for a mixed group most of whom had been treated with both surgery and radiotherapy [101]. Radiotherapy for cervical cancer is associated with FI in 25% of cases compared to 8% for cervical cancer patients treated exclusively by surgery [102]. The mechanism through which radiotherapy contributes to FI is believed to be a decrease in rectal compliance [103], leading to increases in symptoms of urgency and loose stools [67;102].

f) Neurological Diseases that predispose to FI

1. COGNITIVE IMPAIRMENT

Dementia is a significant predictor of FI both in the community [40] and in nursing homes [12;32;53]. In some community studies, dementia was not found to be a significant predictor after controlling for other risk factors [40;40;55], possibly because patients with severe dementia associated with FI are frequently admitted to nursing homes [104].

In people with a developmental disorder, the prevalence of FI in those with mild learning disability is little different from that of the general population; however, rates for those with moderate and severe learning disability are higher than population norms and are similar to each other. The prevalence of FI is substantially higher in those with a profound learning disability [105]. Nevertheless, around half of those with a profound learning disability will acquire bowel control by adulthood.

2. SPINAL CORD INJURY

Traumatic spinal cord lesions result in substantial or complete denervation of pelvic floor muscles and loss of voluntary control over the external anal sphincter. However, many of these patients avoid FI because they are constipated due to delayed whole gut transit and/or hyper-reflexia of the external anal sphincter. Occasional FI is reported by 33-66% [106-108] but
frequent FI (more than monthly) is limited to 11% [109] to 14% [108;110]. Approximately 70% require mechanical or manual assistance to initiate defecation [110]. In patients with congenital spinal cord lesions (spina bifida), anorectal dysfunction may be more common; 53% in one study [111] and 34% in another survey [112] report that they soil regularly. As with traumatic spinal cord lesions, the majority of patients with spina bifida are constipated, which reduces the frequency of FI that would otherwise occur in these patients because they have partial or complete disruption of the efferent innervation to the pelvic floor muscles [113].

3. Stroke

Two large studies have assessed the incidence of FI following stroke. In the Copenhagen Stroke Study of 935 consecutive admissions for stroke [114], 34% were fully incontinent and 6% were partially incontinent on admission to the hospital; 6 months later, 5% were fully incontinent and 4% were partially incontinent. In a study of 1069 patients taken from the South London Stroke Register [115], 29.7% were faecally incontinent 7-10 days after stroke, 10.8% were still incontinent at 3 months, 10.9% at one year, and 15.0% at 3 years. These data suggest that FI is transient for the majority of patients affected, but the prevalence of FI remains elevated compared to population norms at one year and shows little further improvement. A study of 186 stroke patients in Spain showed a similar pattern: 56% had FI at admission, and 22% remained incontinent 6 months later. Risk factors for FI included age, severity of stroke, diabetes, and comorbidity of other diseases [114].

4. Traumatic brain injury

An excellent study [116] of the prevalence of FI following traumatic brain injury was carried out in 1,013 patients consecutively enrolled in any of 17 acute rehabilitation facilities. Prevalence rates were 68% at admission, 12.4% at discharge, and 5.2% at one year follow-up. The risk of incontinence at each time point was significantly related to all measures of the severity of brain injury including Glasgow Coma Scores and length of stay. In addition, at discharge from the rehabilitation facility, FI was significantly associated with pelvic fracture, urinary tract infection, and patient age (older patients were more likely to be incontinent); at one-year follow-up, FI was significantly associated with urinary tract infection and patient age. Patients with FI were more likely to be discharged to an institution rather than to return to their homes.

5. Diabetes mellitus

Bytzer and colleagues [117] carried out a large population-based postal survey in 8,657 adults including 423 with self-reported diabetes mellitus (DM). The response rate was 60%. When patients with DM were contrasted to the remainder of the sample the frequency of FI occurring at least “sometimes” was 12.8% vs. 3.8% (p<0.001) and the prevalence of FI occurring “often” was 2.6% vs. 0.8%. The odds ratio (after adjusting for confounders) was 2.74 (CI, 1.40-5.37). The prevalence of FI was shown to be related to self-reported degree of glycemic control. These results were confirmed by two other studies that recruited patients from a diabetes register [118] or a diabetes clinic [60]. The risk of FI among patients with DM is known to be related to weakness of anal canal resting and squeeze pressures and impaired sensation in the rectum [119;120], and these physiological defects are related to duration of DM and the presence of microcirculatory abnormalities and autonomic and peripheral neuropathies [120].

6. Multiple sclerosis

FI is reported by 29-51% [121-123] of multiple sclerosis patients living in the community, and it is frequent in 5% [121] to 25% [123]. Among 14,000 nursing home residents with multiple sclerosis, FI was present in 58% and occurred more than twice a week in 7.5% [124]. Incontinence in this group is associated with weak strength of contraction of pelvic floor muscles, a low threshold for elicitation of the internal anal sphincter inhibitory reflex, and impaired sensation for rectal filling [125;126]. Approximately half of patients with multiple sclerosis are also constipated, but constipation seems to occur about equally often in multiple sclerosis patients with and without FI [123].

3. SUMMARY OF EVIDENCE ON RISK FACTORS FOR FI AND POTENTIAL FOR PREVENTION

1. There is a high prevalence of FI in community-dwelling populations

2. High risk groups fall into four main categories and include:

1. Patient characteristics
   • Increasing age
   • Nursing Home residence
   • Gender: equivocal evidence
     - Younger: 6 studies women>men; 8 studies no difference
     - Older men>women (one study)
   • Race: no difference except obstetric injuries
   • Obesity, poor general health and physical limitations, urinary incontinence & pelvic organ prolapse, endurance running are all associated with FI
   • Neurological disease or injury (learning disability, dementia, spinal cord injury, multiple sclerosis, spina bifida, stroke, head injury, diabetes mellitus)

2. Patients with gastrointestinal symptoms and disorders
   • Diarrhoea or loose stools (community & NH)
- Drugs (antibiotics, SSRIs, laxatives, digoxin, orlistat), dietary supplements (lactose, fructose, artificial sugars, olestra) foods (prunes, figs)

• Urgency (independent of stool consistency)
• Constipation ("overflow")
• Irritable bowel syndrome (IBS) (OR 2-8)
• Inflammatory bowel disease (IBD) (diarrhoea + perianal)
• Haemorrhoids (before and after surgery)
• Congenital anomaly (imperforate anus)

3. Obstetric factors (note the disparity population vs. selected clinic studies)
• Parity for AI (1st vaginal delivery, subsequent deliveries: clinic populations)
• Sphincter laceration for AI & FI (7 studies found increased risk, 2 not)
• Instrumental delivery (forceps 5 studies found increased AI risk, 2 not; vacuum equivocal)
• Episiotomy: midline ? risk; mediolateral not protective
• CS: inconclusive, tending to not protective
• Large baby, prolonged 2nd stage: equivocal

4. Sequelae of surgical procedures
• Colectomy & ileo-rectal anastomosis or pouch: diarrhoea + pressures: 18-49% FI
• Sphincterotomy: 11% FI in long term
• Haemorrhoidectomy: 33% AI
• Radical prostatectomy: 9-32% (retropubic vs. perineal)
• Pelvic radiotherapy 14-46% (diarrhoea + compliance)

4. RECOMMENDATIONS FOR PRACTICE ON PREVENTION

1. Primary prevention:
• Public health measures to prevent diarrhoeal diseases (Grade B/C)
• Treat reversible causes of diarrhoea (C)
• Obstetric: no convincing evidence of role for preventive caesarean section; avoid midline episiotomy; restrictive episiotomy protocols (A)
• Discourage the use of internal anal sphincter division for treatment of anal fissure and haemorrhoids (A)

2. Secondary prevention (Table 4):
• Active case finding/screening in high risk groups (C)
• Proactive bowel management in high risk groups (eg neurological) (C)
• Optimise stool consistency in people with loose stools (all ages); hard stools (children and older pops) (B)
• Treat obesity? (D)
• Consider medication alternatives in patients with FI & medication-induced diarrhoea (C)
• Alert patients to risk of FI following colorectal surgery (C)

Table 4. Targets for Secondary Prevention Through Early Recognition

<table>
<thead>
<tr>
<th>Patient characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia/cognitive impairment</td>
</tr>
<tr>
<td>Physical limitations/ impaired mobility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diseases and disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Pelvic organ prolapse</td>
</tr>
<tr>
<td>Hemorrhoids, grade 3 and 4</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>CNS injury: stroke, head injury, Alzheimer's, Spinal cord injury: traumatic cord injury, spina bifida</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Congenital anorectal anomalies: imperforate anus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical interventions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery with sphincter laceration</td>
</tr>
<tr>
<td>Instrumented vaginal delivery</td>
</tr>
<tr>
<td>Colectomy, with or without ileal reservoir</td>
</tr>
<tr>
<td>Internal anal sphinterotomy for anal fissure, hemorrhoids, Hirschprung's disease</td>
</tr>
<tr>
<td>Prostatectomy, especially by perineal approach</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs and Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that cause diarrhea as a side-effect</td>
</tr>
<tr>
<td>Foods that cause diarrhea: dairy products in lactase deficient individuals, some fruits</td>
</tr>
<tr>
<td>Food additives that cause diarrhea or gas: artificial sweeteners</td>
</tr>
</tbody>
</table>

| Radiological treatment of pelvic cancer |
5. RECOMMENDATIONS FOR RESEARCH ON PREVENTION

- Longitudinal studies to map natural history, especially in women with obstetric risk factors
- Prevention studies in childbearing women and other high risk groups
- Colorectal surgery and radiotherapy techniques
- Bowel management strategies in high risk groups (e.g. neurological)
- Understanding mechanisms of FI in men
- Frail Elderly: community prevention/ screening/ early treatment to prevent NH admission
- Measures to prevent/reduce FI in nursing homes (functional FI, staffing etc)

III. EDUCATION & “LIFESTYLE” INTERVENTIONS

1. BACKGROUND

Most patients do not know how the bowel works and what might improve bowel function. Many also have attitudes to defaecation that are influenced by stigma and taboos prevalent in their particular family and wider cultural group within a society [127].

Expert opinion supports the use of general health education, patient teaching about bowel function and advice on lifestyle modification [128;129], but the evidence base is small. Unlike urinary incontinence, few “lifestyle” associations have been identified with FI and little is known about whether interventions designed to reduce potential risk factors might improve FI. Diet and fluid intake are covered in Section 4.

2. SEARCH

The following keywords were searched: “anal, anorectal, bowel, faecal, fecal, rectal, stool” and “continent$ or incontinent$,” or “diarrhea, diarrhoea” and the relevant lifestyle or intervention term: exercise; irrigat$ and rectal or rectum or anal or transanal; smoking, tobacco smoke pollution, tobacco use disorder, and tobacco$ or cigarette$ with use$ or abuse$ or smok$; toileting and toilet$; psycholog$ or effect$ with carer, caregiver, spouse, family, families or parent$ and nursing or care. The following databases were searched: CINAHL 1982- March, 2008 MEDLINE 1955- March, 2008. The Cochrane library and a recent systematic review of the epidemiology and prevention of urinary and FI was also reviewed [6]. All seemingly relevant abstracts were reviewed then salient articles were retrieved and reviewed, and the reference lists searched for further studies.

3. REVIEW OF EVIDENCE ON THE EFFECT OF EDUCATION AND LIFESTYLE CHANGES ON FI

a) Weight reduction

Obesity is a well-documented risk factor for FI (Section 2 above). The only data available about the association of weight loss and FI reduction is in morbidly obese individuals undergoing weight reduction surgery and findings conflict. One preliminary report of surgical intervention [130], is published only in abstract form so far and is included because of limited studies available. In that study, bariatric surgery was not beneficial: 159 massively obese patients underwent either gastric bypass surgery or gastric banding and were asked approximately 2 years later to report retrospectively on their continence status before and after surgery. A higher than expected proportion of them reported FI prior to surgery (23% solid, 47% liquid FI), but FI was worse rather than better in more than half of these patients following surgery despite an average 48kg weight loss. It is possible that diarrhoea, a common consequence of bariatric surgery and which exacerbates FI, might account for this worsening of FI, but this was not noted in the preliminary report. In contrast, a second study [49] reported a significant decrease in the prevalence of FI of solid or liquid stool from 19.4% preoperatively to 8.6% at 12 months (p= .018; 95% CI = 2.1–19.4%) in women who underwent bariatric surgery for morbid obesity (mean (sd) body mass index (BMI) = 48.9 (7.2) kg/m²). In a single group cohort study (i.e., no control group), 93 women (aged 20–55 years) received a laparoscopic Roux-en-Y gastric bypass and reported data about FI by answering two questions before and after surgery. Any association between weight loss and FI reduction was not reported.

b) Physical exercise and work

One study in a nursing home population found that a structured daily exercise programme, combined with increased fluid intake and regular toileting opportunities, significantly improved FI and increased the percentage appropriate toilet use compared with controls [131;132]. However, lack of exercise is not an established risk factor for FI or AI (see Section 2 above).

c) Smoking

Nicotine is thought to slow upper gut motility and increase total transit time [133], but it seems that it can speed recto-sigmoid transit [134], and this stimulation of distal colonic motility may exacerbate a tendency to faecal urgency. This fits with many anecdotal reports that smoking a cigarette facilitates initiation of defaecation. Smoking is a known risk factor for urinary incontinence and genital prolapse (OR 2.9) [135],
presumably via chronic coughing. No association has been found between antenatal smoking and postnatal FI [136]. In a survey of 271 pairs of identical twin sisters, smoking was not significantly related to FI or flatus incontinence [137]. In a study of community-living elderly men and women, smoking was not predictive of prevalent or incident FI [55]. Smoking cessation is anecdotally reported to be useful for reducing urgency of defaecation, but no formal studies were identified.

c) Medication side-effects

Medication used specifically to treat FI is covered in section 6 below. A vast number of drugs have direct or indirect effects on the gastrointestinal system, tending to cause constipation, diarrhoea, or either in different people. A careful drug history (including all over the counter or “herbal” preparations) should be taken in each person with FI. It is beyond the scope of this chapter to review drug effects in detail, and prescribers should be aware of the possible unintended side-effect of FI. No studies were identified that evaluated the benefits of patient or provider education regarding the gastrointestinal side-effects of medications.

One single case report was found reporting that a combination of olestra in the diet and orlistat given to treat obesity led to symptoms of FI, which resolved when the olestra was stopped [138]. Patients reporting soiling while on treatment with orlistat for obesity have been found to have pre-existing impaired anorectal function, thus predisposing them to symptom development [139].

d) Toilet facilities

In individuals who have physical or mental impairments, an adverse physical or social environment may impair the ability to maintain continence. This is particularly relevant to those in institutional settings; use of physical or chemical restraints in institutions also limit or delay access to toilet facilities (see Committee 13). Adverse environmental factors include: (a) toilet facilities that are inaccessible or that lack privacy so that the person avoids using the toilet; (b) care providers who are insensitive to the individual’s needs and bowel habit; (c) clothes which are difficult to manipulate in a hurry; and a variety of other factors which vary with abilities of the individual. The toilet itself may be too high, leaving the feet dangling and thus making abdominal straining difficult. The toilet may be too low, making sitting and rising difficult for those with immobile hips. A social environment in which care-givers are overworked and harassed may lead the patient to repeatedly ignore the call to stool, in the hope of finding a quieter time later. Commode use is reviewed in Chapter 20.

There are many adaptations that can be made to a toilet to facilitate access and stability in use [140]. Effective bowel evacuation is helped by sitting well-supported, with feet slightly raised to enable appropriate use of abdominal effort if needed, and leaning forward slightly [141]. Horizontal grab rails assist pushing up from a seated position, while vertical ones can enable pulling up. A raised seat or foot blocks can adjust the height as needed. For lateral transfer from a wheelchair, both seats need to be at the same height. Where it proves impossible for a person to use the toilet, alternative commodes or chemical toilets are available with appropriate features for the individual’s needs. No studies were found examining the effect of modifying the physical or social environment in treating FI.

e) Patient and care-giver education and attitudes

The strongest data on education and lifestyle comes from a single RCT. Patients were randomised to nurse-led education and advice alone, or education with the addition of exercises and/or, biofeedback. The education and advice group showed reduced frequency of FI and was as effective as biofeedback or exercises [142]. Other support for the benefits of patient education comes from a study reported in abstract form [143] which showed that education and standard medical care, when provided systematically to a group of FI patients who had failed prior attempts at medical management, led to a successful outcome in 38%. Success in this trial was defined as a patient’s report that they had experienced adequate relief of bowel symptoms.

An RCT of a combination nurse-led intervention for bowel problems in 146 stroke patients found that a single educational visit with a detailed information booklet improved bowel dysfunction up to 6 months later, and changed diet and fluid behaviour up to one year later compared to controls who received routine care. The intervention group were more likely to have sought professional help from their family practitioner for bowel problems, demonstrating a heightened awareness of the possibility of treatment [144]. However, there was no difference in the rates of FI between the intervention and control groups.

For people with dementia or other severe intellectual impairments, expert opinion holds that the attitude and management methods adopted by care providers is as important as bowel function in maintaining continence [144]. No controlled studies on this subject were found. However, one quasi-experimental study examined care-givers’ knowledge and compliance before and after an educational intervention [145]. Forty home care-givers of people with dementia, over half of whom had some degree of FI, completed a study-specific questionnaire before and after receiving a videotape and information booklet entitled “a practical approach to maintaining bowel control in people with dementia”. Ninety percent of the care-givers accessed the information and there was an improvement in post-intervention knowledge scores measured on a
55-point scale, with the mean score increasing from 23 pre-test to 32 post-test (p=<0.001). However, it is not known if this improved knowledge translates into improved care or reduced FI.

f) Complementary therapies

No hypnosis treatment study was found which included FI as an outcome variable. Psychotherapy does not appear to enhance the effectiveness of behavioural interventions for FI in children [146], but no studies were found in adults. Likewise, there have been no studies of the use of acupuncture, reflexology, homeopathy or any other complimentary approach reported in the literature.

4. SUMMARY OF EVIDENCE ON EDUCATION AND LIFESTYLE INTERVENTIONS IN FI

There is at present limited evidence for any lifestyle intervention for FI.

- Obesity: FI may improve after bariatric surgery (Level 3)
- Smoking: not predictive; no studies
- Medication side effects may cause FI related to diarrhoea

5. RECOMMENDATIONS FOR PRACTICE ON EDUCATION AND LIFESTYLE

- Medication side effects: consider alternatives if causing diarrhoea (C)
- Toilet access for people with disabilities (C)
- Education
  - of patient (B/C)
  - of carer (C)
- Complementary therapies: no evidence (D)

There is insufficient evidence to recommend or discourage most lifestyle modifications either for the prevention or treatment of FI. Based on the consensus of experts (Level 3 evidence) the committee recommends patient education about the causes of FI and a systematic effort to remove barriers to effective toileting as an intervention that is likely to be beneficial. This may be provided at relatively low cost and involves no significant risk to the patient.

6. RECOMMENDATIONS FOR RESEARCH ON EDUCATION AND LIFESTYLE

- Based on encouraging preliminary reports that patient education, combined with conservative medical management, can reduce the frequency of FI, we recommend further research. An RCT may not be possible due to the challenge of identifying a suitable control for expectancy and attention, but a study which demonstrates a sustained benefit from a limited educational intervention (provided to patients or caregivers), would provide useful guidance for clinical management.

- Further investigation of the benefits for FI of weight reduction, especially in moderately obese patients without bariatric surgery.
- Exercise programmes, when incorporated into a multi-component intervention, have produced promising preliminary results and should be tested further. Such trials should differentiate between constipation-associated FI and diarrhoea-associated FI as exercise may be more beneficial to the former group.
- Evaluation of the incremental or additive value of different lifestyle interventions in the patient pathway.
- Research on the contribution of complementary therapies.

IV. DIET AND FLUID INTAKE

1. BACKGROUND: RATIONALE FOR DIETARY INTERVENTIONS

The basis for investigating diet modification as a strategy for managing FI comes from anecdotal reports of this practice by patients to clinicians and recent qualitative and survey research reports. Community-living adults and elderly individuals, especially women, report that they manipulate their diet and eating patterns as a strategy for managing their FI [30; 147; 148]. Dietary manipulation is employed by the approximately 20% of patients with irritable bowel syndrome (IBS) who also have FI [129; 149] and by the approximately 19% to 40% of patients with inflammatory bowel disease who have FI [56; 66; 129; 150-152].

Empirical observations of a suspected relationship between diet and changes in bowel pattern are not limited to FI but have been reported by individuals with constipation, those with IBS with constipation (IBS-C) and some healthy individuals, and together with physiological principles of gastrointestinal (GI) function, supported an investigation of the evidence and discussion of possible mechanisms.

2. LITERATURE SEARCH

The following databases were searched for studies to include in this review of dietary interventions for FI management: CINAHL (1982 to March, 2008) and Medline (1966 to March 2008). The Cochrane library and a recent systematic review of the epidemiology and prevention of urinary and FI was also reviewed [6] (Table 5).

The following key words were linked with anal, anorectal, bowel, faecal, fecal, rectal, stool and “continent$ or incontinent$, “ or “diarrhea, diarrhoea,
### Table 5. Randomised trials of the effects of dietary interventions on faecal incontinence

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and sample</th>
<th>Intervention and Outcomes</th>
<th>Findings</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Bliss et al. [175] | - Randomised, parallel-group, placebo-controlled, single-blind trial.  
- The participants, statisticians, laboratory technician, and participants' clinicians were blinded.  
- 39 adults (79% female) completed the study.  
- Subjects had faecal incontinence of loose or liquid stool at least weekly.  
- A block scheme resulted in equal numbers (n=13) in each group.  
- Groups' characteristics were comparable in the baseline period. | - One of the following soluble fibre supplements mixed into fruit juice: 25 g of psyllium source per day, 25 g of gum arabic source per day, or placebo (0.25 g of pectin source per day).  
- Based on the percent of fibre in each of the sources, the total amount of dietary fibre administered was: 7.1 g of psyllium per day, 21.5 g of gum arabic per day, or 0.2 g of the pectin placebo.  
- The supplements were taken for 31 days in addition to usual diet intake, determined by a prospective diet record for 8 days in each period.  
- Participants prospectively reported faecal incontinence on a daily stool diary for 8 days in each period.  
- The proportion of incontinent stools during the baseline and fibre supplementation periods was the primary measure.  
- Secondary clinical measures included stool consistency and frequency, stool wet and dry weights, and percentage water content of stool. The adverse event of flatulence was monitored daily by self-report of the participants on the stool diary.  
- Secondary measures of the effects of the fibres on the stools included the water-holding capacity of stool solids, total fibre content of stool, stool pH, and faecal short chain fatty acids. | - The rate of faecal incontinence for the groups ingesting psyllium or gum arabic were significantly lower than those taking the placebo.  
- The rate of stool with loose and unformed or liquid consistency for the groups ingesting psyllium or gum arabic were significantly lower than those taking the placebo.  
- There was no significant difference in baseline diet intake among groups.  
- The water-holding capacity of stool solids was highest for the group ingesting psyllium.  
- Faeces did not differ between the baseline and fibre supplementation periods or among fibre groups.  
- There were no differences among the groups in stool frequency, wet or dry weight of stool, weight of stool solids, total fibre content of stool, stool pH, or short chain fatty acids. | - The inclusion and exclusion criteria were reported.  
- Sample size was based on a power analysis.  
- The timing of supplement consumption and allocation concealment were not provided.  
- How power was calculated was not explained.  
- Small group sizes reduced generalizability of findings. | - Details of the procedures for random assignment and allocation concealment were not provided.  
- Supplements were pre-mixed and ready-to-take. Adherence to taking the supplements was determined by self-report.  
- 95% of subjects completed the study and reasons for attrition were reported.  
- Measures of stool characteristics were made using standard objective laboratory procedures. |
Table 5. Randomised trials of the effects of dietary interventions on faecal incontinence

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and sample</th>
<th>Intervention and Outcomes</th>
<th>Findings</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Levati et al.  | A double-blind, randomized, cross-over design | - Treatment A: self-titrated dose of loperamide (starting at 2 mg twice per day, 1 rounded teaspoon of a food thickener containing maize starch, methylcellulose, and linseed gum twice per day, and a diet advice sheet about a low-fibre residue diet.  
- Treatment B: same self-titrated dose of loperamide, one rounded teaspoon of psyllium hydrocolloid fiber in water twice per day, and a diet advice sheet about a high and low-fiber residue diet.  
- Participants self-reported anal incontinence outcomes for the last 4 weeks of the 6 weeks of each fiber treatment using the patient weighted FISI. FISI score during each treatment period was the primary measure of anal incontinence.  
- Secondary clinical measures included a fecal incontinence specific quality of life scale and the SF-36, a measure of general health status. | - 67% of treatment A fiber and 73% of treatment B fiber were taken as determined by weighing the container containing the fiber source at the end of each fiber phase.  
- The mean difference in the FISI score between treatments was -0.8 (95% confidence interval = -4.9 to 3.3) and was not statistically significant.  
- There were no adverse events. It was noted that some subjects reported having a dry mouth and thought the supplements had low palatability. | - There were two power calculations based on a five-point difference in the Fecal Incontinence Severity Index, which was considered by the investigators to be clinically significant. One for a test of paired data and one for tests of unpaired data in the event of high attrition at the crossover point.  
- Subjects were randomly assigned to treatments using a computer-generated list in blocks of 10.  
- Independent pharmacists dispensed the treatments.  
- The interval for data collection during both treatments was the same.  
- 75% of subjects completed the study protocol and reasons for attrition were reported. | - Given the cross-over design, period and sequence effects were not reported prior to combining all subjects on Treatments A or B for analysis.  
- Baseline FISI scores do not appear to be included in the main analysis.  
- There was no theoretical or physiological rationale for use of dietary fiber for leakage of mucus or solid stools.  
- The total amount of fiber in each supplement source was not reported.  
- Participants mixed their own supplements.  
- The definition of an adverse event or the method of reporting them was not provided.  
- Although two different diet advice sheets about high and low residue diets were provided, no record of usual diet intake was analysed.  
- There was no record of the doses of the anti-motility medication that were taken or use of suppositories that were provided for constipation.  
- There was no record of control of concomitant treatments for fecal incontinence during baseline or treatment periods.  
- The FISI was designed and tested using recall of anal incontinence characteristics. How the FISI was used (e.g., daily or by recall) in each treatment phase was not reported. |
signs and symptoms digestive or digestive disease: alcohol, alcoholism, alcoholic beverages, ethanol, drinking; beverages, fluid, fluid intake; liquid, water; coffee, caffeine, cola; diet, dietary therapy, diet, eat, intake, consume, fat, lipid, fibre/fiber, lactose, dairy; prebiotic, probiotic, symbiotic; oligofructose, oligosaccharide, fructans, fructo, fos or fructooligosaccharide; sorbitol or glycol, meglumine; spice, spicy, hot; yogurt, bifidobacteria, Lactobacillus acidophilus, acidophil. All seemingly relevant abstracts were reviewed; then salient articles were retrieved and reviewed, and the reference lists of these articles searched for further studies.

a) Criteria for considering studies for this review

1. Types of studies

Only studies in the English language were reviewed. Systematic reviews and meta-analyses of randomised controlled trials and full-length manuscripts reporting individual studies published in a peer-reviewed journal were considered. Individual studies or reports were required to have one of the following designs as defined in the ICDR review guidelines: randomised, controlled trial; prospective, non-randomised cohort; case-control; or recommendations from an expert consensus panel or Delphi process.

2. Types of study participants

Studies that involved people who were 18 years or older, had FI, and received a dietary intervention were included. People who were tube-fed or had an intestinal ostomy were ineligible.

3. Types of dietary interventions

A dietary intervention was defined as any type of food, supplement, dietary product, or fluid that is purposefully consumed or restricted, limited or avoided to manage FI. Studies were excluded if it was not possible to distinguish any direct effect of the dietary intervention from other interventions introduced simultaneously. For example, a study was excluded if it combined pelvic floor muscle training and a dietary intervention and compared it to another intervention such as drug therapy making it impossible to determine the effect of the dietary intervention alone.

4. Types of outcome measures

FI was required to be a primary outcome measure of the studies. Studies which focused primarily on the outcomes of stool consistency or form, stool amount, volume or bulk, defecation frequency, diarrhoea, or constipation without including any measure of FI were excluded.

b) Method of review

The reviewer examined the list of citations and abstracts yielded from the electronic search strategy. Potentially relevant papers were retrieved in full text. The reviewer was not blind to the journal titles, authors’ names or their institutional affiliations. The quality of the studies was evaluated using the checklist accompanying the CONSORT statement available at http://www.consort-statement.org. The levels of evidence for therapeutic interventions developed by the 3rd ICI 2004 were adopted.

3. Review of evidence on diet and fluids in FI

a) Diet modification

Studies of diet modification primarily used qualitative research methods or surveys and provide background and rationale for examining the effects of diet. A survey about FI and self-care practices administered to community-living elderly people showed that many of the respondents changed their diet and skipped meals as a management strategy for FI. Changing diet was a significantly more common practice among women (35.4%) compared to men (12.5%) [147]. A qualitative interview of women with FI revealed that one avoided eating anything on days they were going to be away from home or restricted the amount eaten while out in public [148]. Many also restricted foods that they thought worsened FI (for example, fried or spicy foods or caffeinated beverages and chocolate), or foods that increased flatulence (for example, cabbage, onions); a few purposely ate certain foods as a therapy to decrease FI (for example, yogurt).

Using a trial and error approach, women with FI often modified their diet based on recommendations for other gastrointestinal problems (e.g., lactose intolerance and IBS) that were available in the professional or lay literature [148]. The effectiveness of these diet modifications was unmeasured and variable. Concerns of diet manipulation are nutritional deficiencies and subsequent poor health. However, Bliss et al. [153] found few significant differences in the nutritional composition of usual diets of persons with FI compared to the usual diets of age and gender matched controls with normal bowel function. The group with FI had a greater intake of carbohydrates, manganese, and vitamin B1.

b) Fluid intake

FI is associated with constipation in nursing homes (see section 2). Approximately 30% of elderly residents in long-term care institutions have faecal impaction, and general clinical recommendations for FI management in these cases are for an adequate intake of fluid to prevent hard stool consistency and constipation. However, there are no empirical data to support the recommendation of increased fluids either for constipation or for FI, and there is no evidence that the diets of patients with FI or constipation are deficient in fluids.

c) Dietary fibre, prebiotics, probiotics, and synbiotics

A prebiotic is a general term describing a food ingredient that is not digested in the human small intestine and thus stimulates the growth and/or activity of...
of one or more types of bacteria in the colon that have the potential to improve the health of the host. Because of its ability to stimulate growth of bacteria in the colon, dietary fibre can be considered a prebiotic. Fructo-oligosaccharides and galacto-oligosaccharides are popular prebiotics. A probiotic is a food supplement containing live non-pathogenic and non-toxic microbes that have the potential to affect the balance of colonic microbes or improve the host’s health. Bifidobacteria and lactobacilli are the most commonly used probiotics, and yogurt which has active microbial cultures can be considered a probiotic. A synbiotic refers to a product that combines a prebiotic and probiotic. Probiotics have been investigated for their potential to improve the health of the host. Because the presence of lactose creates an osmotic shift of intestinal water into the small intestine and speeds transit. In the large intestine, fermentation of lactose by colonic bacteria may result in flatulence, distension, diarrhea, and cramps. However, the majority of adults who have lactase deficiency can tolerate a small amount of lactose in foods [160]. Yogurt is usually well tolerated by lactose maldigesting individuals because the lactose is partially digested by the beta-galactosidase of the bacteria used to ferment the yogurt. However, yogurt has not been found to aid the digestion or tolerance for additional lactose simultaneously consumed with it [161].

Due to its prevalence in approximately two-thirds of the world’s population, hypolactasia is currently regarded as a normal physiological pattern rather than a disease [162]. The prevalence ranges from highs of nearly 100% in some Asian countries and 70% in Italy to lows of 2% in Scandinavia and 15% in U.S. Whites [163]. Malabsorption of fructose and sorbitol results in osmotic diarrhea and adverse symptoms, similar to lactose. A diet reduced in fructose and sorbitol content is suggested for some patients with irritable bowel syndrome to reduce adverse GI symptoms [164].

Caffeine, of which coffee is a popular source, induces a desire to defecate [165-169]. Caffeine has also been observed to stimulate defaecation urgency in some patients with FI [158]. However, regular consumption of coffee was not associated with prevalent or incident FI in elderly men and women [55], and no studies were found on caffeine restriction to improve FI.

Chronic consumption of alcohol has been associated with accelerated gastric emptying and small bowel transit in animal studies whereas a single large dose has an inhibitory effect on these parameters [170-172].

Excessive alcohol consumption leads to injury of the duodenal and upper jejunal mucosa and inhibition of sodium and water absorption. There is an increased prevalence of bacterial overgrowth in the small intestine of alcoholics, which may contribute to loose stools, diarrhea, incontinence, and other GI symptoms [173]. No studies were found in which alcohol restriction was reported to reduce FI.

e) Review of RCT evidence on diet and fluid intake

Two studies were found that met the inclusion criteria for review [174;175]. The methods, strengths and limitations of the studies are presented in Table 5. In the Bliss study, subjects were community-living adults living in the United States with incontinence of loose or liquid stools . The intervention was supplementation with one of two soluble dietary fibres compared to placebo. This study provided level 1 evidence suggesting that dietary fibre can reduce the rate of FI in patients with loose stool [175].

In the second study, subjects were outpatients of a colorectal service in Australia who were incontinent of mucus, liquid, or solid stools. Two combination treatments consisting of an antimotility medication, a diet advice sheet and a fibre supplement or placebo were compared.
This study was not limited to patients with FI of loose or liquid stools (i.e., other types of FI were included), and the study showed no additional benefit of a dietary fibre supplement over use of the antimotility medication, loperamide, for reducing incontinence of flatus, mucus or solid or liquid stool [174]. Differences in the findings of these studies (Table 5) may be explained in part by differences in the interventions, level of control of threats to internal validity, and lack of some analysis data.

4. SUMMARY OF EVIDENCE

Patients consider diet a factor affecting the severity of their FI and they use diet modification as a self-care strategy (level 3 evidence). Dietary fibre supplementation appears to be a safe and tolerable intervention. However, findings from two randomised trials about its effectiveness differ.

5. RECOMMENDATIONS FOR PRACTICE ON DIET AND FLUIDS

- Soluble dietary fibre is recommended for the management of FI associated with loose stool. This recommendation is made despite inconsistent results between two RCTs because the methodology for the positive study was significantly better than that of the other study. (Evidence level 1. Recommendation Grade B).
- Dietary fibre is not recommended as an adjuvant to antimotility medication for managing AI when stools are not loose or liquid. (Evidence level 2 Grade B).
- Patients should be asked about dietary restrictions and meal skipping.

6. RECOMMENDATIONS FOR RESEARCH ON DIET AND FLUIDS

Further studies on the effect of dietary fibre and other diet modifications on FI are encouraged to build a greater body of evidence. Because dietary fibres differ in their chemical composition and properties, future studies are recommended to determine the optimal type and amount of fibre to use for FI. Whether a dietary intervention can augment other behavioural interventions, such as pelvic floor muscle exercises or bowel training, needs further study.
- Role of fibre and fluid in constipation/impaction related FI
- Effect of diet and eating pattern as a management strategy for FI
- Role of caffeine restriction in the treatment of FI and AI

There are several recommendations for methodological rigour in future studies. Theory-based, adequately powered, controlled trials are sought. Studies should control for variability in an individual’s baseline severity of incontinence and any adjuvant therapies. Monitoring adherence to the dietary intervention is recommended. A common set of outcome measures that includes tolerance to diet interventions is recommended. Reporting outcomes of FI in addition to those of AI (which incorporates flatus incontinence) is recommended.

V. BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

1. BACKGROUND

Constipation is a well-established risk factor for FI in children and older people but has not been found to be a consistent risk factor for FI in young and middle aged adults. Frail older people are covered in section 9. The use of rectal medications and enemas is covered in section 6. This section is limited to studies in younger adults.

2. SEARCH

The following keywords were searched: “anal, anorectal, bowel, faecal, fecal, rectal, stool” and “continent$ or incontinent$, “ or “diarrhea, diarrhoea” and the relevant lifestyle or intervention term: bowel$ and train$ or retrain$; digital$ and stimulat$); crede or massage; enema; and suppositor$. The following databases were searched: CINAHL 1982- March, 2008 MEDLINE 1955- March, 2008. The Cochrane library and a recent systematic review of the epidemiology and prevention of urinary and FI was also reviewed [6]. All seemingly relevant abstracts were reviewed, after which salient articles were retrieved and reviewed, and the reference lists searched for further studies.

3. REVIEW OF EVIDENCE ON BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

a) Bowel habit

Expert opinion supports the importance of attempting to establish a regular, predictable pattern of bowel evacuation by patient teaching and adherence to a routine [128;176]. Because peristaltic contractions of the colon that are associated with defaecation increase in frequency following awakening from sleep and following meals [177;178], the period after breakfast is the best time for scheduled defaecation. However, no studies have evaluated the effectiveness of this in young and middle aged adults.

b) Resisting urgency

The sensation of a strong urge to defaecate is frequently associated with diarrhoea, and it is a recognized risk factor for FI in adults [179]. In contrast to urinary incontinence, particularly the overactive bladder syndrome (Committee 14) for which a body of knowledge has developed on the efficacy of bladder...
training techniques (i.e., voiding at specific intervals rather than in response to urge and deferment techniques), the possibility of bowel retraining for resisting urgency to defeate is relatively unexplored. Some biofeedback protocols focus on altering rectal sensory thresholds (see below).

One RCT compared patients who received education, including urgency resistance techniques [158] and dietary advice, to a group of patients who received the same training plus anal sphincter exercises with or without home or clinic biofeedback. There were no significant difference in outcomes [142]. However, this study did not assess the effectiveness of the behavioural training compared to an appropriate control group.

c) Evacuation training

A common factor in the genesis of pelvic floor problems may be chronic straining with perineal descent from constipation; this may lead to pelvic floor damage (direct or neurological) [180;181] and may be associated with pelvic organ prolapse or urinary or FI. In one small study women who reported straining were more likely to develop urogyneacologic symptoms such as prolapse and stress urinary incontinence [182]. However, straining has not been shown to be a risk factor for FI. No studies were identified examining the effect of treating constipation or decreasing straining on preventing or treating FI in non-institutionalised adults.

Clinically, many patients with FI are taught evacuation techniques or are encouraged to use laxatives, enemas or suppositories in an attempt to ensure that the rectum remains empty most of the time, thus giving less chance of FI. This is known to improve continence in children and elderly patients (Section 9), but there is no evidence that it improves FI in young and middle-aged adults.

Committee 10 has reviewed the evidence for digital rectal stimulation and manual evacuation. The use of these techniques to assist complete evacuation in non-neurological populations has not been evaluated.

One RCT of a combination treatment package for FI included training on evacuation techniques and noted that patients reported improved ease of evacuation after treatment [142]. No separate data on FI were presented. No studies were found utilising specific evacuation training to treat FI in younger adults.

d) Behaviour modification

Toilet training with rewards, either alone or in combination with laxatives has been found helpful in children with FI [183]. It is not known if a similar approach might be applicable to adults with learning difficulties or frail older people in institutional settings, although a behavioural approach to such problems has been recommended based on expert opinion [184]. Adults with learning difficulties may respond to formal behaviour modification techniques, but only small case series are currently available as evidence [185]. Similarly there are no controlled studies of training in adults with non-retentive FI [186].

e) Rectal irrigation

Irrigation of the lower bowel has been used for many years to manage both FI and constipation. Surgical construction of a portal for antegrade irrigation is covered in Chapter 17. Various equipment has been used for retrograde irrigation, including a stoma irrigation cone held in place manually against the anus [187], a mechanical pump [188] and more recently purpose-designed anal irrigation equipment [189;190]. Use in FI secondary to spina bifida has been widespread [189].

One single RCT was found in the literature. Rectal irrigation with tap water was found in an RCT to improve bowel management, constipation and FI in patients with problematic bowel management following spinal cord injury [190]. This warrants further evaluation in other populations as uncontrolled case series report possible efficacy in FI without neurological injury [188;191]. Benefit may be maintained with continued use in up to 50% in the long term [192].

f) Combination therapies

It is recognised that in many people, the symptom of FI is the result of a complex combination of disordered anatomy and physiology, stool consistency and gut motility, emotional and psychological status and restricted access to toilet facilities, amongst other factors (see Committee 5). Hence in clinical practice most patients receive a combined approach addressing diet, medications, lifestyle, muscle function and bowel habit simultaneously, depending on the result of initial assessment [193;194]. However, with the exception of one study [142] the few well-conducted studies on the conservative management of FI in adults have usually focused on evaluating a single intervention such as biofeedback, often not specifying what other advice (that might confound the results) was given to patients.

Norton et al compared a combination of conservative measures, including patient teaching, advice on diet, medication titration, and bowel retraining, with the same measures combined with anal sphincter exercises and/or biofeedback [142]. No statistically significant differences were detected between the four groups on any of the outcome measures (including diary, symptom questionnaire, manometry, anxiety, depression and quality of life). Over 50% of those randomised (171 patients) reported improved continence. Of those completing the protocol, 74% felt that they remained improved at one year following the end of treatment. The authors of this study suggest that the most effective element may have been
education and therapist-patient interaction rather than specific interventions.

In children a combination of behavioural training techniques and laxative therapy is as effective alone as it is when combined with biofeedback (183). Anecdotally, laxatives may enhance the effect of behaviour modification alone.

4. SUMMARY OF EVIDENCE

There is very limited evidence in this area. In particular there are:

- No studies in adults with learning disabilities
- No studies in frail elders or Nursing Home patients
- No studies in neurological patients
- One study in adults (combination intervention: [142]): retraining alone is possibly as effective as biofeedback
- One RCT of rectal irrigation in SCI has found benefit for FI, constipation, time spent & QoL [190] (Level of evidence 2)

5. RECOMMENDATIONS FOR PRACTICE ON BOWEL TRAINING

- Attempt to establish a bowel routine (C)
- Urgency resistance training possibly useful for urgency (D: need for research)
- No evidence on behaviour modification methods (D: need for research)
- Digital stimulation and manual evacuation useful in neurological patients (C)
- Rectal irrigation is useful in SCI (B) and has potential in other patients with FI (D)

6. RECOMMENDATIONS FOR RESEARCH

Research is needed in all areas.
Combination studies with urinary incontinence are recommended.

6. DRUG TREATMENT OF FI

1. GOALS

The goals of this section are to identify the drugs and other medical interventions that have been used to treat FI and to evaluate the evidence regarding their efficacy. The medical management of FI has focused exclusively on three mechanisms:

1. Reduction of diarrhoea. Diarrhoea is consistently found to be a strong risk factor for FI (see Section 2 above).
2. Increasing resting anal canal pressure. Low resting anal canal pressure is a risk factor for passive FI, and is commonly seen following some types of anorectal surgery (e.g. sphincterotomy, ileal pouch procedures, abdominoperineal pull-through for imperforate anus).
3. Treatment or prevention of constipation. Constipation is frequently found to be a risk factor for FI, especially in children and the elderly (see Section 2 above).

2. SEARCH METHODS

1. The Medline database and the Cochrane reviews [183;195] were searched for studies in any language and any year through March 2008 which matched the following search terms:
2. “Faecal incontinence” OR “anal incontinence” AND “drug” OR “medical management” OR “medical treatment.”
3. “Faecal incontinence” OR “anal incontinence” AND “loperamide” OR “diphenoxylate.”
4. “Faecal incontinence” OR “anal incontinence” AND “laxative” OR “polyethylene.”
5. “Faecal incontinence” OR “anal incontinence” AND “phenylephrine gel.”

Additional articles were identified by examining systematic reviews [195-197].

3. REVIEW OF EVIDENCE ON MEDICATION AND FI

a) Treatment of diarrhoea-associated FI with antidiarrhoeal drugs.

1. LOPERAMIDE AND DIPhenoxylate

The most extensively tested drug treatment for diarrhoea-associated FI is loperamide. We identified 6 studies in adult subjects [174;198-202] and 3 studies in children [203-205]. These studies all have methodological weaknesses including small sample sizes and use of crossover designs or they are case series. These studies generally support the efficacy of loperamide for decreasing diarrhoea-associated FI. Three of these studies are briefly summarized below:

Palmer and colleagues [198] compared loperamide (average of 4.6 mg per day) to codeine (average of 103 mg per day) and diphenoxylate (average of 12.5 mg per day) in 30 patients with diarrhoea, of whom 19 had FI prior to treatment. However, FI was not the primary outcome measure. Loperamide was superior to diphenoxylate and similar to codeine with respect to decreased stool frequency, improved stool consistency, and reduced side-effects. Although not statistically significant, there was a trend for less FI while taking loperamide compared to diphenoxylate.

Haeford and colleagues tested diphenoxylate against placebo in 15 patients with diarrhoea-associated FI and reported a tendency for decreased FI.
Mechanism of action in this patient population.

benefit for diarrhoea [209] and a worsening of FI [210] pelvic cancer [208]. However, subsequent large sucralfate might reduce diarrhoea secondary to stomach lining. An early study suggested that aluminium hydroxide used primarily for the treatment benefit for treating FI. Sucralfate is a formulation of and other tricyclic antidepressants are of possible complexes.” This study suggests that amitriptyline pressure and decreased numbers of “rectal motor authors attributed the benefits to increased anal resting became continent and 3 reported improvement. The authors were selected for study because they had previously been found to soil while taking orlistat. In this study, loperamide decreased soiling and FI and increased resting anal canal pressure. Lauti’s group [206] compared loperamide plus fibre supplementation to loperamide with a low fibre diet and placebo fibre supplement in the first adequately powered study. This was a double-blind crossover study with order of treatments counterbalanced. Results showed a significant improvement in continence relative to baseline in both groups, but the addition of fibre to loperamide did not increase benefit. This suggests that loperamide may be more effective than fibre supplementation alone for the treatment of diarrhoea-associated FI. An earlier study by Bliss and colleagues [175], which is reviewed in Section 4, showed that fibre supplementation with either psyllium or gum agar improved diarrhoea-associated FI more than placebo.

2. OTHER ANTIDIARRHOEAL DRUGS

Santoro and colleagues [207] carried out an uncontrolled study of the tricyclic antidepressant, amitriptyline, given 20 mg at bedtime, in 18 patients with FI; diarrhoea was not required. Thirteen of 18 became continent and 3 reported improvement. The authors attributed the benefits to increased anal resting pressure and decreased numbers of “rectal motor complexes.” This study suggests that amitriptyline and other tricyclic antidepressants are of possible benefit for treating FI. Sucralfate is a formulation of aluminium hydroxide used primarily for the treatment of duodenal ulcers; it has the property of coating the stomach lining. An early study suggested that sucralfate might reduce diarrhoea secondary to radiation proctitis in patients receiving radiotherapy for pelvic cancer [208]. However, subsequent large randomized controlled trials have shown no significant benefit for diarrhoea [209] and a worsening of FI [210] in this patient population.

Mechanism of action Three possible mechanisms of action have been identified in the these studies of the drug treatment of diarrhoea-related FI: Loperamide, diphenoxylate, and amitriptyline appear to work in part by decreasing bowel movement frequency through an effect on motility and absorption. Fibre supplements (reviewed in Section 4 above), on the other hand, work by binding more water into the stools. Resting anal canal pressures were reported to be increased in response to loperamide [199;200] and amitriptyline [207].

b) Increasing anal canal pressure in patients with passive FI

A subgroup of patients with FI have passive incontinence, defined as FI that is not preceded by a sensation of urgency to defecate and that occurs without awareness. This is believed to be related to decreased resting pressure in the anal canal due to an impaired internal anal sphincter and/or to decreased sensation for rectal distension. A specific aetiology for passive FI is the patient with a colectomy (usually for ulcerative colitis) with a surgically constructed ileal reservoir connected to the anal canal [87].

1. PHENYLEPHRINE GEL

Phenylephrine gel, an alpha-1 adrenergic agonist, has been investigated for the treatment of passive FI in several studies [211;211-215]. In an initial study of 36 patients with intact sphincters, no significant benefit was seen [214]. Two subsequent studies [211;215] suggested a benefit of phenylephrine gel, but a recent randomized controlled trial in 35 patients with passive incontinence secondary to low anterior resection failed to show a benefit [213]. Thus, the clinical utility of phenylephrine gel (if any) may be limited to patients with passive incontinence associated with ileal pouches.

L-erythро methoxamine gel, an alpha-1 adrenoceptor agonist similar to phenylephrine, has also been shown in two proof-of-concept studies to increase internal anal sphincter resting pressure [216;217], although no clinical trial data are available as yet.

2. VALPROATE SODIUM

The gamma-amino butyric acid transaminase inhibitor, valproate sodium, also increases anal canal resting pressure. It was compared to placebo in a double-blind, randomised crossover study [218] in 17 patients with diarrhoea-related FI secondary to colectomy and ileoanal anastamosis. The drug decreased FI episodes and stool frequency relative to baseline and increased anal canal pressure, whereas placebo did not have these effects. In a second randomized controlled trial by the same investigators [219], 12 patients with ileal pouches were treated with valproate sodium or placebo. There was a significant improvement in anal canal pressures, pouch capacity, and continence. Therefore, valproate sodium is of possible benefit in this population.

c) Drug treatment of constipation-associated FI

Constipation-associated FI, sometimes referred to as “overflow incontinence”, occurs more frequently at the two ends of the lifespan. The prevalence of FI in children is estimated to be 0.8% [220] to 3% [221] and in 35% [63] to 96% of cases, FI in children is associated with constipation. FI occurs in 46% [222] to 47% [12] of nursing home residents and is more common in those with constipation [223]. However, the proportion of faecally incontinent nursing home residents whose FI is attributable to constipation is not known. Constipation-associated FI is also common in patients with spinal cord injury, occurring in an estimated 33% [106].
Constipation-associated FI in nursing homes is often treated with the prescription of daily or frequent laxatives. However, we found only two RCTs which tested the effectiveness of laxatives for treating FI associated with constipation in adults. Ryan [224] randomised 87 new admissions to a single nursing home to receive either 15 ml daily of sorbitol for up to 15 days or routine care without the use of a laxative. Patients were enrolled whether or not they had constipation or FI. The outcome measures recorded by nurses were amount of nursing time required for the care of FI and amount of soiled linen. Patients treated with sorbitol were found to have significantly less soiled linen, and they tended to require less nursing time. Limitations of the study included (a) analysing the aggregate amount of soiled linen used by each group rather than the proportion of the subjects in each group who had FI; (b) failure to control for expectancy by providing a placebo treatment to members of the control group; and (c) failure to include all randomised subjects in the data analysis, i.e. failure to use an intention to treat analysis.

A second study [225] compared daily enemas to no treatment in 206 nursing home residents who had FI and documented constipation. This was an open label RCT. Results showed no difference between groups either for frequency of FI or for amount of soiled linen. However, post hoc subgroup analysis showed that patients with complete rectal emptying by digital examination exhibited a significantly greater improvement than the group that continued to have a faecal impaction. Strengths of this study were the large sample size, randomisation, strict inclusion criteria, and assessment of whether the enema regimen in fact eliminated faecal impaction. A weakness was that the post hoc analysis of the physical examination data suggest that the trial is not interpretable since the daily enema regimen did not eliminate faecal impaction in most patients.

A double-blind RCT testing the effectiveness of the prokinetic (motility stimulant) drug cisapride in paediatric FI found no evidence for efficacy [226] and adverse events led the US Food and Drug Administration to restrict access to this drug. An alternative prokinetic drug, tegaserod, has been approved for the treatment of chronic constipation in adults, but has not been tested for its effectiveness in patients with constipation-associated FI.

Several trials [227,228], including one high quality RCT [229] have compared laxatives alone to the combination of laxatives plus biofeedback in children with constipation-associated FI. For this indication, biofeedback is designed to teach the patient to relax the pelvic floor muscles during attempts to defecate in order to overcome a tendency to paradoxically contract these muscles and to obstruct defecation. The RCT by van der Plas and colleagues [229] showed that combined treatment was associated with a higher success rate at the end of training (39% vs. 19%), but by follow-up 12 months later, there were no differences between groups.

Other studies support these findings by showing either no difference between the laxative only group and a biofeedback group [227] or faster acquisition of continence in the biofeedback group but no long-term difference in success rate [228].

These trials suggest that laxatives alone are as effective as biofeedback for constipation-associated FI in children in the long term, but they were not designed to show that laxatives are superior to placebo or to no treatment.

4. SUMMARY OF EVIDENCE ON MEDICATION AND FI

- Loperamide is useful for diarrhoea-associated FI. There is some evidence that the loperamide may be superior to diphenoxylate (level 2 evidence).
- There is a possibility that medication may improve FI associated with faecal impaction in a nursing home population if impaction is resolved.

5. DRUG TREATMENT OF FI: RECOMMENDATIONS FOR CLINICAL PRACTICE

- Treat FI with diarrhoea with anti-diarrhoeal medication (C): titrate the dose to individual response (C).
- We are unable to recommend sphincter modifying drugs (D).
- Use oral or rectal laxatives/evacuants to treat constipation-associated FI (C): no evidence on the most effective agent. Need to confirm impaction is resolved (C).
- For constipation-associated FI, there is level 2 evidence suggesting that daily or more frequent oral laxative regimens may be effective for the treatment of constipation-associated FI in nursing home residents [224] and children [230], but there are conflicting data [225,231].

6. DRUG TREATMENT OF FI: RECOMMENDATIONS FOR RESEARCH

- Additional, well-designed studies are needed to validate the common clinical practice of using laxatives to treat constipation-associated FI.
- There is a need for further research on preparations, doses and combination therapies for all types of FI and all patient subgroups.
VII. BIOFEEDBACK AND/OR ANAL SPHINCTER / PELVIC FLOOR MUSCLE TRAINING

1. BACKGROUND

Biofeedback can be defined as the use of an instrument that delivers a concurrent measurement of selected biological responses to enable the individual to alter his/her physiological response in directions associated with improved function [232].

The earliest reported application of biofeedback to treat FI used a simple pressure device in the anal canal to reinforce external anal sphincter (EAS) contraction [233], a procedure somewhat analogous to the vaginal perineometer that was used by Kegel to treat stress urinary incontinence [234]. However, the seminal biofeedback procedure [235] for FI, which was followed in a series of studies, used a 3-balloon manometry probe to reinforce changes in 3 distinct physiological variables rather than just EAS contraction. The responses that were reinforced with this protocol included: (a) the perception of sensory cues associated with rectal distension and potential loss of stool; (b) a short-latency EAS contraction; and (c) inhibition of activity that would increase rectal pressure (i.e. contraction of the abdomen rectus and diaphragm). The overall goal of this protocol was to strengthen the presumed EAS reflex contraction that normally counteracts the internal anal sphincter inhibitory response to rectal distension. However, reinforcement for EAS contraction was contingent upon maintaining stable rectal pressure, because increases in rectal pressure during stool urgency can overcome relative sphincter closure pressure, and thus would be counterproductive to retention. Subsequently, the EAS response to rectal distension was determined to be a learned, rather than an involuntary response. As a result, the theoretical basis for the use of operant conditioning (biofeedback) in the treatment of bowel disorders was established [236].

There is no standardisation in the biofeedback literature for FI. Studies use different instrumentation, training procedures, adjunctive strategies, samples, outcome measures, and follow-up periods. Therefore, straightforward comparison of study outcomes and statistical analysis of multiple outcomes is difficult. Most biofeedback protocols can be placed into one of three general categories on the basis of the procedures used for training and include:

1) Strength training, defined as the reinforcement of anal sphincter and/or pelvic floor muscle (PFM) contraction to improve EAS strength, speed or endurance without attention to sensation.

2) Sensory training, defined as the reinforcement of heightened sensitivity to stepwise reductions in rectal distension volumes without emphasis on improvements in sphincter strength.

3) Coordination training, enhancing deliberate voluntary anal contraction in response to rectal filling and thus countering the effect of the recto-anal inhibitory reflex in lowering anal pressure, usually combined with the reinforcement of rectal sensitivity, a rapid EAS response in the absence of rectal pressure changes and also sustained EAS contraction to improve sphincter strength.

These approaches can be combined. Variations of these procedures include the reinforcement of tolerance to progressively larger volumes of rectal distension and control of urgency. Instrumentation used to measure and reinforce the changes in biological activity include pneumatic and perfusion manometry, surface electromyography (EMG) and transanal ultrasound. Some workers have suggested the use of a multivariable EMG protocol that mirrors the manometric protocol by substituting surface abdominal EMG electrodes for the rectal pressure balloon to measure extraneous abdominal muscle wall contraction that is associated with increases in rectal pressure. An EMG probe is placed within the anal canal or vagina to measure external anal sphincter or pelvic floor muscle activity.

Historically, the use of pelvic floor muscle training (PFMT) without biofeedback has seldom been used as a primary treatment for FI, unlike its application for UI where PFMT has been recommended as an intervention prior to the use of biofeedback. For FI, most exercise protocols have used PFMT secondarily to augment the biofeedback protocol.

2. LITERATURE SEARCH

A search of Medline, Cinhall and Embase (1970-April 2008) was conducted using the search terms “biofeedback”, “exercise therapy”, “pelvic floor” and “fecal incontinence”, limited to randomised controlled trails (RCTs) in adults. The search was supplemented by a crosscheck of citations in the identified papers and other systematic reviews.

A Cochrane review [237] of randomised or quasi-randomised studies found 11 eligible studies that used biofeedback and/or PFMT to treat FI. Our current review found three additional studies [238-240]. A total of 14 studies were therefore identified by this search. One study was published in a very brief German abstract only, with no extractable data [239], and a further two were in abstract form only [240:241] and so were excluded, leaving 11 studies for the review (Table 6). In addition, a large number of uncontrolled studies were identified. These are only quoted where they serve to augment the evidence.
<table>
<thead>
<tr>
<th>Author, year country</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis 2004 UK [3]</td>
<td>38 females undergoing anal sphincter repair Mean age 60 (range 26-78)</td>
<td>Manometric BFB starting 3 months after surgery: 1 hour/week for 6 weeks (exercise and sensory training) N = 14 completed</td>
<td>Usual care N = 17 completed</td>
<td>31 completed at 12 months after surgery. VAS for subjective outcome: NSD QoL: NSD Score: NSD Manometry: NSD</td>
<td>No ITT analysis. Scores, satisfaction and manometry improved in both groups compared to 3 months post-surgery. Paper focuses on before-after changes within groups and does not report detailed differences between groups.</td>
</tr>
<tr>
<td>Fynes 1999 Ireland [249]</td>
<td>40 females with obstetric related FI. Mean age 32 years (range 18-48).</td>
<td>Weekly anal EMG BFB + electrical stimulation (20 Hz &amp; 50 Hz) with physiotherapist (&quot;augmented BFB&quot;).</td>
<td>Weekly vaginal manometric BFB with nurse specialist.</td>
<td>At end of 12 weeks treatment: Score: improved more in augmented group (p = &lt;0.001)</td>
<td>No ITT analysis. Paper focuses on before-after changes within groups and does not report detailed differences between groups.</td>
</tr>
<tr>
<td>Ilnyckyj 2005 Canada [371]</td>
<td>23 females with regular and frequent FI. Mean age 59 years (range 26-75). Excluded IBS.</td>
<td>Education + manometric BFB n = 7 completed</td>
<td>Education + PFMT n = 11 completed</td>
<td>18 completed. Success = no FI in last week of study: BFB 6/7 (86%) PFMT 5/11 (45%) p = 0.2</td>
<td>No ITT analysis. Underpowered to detect a difference?</td>
</tr>
<tr>
<td>Latimer 1984 Canada [246]</td>
<td>8 subjects (4 children) range 8-72 years</td>
<td>4 phases: A: one month diary B: PFMT with balloon and verbal feedback C: rectal sensory training D: 3 balloon BFB</td>
<td>Varied order of phases</td>
<td></td>
<td>Complex design Underpowered to detect a difference</td>
</tr>
<tr>
<td>Author, year country</td>
<td>Population</td>
<td>Intervention</td>
<td>Control</td>
<td>Outcome</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>Miner 1990 UK [245]</td>
<td>25 consecutive patients with FI. 8 men. Age range 17-76 years.</td>
<td>1. Rectal sensation training 2. Strength or coordination training (crossed over)</td>
<td>1. Sham rectal sensation training 2. Coordination or strength training (crossed over)</td>
<td>End of active vs. sham: active reduced FI.</td>
<td>No ITT analysis. Complex cross-over design and small sample size. Both groups improved: + 24 month follow up: improvement maintained</td>
</tr>
<tr>
<td>Naimy 2007 Norway [238]</td>
<td>49 females after 3rd or 4th degree obstetric tear (referred or identified via survey). Mean age 36 (range 22-44)</td>
<td>BFB: EMG, anal probe, home exercises (fast, 10 second and endurance squeezes). 20 mins, twice daily at home for 8 weeks + 2 sessions with therapist</td>
<td>Electrical stimulation at 30-40 Hz, pulse width 200 µs, limit at 80mAmp, anal probe 20 mins, twice daily at home for 8 weeks + 2 sessions with therapist</td>
<td>40 completed. Score: NSD QoL: NSD Both groups subjectively improved,</td>
<td>No ITT analysis. Compared median changes pre-post treatment between groups rather than direct comparison. Both groups improved subjective perception of control, but no changes shown in other parameters. Mostly mild FI: limits potential to benefit?</td>
</tr>
<tr>
<td>Solomon 2003 Australia [252]</td>
<td>120 patients who had failed diet and medical management. Mean age 62 years 13 men.</td>
<td>5 monthly 30 minute sessions. 3 groups: 1. PFMT taught digitally 2. PFMT + anal ultrasound BFB 3. PFMT + manometric BFB</td>
<td>See groups</td>
<td>102 completed. End of treatment: Score: NSD QoL: NSD Manometry: NSD Subjective: NSD</td>
<td>No ITT analysis. All groups improved equally and significantly.</td>
</tr>
<tr>
<td>Whitehead 1985 USA [244]</td>
<td>18 older patients recruited from clinics or newspaper advert. Mean age 73 years (range 65-92). 3 men, 6 double incontinence.</td>
<td>4 weeks habit training + PFMT (50 squeezes per day for 10 seconds)</td>
<td>4 weeks habit training alone</td>
<td>End of treatment: No statistical analysis given of difference between groups</td>
<td>No ITT analysis. If still incontinent after 4 weeks, all received BFB.</td>
</tr>
</tbody>
</table>

Key: NSD = no statistically significant difference  
ITT = intention to treat analysis
from RCTs, for example on possible mechanisms of efficacy or sustainability of effect. All RCTs that included at least one arm where patients were given instrumented biofeedback or instructions/coaching in PFMT to treat FI in adults were eligible for inclusion.

3. REVIEW OF THE EVIDENCE

The 11 studies included a total of 592 patients. The median sample size was 40 (range 8-171). Only one study mentions an intention to treat analysis [142], three trials did not mention number of drop-outs. Of those that do mention drop-outs, a total of 18% of recruited subjects failed to complete.

The majority (90%) of patients in the 11 RCTs were female. Ages ranged from 8-92 (studies primarily of children were excluded). Aetiology and symptom severity was highly heterogeneous. However, some studies did select subjects according to specific problems such as obstetric injury [238;242;243] or older people [244] or following sphincter repair (3). All studies were from a single hospital centre. All but one [238] were from English-speaking countries. Methodological quality was variable, and in many cases unclear.

Two studies attempted a component analysis to determine whether rectal sensory training or EAS strength training was more effective in reducing FI. They concluded that the primary mechanism responsible for symptomatic improvement was increased rectal sensitivity [245;246]. However, both studies were small, underpowered, and involved a complex cross-over design which makes analysis difficult due to carry over effects [247]. Also limitations in the applied strength training procedures preclude valid comparisons of strength vs. sensory training methods in these studies.

Other studies have investigated the additional benefits of aspects of therapy. In a between-group design, one study [248] compared out-patient intra-rectal EMG strength training to EMG plus sensory training using an intra-rectal balloon, EMG plus home biofeedback training, and EMG, sensory training plus home biofeedback. No added benefit was found when the more comprehensive protocols were used, but small group sizes make this study inconclusive.

One study using a between-group design of 4 different treatments, compared management and advice that included the use of diet advice, urge resistance training and anti-diarrhoeals to the same protocol plus: EAS exercise; EAS exercise and clinic biofeedback; or EAS exercise, biofeedback and the use of a home trainer [142]. There were no statistically significant differences between the four groups.

In addition to diet and bowel management, another adjunctive treatment that has been used with biofeed-

back is electrical stimulation [243;249]. The first of these studies found some benefit from the electrical stimulation (however the biofeedback methods and therapist were also different between groups). The second study found no difference with or without electrical stimulation.

Some studies have added home biofeedback equipment [142;248]. There was no evidence of additional benefit over clinic biofeedback.

Most studies report that patients are instructed in home exercises but many do not specify the precise instructions given to the patients. Some studies state that subjects were simply instructed to contract the EAS with any feeling of rectal distension at home, while others provided structured sphincter exercise programmes. Some have taught exercise with biofeedback or digitally, while others have not mentioned the method of teaching. There was no measure of compliance with exercises. A relationship between long-term improvement and continued exercise has not been established. In one uncontrolled study, [250] only 26% of the subjects reported that they continued to perform PFM exercise at 12 month follow-up even though all subjects who improved initially (71%) maintained the gains at follow-up. No controlled study has examined intensity of follow-up, although one case series suggests that telephone follow up can be as effective as face-to-face clinic visits [251].

One study [248] compared 4 different biofeedback protocols but did not have a non-biofeedback control group. Before patients were randomised to the different biofeedback protocols, they underwent medical and bowel management but the time period of initial intervention was unspecified. Although there was an overall 74% reduction in stool incontinence after biofeedback, no difference in effect was found between the different protocols. However, interpretation of effects was hampered by small group size.

Another study compared manometric biofeedback, anorectal ultrasound biofeedback and sphincter exercise taught with digital examination alone [252]. All groups showed modest improvements in bowel control with 70% of the subjects reporting at least some clinical improvement. Improvements in bowel control were associated with modest changes in anorectal measures. However, neither manometric or ultrasound biofeedback provided added benefit to digitally taught sphincter exercise on any of the nine outcomes measures.

Another RCT [142] used four groups to compare the effects of a behavioural treatment from a specialized nurse that included advice on bowel management, diet, urgent control and the use of anti-diarrhoeal medication, to the same behavioural management but with the addition of: sphincter exercises; exercises plus clinically administered biofeedback; or exercises, clinical biofeedback and home biofeedback. Each
group received a median of five (range 1-9), 45-90 minute treatment sessions. No difference was found between groups on ratings of bowel control or physiological measures. These findings suggest that biofeedback did not provide any additional benefit to behavioural and medical management. When outcomes were collapsed across all subjects, modest reductions in symptoms of 54% and 53% were reported to occur in the advice and biofeedback groups, respectively. Although manometric indices of sphincter function improved across all groups, an unexpected and unexplained numerical decrease in squeeze pressure was reported in one of the biofeedback groups, and minimal change was reported in the other biofeedback group. However, the outcome analysis was appropriately conducted on an intention to treat basis. In this study a 20% drop out rate was reported, which is consistent with other studies that have also reported drop out rate. But unlike Norton, most studies have reported outcomes only on subjects completing treatment rather than on an intention to treat basis. As result of the more stringent analysis, the Norton outcomes appear to be lower than many of the other reports.

While there was little difference between groups in the RCTs, it should be noted that on a before-after analysis, all studies showed at least some improvement in patient symptoms or other parameters. This is consistent with the majority of case series. There are over 70 uncontrolled studies of BFB and/or PFMT for FI. All but one [253] report benefit to patient symptoms and a variety of other outcome measures. Most studies report an overall response rate that combines improvement and cure rates. Reported improvement ranges from 0% [253] to 100% [254], with the majority being in the range of 50-80% [255;256].

**a) Long-term follow-up**

There are few long term follow up studies. One RCT found little fall-off in efficacy at one year [142]. One uncontrolled study found that a majority of patients maintained, and in some cases exceeded, improvements reported immediately after treatment [247]. The long-term positive outcome in this study was attributed to the 83% home exercise compliance during the active treatment phase. An uncontrolled study reports that 63% of patients were continent at one year [257] and another study reported that most responders are still improved at 5 years [258].

**b) Mechanism of treatment benefits**

Many studies have reported changes in physiological variables such as resting and squeeze pressures and changes in rectal sensory threshold volumes as an outcome of biofeedback training. A few studies also have reported changes in the duration of EAS contraction [142] with researchers concluding that the ability to sustain an EAS contraction is more important than maximum squeeze pressure. Two uncontrolled studies found that it was the subjects who learned to extend the duration their sphincter contraction who developed continence [259;260] after biofeedback training. This notion was supported by a study that compared the EAS fatigue rates of healthy controls to patients with constipation, seepage and stool incontinence and found that the EAS fatigue rate in incontinent patients was significantly greater compared to healthy controls and those with seepage [261].

Several studies report that improved rectal sensation is most consistently linked to improvements in continence as a result of biofeedback training [245;246;262]. Conversely, changes in sphincter strength are not consistently found to be associated with reductions in incontinence [245;263-267] and in two studies, squeeze pressure was found to increase even in those patients that did not improve in bowel control [250;268]. These inconsistencies have lead to questions regarding the mechanism(s) presumed to be responsible for symptom reduction as a result of biofeedback training [269]. They may also call into question the use of such proxy measures of patient improvement, as symptoms are only loosely related to physiology test findings.

**c) Identifying people likely to benefit from biofeedback**

There are no established criteria that might predict which patients would most likely benefit from biofeedback or exercise therapy. One case series found that in addition to a rectal sensory threshold of 50ml or less, a lower EAS and IAS response threshold and an urgency threshold less than 100ml were associated with better outcomes after biofeedback [250]. Another study noted that positive outcomes were associated with those patients 55 years and older and having normal defecation patterns, while poorer outcomes were associated with those younger than 55 and having abnormal evacuation patterns [270]. One study noted that the need for more than 3 biofeedback sessions and a poor early response to biofeedback predicted poor long-term improvement at follow-up [258].

Several reports noted that improvements were not associated with the presence or absence of anal sphincter defects found with ultrasound [142;261;271;272], but one study found that less robust improvements were obtained in those having passive incontinence rather than urgency incontinence [271]. In the one study that found that no functional improvement was obtained with biofeedback, all subjects had severe pudendal nerve neuropathy and absent sensation for call to stool [253]. Another study found that patients with spinal cord lesions were least likely to respond to treatment [273]. On the other
hand, one study did find that subjects with pudendal neuropathy could improve bowel control with biofeedback but were less likely to show improvement in EAS strength [266]. However, the effects of bowel management strategies were not controlled. Currently, there is little evidence that shows a relationship between pre-treatment anorectal function as measured by manometry and biofeedback outcomes, with the exception of rectal sensitivity which, if found to be greater than 100ml before treatment, is associated with a poor response to biofeedback [273]. As a result, some studies have excluded patients who have a rectal sensory threshold greater than 100 ml.

Unsurprisingly, one case series has found that those who completed treatment were most likely to benefit [274]. The latter study also found that patients who were older, female and had more severe incontinence were most helped, but this may be compounded by the greater likelihood of these patients completing treatment. One further study found that older and less obese patients were most likely to benefit [142].

d) Comparison of PFMT and BFB

Given that PFMT without BFB has been accepted as a valid treatment for UI, similar protocols may potentially improve FI as well. Two studies that have directly examined the effects of pelvic floor muscle training on FI report similar outcomes [142;252]. When PFMT was used in addition to a comprehensive behavioural management programme, no added benefit was obtained [142]. Both studies found PFMT alone to be as effective as BFB combined with PFMT.

In a RCT which recruited women with urinary incontinence three months postnatally, the intervention group reported less FI at 12 months follow-up [275], although the effect does not appear to last at six years [276]. However, in this study, the effect of PFMT was not studied separately from education and patients were not recruited with FI as their primary problem. Given the limited data available, there is an obvious need to investigate the effectiveness of PFMT alone on FI because there are no known risks associated with its application and its cost is low relative to biofeedback.

4. SUMMARY OF THE EVIDENCE: BIOFEEDBACK AND EXERCISES FOR FI

In general, the outcomes reported from uncontrolled biofeedback studies for FI have been favourable. However, most studies have been small and have a multitude of methodological flaws that include inadequate descriptions of subject characteristics and procedures, the use of heterogeneous samples, and limited follow-up data. Only a handful of the studies have made efforts to control for non-specific effects. In contrast to the mostly favourable outcomes reported in uncontrolled studies, randomised controlled trials have generally found no additional benefit when biofeedback was added to either a comprehensive behavioural and medical management programme [142] or to digitally taught sphincter exercises. There are limitations in all studies to date.

We still lack precise knowledge of the mechanisms responsible for improvement when biofeedback or exercise is used to treat FI, and we do not yet understand the extent to which any specific biofeedback protocol alters parameters of anorectal function. The exception is rectal sensitivity, which is the single physiological parameter that has been reported to most consistently improve with biofeedback. However, not all subjects who show improvements in rectal sensitivity also develop continence. Thus, good rectal sensitivity can be considered a necessary but not sufficient requirement for reliable continence. In contrast to rectal sensation, EAS strength has not been shown to consistently improve with biofeedback even when protocols have been directed to improve EAS function. Hence lies an essential empirical question for the field that must be answered before we can determine whether biofeedback is a useful tool in the treatment of stool incontinence.

For, if changes in sphincter function are not observed when the stated goal of a biofeedback procedure is to improve sphincter strength, the validity of the protocol can be questioned and accordingly, conclusions based on the outcomes must be limited. Protocols then should be appropriately altered to achieve the stated goal of changing EAS function. As in the field of psychophysiology from which biofeedback has evolved, a test of biofeedback effectiveness for any disorder cannot be accepted as an adequate evaluation of the treatment without evidence that the targeted physiology has been changed to a valid criterion of function [277].

Accordingly, any biofeedback protocol for FI should first be shown to have altered some target aspect of anorectal or bowel physiology, before it is be tested as a treatment. Additionally, measurement of these functions has yet to be standardised and validated. Without validation of the biofeedback procedure itself, the analysis of group effects tends to be primarily a test of non-specific effects.

In summary, the primary problems in the biofeedback and pelvic floor muscle literature are:

1. Biofeedback studies for FI have employed a variety of methodologies that range from rectal sensitivity training to sphincter strength training but without standardisation of methodology or outcome evaluation tools.

2. Although uncontrolled studies using biofeedback for FI have reported mostly favourable outcomes, results from larger RCTs have mostly not demonstrated a benefit of biofeedback over
comprehensively administered behavioural and medical management or sphincter exercises alone.

• Only one study has found significant differences between groups [242]

• Rectal sensation may be more important than sphincter strength [245;250]

• Changes in sphincter strength are not necessarily linked to symptoms

• There are few established predictors of outcome of biofeedback or exercises (rectal sensation, IBS, age, weight, sphincter disruption; each have weak or contradictory evidence as predictors)

• PFMT may be as effective as BFB [142;252]; advice alone may be as effective as PFMT [142]

• More than 50% of patients in all groups improve

5. RECOMMENDATIONS FOR PRACTICE

Because recent RCTs have raised questions as to whether biofeedback provides a specific benefit relative to education and good clinical management despite a large body of uncontrolled studies supporting its efficacy, the consensus of the committee is that it is possibly effective but currently unproven. This reinforces the case for using maximal education, lifestyle and dietary interventions before PFMT or BFB, as recommended by recent national guidelines in the UK [278].

• PFM exercises are recommended as an early intervention in the treatment of FI as part of a conservative management bundle of interventions, based upon low cost and morbidity and some, although limited, evidence suggesting efficacy (C).

• The use of biofeedback as a treatment for FI is recommended after other behavioural and medical management has been tried if inadequate symptom relief obtained, given the numerous positive outcomes from uncontrolled trials, limitations in the current RCTs and low morbidity associated with its application. (C).

6. RECOMMENDATIONS FOR RESEARCH

There is a need to conduct further RCTs to determine whether specific biofeedback and pelvic floor muscle exercise protocols can alter the hypothesised target physiological parameters of ano-rectal function (muscle strength and/or sensation) with concomitant changes in bowel control.

• Clear description of modalities and evaluation of different elements of BFB

• Adherence monitoring

• Standardisation of outcome measures

• Long term follow up

• Robust patient-focused outcome measures

• Understanding of physiological effect and relationship to symptom change

• Work on clinically meaningful improvement and distinguishing cure from improvement rates

• The exploration of possible synergies between urinary and faecal incontinence interventions and evaluations should be considered in study designs

VIII. EXTERNAL ELECTRICAL STIMULATION FOR FI

1. BACKGROUND: THE PHYSIOLOGICAL BASIS FOR ELECTRICAL STIMULATION

Sacral nerve stimulation through surgically implanted electrodes and stimulators have been found to be effective for reducing the severity of FI in randomized controlled trials [279;280]. These studies, which are reviewed in detail by Committee 17, provide an impetus for identifying electrical stimulation protocols for the treatment of FI that are less invasive than other surgical approaches such as sphincteroplasty and injection of bulking agents. This section reviews the use of external (surface) electrical stimulation.

Anal electrical stimulation was first described for treatment of FI over 40 years ago, firstly as an implanted stimulator [281] and later as needle EMG stimulation [282]. As technology developed, more comfortable surface electrodes became available either as skin or intra-anal plug devices with a battery box. ES may be provided by a mains-powered machine or by a portable battery-powered stimulator. The advantage of a small device is that it is easier for the patient to use on a daily basis. Development of vaginal and anal electrodes make it possible for the patient to sit, stand or move during a training programme. There is at present no experimental evidence upon which to select optimum electrical stimulation parameters for different symptoms and clinical conditions.

An electric current of sufficient amplitude will excite nerve and muscle tissue in its field. In addition, the current will alter cell membrane potentials and therefore exert an influence on all living cells. The full extent of this influence is not known but studies have shown an increase in axonal budding following denervation and an increase in vascularisation and muscle bulk when the stimulating electrodes are placed in an area of striated muscles [283]. Also normalisation of the reflex activity of the bladder by using electrical stimulation (ES) has been reported [284]. In an animal model (dog) anal stimulation significantly increased anal sphincter pressure and rectal compliance without changing recto-anal inhibitory reflexes. Vaginal
stimulation also reduces rectal tone and increases anal pressure. Pressure increases are dose-dependent.

Maintenance of continence requires volitional cortical control which is dependent upon the sensory feedback from the ano-rectum [285] and the ability to sense rectal distension and impending defecation and to relax or contract the striated muscles of the pelvic floor [286]. Reduced rectal sensitivity is common in patients with constipation and/or FI [287]. The motor control of the pelvic floor muscles is a learned voluntary response albeit often at a subconscious level [236;288].

Functional electrical stimulation activates both sensory and motor axons. The sensory axons send signals to the brain and it is thought may cause plastic changes in the representational area of a body part. The result of this is enlargement of the representation and improvement of awareness of the stimulated body part. This leads to better control of movements. In theory ES may therefore reinforce weak functional signals that come from the pelvic floor musculature during the treatment [289], although this remains to be demonstrated experimentally.

Stimulation parameters such as stimulation frequency, pulse width, on:off ratios, and current intensity are very important as it is possible to cause fatigue and other problems by using incorrect parameters, too long a treatment time or too high an intensity.

2. SEARCH

The following databases were searched for controlled trials up to April 2008 using the terms “faecal/fecal incontinence” and “electrical stimulation”: Scopus, Medline, Embase, Cinahl. The reference lists of relevant studies and the Cochrane review [290] were also considered.

3. RESULTS

Six controlled studies of ES in FI were found (Table 7).

The first controlled study in forty women with obstetric-related FI [249] randomised patients to anal biofeedback and pelvic floor exercises with adjunctive electrical stimulation, or vaginal biofeedback and pelvic floor exercises without electrical stimulation (carried out by a different therapist). Both groups improved symptomatically, with no difference in symptoms between the groups. The stimulation group also improved manometric pressures. However, electrical stimulation was not the only variable in the study, and there was no follow up beyond the 12-week study period. Another attempted controlled study in patients who had FI following repair of obstetric third degree tear, abandoned stimulation because it caused discomfort [291].

Mahony et al studied a group of 60 women with FI secondary to obstetric trauma and compared 12 weeks of anal EMG biofeedback to anal electrical stimulation [243]. They found no difference between the groups in outcome at the end of the treatment period. Healy [292] found no difference in outcome between home electrical stimulation and clinic stimulation with or without biofeedback. Naimy likewise found no difference between patients given electrical stimulation plus home exercises and those given clinic biofeedback plus home exercises [238]. Norton reported no difference between stimulation at 35Hz and 1Hz, suggesting any effect may be sensory rather than motor [293]. Osterberg (2) compared stimulation with surgical levatorplasty and found few differences in outcome at 2 years. In all studies a significant proportion of patients reported improvement compared to pre-treatment, whatever treatment was given.

4. SUMMARY OF EVIDENCE ON ELECTRICAL STIMULATION FOR FI

A Cochrane review of trials of electrical stimulation for FI has concluded that “At present, there are insufficient data to allow reliable conclusions to be drawn on the effects of electrical stimulation in the management of FI. There is a suggestion that electrical stimulation may have a therapeutic effect, but this is not certain. Larger, more generalisable trials are needed “ [294].

Because there is a lack of consistency in electrical stimulation protocols and also a failure to use physiological principles when employing electrical stimulation, direct comparisons between studies are impossible. There are many parameter and clinical applications that have not yet been investigated. We know little about which patients are likely to benefit from ES. Sensory awareness of the body schema and the possibility of improving this cortically by using ES may be important in motor re-learning for those patients with severe sensory lost, but this has not been investigated.

5. RECOMMENDATIONS FOR PRACTICE ON ELECTRICAL STIMULATION FOR FI

Based on currently available evidence it is not possible to recommended electrical stimulation for FI.

6. RECOMMENDATIONS FOR RESEARCH ON ELECTRICAL STIMULATION FOR FI

- Randomised controlled trials with adequate sample sizes are necessary to investigate all aspects of the effectiveness of ES in FI.

- The effect of electrical stimulation in changing consciousness of the pelvic floor is one of the interesting future areas for research.

- When planning future research basic knowledge of electrical stimulation parameters and their likely physiological effects is essential.
<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 women with H after 3rd degree tear. Mean age 36 (range 22-44).</td>
<td>Anal stimulation (Nero Trac ETS + anumform probe). 30-40Hz, pulse width 200, turn up to tolerance. Max 60 mAmp. 3 seconds on/off. 2 sessions with therapist. 2 x 20 mins sessions daily at home for 6 weeks.</td>
<td>Biofeedback (Nero Trac ETS + anumform probe) 2 sessions with therapist. 2 x 20 mins sessions daily at home for 6 weeks.</td>
<td>40 completed. No difference or change in Wexner score, or quality of life. No difference in subjective evaluation of effect: both groups subjectively improved</td>
</tr>
<tr>
<td>56 women with FI. Mean age 55 (range 40-78). Excluded significant sphincter defects.</td>
<td>3 months of home stimulation using ETS 90 + Anumform probe. 1 hour daily. Frequency: preset programme 3.10.20.30 &amp; 40 Hz. 4 seconds on/off. Intensity patient controlled.</td>
<td>Comparison 1: 3 months of hospital physiotherapy treatment once weekly. Alternate electrical stimulation with electrical stimulation (10 &amp; 40 Hz) + biofeedback for 15 minutes each. Comparison 2: 1 twice weekly hospital electrical stimulation without biofeedback</td>
<td>46 completed. No intention to treat analysis. No difference in squeeze pressure. Wexner score, quality of life between groups. Both groups significantly improved squeeze pressure, Wexner score and quality of life (some parameters) compared to pre-treatment.</td>
</tr>
<tr>
<td>50 patients (9 males). Median age 55 (range 30-77). Blinded to intervention group.</td>
<td>Daily home stimulation using Elora 4 Dammeter + Anumform anal probe at 35Hz for 8 weeks, with no other intervention. 20 minutes for 3 weeks then 40 minutes for 5 weeks. Ramp up pulse, 5 sec on/off, 300ms pulse width</td>
<td>&quot;Sham&quot; stimulation at 1Hz (n = 43) to same daily protocol.</td>
<td>70/00 completed. Intention to treat analysis. No difference between groups in subjective rating of outcome, frequency of FI, use of pads, satisfaction, effect on life or anal pressures. Both groups reported subjectively improved bowel control and frequency of FI.</td>
</tr>
<tr>
<td>70 patients randomised. Age range 43-61. 7 men. Excluded sphincter defect &amp; rectal prolapse.</td>
<td>Anal plug stimulation using MS210 Medicon (n = 28 completed). 28Hz, 1.8 sec on, 3 sec off. 12 x 20 minute sessions over 4-5 weeks.</td>
<td>Surgical levatorplasty, anterior in women, posterior in men (n = 39 completed).</td>
<td>Evaluation at 3, 12 &amp; 24 months. No difference in patient evaluation of improvement in FI, use of pads or urgency at any time point. Surgical group reported higher quality of life on several parameters. Both groups significantly improved continence, decreased pad use and lessened social handicap at each time point compared to pre-treatment. There was no difference or change in physiological parameters.</td>
</tr>
<tr>
<td>40 women with FI after obstetric trauma. Mean age 32 (range 18-48).</td>
<td>12 x weekly 30 minute sessions of physiotherapist delivered anal biofeedback (fast and slow squeezes) and electrical stimulation (Incare PHS 9400). 20Hz 10 minutes (ramped, 5 sec on, 1 sec off), then 50Hz (8 sec on, 30 sec off).</td>
<td>12 x weekly 30 minute sessions of nurse delivered vaginal biofeedback (Pentron pressure probe).</td>
<td>Significant difference in favour of stimulation group in improvement or cure of FI.</td>
</tr>
</tbody>
</table>
IX. Faecal Incontinence in Frail Older People

1. BACKGROUND

FI in older people is a distressing and social isolating symptom and is associated with increased risk of morbidity [8;37], mortality [32;295], and dependency [8;295]. Frailty, defined by having multiple comorbid chronic illnesses and/or limitations to physical activity (see Section 2), is an independent risk factor for FI. Many older individuals with FI will not volunteer the problem to their general practitioner or nurse, and regrettably, health care providers do not routinely enquire about the symptom. This ‘hidden problem’ can therefore lead to a downward spiral of psychological distress, dependency, and poor health. The condition can especially take its toll on informal care providers of home-dwelling patients [296], with FI being a leading reason for requesting nursing home placement [297;298].

Even when older people are noted by health care professionals to have FI, the condition is often managed passively, especially in the long-term care setting where it is most prevalent. Current surveys show that the level of awareness regarding appropriate assessment and treatment options is limited among primary care physicians [299]. The importance of identifying treatable causes of FI in frail older people rather than just managing passively (e.g. pads provision without assessment) is strongly emphasised in national and international guidance [1;278;297], but audits show that adherence to such guidance is generally poor, with non-integrated services, and sub-optimal delivery by professionals of even basic assessment and care [35;300].

This section covers specific issues for frail older people with FI. As this group frequently has co-existing urinary incontinence, it should be read in conjunction with Chapter 11. Healthy older people should be managed using the interventions covered previously in this chapter.

2. SEARCH

The PUBMED database was searched up to March 2008 using the following keywords:

1. ‘anal, bowel, faecal, fecal’ and ‘incontinence’
2. constipation
3. ‘urinary’ and ‘incontinence’
4. laxatives, enemas, suppositories
5. other relevant phrases such as ‘comprehensive geriatric assessment’ ‘stroke’

Additional articles were identified by examining reference lists, and the Cochrane other recent systematic reviews.

3. SUMMARY OF EVIDENCE ON PREVALENCE AND RISK FACTORS FOR FI IN FRAIL OLDER PEOPLE

The prevalence and risk factors for FI are detailed in Section 2. Summarized below are key points that are specific to the frail elderly population. The level of evidence is given in brackets.

- FI affects 1 in 5 older people (aged 65+) living in the community, and half of those resident in care homes (Level of evidence 1)
- The prevalence of FI increases with age alone, particularly in the 8th decade and beyond (1)
- The prevalence of FI is higher in the acute hospital and nursing home setting than in the community (1), thus the group most affected is frail older people.
- The prevalence of FI in frail older men is equal to or greater than in women (2). This predominance of older men over women with FI is most striking among nursing home residents (2).
- The prevalence of FI varies dramatically between institutions in nursing home studies (2)
- FI usually coexists with urinary incontinence in frail older people (1)
- Aside from age, the following are primary risk factors for FI in older people (2):
  - Loose stool
  - Impaired mobility
  - Dementia
  - Neurological disease
  - Chronic medical conditions
  - Depression
- Loose stool is a primary cause of transient FI in older people (2)
- Faecal loading and constipation are clinically linked to FI, but there is little epidemiological work assessing this association (3)
- Physicians and nurses in primary care, acute hospital, and long-term health care settings do not have a high awareness of FI in older people (2)
- Within nursing homes, there is a low rate of referral by nursing staff of residents to primary care physicians or continence nurse specialists for further assessment of FI (2), and there is a tendency toward passive management (e.g. use of pads only without further evaluation) (2). Faecal loading is often present in older care home residents with FI (2)
- Older people may be reluctant to volunteer the symptoms of FI to their health care provider for social or cultural reasons, or due to a popular misperception that the condition is part of the ageing process and therefore ‘nothing can be done about it’ (2)
- FI is associated with reduced quality of life, and poor health perception (2)
4. RECOMMENDATIONS - IDENTIFYING FAECAL INCONTINENCE IN FRAIL OLDER PEOPLE

- Bowel continence status should be established by direct questioning and/or direct observation in:
  - all nursing and residential home residents
  - hospital inpatients aged 65 and over
  - people aged 80 and beyond living at home
  - older adults with impaired mobility
  - older adults with impaired cognition
  - older adults with neurological disease
  - older adults with chronic disease

- Primary care staff, hospital ward staff, and long-term care staff should routinely enquire about FI in frail older patients

- Enquiry about FI should be systematic and include stool consistency, severity of FI and impact on activities of daily living and quality of life

- Health care providers should be sensitive to cultural and social barriers discouraging patients from talking about the condition

- Frail older patients with restricted ability to access primary care such as nursing home residents, and those with mobility, chronic illness, or cognitive impairments, should be screened for FI through systematic case-finding methods

- Systematic outreach programmes which make it easier for frail older people and those who care for them to volunteer the problem to their primary care provider should be implemented

- There are significant geographic variations in provision of specialist expertise in bowel care (both medical and nursing) nationally and globally, which may affect case-finding in older people

- Further examination of underlying reasons for the variations in prevalence of FI between nursing homes (standards of care, patient case-mix, reporting) is needed

- Urinary and FI often coexist; continence care workers (e.g. nurse specialists) should be trained in identification and management of faecal as well as urinary incontinence in older people

- Key requirements to improving detection in the practice setting should be implemented:
  - (a) education of health care workers to embed both a sense of value in identifying FI, plus confidence that the condition can be treated
  - (b) protocols should be in place clarifying all details of screening enquiry (who will ask, how to ask, when to ask, and who to ask)
  - (c) patients and carers should have access to educational materials at the point of enquiry

5. THE AGEING LOWER BOWEL AND PATHOPHYSIOLOGY IN OLDER ADULTS WITH FAECAL INCONTINENCE

Chapter 4 covers the pathophysiology of FI. This section considers factors specific to frail older people.

a) Quality of data

The findings from physiological studies of the lower bowel in older adults tend to be variable due to a) a variety of different techniques used in measuring anorectal function, b) unclear definition of the normative range of manometric measures for older people, c) poor matching between cases and controls of clinical factors which may affect gut function (e.g. level of mobility), or inaccurate clinical information and d) usually small subject numbers. Studies reviewed are cohort case-control to evaluate age-effect [301-304], young-old healthy subject comparisons [305;306], and age- and sex-matched case-control studies of continent versus incontinent patients [154;307;308].

b) Anorectal function in healthy older adults

Studies of age effect in healthy volunteers have shown a linear reduction with ageing in squeeze pressures (external anal sphincter tone) in women after the age of 70, and in men from the 9th decade onwards [301;302]. Age beyond 70 years was associated with reduction in basal pressures (internal anal sphincter tone) in both genders, but to a greater degree in women [301;302;306]. The internal sphincter thickness and diameter is significantly increased in older versus younger nulliparous women with, however, reduced functionality in this smooth muscle [309].

Rectal motility appears to be unaffected by healthy ageing [305], but an age-related increase in anorectal sensitivity thresholds, and reduced rectal compliance has been observed, starting at an earlier age in women than men [303].

c) Anorectal function in older adults with faecal incontinence

One study demonstrated prolonged pudendal nerve terminal motor latency (>2.2ms) in 34% of women aged over 50 with FI, though no relationship was observed between pudendal neuropathy and basal or squeeze pressures [310]. Advancing age was however related to declining basal pressures. Another study similarly found an age-related increase in pudendal neuropathy in incontinent women, again unrelated to squeeze pressures [311]. Single fibre EMG in incontinent patients aged over 70 years showed increase in polyphasic potentials in the external anal sphincter muscles compared with continent subjects, indicating some local reinnervation of these muscles following neurogenic damage [308]. A study comparing anorectal function in young (mean age 42) and old (mean age 72) women with FI (patients with constipation and/or pelvic floor dysfunction excluded) showed that older women were more likely to have
bilateral pudendal neuropathy, but less likely to have a sphincter deficit of >90 degrees and thin perineal body [304], although the validity of this test is questionable (Committee 7). Anorectal physiology was similar aside from a trend toward lower resting tone in older women.

An examination of anorectal function in elderly medically frail incontinent patients and continent age- and sex-matched controls showed that individuals with FI had reduced internal anal sphincter pressures, and a lower threshold for expulsion of a rectal balloon (307). Patients with FI and dementia were more likely to exhibit multiple rectal contractions in response to rectal distension, though the role of these ‘uninhibited’ contractions in causing incontinence was unclear [307;312].

A similar matched case-control study showed that elderly patients with rectal impaction and soiling had impaired rectal sensation (needing a larger volume before feeling the presence of a rectal balloon and the desire to void), lower rectal pressures during rectal distension, and impaired anal and perianal sensation (‘rectal dyschezia’) [154]. Basal and squeeze pressures were however unimpaired in these patients, and the rectoanal inhibitory response was well-preserved. The authors concluded that overflow FI is primarily due to locally secreted mucus from around an irritative rectal faecal mass leaking out, despite well-preserved anal sphincter integrity.

**SUMMARY OF EVIDENCE ON FAECAL INCONTINENCE AND THE AGEING GUT**

- Anorectal function in healthy older persons is characterised by a tendency towards an age-related reduction in internal anal sphincter tone (Level of evidence 2), and a more definite decline in external anal sphincter tone, especially in older women (2)
- An age-related decline in anorectal sensitivity in women has been observed (2), but rectal motility is well-preserved (2)
- Ageing alone however, appears to have little impact on anorectal function until later old age – from the 7th decade upwards in women and even later in men (2)
- Age-related internal anal sphincter dysfunction (reduced anal resting tone) is an important factor in FI in later old age (3)
- Pudendal neuropathy is an age-related phenomenon in women with FI (2), and a likely predisposing factor for FI (2) although the validity of this test is questioned.
- Stool impaction predisposing to overflow is related to rectal dyschezia in frail older adults, a condition characterised by reduced tone, increased compliance and impaired sensation (3)
- Overflow FI is due primarily to mucus secretion from around a rectal faecal bolus, rather than to impaired sphincter function (3)

**RECOMMENDATIONS - PATHOPHYSIOLOGY OF FI IN OLDER PEOPLE**

- Overall, the physiological data suggests that FI should not be considered an inevitable consequence of ageing
- Older adults with FI should be evaluated for age-related reduction in internal and external sphincter function
- Older patients with FI require a digital examination to identify rectal stool impaction causing overflow
- Patients who are unaware of the presence of a large faecal bolus in the rectum may have rectal dyschezia, and should be considered at risk of recurrent impaction with overflow

**6. CLINICAL CAUSES OF FI IN OLDER PEOPLE**

The evidence for this review is poor and the following section is based largely on case series and expert opinion rather than robust empirical data. The causes of FI in older people are often multifactorial. The aim of this section is to categorise the causes of FI in the frail older adult in a clinically meaningful way emphasising the identification of potentially reversible factors. Comprehensive geriatric assessment (assessing medical, functional and psychosocial factors in addition to the bowel) is key to identifying all contributing causes for FI in frail older people.

**6.1 OVERFLOW INCONTINENCE SECONDARY TO CONSTIPATION AND STOOL IMPACTION**

Constipation is the most important cause of FI in frail older people, as it is treatable, preventable, and frequently overlooked. In a UK hospital, faecal impaction was a primary diagnosis in 27% of acutely hospitalised geriatric patients admitted over the course of a year [154]. A more recent survey found that faecal loading was present in 57% of older acute hospital inpatients with FI (31). Care home studies show that 52-70% of care home residents have faecal loading underlying FI [25;31]. In a Finnish study, the prevalence of constipation (defined as self-reported difficult evacuation or infrequent bowel movements) was 57% in women and 64% in men living in residential homes, and 79% and 81% respectively in the nursing home setting [223]. The high prevalence of constipation in nursing homes is all the more striking in that 50-74% of long-term care residents use one or more daily laxative [34;223;313-315].

A prospective study in the US looked at baseline characteristics predictive of new-onset constipation in elderly nursing home patients using the Minimum Data Set instrument [316]. Constipation was defined as having two or fewer bowel movements per week or straining on more than 25% of occasions. Seven percent (n=1,291) developed constipation over a 3-month period. Independent predictors were white
OLDER PEOPLE AND RISK FACTORS FOR CONSTIPATION IN SUM

PREVALENCE

are summarised below.

constipation (and their supporting level of evidence)

epidemiological data regarding risk factors for constipation (and their supporting level of evidence) are summarised below.

SUMMARY OF EVIDENCE ON PREVALENCE AND RISK FACTORS FOR CONSTIPATION IN OLDER PEOPLE

- The prevalence of both self-reported and symptomatic constipation are high in frail older people (Level of evidence 2)
- Women predominate over men in prevalence rates of self-reported constipation and related symptoms among older people, though this gender difference is less marked beyond the age of 80 (2)
- Nursing home residents have a higher prevalence than community-dwelling individuals of all constipation-related symptoms, including infrequent bowel movements, straining, and hard stool (2)
- Faecal loading is often present in older patients with FI in the acute hospital (3) or care home setting (2)
- Advancing age increases the risk for heavy laxative use and symptom-based constipation among nursing home patients (3)
- The prevalence of constipation in nursing homes is high despite heavy laxative usage (2) implying that a) laxative prescribing may be ineffective, and b) non-pharmacological approaches to treatment are under-utilised in this setting.
- Frail older people are at greater risk of faecal impaction and overflow FI and other complications of constipation (2)
- There are numerous potentially modifiable risk factors for symptomatic constipation in frail older people (2). These include:
  - Polypharmacy (2) [223;316-318]
  - Anticholinergic drugs (2) [319] [314]
  - Opiates (2)
  - Iron supplements (3) [320]
  - Calcium channel antagonists (3) [321]
  - Nonsteroidal anti-inflammatory drugs (2) [322;323]
  - Immobility (2) [223;319;324]
  - Institutionalisation (3) [223]
  - Parkinson’s disease (2) [316;319;325]
  - Diabetes mellitus (2) [326;327]
  - Dehydration (2) [316] [328]
  - Diet deficient in fibre (3) [318] [329]
  - Dementia (2) [154;307;316]
  - Depression (3) [318;330]

6.2 OTHER CLINICAL CAUSES

a) Functional incontinence

Functional incontinence occurs in individuals who are unable to access the toilet in time due to impairments in mobility, dexterity, vision, intellect / awareness. These patients may even have normal lower gut function. Epidemiological studies in older people (see above) have repeatedly shown that poor mobility is a strong risk factor for FI after adjustment for other variables [8;32;40;53;296]. It is also a primary risk factor for constipation in older people [223;319;324]. While these studies particularly examined immobility as a risk factor, it is likely that problems of impaired sensation and dexterity are also contributory.

b) Dementia-related incontinence

Some patients with advanced dementia lack cortical control of the defecation process, and so tend to void formed stool once or twice daily following mass peristaltic movements. One study identified dementia as the primary cause of FI in 46% of nursing home residents [25], and the condition has been identified as an independent risk factor in epidemiological studies [32;40;53]. These individuals are very commonly incontinent of urine also [40].

c) Comorbidity-related incontinence

The following diseases may cause FI, and are more common in older people:

1. STROKE

FI affects 30-56% of individuals acutely after stroke, 11% at 3 months, and 11-22% at 12 months [114;115]. Major FI is four and a half times more prevalent in stroke survivors than the non-stroke population [331]. FI may develop months after acute stroke and can be transient, consistent with constipation with overflow as one possible cause [115;332]. Epidemiological data suggest that FI is associated more with disability-related factors (particularly functional difficulties in using the toilet, and anticholinergic medications) than stroke-related factors (e.g. severity and lesion location) [115;331;333].

2. DIABETES MELLITUS

Prospective data show that diabetes is a risk factor for the development of FI, especially in men [55]. FI may occur in people with diabetic neuropathy affecting the gut through the dual mechanisms of a) bacterial overgrowth resulting from severe prolongation of gut transit causing the characteristic nocturnal diarrhoea [326] and b) multifactorial anorectal dysfunction. Case-control studies show that diabetic patients with FI have reduced basal and squeeze pressures, spontaneous relaxation of the internal anal sphincter, reduced rectal compliance, and abnormal rectal sensation [327;334]. Diabetic anorectal dysfunction predisposing to FI can be further exacerbated by acute hyperglycaemia [335].
3. SACRAL CORD DYSFUNCTION

The neuropathophysiology of rectal dyschezia [154] is compatible with diminished parasympathetic outflow from the sacral cord. Rectal dyschezia is characterised by impaired rectal sensation (needing a larger volume before feeling the presence of a rectal balloon and the urge to void), lower rectal pressures during rectal distension, and impaired anal and perianal sensation, and is clinically associated with recurrent rectal impactions and continuous faecal soiling [154]. Common conditions in older persons that could impair sacral cord function are ischaemia and spinal stenosis.

4. ANORECTAL INCONTINENCE

Studies of older people with FI suggest that age-related internal anal sphincter dysfunction is an important contributing factor [310;312], as it lowers the threshold for balloon (stimulated stool) expulsion [312]. A study of women with anorectal FI compared underlying causes in young (mean age 42) and old (mean age 72) patients - the younger women were more likely to have an anal sphincter defect only, while the aetiology was more multifactorial in the older group, including a significantly higher occurrence of haemorrhoidectomy, diabetes, rectal and vaginal prolapse and pudendal neuropathy [304]. Later-life FI is linked to childbearing via structural damage to the external anal sphincter, and pelvic musculature [336]. Uterovaginal prolapse and rectocele have been shown to be a predominant independent risk factor for FI in women attending urogynaecology clinics [337;338]. Rectal prolapse is also a condition associated with FI which occurs more commonly in older adults [302].

5. LOOSE STOOLS

Loose stool increases the risk of incontinence in normally continent older adults by overwhelming a functional but age-compromised sphincter mechanism. Frail older individuals are particularly susceptible to bowel leakage in the context of loose stools [25;32]. Forty-four percent of cases of FI in a prospective nursing home study were related primarily to acute diarrhoea [32].

POSSIBLY REVERSIBLE CAUSES OF LOOSE STOOLS IN FRAIL OLDER ADULTS ARE:

i) Excessive use of laxatives

One-third of community-dwelling people aged 65 and over regularly take laxatives, far exceeding the prevalence of constipation in this population [339]. In the nursing home, laxative use (in particular ‘Codanthermer’ a Docusate-stimulant combination agent) has been linked to FI [34].

ii) Drug side-effects e.g.

Proton-pump inhibitors, selective serotonin re-uptake inhibitors, magnesium-containing antacids, choline-sterase inhibitors.

iii) Lactose intolerance

An age- and ethnicity-related phenomenon - Goulding et al. found a lactose malabsorption rate of 15% in healthy women aged 40-59 years as compared with 50% in those aged 60-79 [340].

iv) Antibiotic-related diarrhoea

Among hospitalised patients, age, female gender and nursing home residency significantly increases the risk for Clostridium difficile-associated diarrhoea associated with antibiotic use [341]. The diarrhoea also takes longer to resolve following treatment of C.Difficile in frailer older patients [341]. In a case-control study of hospitalised patients, Tal et al found FI to be a risk factor for recurrent C. Difficile (53% of patients studied), in addition to prolonged fever during initial infective episode, and H2-antagonist treatment [342].

v) Cancer

Loose stools should also be considered a possible indicator of colorectal cancer, and all patients with this symptom should be screened clinically for neoplastic and systemic illness. A study comparing underlying aetiologies in younger and older (age >70) men with FI found colon cancer to be significantly more common in the older group [343]. Where a change in bowel in habit is identified, colonoscopy or other imaging should be considered to rule out a colorectal cancer.

SUMMARY OF EVIDENCE ON CAUSES OF FI IN FRAIL OLDER PEOPLE

- Overflow incontinence secondary to stool impaction is a primary cause of FI in frail older people (Level of evidence 2).
- There are multiple potentially modifiable causes of constipation in older people (2), which are likely also to be risk factors for overflow FI.
- Frail older people (particularly those with neurological disability) may be incontinent because they are unable to use the toilet for physical functional reasons (2).
- Dementia is an important cause of FI in frail older people (2).
- FI is a common complication following stroke (2), but factors other than stroke status itself are contributory causes for incontinence in stroke survivors (2).
- Older people with diabetes (particularly if associated with autonomic neuropathy) are at risk of FI secondary of anal sphincter dysfunction (2)
- Loose stools predispose older people to soiling (1), and have numerous potentially reversible causes. Loose stools may however be indicative of underlying colonic disease such as colorectal cancer or colitis (2).
RECOMMENDATIONS - IDENTIFYING REVERSIBLE CAUSES OF FI IN OLDER PEOPLE

- The following potentially modifiable risk factors for FI should be carefully identified in all cases:
  1. Constipation causing impaction and overflow
  2. Loose stool
  3. Impaired mobility
  4. Difficulty with using the toilet (acute or chronic)
  5. Delirium (as a reversible cause of cognitive impairment)
  6. Anal sphincter weakness
  7. Impaired vision and/or manual dexterity
  8. Medications
    - All older people with FI should be assessed for reversible causes, regardless of their institutionalisation status
    - All frail older people with overflow FI should be assessed for potentially modifiable causes of constipation
    - The symptom of loose stools should be elicited in all older people with any degree of FI, and underlying causes rigorously sought
    - Evaluate nursing home administrative factors such as poor resident:staff ratios as a reversible cause of FI
    - Colorectal carcinoma may present with the symptom of loose stools, and this diagnosis should be considered where a change in bowel habit, or other indicators (rectal bleeding, abdominal pain, weight loss, anaemia) are present.

7. ASSESSMENT AND DIAGNOSIS OF FI IN OLDER ADULTS

The algorithm (Figure 2) summarises the clinical evaluation and management of FI in this population. The emphasis is on a structured comprehensive clinical approach, which can be undertaken by doctor or nurse specialist. In most cases the clinical approach will provide sufficient diagnostic information on which to base a feasible management plan without resorting to more specialised tests and assessments. The clinical usefulness of anorectal function tests and defecography in assessing FI in older people is limited by a) lack of normative data from healthy elderly, b) few standardised test protocols, and c) poor association between detected abnormalities and symptoms [344-346].

There is however much room for improvement in this clinical area; current surveys indicate a lack of thoroughness by doctors and nurses in assessing FI in older people in all settings (community, acute hospital, and nursing home), with failure to obtain an accurate symptom history or to perform rectal examinations [35;347]. A national UK audit of older patients with FI in primary care, acute hospital, and care home settings showed that only 50% of individuals within each setting had a history taken, and only 22-33% had a documented basic examination (history and rectal) [35]. Cause(s) for FI was documented in 27-49%, the 27% being in the acute hospital sector.

a) Results of search

Self-report of bowel symptoms relating to FI have been shown to be reliable and reproducible in older cohorts, including those in long-term care [348-350]. A study of women aged 65 years and older who were hospitalised with fractured neck of femur showed that proxy responses (proxy nominated by patient) for questions concerning FI has also been shown to concord well with index responses given by the patients [351].

Documentation of the type of incontinence is diagnostically very important [297]. There is a strong association between loose stool and FI in older people. Urgency is more associated with diarrhoeal disease (e.g. infective). Constant passive leakage of loose stool or stool-stained mucus is characteristic of overflow around an impaction, while patients with anal sphincter dysfunction tend to leak small amounts of stool. A symptoms study in adults with FI showed that where external anal sphincter weakness predominates the patient often reported urgency prior to leaking (urge FI), while those with internal sphincter dysfunction tended to have passive leakage of stool (passive FI) [352]. Patients with dementia-related incontinence often pass complete bowel movements, especially after meals in response to the gastrocolic reflex.

Assessment of FI must include an assessment for constipation. Based on international consensus, constipation is defined according to self-report of a combination of at least two of the following symptoms: usually 2 or less bowel movements per week over at least 3 months, hard stool, straining on more than 25% of evacuations and, feeling of incomplete evacuation [322;353].

It is important to identify the constipation subtype of rectal outlet delay in older people, as it affects 21% of community-dwellers aged 65 and over [322], and may lead to rectal impaction and FI. It is defined as: feeling of anal blockage during evacuation and prolonged defaecation (more than 10 minutes) and/or need for manual evacuation. Constipated older people tend to suffer primarily from difficulties with rectal evacuation and symptoms of straining and hard stool rather than from reduction in stool frequency [354].

Objectively however, the clinical definition of constipation relies on evidence of excessive stool
Figure 2: Multifactorial assessment and intervention protocol

1. Physical function history
   - Functional toileting problems?
   - Weak pelvic floor and/or sphincters?
   - Rectal stool impaction?
   - Rectal outlet delay?
   - Constipation?

2. Digital rectal examination
   - Glycerine suppositories daily and as required
     If ineffective, Bisacodyl suppositories daily and as required
     Written instruction on suppository insertion
     Advise footstool use during evacuation
     Phosphate enemas for severe impaction

3. Bowel symptom history
   - Faecal incontinence?
   - Impaction rectally or on abdominal xray?
     - Yes
     - No
       - Senna 2-3 tablets at night + lactulose 15 mls daily with instruction on dose titration according to ease of evacuation
       - Fybogel 1-3 daily with fluids instead of lactulose if diverticular disease or if weak anal sphincters
       - Polyethylene glycol 1 sachet for 3 days for colonic impaction without obstruction, then continue as above

4. Education (targeted verbal information with provision of booklet)
   - What is normal bowel function?
   - How stroke affects bowels?
   - Symptoms and tests
   - Diet (with food lists)
     - Fibre, fruit, vegetables
   - Caffeine avoidance
   - Fluids
   - Exercise
   - Regular toilet habits
   - Abdominal massage
   - Skin care
   - Pads
   - Odour control
   - When should I see my doctor
   - Helpful addresses
   - Alert patient and GP to drugs causing possible bowel-related side-effects

Explore problems with toilet access
In hospital: Ensure privacy
Use toilet (or sani-chair) rather than commode
Avoid bedpans
In community: Recommend community
OT/Physio assessment

Anal sphincter and pelvic muscle strengthening exercises

Loperamide 2mg up to 3 times daily according to symptoms
Anal sphincter strengthening exercises
Holding on exercises (bowel retraining)
Retention in the rectum and/or colon. Such objective assessment is particularly important in frail older people who may:

- be unable to report bowel-related symptoms due to communication or cognitive difficulties
- have regular bowel movements despite having rectal or colonic stool impaction
- have impaired rectal sensation and rectal dyschezia and so be unaware of symptoms associated with a large faecal bolus in the rectum [154].
- have non-specific signs or symptoms (such as delirium, leucocytosis, anorexia, functional decline) in association with severe faecal impaction

Digital examination can reasonably assess anal sphincter tone in the clinical setting. Easy finger insertion with gaping of the anus on finger removal indicates poor internal sphincter tone, while reduced squeeze pressure around the finger when asking the patient to ‘squeeze and pull up’ suggests external sphincter weakness. Digital assessment of squeeze and basal tone has been shown to be as sensitive and specific as manometry in discriminating sphincter function between continent and incontinent patients aged over 50 [355].

A digital rectal examination is essential for identifying stool impaction, although an empty rectum does not exclude the diagnosis of constipation [324]. Incontinent patients without evidence of rectal stool impaction should ideally undergo a plain abdominal radiograph in order to a) establish or rule out the diagnosis of overflow, b) measure the extent and severity of faecal loading, c) evaluate the degree of bowel obstruction secondary to impaction, and d) rule out acute complications of impaction such as sigmoid volvulus and stercoral perforation [356;357].

Certain symptoms associated with FI (abdominal pain, rectal bleeding, recent change in bowel habit, weight loss, anaemia) should prompt further consideration of underlying neoplasm [358]. Colorectal cancer is associated with both constipation and use of laxatives, though this risk association is likely to be confounded by the influence of underlying habits [359]. Chronic constipation alone is generally not considered an appropriate indication for lower endoscopy [360]. However, as the prevalence of colorectal cancer increases with age, the index of suspicion should be higher in older adults [361]. It should be noted that bowel preparation for lower endoscopy or barium enema may itself cause FI. Furthermore, a prospective study of 649 patients showed that dementia and stroke were independent predictors of inadequate colonic preparation [362].

Evaluation of toilet access should be multidisciplinary, and include a broad functional assessment (e.g. Barthel Index), mobility test (e.g. ‘up and go’ test), visual acuity test (count fingers), upper limb dexterity assessment (undoing buttons), and cognitive measure (e.g. Abbreviated Mental Test Score). An even more practical assessment is to watch someone transfer and manage clothing.

Appropriateness of the commode design for the individual concerned should be considered (e.g. trunk support, adaptability, mobility, foot support etc.) [35;363] (see Chapter 20). For community patients, the health care provider should be aware of the physical layout of the patient’s home, and in particular bathroom details (location, distance from main living area, width of doorway for accommodating walking aids, presence of grab rails or raised toilet seat). Low lighting levels, high degree of clutter and hard to manage clothing may also be relevant.

FI is a primary independent risk factor for pressure sores in frail older people [296;364], so evaluation of skin integrity (with pressure ulcer risk assessment) is important. Pelvic examination is also relevant in view of the association between urogenital prolapse (particularly rectocele) and FI in older women [337;338;365].

Bowel-specific quality of life scores have not specifically validated in the frail older population.

A UK RCT evaluated a multi-component assessment and treatment intervention for constipation and/or FI in frail older stroke patients, using an approach summarised in Figure 1 [144]. The assessment was undertaken in patients’ homes, outpatient clinics and hospital wards by a non-specialist nurse who had received simple training in bowel care. The structured assessment showed that the majority of patients had more than one bowel problem. Forty-eight (66%) had constipation, 41 (56%) rectal outlet delay and 16 (22%) rectal impaction. Twenty-two (30%) reported FI, of whom 12 had constipation with overflow. Thirty (41%) had reduced internal sphincter tone, 40 (55%) weak external sphincter tone, and 27 (37%) excessive pelvic floor descent. Thirty-four (47%) had difficulties with toilet access.

**SUMMARY OF EVIDENCE ON ASSESSMENT OF FI IN FRAIL OLDER PEOPLE**

- Evidence shows that current assessment of FI in frail older adults in routine healthcare settings is suboptimal (Level of evidence 2)
- Structured assessment of frail older people with bowel problems are likely to demonstrate multi-factorial causes for FI and constipation (2)
- Structured nurse-led assessment is a feasible approach in various healthcare settings (2)
- Documentation of the type of incontinence and related bowel symptoms by self-report, proxy report or observation is feasible (2) and diagnostically important (2)
• Constipation can be characterised clinically according to standardised symptom-based definitions in patients able to give a history (2)

• Rectal examination can reveal faecal impaction in patients with overflow (2)

• Digital assessment of sphincter tone can effectively estimate anal sphincter function in assessment of adults with FI (3)

• Anorectal function tests and defecography show poor association between abnormal findings and symptoms in older people with FI (3)

• FI-related quality of life measures have not been specifically validated in frail older persons

**RECOMMENDATIONS ON ASSESSMENT OF FI IN FRAIL OLDER PEOPLE (ALL GRADE C)**

- The emphasis in older people is on a structured clinical approach to identify multiple causes of FI, including cognitive and functional assessments. A standardised assessment of FI in frail older people is required to ensure proper identification of underlying causes. These assessments can feasibly be undertaken by nurses or doctors both in institutions, and in patients persons

- Physicians should prioritise assessment of FI of frail older people (especially in nursing homes). Nurses may be more aware of the problem, but should be specifically trained to look for underlying causes. A feasible practice-based approach is targeted training of non-specialist nurses providing routine care

- Hospital wards, primary care practices, and long-term care institutions internationally should have appropriate multidisciplinary protocols of case-finding and risk assessment

- Carers should be trained to routinely perform rectal examinations to evaluate stool retention

- A careful bowel symptom history (FI and constipation) and assessment of bowel pattern should form part of the assessment

- Digital assessment of sphincter tone should be performed in all older people with FI

- Ano-rectal physiology tests are not generally required in the frail elderly as they do not tend to alter the clinical examination conclusions or the management plan

- In the initial assessment of an older patient with FI, those without evidence of rectal stool impaction should undergo a plain abdominal radiograph to rule out higher impaction and other problems

- FI can be the presenting symptom of colorectal cancer and may require investigation by colonoscopy or barium enema. Bowel preparation should be carefully planned in frail older people to avoid causing acute diarrhoea, and/or inadequate clear-out

- Pelvic examination should form part of the assessment for FI, in particular to identify prolapse and rectocoele

- The impact of FI on patient and carer quality of life and usual activities should be qualitatively assessed, as well as patient attitude to their condition

- Evaluation of ability to access and use the toilet should be multidisciplinary

8. TREATMENT OF FI IN OLDER ADULTS

a) Quality of data

There are very few published trials of treatment of FI in older people, and no trials on prevention of FI. The studies reviewed had small numbers [25;144;244], problematic methodology (e.g. not applying intent-to-treat analysis, unclear reporting of drop-outs) [25;32;225], and were all non-blinded. Randomised controlled trials examining effective laxative treatment for constipation in older adults generally lack power, and are therefore unlikely to detect effects of treatment [366]. Issues of surgery, biofeedback, containment (pads and anal plugs) and skin care are covered elsewhere in the chapter.

b) Treatment of faecal impaction and overflow FI in older people

(See also section VI.3.c). One trial evaluated a therapeutic intervention in 52 nursing home residents with FI, based on treatment recommendations to general practitioners [25]. Patients with rectal impaction and continuous faecal soiling were classed as having overflow and recommended treatment with enemas until no further response followed by lactulose - complete resolution of incontinence was achieved in 94% of those in whom full treatment compliance could be obtained. Compliance with the recommended treatment was obtained in 67% of patients.

A French nursing home study of 206 frail elderly nursing home residents found that treatment of constipation was only effective in improving overflow FI (incontinence at least once weekly associated with impaired rectal emptying) when long-lasting and complete rectal emptying (monitored by weekly rectal examinations) was achieved using daily lactulose plus daily suppositories, plus weekly tap-water enemas. The number of FI episodes was reduced by 35% and staff workload (based on soiled laundry counts) fell by 42% in those with effective bowel clearance. However,
complete rectal emptying was only achieved in 40% of people receiving this regimen.

Over half of nursing home residents take laxatives at least once daily, prompting speculation that non-pharmacological approaches to optimise management of constipation may be under-utilised in this setting [34].

A 1997 a systematic review of laxative treatment in elderly persons found that the few published randomized controlled trials were potentially flawed due to small numbers and other methodologic concerns [366]. In the 10 years since that review, there has been little rigorous research specific to the older population. The following conclusions are drawn from the recent meta-analytical reviews [323;366] of efficacy of laxatives in treating chronic constipation in adults (it should be noted that none of these studies had relief of constipation-related FI as an outcome measure):

- Availability of published evidence is poor for many commonly used agents including senna, magnesium hydroxide, bisacodyl and stool softeners
- In trials conducted in older people, significant improvements in bowel movement frequency were observed with a stimulant laxative (cascara) (Level of evidence 3) and with lactulose (2), while psyllium (2) and lactulose (2) were individually reported to improve stool consistency and related symptoms in placebo-controlled trials
- Level (1) evidence supports the use of polyethylene glycol (PEG) in adults
- Level (2) evidence supports the use of lactulose and psyllium in adults
- None of the currently available trials include quality of life outcomes
- In trials conducted in older adults (>55 years) there is little evidence of differences in effectiveness between categories of laxatives
- A stepped approach to laxative treatment in older people is justified, starting with cheaper laxatives before proceeding to more expensive alternatives
- Note that none of these studies had relief of constipation-related FI as an outcome measure.

Polyethylene glycol (PEG) is a potent hyper-osmolar laxative. An RCT evaluating its use in treatment of faecal impaction (in combination with daily enemas) in elderly nursing home residents, showed greater efficacy than lactulose, without the dehydration or haemodynamic side-effects. Another RCT of adults (aged 17-88) with fecal loading on Xray or rectal examination, and bowels not open for 3-5 days showed that 1L (or 8 sachets) a day of PEG plus electrolytes (Movicol®) for 3 days resolved impaction in 89% of patients, with few adverse effects. The current evidence base suggests that the role of PEG in older people is for acute disimpaction (ensuring that easy toilet access is guaranteed), and for regular use as a laxative only in high risk people whose constipation has proved resistant to milder and cheaper alternatives (e.g. senna).

Enemas and suppositories have a role in both acute disimpaction, and in preventing recurrent impactions in susceptible patients [25;225]. They induce evacuation as a response to colonic distension. Frail elderly patients with recurrent episodes of overflow FI despite regular laxative and suppository use can benefit from weekly enemas. Regular use of phosphate enemas should be avoided in patients with renal impairment as dangerous hyperphosphatemia may occur [367]. Tap water enemas are the safest type for regular use, although they take more nursing administration time than phosphate enemas, and are not available in certain countries. Soapsuds enemas should never be administered to older patients. Arachis oil retention enemas are particularly useful in loosening colonic impactions. In patients who have a firm and large rectal impaction, manual evacuation should be performed before inserting enemas or suppositories, using local anesthetic gel if needed to reduce discomfort.

The value of treating constipation in preventing FI in frail older people has not yet been reported.

c) Treatment of dementia-related FI

Prompted toileting programmes significantly increased the number of continent bowel movements in an uncontrolled study of elderly nursing home residents in the US with dementia-related incontinence over a period of a few weeks, but no impact was seen on frequency of FI [368]. A further nursing home RCT showed that prompted toileting in frail residents significantly reduced the frequency of FI and increased the rate of appropriate toilet use in the intervention group, but did not overall impact the primary outcome measure of pressure ulcers [132].

A bowel programme in 25 nursing home residents with dementia-related FI consisting of daily codeine phosphate and twice weekly enemas achieved continence in 75% of those fully treated [25].

d) Treatment of anorectal FI in older adults

Biofeedback treatment for FI in older people resulted in a 75% reduction in incontinent episodes short-term in one small study of a highly selected group of patients with no cognitive impairment, good motivation and intact anorectal sensation [244]. Pelvic floor retraining is effective treatment in older women with urinary incontinence [369], and there is no evidence to suggest that frail older people without significant cognitive problems are any less able to adhere to such programmes.
There is no data on the use of Loperamide in frail older people. Expert opinion suggests that it should be used only with extreme caution and monitoring for impaction in this patient group.

e) Treatment of loose stools in frail older people

For prevention of C. Difficile in frail older hospital inpatients (and consequent loose stool with FI in those with weak sphincters), strict antibiotic policies and hand washing by all staff before and after contact with patients have been shown to reduce the risk of infectious disease. Preliminary trials suggest that use of probiotic yogurt drinks started simultaneously with antibiotic prescribing and continued for 2 weeks after course completion can reduce antibiotic-related diarrhoea and C.Difficile incidence.

f) Multi-component treatment of FI in frail older people

While a multidimensional approach to FI treatment would clearly be indicated in view of the multifactorial causation in older people, there are few published studies of multicomponent interventions. A UK RCT in frail older stroke survivors with constipation and/or FI evaluated a one-off assessment leading to targeted patient/carer education with a booklet, and treatment recommendations to the routine health care provider [144]. At one year follow-up the intervention group (as compared with controls receiving usual care) were more likely to be altering their diet and fluid intake to control their bowels, and at 6 months had significantly more 'normal' defecations. This type of evaluation does not define any specific action that had a particular beneficial effect, but does test a multicomponent approach that non-specialist doctors and nurses could feasibly apply in various settings (see Figure 1).

A US study specifically looked at self-care practices among 242 home-dwelling older people with FI [147]. Most commonly used practices were dietary change, wearing pads, and limiting activity.

A UK study asked frail older patients with FI about privacy during defecation [370]. Adequate privacy was reported by only 23% of nursing home residents, and 50% of hospital inpatients. Lack of privacy, particularly in dependent older people in institutions, is a major care issue.

SUMMARY OF EVIDENCE ON THE TREATMENT OF FI IN FRAIL OLDER PEOPLE

- Current evidence shows that stimulant laxatives, osmolar laxatives (PEG and lactulose), suppositories and enemas can be effective in treating faecal impaction in older people at risk of overflow (Level of evidence 2).
- Complete rectal clearance is required to reduce overflow FI (2), but may be hard to achieve in frail older patients (2). Weekly digital rectal examination is helpful in monitoring the effectiveness of a bowel clearance programme (2).

- Structured approaches to bowel care (including prompted toileting) can reduce the frequency of FI in the nursing home setting (2)
- Older people with FI may benefit from biofeedback and sphincter strengthening exercises if they are able to comply (3)
- Loperamide can reduce frequency of FI, particularly when associated with loose stool (once infection and other causes have been excluded) but should be used with caution (2)
- Changes in antibiotic prescribing and use of probiotics in antibiotic users can reduce the risk of C.Difficile and antibiotic related diarrhoea in older people (2)
- Multicomponent structured nurse-led assessment and intervention can improve bowel symptoms and alter bowel-related habits in older stroke patients (2)
- Self-care practices are prevalent in older people with FI, especially in those with more severe FI (3)
- Dependent older people with FI in care homes and hospital often lack privacy during defecation (3)

RECOMMENDATIONS - TREATMENT OF FI IN FRAIL OLDER PEOPLE (ALL GRADE C)

- Patients identified as having constipation with overflow should have effective bowel clearance (using a combination of laxatives and enemas), and then maintenance therapy with stimulant or osmotic laxatives
- Regular digital rectal examinations should be performed to assess the effectiveness of a bowel clearance programme in frail older people with overflow
- Suppositories are useful in treating rectal outlet delay and preventing recurrent rectal impaction with regular use
- Loperamide is a useful treatment in anorectal FI, in the absence of constipation, but should be used with caution
- Causes of loose stool must be identified and treated. In the case of C. Difficile, appropriate preventive measures should be taken, particularly in frail older people who are at risk of recurrent infection
- All frail older people with FI should have a structured multidisciplinary assessment and treatment of their bowel problem. Figure 1 summarises a structured approach that can be used in multiple health care settings.
**8. AREAS FOR FURTHER RESEARCH ON FI IN FRAIL OLDER PEOPLE**

- Patient and carer education (using verbal and written materials) should be undertaken to promote self-efficacy and other coping mechanisms, and where appropriate self-management (e.g. reducing risk of constipation and impaction through dietary and lifestyle measures, advice on how to take loperamide). Advice on skin care, odour control, and continence aids is also important.
- Privacy and dignity of care during defecation should be afforded to all older people in institutionalised settings. Particular attention should be paid to this in patients with FI, as privacy may be relatively overlooked in their care.
- Greater emphasis needs to be placed on systematic and effective management of FI in older people backed up by sound communications between all health care providers, especially in the nursing home and acute hospital setting.
- Education of health care providers with regards to heightening awareness of the problem plus methods of identification, assessment and management of FI in older people should be broad-ranging and include geriatricians, general practitioners, hospital physicians, hospital, community, general practice and long-term care nurses, and related disciplines (physiotherapists, occupational therapists, dieticians, pharmacists).
- Cyclical national audit with provider accountability, of current practice in managing FI in older people is needed to lay the ground-work for standardized care, and provide a culture of continuous quality improvement. Such audit tools should be developed using standardized consensus methodologies (35). Incentives to providers could be benchmarking their practice against national averages, opportunities to share successful practice change strategies, and professional validation linked to good practice.

**• Trials of laxative and nonpharmacological treatment and prevention of faecal impaction and overflow are needed to optimise standards of prescribing and care.**

**• Multicomponent interventions to treat FI in frail older people should be evaluated in applied research projects to assess effective ways of delivering this type of intervention within routine health care settings.**

**• Multidisciplinary study assessing the feasibility and efficacy of a step-wise approach to the management of dementia-related FI in nursing home residents (prompted toileting in those with mild to moderate dementia, scheduled toileting plus suppositories next step, and a bowel programme of controlled evacuation in those with persistent incontinence) would provide useful evidence.**

- The challenges of undertaking RCT’s in frail older people are summarised in the chapter on urinary incontinence in frail elderly (Committee 11). In particular, it is important to balance feasibility and practicality versus high strength intervention, i.e. a team of specialist continence nurses in nursing homes are likely to have an impact, but at what cost, and what carry-over will there be when they are gone? Other methodologies (e.g. pre-post with multivariate case-mix adjustment) should also be considered.

**• Evaluation of case-finding methods for FI in different settings including the fundamentals of staff education, screening protocols, patient’s educational information would be very informative.**

**• Testing the feasibility of providing an integrative approach to assessment of FI in the frail older person, including a range of health and social care providers and different health care settings (acute, intermediate or sub-acute, long-term care, and community) would be relevant to national implementation of bowel care improvement programmes.**

**• Examination of the variability of FI rates between nursing homes within single nation states, (taking into consideration case-mix) will highlight problems areas both organizationally and clinically. Nursing home administrative factors such as resident:nurse staff ratios should be evaluated as a contributing factor to FI.**

**• Further epidemiological studies are required to document causes of FI in frail older people in different health care settings. Such studies should include evaluation of unmet need for patients and carers.**

**• Evaluation of aetiologies, and in particular the pathophysiological basis for high prevalence of FI in older men. Evaluation of potentially preventable causes of loose stools in institutionalized older people, and impact of their treatment on FI.**

**• Nurse-led initiatives are needed to develop care pathways for assessing of bowel problems in frail older people with a view to establishing integrated service delivery.**

**• Examine the research question, ‘Do educational interventions by health care providers to informal carers of home-dwelling older people with FI reduce carer burden and improve quality of life for patient and carer?’**
X. CONCLUSIONS, RECOMMENDATIONS AND ALGORITHM

1. PREVENTION

a) Primary prevention:
   • Public health measures to prevent diarrhoeal diseases (Grade of recommendation B/C)
   • Treat reversible causes of diarrhoea (C)
   • Obstetric: no convincing evidence of role for preventive caesarean section; avoid midline episiotomy; restrictive rather than liberal episiotomy protocols (A)
   • Discourage the use of internal anal sphincter division for treatment of anal fissure and haemorrhoids (A)

b) Secondary prevention:
   • Active case finding/screening in high risk groups (C)
   • Proactive bowel management in high risk groups (e.g. neurological) (C)
   • Optimise stool consistency in people with loose stools (all ages); hard stools (children and older populations) (B)
   • Treat obesity? (D)
   • Consider medication alternatives in patients with FI & medication-induced diarrhoea (C)
   • Alert patients to risk of FI following colorectal surgery (C)

c) Recommendations for research on prevention
   • Longitudinal studies to map natural history, especially in women with obstetric risk factors
   • Prevention studies in childbearing women and other high risk groups
   • Colorectal surgery and radiotherapy techniques
   • Bowel management strategies in high risk groups (e.g. neurological)
   • Understanding mechanisms of FI in men
   • Frail: community prevention/screening/early treatment to prevent NH admission
   • Measures to prevent/reduce FI in nursing homes (functional FI, staffing etc)

2. EDUCATION AND LIFESTYLE
   • Medication side effects: consider alternatives if causing diarrhoea (C)
   • Toilet access for people with disabilities (C)
   • Education
     - of patient (B/C)
     - of carer (C)
   • Complementary therapies: no evidence (D)

There is insufficient evidence to recommend or discourage most lifestyle modifications either for the prevention or treatment of FI. Based on the consensus of experts (Level 3 evidence) the committee recommends patient education about the causes of FI and a systematic effort to remove barriers to effective toileting, are both interventions that are likely to be beneficial. They may be provided at relatively low cost and they involve no significant risk to the patient.

Recommendations for research on education and lifestyle

• Based on encouraging preliminary reports that patient education, combined with conservative medical management, can reduce the frequency of FI, we recommend further research. An RCT may not be possible due to the challenge of identifying a suitable control for expectancy and attention. A study which demonstrates a sustained benefit from a limited educational intervention (provided to patients or caregivers), would provide useful guidance for clinical management.

• Further investigation of the benefits for FI of weight reduction, especially in moderately obese patients without bariatric surgery.

• Exercise programmes, when incorporated into a multi-component intervention, have produced promising preliminary results and should be tested further. Such trials should differentiate between constipation-associated FI and diarrhoea-associated FI as exercise may be more beneficial to the former group.

• Evaluation of the incremental or additive value of different lifestyle interventions in the patient pathway.

Research on the contribution of complementary therapies.

3. DIET AND FLUIDS
   • Soluble dietary fibre is recommended for the management of FI associated with loose stool. This recommendation is made despite inconsistent results between two RCTs because the methodology for the positive study was significantly better than that of the other study. (Evidence level 1. Recommendation Grade B).

   • Dietary fibre is not recommended as an adjuvant to antimotility medication for managing AI when stools are not loose or liquid. (Evidence level 2 Grade B).

   • Patients should be asked about dietary restrictions and meal skipping.
Recommendations for research on diet and fluids

Further studies on the effect of dietary fibre and other diet modifications on FI are encouraged to build a greater body of evidence. Because dietary fibres differ in their chemical composition and properties, future studies are recommended to determine the optimal type and amount of fibre to use for FI. Whether a dietary intervention can augment other behavioural interventions, such as pelvic floor muscle exercises or bowel training, needs further study.

- Role of fibre and fluid in constipation/impaction related FI
- Effect of diet and eating pattern as a management strategy for FI
- Role of caffeine restriction in the treatment of FI and AI

There are several recommendations for methodological rigour in future studies. Theory-based, adequately powered, controlled trials are sought. Studies should control for variability in an individual’s baseline severity of incontinence and any adjuvant therapies. Monitoring adherence to the dietary intervention is recommended. A common set of outcome measures that includes tolerance to diet interventions is recommended. Reporting outcomes of FI in addition to those of AI (which incorporates flatus incontinence) is recommended.

4. BOWEL TRAINING

- Attempt to establish a bowel routine (C)
- Urgency resistance training possibly useful for urgency (D: need for research)
- No evidence on behaviour modification methods (D: need for research)
- Digital stimulation and manual evacuation useful in neurological patients (C)
- Rectal irrigation is useful in SCI (B) and has potential in other patients with FI (D)

Recommendations for research on bowel training

Research is needed in all areas.

Combination studies with urinary incontinence are recommended.

5. DRUG TREATMENT OF FI

- Treat FI with diarrhoea with anti-diarrhoeal medication (C); titrate the dose to individual response (C)
- We are unable to recommend sphincter function modifying drugs (D)
- Use oral or rectal laxatives/evacuants to treat constipation-associated FI (C): no evidence on the most effective agent. Need to confirm impaction is resolved (C)
- For constipation-associated FI, there is level 2 evidence suggesting that daily or more frequent oral laxative regimens may be effective for the treatment of constipation-associated FI in nursing home residents and children, but there are conflicting data.

Drug treatment of FI: recommendations for research

- Additional, well-designed studies are needed to validate the common clinical practice of using laxatives to treat constipation-associated FI.
- There is a need for further research on preparations, doses and combination therapies for all types of FI and all patient subgroups.

6. BIOFEEDBACK AND/OR ANAL SPHINCTER / PELVIC FLOOR MUSCLE TRAINING

Because recent RCTs have raised questions as to whether biofeedback provides a specific benefit relative to education and good clinical management despite a large body of uncontrolled studies supporting its efficacy, the consensus of the committee is that it is possibly effective but currently unproven. This reinforces the case for using maximal education, lifestyle and dietary interventions before PFMT or BFB, as recommended by recent national guidelines in the UK.

- PFM exercises are recommended as an early intervention in the treatment of FI as part of a conservative management bundle of interventions, based upon low cost and morbidity and weak evidence suggesting efficacy (C).
- The use of biofeedback as a treatment for FI is recommended after other behavioural and medical management has been tried if inadequate symptom relief is obtained, given the numerous positive outcomes from uncontrolled trials, limitations in the current RCTs and low morbidity associated with its application (C).

Recommendations for research

There is a need to conduct further RCTs to determine whether specific biofeedback and pelvic floor muscle exercise protocols can alter physiological parameters of ano-rectal function with concomitant changes in bowel control.

- Clear description of modalities and evaluation of different elements of BFB
- Adherence monitoring
- Standardisation of outcome measures
- Long term follow up
- Robust patient-focused outcome measures
7. ELECTRICAL STIMULATION FOR FI

Based on currently available evidence it is not possible to recommended electrical stimulation for FI.

Recommendations for research on electrical stimulation for FI

• Randomised controlled trials with adequate sample sizes are necessary to investigate all aspects of the effectiveness of ES in FI.
• The effect of electrical stimulation in changing consciousness of the pelvic floor is one of the interesting future areas for research.
• When planning future research basic knowledge of electrical stimulation parameters and their likely physiological effects is essential.

8. FI IN FRAIL OLDER PEOPLE

Bowel continence status should be established by direct questioning and/or direct observation in:
• all nursing and residential home residents
• hospital inpatients aged 65 and over
• people aged 80 and beyond living at home
• older adults with impaired mobility
• older adults with impaired cognition
• older adults with neurological disease
• older adults with chronic disease

Appropriate investigation and active treatment is needed in all older adults with FI (see Chapter for details).

REFERENCES


49. Lustyk MK, Jarrett ME, Bennett JC, Heitkemper MM. Does


133. Schnelle JF, Alessi C, Simmons SF, Al-Sa marril NR, Beck
148. Hansen JL, Bliss DZ, Penden-McAlpine C. Dietary strategies

147. Bliss DZ, Fischer LR, Savik K. Self-care practices of the


146. Taitz LS, Fischer LR, Savik K. Self-care practices of the


243. Mahony RT, Malone P, Nalty J, Behan M, O’Connell PR,


294. Hosker G, Norton C, Brazzelli M. Electrical stimulation for
293. Norton C, Gibbs A, Kamm MA. Randomised trial of electrical
291. Sander P, Bjarnesen J, Mouritsen L. Anal incontinence in
290. Hosker G, Cody JD, Norton C. Electrical stimulation for
289. Peticca L. Combined biofeedback, physiotherapy and
287. Gladman A, Scott SM, Chan CLH, Willis NS, Lunniss PJ.
286. Salvioli B. Rectal compliance, capacity, and rectoanal
285. Hobday DI. A study of the cortical processing of ano-rectal
284. Fall M, Lindstrom S. Electrical stimulation: a physiologic
282. Haskell B, Rovner H. Electromyography in the management
281. Caldwell KPS. The electrical control of sphincter
280. Leroi AM, Parc Y, Lehur PA, Mion F, Barth X, Rullier E, et
275. Caldwell KPS. The electrical control of sphincter
274. Haskell B, Rovner H. Electromyography in the management
273. Caldwell KPS. The electrical control of sphincter
272. Haskell B, Rovner H. Electromyography in the management
271. Caldwell KPS. The electrical control of sphincter
270. Haskell B, Rovner H. Electromyography in the management
radiograph the assessment of constipation. Z Gastroenterol 1990;28:335-8.


Committee 17

Surgery for Faecal Incontinence

Chairman

*R.D. Madoff* (USA)

Members

*S. Laurberg* (Denmark),
*K.E. Matzel* (Germany),
*A.F. Mellgren* (USA),
*T. Mimura* (Japan),
*P.R. O’Connell* (Ireland),
*M.G. Varma* (USA)
# CONTENTS

<table>
<thead>
<tr>
<th>Introduction</th>
<th>IX. Injectable Biomaterials</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Surgery for Adult Faecal Incontinence</td>
<td>X. Colectomy</td>
</tr>
<tr>
<td>I. Sphincter Repair</td>
<td>XI. Antegrade Continence Enema</td>
</tr>
<tr>
<td>II. Sphincteroplasty</td>
<td>B. Surgery for Pediatric Faecal Incontinence</td>
</tr>
<tr>
<td>III. Postanal Repair</td>
<td>I. Anorectal Malformations</td>
</tr>
<tr>
<td>IV. Non-Stimulated Muscle Transposition</td>
<td>II. Other Causes of Faecal Incontinence</td>
</tr>
<tr>
<td>V. Stimulated Muscle Transposition</td>
<td>III. Other Surgeries</td>
</tr>
<tr>
<td>VI. Artificial Anal Sphincter</td>
<td>C. Conclusions</td>
</tr>
<tr>
<td>VII. Sacral Nerve Stimulation</td>
<td>References</td>
</tr>
<tr>
<td>VIII. Posterior Tibial Nerve Stimulation</td>
<td></td>
</tr>
</tbody>
</table>

---

**A. Surgery for Adult Faecal Incontinence**

- I. Sphincter Repair
- II. Sphincteroplasty
- III. Postanal Repair
- IV. Non-Stimulated Muscle Transposition
- V. Stimulated Muscle Transposition
- VI. Artificial Anal Sphincter
- VII. Sacral Nerve Stimulation
- VIII. Posterior Tibial Nerve Stimulation

**B. Surgery for Pediatric Faecal Incontinence**

**C. Conclusions**

**References**
Therapy for faecal incontinence is readily divided into non-surgical and surgical therapy. Selection of specific therapy is based upon a number of considerations, including the severity of incontinence and structural integrity of the anal sphincter.

Conservative therapy is most applicable to relatively mild cases of incontinence. Biofeedback retraining can be attempted for incontinence of any cause or severity, as the therapy is painless and risk-free. These treatments are discussed in detail elsewhere in this monograph.

The most widely accepted surgical therapy for faecal incontinence is overlapping sphincteroplasty. Typical of other well-established therapies, the evidence base supporting this approach is paradoxically less robust than that supporting more recent treatment options. Sphincteroplasty is useful only in cases in which there is an anatomic sphincter defect, and it has been reported to provide satisfactory results in many case series. However, several recent studies have now shown that results of sphincteroplasty deteriorate with time [1, 2].

A number of operations were developed in the early to mid 20th century to provide a treatment option for patients whose native sphincter was either intact but weak or not repairable. Muscle transposition procedures using either gluteus maximus or gracilis were devised to create a functional biological neosphincter, but the approach did not gain widespread popularity. The Parks postanal repair was devised in 1975 to treat patients with incontinence due to pelvic neuropathy [3].

Dissatisfaction with available operations for faecal incontinence led to development of a variety of novel procedures during the last 20 years. The stimulated (dynamic) graciloplasty and the artificial anal sphincter were devised as salvage procedures for patients who had failed or were not candidates for standard therapy. A more recent approach is the use of sacral nerve stimulation, which was adopted for this purpose from its previously better-defined role in urinary voiding dysfunction. Moreover, there has also been a trend towards development of minimally invasive approaches to faecal incontinence, such as the use of injectable biomaterials.

Several important caveats apply to interpretation of the results of surgery for faecal incontinence reported in the literature. First, the vast majority of reports are uncontrolled case series. Randomized controlled studies are rare, and those reported include only small numbers of patients [4]. Second, numerous quantitative measures have been used to report outcomes, but only recently have any of these been validated, such as the Faecal Incontinence Quality of Life (FIQL) instrument. Third, criteria for “successful” outcomes have been variable and often arbitrary. Fourth, the quality of data reported is variable, though it has generally improved with the passage of time. Chart review has been supplanted by patient questionnaires and interviews by independent data auditors; daily continence diaries, the most stringent form of data collection, have become increasingly commonplace (though not routine). Despite the fact that studies using lax data collection are certain to report better results than those using methodology that is more stringent, of necessity, composite reviews of surgical results include studies using various methods of data collection. Finally, results are not always reported on an intention to treat basis, particularly in the implantable device literature.

SEARCH METHODS
PubMed search was conducted to identify studies published on the use of surgery for faecal incontinence in children and adults. Keywords used were faecal incontinence and surgery. Full text copies of studies deemed to be potentially relevant were obtained. Priority was given to systematic reviews, randomized controlled trials, and controlled clinical trials; if those were unavailable or inadequate, comparative observational studies, case series, case reports and narrative reviews were also included. Reviewers were not blinded to the names of studies’ authors, institutions or publications. In view of the nature of the guideline, priority was given to the reports with large number of
A meta-analysis of 717 vaginal deliveries found an incidence of anal sphincter injury is higher [6, 7]. 

It can be prospectively looked for with endoanal ultrasound, second and subsequent deliveries [5]. When following primiparous delivery and 0.5-1% following anal sphincter injury (grade 3 or 4 tear) is low, 3-5% in Western obstetric practice, the incidence of overt other pathology particularly surgery for anal fistula. 

Mechanisms are more commonly involved in primary repair of injury that is the result of blunt or penetrating trauma. Occasionally, the anal sphincter mechanism is damaged during anorectal surgery for other pathology particularly surgery for anal fistula. 

In Western obstetric practice, the incidence of overt anal sphincter injury (grade 3 or 4 tear) is low, 3-5% following primiparous delivery and 0.5-1% following second and subsequent deliveries [5]. When prospectively looked for with endoanal ultrasound, the incidence of anal sphincter injury is higher [6, 7]. 

A meta-analysis of 717 vaginal deliveries found an incidence of new anal sphincter defects of 27% in primiparous and 9% in multiparous women using 2D endo-anal ultrasound [8]. 3D ultrasonography suggests that the incidence is somewhat less, perhaps 11%, following primiparous delivery [9]. The risk factors for sphincter injury include instrumental vaginal delivery, prolonged second stage of labor, fetal macrosomia, and a persistent occipito-position of the fetal head [7, 10-12]. Midline episiotomy is associated with higher incidence of anal sphincter injury and the angle of mediolateral episiotomy may also influence perineal outcome [13]. A policy of restrictive use of episiotomy may reduce the incidence of anal sphincter injury [14]. 

Obstetric injury of the perineum is classified as a first degree tear if confined to vaginal epithelium and skin, second degree if the perineal muscles are torn, third degree if the anal sphincter muscles (external: EAS; internal: IAS) are torn, (3a: less than 50% EAS torn; 3b: more than 50% EAS torn; 3c: IAS torn), or fourth degree if both EAS and IAS and rectal or anal mucosa are torn [15]. Primary repair of an obstetrical tear is correctly termed anal sphincter repair and is usually performed by the obstetrician immediately after delivery most commonly in the delivery room under local or epidural anesthetic. By tradition, the technique of repair has been a direct oppositional repair of the severed external anal sphincter. The internal anal sphincter, if divided, is difficult to identify separately and when separately repaired it is usually en block with the anal canal mucosa in a complete or 4th degree tear. There have been four randomized clinical trials [16-19] and one meta-analysis [20] that have investigated different techniques of immediate primary repair of the external anal sphincter following obstetric injury. 

There was a trend towards better outcome with an overlap repair; however, the meta-analysis concluded that it would be inappropriate to favor one type of repair over another [20]. [LEVEL OF EVIDENCE: 1] With regard to management of the internal anal sphincter, Mahoney et al [21] have shown persistence of an IAS defect to be adversely associated with continence outcome in a series of 500 consecutive women assessed following repair of a 3rd or 4th degree tear. 

It has been suggested that primary anal sphincter repair might be best performed by a colorectal surgeon rather than an obstetrician [22]. Nordenstam et al [23] concluded, in a single institution study of 156 women, that technique and expertise impact on the outcome of primary repair and that if needed, the repair could be safely delayed until such expertise was available. Soerensen et al [24] have found no adverse outcome with delayed primary repair. [LEVEL OF EVIDENCE: 2] 

There have been two randomized trials of post-operative management of the bowel after primary anal sphincter repair. These have shown benefit in use of a laxative rather than a constipating regimen but no advantage to the addition of a stool bulking agent [25, 26]. [LEVEL OF EVIDENCE: 1] 

Alteration in faecal continence occurs in approximately 13-17% of women following primiparous vaginal delivery [6, 27, 28]. The prevalence is greater if urgency of defecation is included as a symptom [7]. Incontinence to flatus has been reported in up to 27% of 7,879 women surveyed 12 weeks after delivery [29]. [LEVEL OF EVIDENCE: 2] The prevalence is significantly higher in women who have undergone anal sphincter repair. Fenner et al [30] found that women who had sustained third and fourth degree tears were more likely to have bowel incontinence than women without anal sphincter injury 6 months following delivery. This was more pronounced in women with a history of 4th degree tear. Mahoney et al [21] studied 500 consecutive women after repair of a recognized 3rd or 4th degree tear and found some alteration in continence in 50% at 3 months post partum. The median Cleveland Clinic Continence score [31] in this cohort was 2 (range 0-19) and 4.4% of defecation is included as a symptom [7]. 

Non-English language papers were noted but excluded from the review unless they contained an English-language abstract providing sufficient information.

A. SURGERY FOR ADULT FAECAL INCONTINENCE

I. SPHINCTER REPAIR

Anal sphincter repair is the term used to describe primary repair of the anal sphincter mechanism following direct trauma. The most common indication is following childbirth and repair in this situation is usually performed by the attending obstetrician. Colorectal surgeons are more commonly involved in primary repair of injury that is the result of blunt or penetrating trauma. Occasionally, the anal sphincter mechanism is damaged during anorectal surgery for other pathology particularly surgery for anal fistula. 

In Western obstetric practice, the incidence of overt anal sphincter injury (grade 3 or 4 tear) is low, 3-5% following primiparous delivery and 0.5-1% following second and subsequent deliveries [5]. When prospectively looked for with endoanal ultrasound, the incidence of anal sphincter injury is higher [6, 7]. 

A meta-analysis of 717 vaginal deliveries found an incidence of new anal sphincter defects of 27% in primiparous and 9% in multiparous women using 2D endo-anal ultrasound [8]. 3D ultrasonography suggests that the incidence is somewhat less, perhaps 11%, following primiparous delivery [9]. The risk factors for sphincter injury include instrumental vaginal delivery, prolonged second stage of labor, fetal macrosomia, and a persistent occipito-position of the fetal head [7, 10-12]. Midline episiotomy is associated with higher incidence of anal sphincter injury and the angle of mediolateral episiotomy may also influence perineal outcome [13]. A policy of restrictive use of episiotomy may reduce the incidence of anal sphincter injury [14]. 

Obstetric injury of the perineum is classified as a first degree tear if confined to vaginal epithelium and skin, second degree if the perineal muscles are torn, third degree if the anal sphincter muscles (external: EAS; internal: IAS) are torn, (3a: less than 50% EAS torn; 3b: more than 50% EAS torn; 3c: IAS torn), or fourth degree if both EAS and IAS and rectal or anal mucosa are torn [15]. Primary repair of an obstetrical tear is correctly termed anal sphincter repair and is usually performed by the obstetrician immediately after delivery most commonly in the delivery room under local or epidural anesthetic. By tradition, the technique of repair has been a direct oppositional repair of the severed external anal sphincter. The internal anal sphincter, if divided, is difficult to identify separately and when separately repaired it is usually en block with the anal canal mucosa in a complete or 4th degree tear. 

There have been four randomized clinical trials [16-19] and one meta-analysis [20] that have investigated different techniques of immediate primary repair of the external anal sphincter following obstetric injury. There was a trend towards better outcome with an overlap repair; however, the meta-analysis concluded that it would be inappropriate to favor one type of repair over another [20]. [LEVEL OF EVIDENCE: 1] With regard to management of the internal anal sphincter, Mahoney et al [21] have shown persistence of an IAS defect to be adversely associated with continence outcome in a series of 500 consecutive women assessed following repair of a 3rd or 4th degree tear. 

It has been suggested that primary anal sphincter repair might be best performed by a colorectal surgeon rather than an obstetrician [22]. Nordenstam et al [23] concluded, in a single institution study of 156 women, that technique and expertise impact on the outcome of primary repair and that if needed, the repair could be safely delayed until such expertise was available. Soerensen et al [24] have found no adverse outcome with delayed primary repair. [LEVEL OF EVIDENCE: 2] 

There have been two randomized trials of post-operative management of the bowel after primary anal sphincter repair. These have shown benefit in use of a laxative rather than a constipating regimen but no advantage to the addition of a stool bulking agent [25, 26]. [LEVEL OF EVIDENCE: 1] 

Alteration in faecal continence occurs in approximately 13 - 17% of women following primiparous vaginal delivery [6, 27, 28]. The prevalence is greater if urgency of defecation is included as a symptom [7]. Incontinence to flatus has been reported in up to 27% of 7,879 women surveyed 12 weeks after delivery [29]. [LEVEL OF EVIDENCE: 2] The prevalence is significantly higher in women who have undergone anal sphincter repair. Fenner et al [30] found that women who had sustained third and fourth degree tears were more likely to have bowel incontinence than women without anal sphincter injury 6 months following delivery. This was more pronounced in women with a history of 4th degree tear. Mahoney et al [21] studied 500 consecutive women after repair of a recognized 3rd or 4th degree tear and found some alteration in continence in 50% at 3 months post partum. The median Cleveland Clinic Continence score [31] in this cohort was 2 (range 0-19) and 4.4%
had a score >9, a score deemed to be socially disruptive [32]. [LEVEL OF EVIDENCE: 2]

Management of subsequent labor following a previous anal sphincter tear must take account of obstetric risk factors, symptoms of incontinence and patient preferences. Harkin et al [12] found an approximately 5 fold increase in the incidence of recurrent sphincter tear compared to the incidence of first sphincter injury during second labor. Fynes et al [33] found that women with altered continence after first vaginal delivery were at risk of deterioration if delivered vaginally on their second pregnancy. Caesarian delivery before the onset of the second stage of labor was found to be protective [33]; however, in a systematic review, Nelson et al [34] found that pregnancy rather than delivery was a more important indicator of post partum continence. [LEVEL OF EVIDENCE: 3]

A number of studies have looked at long term outcomes after repair of a 3rd or 4th degree tears and all have shown an increasing prevalence of continence disorders with age. These findings parallel those of the general population of parous women who have not had a recognized tear [35-37]. Eogan et al [38] found in a study of women 10, 20 and 30 years following delivery that onset of menopause was the most significant determinant of symptoms, whereas Mous et al [39] found the incidence of incontinence increased with age irrespective of menopausal status. Fornell et al [40] found that subjective and objective anal function after an sphincter injury deteriorates with time and subsequent deliveries. A persistent defect in the internal anal sphincter was found to be an important determinant, an observation supported by Mahony et al [21]. [LEVEL OF EVIDENCE: 3]

II. SPHINCTEROPLASTY

The term anal sphincteroplasty is used to describe secondary or delayed reconstruction of the anal sphincter musculature, injury to which has either not been recognized at the time of injury or the outcome of primary repair has been unsatisfactory. Anterior sphincteroplasty is the most common type of reconstruction performed because of the association with obstetric injury. In this situation, the anal sphincter muscles and perineal body have separated, leaving a large defect in the anterior quadrants with horseshoe type configuration to the anal sphincter mechanism. Occasionally, the defect is such that the anal and vaginal mucosa have healed to form a cloacal defect. Anal sphincter defects related to previous anal fistula surgery or direct trauma are usually less complex and are not associated with a deficient perineum. The results of sphincteroplasty are shown in Table 1 [1, 2, 41-56].

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Continent % (excellent / good)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleshman et al [41]</td>
<td>1991</td>
<td>55</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>Engel et al [42]</td>
<td>1994</td>
<td>55</td>
<td>15</td>
<td>79</td>
</tr>
<tr>
<td>Londono-Schimmer et al [43]</td>
<td>1994</td>
<td>94</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Oliveira et al [44]</td>
<td>1996</td>
<td>55</td>
<td>29*</td>
<td>71</td>
</tr>
<tr>
<td>Gilliland et al [45]</td>
<td>1998</td>
<td>77</td>
<td>24*</td>
<td>55$</td>
</tr>
<tr>
<td>Young et al [46]</td>
<td>1998</td>
<td>54</td>
<td>18*</td>
<td>86$</td>
</tr>
<tr>
<td>Malouf et al [1]</td>
<td>2000</td>
<td>55</td>
<td>77</td>
<td>49</td>
</tr>
<tr>
<td>Karoui et al [47]</td>
<td>2000</td>
<td>74</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Osterberg et al [48]</td>
<td>2000</td>
<td>51</td>
<td>12</td>
<td>58</td>
</tr>
<tr>
<td>Morren et al [49]</td>
<td>2001</td>
<td>55</td>
<td>40</td>
<td>56</td>
</tr>
<tr>
<td>Tan et al [50]</td>
<td>2001</td>
<td>50</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Bravo Gutierrez et al [51]</td>
<td>2004</td>
<td>130+</td>
<td>120</td>
<td>6</td>
</tr>
<tr>
<td>Norderval et al [52]</td>
<td>2005</td>
<td>71</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>Zorcolo et al [53]</td>
<td>2005</td>
<td>93</td>
<td>70*</td>
<td>55</td>
</tr>
<tr>
<td>Trowbridge et al [54]</td>
<td>2006</td>
<td>86</td>
<td>67</td>
<td>11</td>
</tr>
<tr>
<td>Banisic et al [55]</td>
<td>2006</td>
<td>65</td>
<td>80*</td>
<td>48</td>
</tr>
<tr>
<td>Madoff [56]</td>
<td>2004</td>
<td>891</td>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>

# metanalysis  * Median follow-up  + 130/190 available for 10 year follow-up  $ defined as “successful”
The decision to perform anal sphincteroplasty is a function of symptoms and the anatomical extent of the sphincter defect [56]. In assessing symptoms, one of several continence scores should be used [31, 57, 58]. The two most commonly applied are the Cleveland Clinic Continence Score [31] and the St Mark's Continence Score [59]. In addition, a quality of life instrument should be applied [32]. Endoanal ultrasound is helpful in defining the extent of anal sphincter injury. 3D endoanal ultrasonography may provide further information [9]. Pelvic floor assessment using fMRI [60] or multiple contrast defecating proctography [61] is valuable in the assessment of a more global pelvic floor injury. [LEVEL OF EVIDENCE: 4]

Other causes of disordered continence should be excluded, e.g., inflammatory bowel disease, colorectal cancer and neurological lesions. Patients with background IBS are more likely to be symptomatic than those more predictable bowel habit and equivalent anal sphincter defects [62]. Pelvic floor electrophysiological assessment, while not essential, should be comprehensive and not confined to measurement of pudendal nerve terminal motor latency [63].

For symptomatic patients with a less than one quadrant anal sphincter defect, a trial of dietary modification, stool regulating drugs and physiotherapy is appropriate. There are limited data regarding the role of biofeedback with or without electrical augmentation [64, 65]; however, a recent Cochrane review concluded there were insufficient data to allow definitive assessment [66].

For patients with a more than one quadrant anal sphincter defect, anal sphincteroplasty is appropriate [4, 15, 56]. Preoperative counseling should identify post operative wound healing as the most common difficulty. The majority of patients can expect significant improvement in continence after the procedure, with a mean of 66% reporting excellent or good results in the short term [56]. [LEVEL OF EVIDENCE: 3]

Concomitant repair of a cloacal defect or vaginal fistula should be undertaken [67, 68]. There is no evidence that a defunctioning colostomy improves outcome.

Anal sphincteroplasty can be performed in the lithotomy or in the prone jack-knife position. Full bowel preparation is often performed but not mandatory, although most surgeons at a minimum would give a cleansing enema pre-operatively. The conventional incision is an inverted ‘V’ that may be closed as an inverted ‘Y’ as described by Parks [69]. If anterior levatorplasty and particularly if rectocele repair is contemplated, then a posterior fourchette incision with the patient in lithotomy may have advantages [50]. The external anal sphincter is usually repaired using an overlapping technique without separate identification and repair of the internal anal sphincter [15]. There has been one small randomized trial of direct versus overlapping sphincteroplasty which showed similar outcomes [70].

Initial success of sphincteroplasty is related to whether the anal sphincter defect is corrected [42, 71]. Early failure is usually associated with a persisting defect, identifiable using endoanal ultrasound [72]. This may be amenable to a further attempt at repair [71, 73, 74]. There is, however, increasing evidence that continence outcomes deteriorate with long-term follow-up [15, 56]. In the largest study reported to date, Bravo Gutierrez et al [51] found that only 6% of patients retained full continence 10 years following anal sphincteroplasty. The effect of age at time of operation on long-term function is controversial [75, 76]; however, long-term atrophy of the sphincters may be relevant [15]. [LEVEL OF EVIDENCE: 2]

Pre-operative physiologic testing may be helpful in the overall management of patients with faecal incontinence. However, the value of anal manometry and pelvic floor electrophysiological assessment as prognostic indicators for outcome following sphincteroplasty is controversial. There are no established parameters that reliably predict outcome following sphincteroplasty [77, 78].

III. POSTANAL REPAIR

Postanal repair was first reported by Sir Alan Parks in 1975 [3]. This procedure was designed to increase the length of the anal canal, restore the anorectal angle and re-create the flap valve mechanism, which at the time was thought essential for maintaining faecal continence. Success rates ranged from 15% to 83%, depending on the definition of the success, the length of follow-up, and possibly the cause of incontinence. The published studies regarding postanal repair include two systematic reviews of randomized controlled trials (level 1) [4, 79], two randomized controlled trials (level 1 [80] and 2 [81]), two non-randomized cohort studies (level 2) [82, 83], 8 case series of good quality (level 3) [84-91] and 10 case series of poor quality (level 4) [3, 92-100]. The results of postanal repair are shown in Table 2 [3, 80-100].

Subsequent observational studies with a median follow-up of more than 5 years revealed that continence deteriorated with time. Despite 60% to 80% of patients reporting persisting improvement, only one-third were actually continent to liquid or solid stool [86, 89, 100]. Even in the most recent study reporting the “long-term” outcome of postanal repair [91], only 23% were continent to liquid or solid stool, while 68% improved symptomatically with a median follow-up of 3 years. Possible explanations for deterioration of continence following initial improvement included unrecognized denervation and/or muscular injury of the sphincter and pelvic floor musculature,
**Table 2. Postanal Repair for Faecal Incontinence**

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients (female)</th>
<th>Median or mean follow-up: months (range)</th>
<th>Continent to solid and liquid (%)</th>
<th>Symptomatic improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parks [3]</td>
<td>1975</td>
<td>75 (68)</td>
<td>ns ( 180 or less )</td>
<td>83%</td>
<td>ns</td>
</tr>
<tr>
<td>Browning and Parks [84]</td>
<td>1983</td>
<td>42 (36)</td>
<td>ns ( 1 or less )</td>
<td>81%</td>
<td>ns</td>
</tr>
<tr>
<td>Keighley [92]</td>
<td>1984</td>
<td>89 (ns)</td>
<td>ns (6 or more)</td>
<td>63%</td>
<td>84%</td>
</tr>
<tr>
<td>Ferguson [93]</td>
<td>1984</td>
<td>9 (8)</td>
<td>ns (ns)</td>
<td>67%</td>
<td>ns</td>
</tr>
<tr>
<td>van Vroonhoven and Schouten [94]</td>
<td>1984</td>
<td>16</td>
<td>ns ns</td>
<td>63%</td>
<td>75%</td>
</tr>
<tr>
<td>Henry and Simson [95]</td>
<td>1985</td>
<td>242 (193)</td>
<td>11 (0.5 - 27)</td>
<td>60%</td>
<td>ns</td>
</tr>
<tr>
<td>Habr-Gama et al [96]</td>
<td>1986</td>
<td>42 (39)</td>
<td>12 (12)</td>
<td>52%</td>
<td>ns</td>
</tr>
<tr>
<td>Womack et al [82]</td>
<td>1988</td>
<td>16 (14)</td>
<td>26 (15 or more)</td>
<td>38%</td>
<td>88%</td>
</tr>
<tr>
<td>Scheuer et al [85]</td>
<td>1989</td>
<td>39 (ns)</td>
<td>ns (ns)</td>
<td>15%</td>
<td>70%</td>
</tr>
<tr>
<td>Yoshioka and Keighley [86]</td>
<td>1989</td>
<td>116 (7)</td>
<td>60 (ns)</td>
<td>24%</td>
<td>81%</td>
</tr>
<tr>
<td>Rainey et al [97]</td>
<td>1990</td>
<td>42 (37)</td>
<td>42 (6 - 95)</td>
<td>31%</td>
<td>71%</td>
</tr>
<tr>
<td>Scott et al [98]</td>
<td>1990</td>
<td>62 (66)</td>
<td>ns (ns)</td>
<td>45%</td>
<td>82%</td>
</tr>
<tr>
<td>Laurberg et al [99]</td>
<td>1990</td>
<td>28 (28)</td>
<td>ns (ns)</td>
<td>32%</td>
<td>75%</td>
</tr>
<tr>
<td>Orrom et al [83]</td>
<td>1991</td>
<td>17 (ns)</td>
<td>15 (ns)</td>
<td>59%</td>
<td>ns</td>
</tr>
<tr>
<td>Deen et al [80]</td>
<td>1993</td>
<td>PAR: 12 (12)</td>
<td>24</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALP: 12 (12)</td>
<td>22 (22 - 28)</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPFR: 12 (12)</td>
<td>28</td>
<td>67%</td>
<td>83%</td>
</tr>
<tr>
<td>Engel et al [87]</td>
<td>1994</td>
<td>38 (34)</td>
<td>43 (15 - 126)</td>
<td>21%</td>
<td>50%</td>
</tr>
<tr>
<td>Jameson et al [88]</td>
<td>1994</td>
<td>36 (33)</td>
<td>6 (6)</td>
<td>50%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 (6 - 72)</td>
<td></td>
<td>28%</td>
<td>53%</td>
</tr>
<tr>
<td>Setti-Carraro et al [89]</td>
<td>1994</td>
<td>34 (34)</td>
<td>73 (61 - 95)</td>
<td>26%</td>
<td>82%</td>
</tr>
<tr>
<td>Rieger et al [100]</td>
<td>1997</td>
<td>19 (ns)</td>
<td>96 (24 - 120)</td>
<td>37%</td>
<td>58%</td>
</tr>
<tr>
<td>van Tets et al [81]</td>
<td>1998</td>
<td>PAR: 11 (11)</td>
<td>3 (3)</td>
<td>27%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPFR: 9 (9)</td>
<td>3 (3)</td>
<td>22%</td>
<td>33%</td>
</tr>
<tr>
<td>Matsuoka et al [90]</td>
<td>2000</td>
<td>20 (20)</td>
<td>36 (12 - 90)</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Abbas et al [91]</td>
<td>2005</td>
<td>44 (44)</td>
<td>36 (24 - 216)</td>
<td>23%</td>
<td>68%</td>
</tr>
</tbody>
</table>
and the presence of occult anal sphincter disruption, particularly in the studies reported before endoanal ultrasonography or magnetic resonance imaging were available. Moreover, physiological and radiological evaluations before and after postanal repair have not demonstrated consistent changes in anal canal length, resting pressure, voluntary contraction pressure, anorectal sensitivity and movement of the anorectal angle [81-84, 101]. These reports of increasingly poor outcomes have diminished the popularity of this procedure significantly. [LEVEL OF EVIDENCE: 3]

Deen et al [80] in a randomized controlled trial comparing three procedures in 36 women with neuropathic faecal incontinence, found that complete continence was achieved in 42% of patients after postanal repair, 33% after anterior levatorplasty, and 67% after total pelvic floor repair. In contrast, van Tets et al [81] conducted a randomized controlled trial comparing postanal repair and total pelvic floor repair in 20 women with neurogenic faecal incontinence. Complete continence to solid or liquid stool was achieved in 27% of patients after postanal repair and in 22% after total pelvic floor repair.

IV. NON-STIMULATED MUSCLE TRANSPOSITION

A variety of muscle transposition procedures have been devised for the treatment of faecal incontinence. Early efforts focused upon the use of transposed skeletal muscle to supplement the function of a weak or disrupted anal sphincter. Early in the 20th century, a number of surgeons utilized gluteus maximus muscle, transposed in a variety of configurations, to create a neosphincter [102, 103]. In 1952, Pickrell et al [104] described the use of transposed gracilis muscle to create a neosphincter for incontinent children.

Published series of gracilis transposition are uncontrolled and demonstrate variable success rates [105-114]. [LEVEL OF EVIDENCE: 3] One study reviewed the functional results of graciloplasty longitudinally in 22 patients followed for a median 63 months [115]. 18 patients (81%) were improved at 6 months, though only one regained normal continence. Results deteriorated in 5 patients during subsequent follow up. Bilateral gracilis transposition has been used successfully in several small series [106, 116].

Success rates following gluteus transposition have likewise been variable [117-121]. [LEVEL OF EVIDENCE: 3] A prospective randomized trial in women with post-obstetric neuropathic incontinence showed similar significant degrees of improvement following both gluteus maximus transposition and total pelvic floor repair [122]. A recent retrospective review of 25 gluteoplasty patients reported restoration of continence in 18 patients (72%) and partial restoration in an additional 4 patients (16%). Donor-site and peri-rectal complications occurred in 16 patients (64%) [123].

V. STIMULATED MUSCLE TRANSPOSITION

The transposition of the gracilis muscle to reconstruct the anal sphincter was first performed in children in 1952 [104]. The blood supply is primarily from a single proximal artery that allows excellent mobility for transposition [124]. Successful electrical stimulation of a previously transposed gracilis muscle was first reported in 1988 [125], and case series from 2 independent centers were simultaneously reported in 1991 [126, 127]. Baeten et al [126] showed improved continence in 8 of 10 patients; Williams et al [127] in 12 of 20.

Even after successful muscle transposition, functional outcomes are limited by two physiological factors. First, patients are unable to consciously maintain tonic contraction of their neosphincters over long periods of time. Furthermore, even if patient volition were not a problem, gracilis muscle is poorly suited to tonic contraction. While the external anal sphincter comprises predominantly slow-twitch, fatigue-resistant type I fibers, the gracilis muscle comprises predominantly type II, fast-twitch fibers that are rapidly fatigable [128]. Graded electrical stimulation transforms type II into type I muscle fibers [129], and use of an implantable electrical pulse generator has been shown to convert transposed gracilis to a muscle with predominantly type I fibers [126-128]. The gracilis muscle is well suited to electrical stimulation due to the relatively constant proximal location of the neurovascular bundle, which is easily identified at surgery [130].

The results of stimulated graciloplasty are shown in Table 3 [131-141]. [LEVEL OF EVIDENCE: 2] In 1995, Baeten reported his results in 52 patients, with 38 (72%) becoming continent after surgery [131]. In a subsequent paper by this group published in 2003, 200 patients followed for a median of 261 weeks were reported [139]. The overall success rate was 72%. Patients with incontinence due to trauma had the best results (82% success), while patients with incontinence due to congenital anorectal malformation had the worst results (52% success). 138 complications were reported, including disturbed evacuation in 32 patients (16%), infection in 24 (12%), pain in 16 (8%) and pulse generator displacement in 12 (6%). Ten patients (5%) had anorectal perforations, 7 of whom eventually obtained a successful outcome. Rosen et al [142] reported restoration of continence in 9 of 10 patients treated by dynamic graciloplasty using a “split-sling” wrap configuration. Sleznezef et al [143] treated 16
patients and 13 had improved continence. However, 8 patients suffered morbidity, resulting in 33 subsequent admissions and 23 reoperations.

Three multicenter prospective trials of dynamic muscle plasty have been performed to date [134-136]. In each of these studies, patients served as their own controls. No randomized prospective trials have been performed.

Madoff et al studied 139 patients from 12 centers, 128 of whom had gracilis wraps and 11 gluteus wraps. [134] Of those patients, 104 were treated for faecal incontinence, and 35 underwent total anorectal reconstruction following abdominoperineal resection for cancer. Success rates for graciloplasty were 71% for patients with acquired incontinence and 50% for those with incontinence due to a congenital abnormality. There were a total of 138 complications for the entire group. Wound complications (41 major and 35 minor) were both the most prevalent and the most consequential. Other complications included pain in 28 patients (22%), hardware problems in 14 (11%) and tendon detachment in 4 (3%). Centers with significant prior experience with the procedure had substantially fewer major wound complications (17.4 vs. 33.1%) and significantly higher success rates (80% vs. 47%).

Mander et al [135] reported the results of dynamic graciloplasty in 64 patients with refractory faecal incontinence treated at 7 centers. Of those patients, 104 were treated for faecal incontinence, and 35 underwent total anorectal reconstruction following abdominoperineal resection for cancer. Success rates for graciloplasty were 71% for patients with acquired incontinence and 50% for those with incontinence due to a congenital abnormality. There were a total of 138 complications for the entire group. Wound complications (41 major and 35 minor) were both the most prevalent and the most consequential. Other complications included pain in 28 patients (22%), hardware problems in 14 (11%) and tendon detachment in 4 (3%). Centers with significant prior experience with the procedure had substantially fewer major wound complications (17.4 vs. 33.1%) and significantly higher success rates (80% vs. 47%).

Baeten et al [136] reported the results of dynamic graciloplasty in 123 patients treated at 20 centers as part of the Dynamic Graciloplasty Therapy Study Group (DGTSG). The aims of this study were to assess both the safety and efficacy of this treatment; 189 adverse events occurred in 91 patients, including one death due to pulmonary embolism. There were 18 major and 31 minor infectious complications. There were 42 instances of therapy-associated pain, occurring variably in the donor leg, at the anal canal, or at the device site. There were 11 lead dislodgements but no problems with lead breakage or pulse generator malfunction. A follow-up study showed full or partial recovery from these complications in 87% of patients. [137] This study, in contrast to others, was based upon data from daily continence diaries. A successful result (defined as a 50% or greater decrease in incontinent events in patients without pre-existing stomas) was achieved in 63% of patients after one year. Another follow-up of this patient cohort demonstrated stable success rates at 18 months (55%) and 24 months (56%) [138]. Statistically significant improvements in the physical and social function scales of the SF-36 were also recorded at 12 months.

A multicenter retrospective trial from Belgium using dynamic graciloplasty treated 60 patients with 27 failures [140]. Continence was achieved in 78% of the group. However, more than half (26 patients) required the use of antegrade continence enemas or other measures to maintain continence. Seven patients had a permanent stoma constructed. Seventy-five complications occurred with 61 total reoperations. Loss of muscle stimulation occurred in 22 patients; 10 were due to issues specific to the stimulator and leads, 4 were due to technical failure of the muscle wrap. Functional outcome was directly associated with a

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Percentage continent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeten et al [131]</td>
<td>1995</td>
<td>52</td>
<td>25.2 months (mean)</td>
<td>73</td>
</tr>
<tr>
<td>Geerdes et al [132]</td>
<td>1996</td>
<td>67</td>
<td>32.4 months (mean)</td>
<td>78</td>
</tr>
<tr>
<td>Cavina et al [133]</td>
<td>1998</td>
<td>31</td>
<td>37.8 months (mean)</td>
<td>85</td>
</tr>
<tr>
<td>Madoff et al [134]</td>
<td>1999</td>
<td>131</td>
<td>24 months (median)</td>
<td>66</td>
</tr>
<tr>
<td>Mander et al [135]</td>
<td>1999</td>
<td>64</td>
<td>16 months (median)</td>
<td>69</td>
</tr>
<tr>
<td>Baeten et al [136]</td>
<td>2000</td>
<td>123</td>
<td>23 months (mean)</td>
<td>74</td>
</tr>
<tr>
<td>Wexner et al [138]</td>
<td>2002</td>
<td>83</td>
<td>24 months</td>
<td>53</td>
</tr>
<tr>
<td>Rongen et al [139]</td>
<td>2003</td>
<td>200</td>
<td>16.3 months (median)</td>
<td>72</td>
</tr>
<tr>
<td>Pennickx et al [140]</td>
<td>2004</td>
<td>60</td>
<td>48 months (median)</td>
<td>55</td>
</tr>
<tr>
<td>Tillin et al [141]</td>
<td>2006</td>
<td>49</td>
<td>43 months (median)</td>
<td>70</td>
</tr>
</tbody>
</table>

* variable definitions; does not necessarily denote perfect continence. Issues of divergence in technique arose from these studies, each of which has seen increasing consensus in the literature despite a lack of randomized trial data. Thus, intramuscular (vs. epineural) electrodes are now universally employed, and diverting stomas and ‘vascular delay’ prior to muscle transposition are no longer utilized.
maintenance of stimulation and initiation of stimulation within 50 days of surgery.

Very few studies have examined the long term results with dynamic muscle wraps. Thornton et al [144] reported on the 5-year follow up of 38 patients who had undergone dynamic graciloplasty. Of the 33 patients available for follow-up by telephone interview, obstructive defecation was a problem for 11% of the cohort and 16% had been converted to a permanent colostomy. Of those with a functioning graciloplasty (22 patients) who reported a faecal incontinence score of less than 12 (range 0-24), 50% reported problems with obstructive defecation and 64% felt their bowel habits had negatively impacted their quality of life. Long-term complications were primarily related to stimulator issues; ten patients required 15 operations to replace stimulator components. However, 72% of patients reported pain, swelling or paresthesias of the donor leg and 27% reported sexual dysfunction.

Tillin et al [141] performed a prospective case-comparison study of 49 patients who had a dynamic graciloplasty and 87 patients who either refused the surgery or were not offered the surgery. The primary outcomes evaluated were symptoms, quality of life, anxiety, and depression. Of the treated group, the procedure failed completely in 15 patients. At two year follow-up, two-thirds of patients were either never or rarely incontinent to liquid or solid stool. Up to 50% of patients with a satisfactory outcome reported disordered evacuation and 8 other patients were deemed failures due to this problem. In comparison to the 87 patients who did not undergo treatment, there were significantly more patients in the dynamic graciloplasty group who reported a greater than 20% improvement in their incontinence scores. However, the treated group also had a significantly worse pain as assessed on a validated pain scale.

Chapman et al [145] performed a systematic review of dynamic graciloplasty for faecal incontinence on behalf of the Australian Safety and Efficacy Register of New Interventional Procedures- Surgical (ASERNIP-S). The authors reviewed 37 original articles published between 1991 and October 2000. All of the papers were judged to be of low-evidence quality, as all but one paper were case series, and the sole comparative study utilized historical controls. Mortality excluding cancer deaths was 1% (95% confidence interval 1-3%) and morbidity 1.12 (95% CI 0.14 - 2.08) events per patient. Success was variably defined between studies, but was reported as ranging from 42-58%. The ASERNIP-S Review Group determined that “the safety of the procedure cannot be determined at the present time due to an incomplete and/or poor-quality evidence base” and that “efficacy is established.” Tan et al [146] examined three treatments for faecal incontinence including dynamic graciloplasty, artificial bowel sphincter and end stoma. They concluded that the most cost effective intervention was an end stoma, the artificial bowel sphincter was most cost-effective after 10 years and that dynamic graciloplasty should only be considered as an alternative in highly specialized centers.

VI. ARTIFICIAL ANAL SPHINCTER

Artificial sphincters have been used for the treatment of urinary incontinence since 1973 [147]. A success rate of 79% with a mean follow-up of 7.2 years has been reported. The device (AMS Sphincter 800® Urinary Control System, American Medical Systems, Minnesota, USA) and its subsequent modifications is a totally implantable system consisting of 3 parts: an inflatable occlusive cuff that is implanted around the native sphincter, a pressure-regulating balloon that is implanted in the prevesical space, and a control pump that is implanted in the labia majora or the scrotum. In 1987, Christiansen & Lorentzen [148] applied this device to a patient with faecal incontinence. The patient had an excellent result with no complications at a follow-up of three months.

Early promising results [149] prompted the modifications of the AMS Sphincter 800®, which eventually culminated in the development of Neosphincter® (American Medical Systems, Minneapolis, USA) that was specifically designed for faecal incontinence and became available in May 1996.

The published studies evaluating the safety and effectiveness of the newest sphincter system (Acticon Neosphincter®) include one randomized controlled trial (level 1) [150], one non-randomized cohort case control study (level 2) [151], 9 non-randomized cohort studies (level 2) [152-160], three systematic reviews of various types of studies with some heterogeneity (level 3) [161-163], one retrospective case control study (level 3) [164], 3 case series of good quality (level 3) [165-167], 4 case series of low quality (level 4) [168-171], and 3 case reports (level 4) [172-174]. The results of these studies except for case reports are shown in Table 4 [150-160, 164-171]. Two studies by Romano et al [175, 176] and two case reports [177, 178] were excluded from the analysis because artificial anal sphincters in those studies were not implanted for faecal incontinence, but as a part of total anorectal reconstruction in patients who had abdominoperineal resection for rectal cancer. [LEVEL OF EVIDENCE: 2]

No mortality was reported, but overall complication rate varied between 11 and 87%. Surgical site infections (9 to 58%) and erosion of the adjacent skin (6 to 32%) were common. Up to 46% of patients underwent revisional surgery, and the proportion of patients with a functioning device at the time of evaluation after follow-up of between 6 and 34 months ranged between
Table 4. Artificial anal sphincter for faecal incontinence with Acticon Neosphincter®

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Mean or median follow-up (months)</th>
<th>Number (%) of functioning devices</th>
<th>Overall complications</th>
<th><em>Success</em> in patients with a functioning device</th>
<th><em>Success</em> in intention to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaizey et al [152]</td>
<td>1998</td>
<td>6</td>
<td>10</td>
<td>5 (83%)</td>
<td>ns</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>Lehur et al [153]</td>
<td>2000</td>
<td>24</td>
<td>20</td>
<td>20 (83%)</td>
<td>42%</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>Dodi et al [154]</td>
<td>2000</td>
<td>8</td>
<td>10.5</td>
<td>6 (75%)</td>
<td>38%</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>O’Brien et al [165]</td>
<td>2000</td>
<td>13</td>
<td>ns</td>
<td>10 (77%)</td>
<td>69%</td>
<td>90%</td>
<td>69%</td>
</tr>
<tr>
<td>Malouf et al [168]</td>
<td>2000</td>
<td>18</td>
<td>26</td>
<td>7 (39%)</td>
<td>67%</td>
<td>ns</td>
<td>39%</td>
</tr>
<tr>
<td>Attomare et al [166]</td>
<td>2001</td>
<td>28</td>
<td>19</td>
<td>21 (75%)</td>
<td>32%</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Devesa et al [155]</td>
<td>2002</td>
<td>53</td>
<td>26.5</td>
<td>26 (49%)</td>
<td>58%</td>
<td>65%</td>
<td>53%</td>
</tr>
<tr>
<td>Wong et al [156]</td>
<td>2002</td>
<td>115</td>
<td>12</td>
<td>75 (65%)</td>
<td>87%</td>
<td>85%</td>
<td>54%</td>
</tr>
<tr>
<td>Ortiz et al [157]</td>
<td>2002</td>
<td>22</td>
<td>28</td>
<td>15 (68%)</td>
<td>77%</td>
<td>60%</td>
<td>41%</td>
</tr>
<tr>
<td>Lehur et al [158]</td>
<td>2002</td>
<td>16</td>
<td>25</td>
<td>12 (75%)</td>
<td>31%</td>
<td>92%</td>
<td>69%</td>
</tr>
<tr>
<td>Parker et al [159]</td>
<td>2003</td>
<td>37</td>
<td>39</td>
<td>17 (46%)</td>
<td>43%</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Michot et al [169]</td>
<td>2003</td>
<td>25</td>
<td>34.1</td>
<td>20 (80%)</td>
<td>20%</td>
<td>79%</td>
<td>60%</td>
</tr>
<tr>
<td>Ortiz et al [151]</td>
<td>2003</td>
<td>8:AAS</td>
<td>44</td>
<td>5 (63%)</td>
<td>75%</td>
<td>CCF-FI score:16→8</td>
<td></td>
</tr>
<tr>
<td>Casal et al [160]</td>
<td>2004</td>
<td>10</td>
<td>29</td>
<td>9 (90%)</td>
<td>60%</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>O’Brien et al [150]</td>
<td>2004</td>
<td>7:AAS</td>
<td>6</td>
<td>6 (86%)</td>
<td>43%</td>
<td>CCF-FI score:19→4.8</td>
<td></td>
</tr>
<tr>
<td>La Torre et al [170]</td>
<td>2004</td>
<td>7</td>
<td>26.3</td>
<td>5 (71%)</td>
<td>43%</td>
<td>100%</td>
<td>71%</td>
</tr>
<tr>
<td>Attomare et al [171]</td>
<td>2004</td>
<td>25</td>
<td>ns: long-term</td>
<td>6 (24%)</td>
<td>76%</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>da Silva et al [164]</td>
<td>2004</td>
<td>11:AAS</td>
<td>12</td>
<td>11 (100%)</td>
<td>55%</td>
<td>CCF-FI score:18→7.5</td>
<td></td>
</tr>
<tr>
<td>Michot et al [167]</td>
<td>2007</td>
<td>9</td>
<td>21.5</td>
<td>8 (89%)</td>
<td>11%</td>
<td>CCF-FI score:19→8.6</td>
<td></td>
</tr>
</tbody>
</table>

CCF-FI: Cleveland Clinic Florida Faecal Incontinence (0: full continence - 20: worst incontinence); AAS: artificial anal sphincter; DG: dynamic graciloplasty; SC: supportive care; GN: gracilis neosphincter; ns: not stated; *Success* is defined as “continence to solid and liquid stool without significant obstructed defecation, otherwise defined in each study.”
24 and 100%, with up to 67% patients having their devices explanted. Most of the patients (78 to 100%) with a functioning device were continent to solid stool, 56 to 95% were continent to solid and liquid stool, and 22 to 67% were completely continent. The success rate in patients with a functioning device was 44 to 100%, and the intention-to-treat success rate was 41 to 83%. Studies of smaller number of patients or shorter follow-up period tend to report better outcomes.

Wong et al [156] has reported the largest, multicenter prospective trial to date. Of 115 patients, 75 patients (65%) retained a functioning device after a median follow-up of 12 months. Overall complication rate was 87%. Forty-six percent of patients underwent revisional surgery and device explantation was required in 37%. Thirty patients (40%) experienced obstructed defecation with 21 reporting to have been impacted. A successful outcome was achieved in 85% of the 61 patients with a functioning device, while the intention-to-treat success rate was 54%.

With a longer follow-up period of presumably 5 years, Altomare et al [171] reported a poorer and “disappointing long-term” results. In their initial report of 28 patients in 2001 [166], 21 patients (75%) retained a functioning device with a median follow-up of 19 months. The success rate in patients with a functioning device was 76%, and the intention-to-treat success rate was 50%. In their follow-up study of the 21 patients who retained the device in their initial report, a further 4 patients had the device removed, because of mechanical failure (2), late infection (1) or untreatable obstructed defecation (1). Out of the 17 patients who continued to have an implanted device, 14 were available for long-term evaluation. Out of the 14 patients, 5 had a revision operation, and 8 no longer activated the device because of obstructed defecation (7) or anal pain (1). Obstructed defecation occurred in 7 patients, who were unable to defecate without an enema. Although 8 patients were reasonably continent to stool, 5 of them were significantly constipated. Over all, out of the initial 25 patients for whom longer follow-up was available, only 6 patients (24%) retained a functioning device, and a good functional result was achieved only in 3 (50%) out of the 6 patients, while the intention-to-treat success rate was only 12%.

O’Brien et al [150] conducted a prospective randomized controlled trial, comparing the artificial anal sphincter (AAS) and a program of supportive care (SC). Out of the 7 patients who underwent the implantation surgery, 6 (86%) retained a functioning device after a 6 month follow-up with complication rate being 43%. The Cleveland Clinic Faecal Incontinence (CCF-FI) score (0: full continence – 20: worst incontinence) significantly decreased from a preoperative mean of 19.0 +1.2 to a postoperative mean of 4.8±4.0 in the AAS group, while it did not change in the 7 patients of SC group with an initial mean of 17.1+2.3 and a final mean of 14.3+4.6 at 6 months. Ortiz et al [151] performed a non-randomized cohort case control study, comparing the AAS and the dynamic graciloplasty (DG). Out of the 8 patients who underwent AAS implantation, 5 (63%) continued to have a functioning device after a median follow-up of 44 months with 75% complication rate. Out of the 8 patients who underwent DG, 4 (50%) retained the stimulator after a median follow-up of 39 months with 63% complication rate. The median CCF-FI score significantly decreased from 16 to 8 in the AAS group, while it did not change from 18 to 18 in the DG group.

A retrospective case control study was reported by da Silva et al [164], comparing the AAS and the gracilis neosphincter (GN) procedure in patients with imperforate anus. All of the 11 patients who underwent the AAS retained a functioning device after a mean follow-up of 12 months with complication rate being 45%. In the 5 patients who underwent the GN, the complication rate was 60% after a mean follow-up of 38.8 months. The mean CCF-FI score significantly decreased in both groups (AAS: before 18 vs. after 7.5; GN: 17.4 vs. 9.4).

There is another artificial sphincter developed and reported by Hajivassiliou et al [179]. Different from the artificial anal sphincter (AAS), Acticon®, this prosthetic bowel sphincter (PBS) is implanted around the rectum at the supralevator plane through an abdominal approach. Finlay et al [180] implanted the PBS in twelve patients with severe faecal incontinence. At a median follow-up of 59 (range 30–72) months, nine of the 12 patients had a functioning device. There were no device-related infective complications after the initial operation, but one patient developed pseudomembranous colitis and had the device removed. The PBS was effective in restoring continence in ten of 11 patients. Median (range) Cleveland Clinic continence scores improved from 16 (7–20) before to 3 (0–7) after surgery. In two patients, the device was eventually removed owing to infection after revisional surgery that was performed due to the displacement of the sphincter component.

The PBS has two potential advantages over the AAS: it may cause less infective complications due to its sterile transabdominal implantation, and it can be applied to a severely incontinent patient with major perineal tissue loss. On the other hand, possible disadvantages include the need for a transabdominal implantation and the possibility of a severe pelvic or intraabdominal infection should an erosion occur.

At present the AAS is more widely used, and its safety and efficacy have been examined by many institutions. The PBS may have some place as an artificial sphincter because of its apparent advantages over the AAS, but its safety and efficacy need to be investigated extensively before widespread implantation is undertaken.
Sacral nerve stimulation (SNS) was first applied for the treatment of faecal incontinence in 1994 by Matzel et al [181] in patients with functional deficits of the anal sphincter but no morphologic defect. The concept of recruiting residual function of an inadequate anorectal continence organ by electrostimulation of its peripheral nerve supply, i.e. the sacral spinal nerves, was adopted from the field of urology in the early 1990's [182], where it has been used since 1981 [183]. The rationale for applying sacral nerve stimulation (SNS) to faecal incontinence was based on both clinical observations and anatomic considerations (from the former, the beneficial effect on bowel habits and anorectal continence function and increased anorectal angulation and anal canal closure pressure seen in urologic patients; from the latter, the demonstration by dissection of a dual peripheral nerve supply of the striated pelvic floor muscles that govern these functions [182] with the sacral spinal nerves being the most distal common location of this dual nerve supply. It was hypothesized that stimulating the sacral spinal nerves could both enhance physiologic function and improve the symptoms of faecal incontinence.

1. TECHNIQUE

SNS has become a minimally invasive technique with low morbidity. The surgical technique can be divided into two stages:

As no other predictors of SNS outcome exist at present, patients are uniformly selected for operative implantation of a permanent neurostimulation device on the basis of clinical improvement during test stimulation. This first stage, termed percutaneous nerve evaluation (PNE), is used to confirm a satisfactory nerve response and then evaluate the clinical effect of stimulation prior to the implantation of a permanent device. Therapeutic trial stimulation is performed for a one to three-week period, a time period sufficient to prove its therapeutic effect - commonly considered if the frequency of episodes of faecal incontinence documented by bowel-habit diary is alleviated by at least 50% and if the improvement is reversible after discontinuation. Two technical options are used for subchronic percutaneous nerve evaluation (PNE): a temporary, percutaneously placed, test stimulation lead (or multiple leads) that will be removed at the end of this phase; or operative placement of a quadripolar lead, the so-called “foramen electrode” close to a target nerve. This electrode can stay in place and be used for permanent stimulation, if the test stimulation is effective. Today most commonly this foramen electrode is placed by a minimally invasive technique that uses a foramen electrode with a modified anchoring device, the so-called “tined lead” placed through a trochar. For screening, both types of leads are connected to an external pulse, the latter with a percutaneous extension cable.

The second stage is implantation of a permanent electrode and neurostimulator if screening is successful. Those with a temporary lead require simultaneous implantation of the pulse generator and the quadripolar lead, most commonly as a tined lead procedure. Those with a foramen electrode already in place for screening will undergo removal of the percutaneous extension before placement of the pulse generator (so-called “two-stage implant” [184]). Bilateral placement of foramen electrodes remains the exception, based either on improved outcome of bilateral stimulation during the screening phase [185] or on conceptual considerations [186]. The pulse generator is placed subcutaneously in the abdominal wall or gluteal area. The pulse generator is activated and stimulation parameters are set early after surgery by telemetry. The pulse generator can be deactivated by the patients with a small, handheld device commonly referred to as a “patient programmer.”

2. PATIENT SELECTION AND INDICATIONS

Today, a variety of causes leading to faecal incontinence can be treated with SNS. During the initial SNS experience, only patients presenting with deficient function but no morphologic defect of the striated anal sphincter and levator ani were eligible for treatment. [182, 187, 188]. However, because of the high predictive value of the test-stimulation, investigators took a more pragmatic, trial and error approach to subsequent patient selection. Patients are now selected for SNS based upon PNE results rather than conceptual considerations of the potential mechanism of action. Test stimulation is indicated, not by an underlying physiologic condition, but by the existence of an anal sphincter with reduced or absent voluntary squeeze function and existing reflex activity, indicating an intact nerve-muscle connection (confirmed by intact anocutaneous reflex activity or by muscular response to pudendal stimulation with the St. Mark’s electrode) [187].

At present, the test stimulation is the only reliable modality to select patients who will likely benefit from permanent therapeutic stimulation. Two studies focused on potential predictors of success of SNS: In a study by Gourcerol et al [189], age was the only variable related with success of temporary stimulation. In patients with a permanent implant, neurologic disorders, delay of the left bulbocavernous reflex and a prolonged or absent bulbocavernous reflex were more frequent in patients with successful outcome. In another cohort analysis, the need for repeated temporary procedures was associated with failure during the screening in univariate and multivariate analysis [190]. A low threshold to obtain motor response during temporary lead placement.
was revealed to be associated with improved outcome only in univariate, but not in multivariate, analysis. Evidence of anal sphincter injury was related to a greater risk of failure during temporary testing, but not with permanent implant.

Contraindications to SNS include pathologic conditions of the sacrum preventing adequate electrode placement (such as spina bifida), skin disease at the area of implantation, anal sphincter damage requiring a sphincter substitute (e.g. artificial bowel sphincter, dynamic graciloplasty), trauma sequelae with micturition disorders or low bladder capacity, pregnancy, bleeding complications, psychological instability, low mental capacity, and the presence of a cardiac pacemaker or implantable defibrillator.

3. MECHANISM OF ACTION

The mechanism of action of SNS remains uncertain. Clinical outcome of SNS has been seen to correlate with results of anorectal physiology studies, but the effect of chronic stimulation varies greatly among published reports [187, 188]. Data are in part contradictory and inconclusive and sometimes not reproducible. The effect appears to be somatomotoric [191-198], somatosensoric [191], based on changes in the autonomic nervous system [191, 193, 199], and not limited to the continence organ per se, but also affecting the central nervous system [200]. Qualitative changes in anal and rectal motility, reduction of spontaneous rectal motility complexes [201, 202], and spontaneous anal sphincter relaxation [201] have been recorded during SNS. An effect on the mucosal neurochemistry during SNS has also been shown with elevation of Substance P and TRPV1 levels [203].

The relevance of each of these effects has not been proven in specific pathophysiological conditions. The mechanism of action is most likely multifactorial and different depending on the underlying condition. [LEVEL OF EVIDENCE: 4]

4. OUTCOME

The results of permanent SNS following the initial and pragmatic, trial-and-error, patient selection process are shown in Table 5 [186, 191-194, 204-220]. Most studies have represented patients with very heterogeneous pathophysiologic conditions. Most commonly, clinical outcome is reported as an improvement in incontinent episodes or days with incontinence during the period of observation, changes in Cleveland Clinic Incontinence score and in quality of life. The studies vary with regard to design and number of patients, but there is general agreement regarding the two-step stimulation for selection for permanent implant.

Matzel et al [208] published a multicenter prospective trial of SNS in 37 patients, 34 of whom underwent a permanent neurostimulator implant. Not only were the frequency of incontinence episodes and the CCIS score improved significantly, but also the ability to postpone defecation. These effects were attained immediately.

In most studies, quantitative measures are used to describe the clinical benefit, such as days with incontinent episodes/period of observation, absolute numbers of incontinent episodes/period of observation, ability to postpone defecation (in minutes), and percentage of improvement. Even though published reports differ with regard to patient population, a general pattern of outcome can be observed: when compared with baseline status, the clinical outcome is significantly improved. [LEVEL OF EVIDENCE: 2]

Melenhorst et al [194] published the largest single center study, with 100 patients undergoing permanent SNS. Late failure occurred in 21 patients as defined by a relapse of symptoms to less than 50% improvement over baseline, implementation of another therapy for faecal incontinence, or patient dissatisfaction. The mean time for definitive failure was 13.6 months (range 3–42.4). There was no evidence of technical failure as lead migration or lead breakage. Leroi et al [210] reported a double-blind, cross-over multicenter study in 34 patients with faecal incontinence treated with SNS. Three months after implantation, patients were randomized in a double-blind manner to on- or off-stimulation for a 2-month period, with reversal of the activation mode after 1 month. Of these, 24 of 27 randomized patients completed the 2-month trial. A significant decrease in median frequency of faecal incontinence episodes was noted during the on-stimulation period compared with the off-stimulation period. No significant change was observed between on and off stimulation for frequency of urgency episodes, delay in postponing defecation, or median number of bowel movements per week (10.2 and 11.1 for on and off, respectively).

There was a trend towards greater improvement in the Cleveland Clinic Incontinence Score during on stimulation compared with off stimulation (8.5 vs 10.5; ns). A total of 24 patients (89%) considered that they had improved during the on period compared with 17 (63%) during the off period.

A report by Rosen et al [191] highlights the effect of SNS in a cohort of patients, 75% of whom suffered from faecal incontinence of neurologic origin. Frequency of incontinence episodes/week was reduced from 6 to 2 at 15 months follow-up.

Recently, some small case series and individual case reports have demonstrated the therapeutic effect of SNS in groups of patients presenting with distinct conditions and well defined anorectal physiology findings, e.g. muscular dystrophy [221], a history of rectal resection for cancer [216], neurologic dysfunction including spinal disc prolapse [217], status after rectal prolapse repair [218], after rectal resection and neoadjuvant chemoradiation [187], and with internal and external sphincter disruption due to Crohn’s disease [219]. [LEVEL OF EVIDENCE: 4]
Table 5. Outcome of Sacral Nerve Stimulation

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Incontinent episodes per week</th>
<th>Incontinence-score (CCIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before SNS (baseline)</td>
<td>After SNS (last FU)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before SNS (baseline)</td>
<td>After SNS (last FU)</td>
</tr>
<tr>
<td>Malouf et al [204]</td>
<td>2000</td>
<td>5</td>
<td>16*</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Rosen et al [191]</td>
<td>2001</td>
<td>16</td>
<td>15*</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Ganio et al [192]</td>
<td>2001</td>
<td>16</td>
<td>15,5</td>
<td>5,8</td>
<td>0</td>
</tr>
<tr>
<td>Rippetti et al [205]</td>
<td>2002</td>
<td>4</td>
<td>24</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Matzel et al [206]</td>
<td>2003</td>
<td>16</td>
<td>32,5</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Althomare et al [207]</td>
<td>2004</td>
<td>14</td>
<td>14*</td>
<td>7</td>
<td>0,5</td>
</tr>
<tr>
<td>Matzel et al [208]</td>
<td>2004</td>
<td>34</td>
<td>24*</td>
<td>16,4</td>
<td>2,0</td>
</tr>
<tr>
<td>Jarrett al. [193]</td>
<td>2004</td>
<td>46</td>
<td>12*</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Rasmussen et al [209]</td>
<td>2004</td>
<td>34</td>
<td>6</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Leroi et al [210]</td>
<td>2005</td>
<td>34</td>
<td>7*</td>
<td>3,5*</td>
<td>0,5*</td>
</tr>
<tr>
<td>Kenefick et al [211]</td>
<td>2006</td>
<td>19</td>
<td>24*</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Holzer et al [212]</td>
<td>2007</td>
<td>29</td>
<td>35*</td>
<td>2,3</td>
<td>0,67</td>
</tr>
<tr>
<td>Hetzer et al [213]</td>
<td>2007</td>
<td>37</td>
<td>13</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Tan et al [214]</td>
<td>2007</td>
<td>53</td>
<td>12</td>
<td>9,5</td>
<td>3,1</td>
</tr>
<tr>
<td>Melenhorst et al [194]</td>
<td>2007</td>
<td>100</td>
<td>25,5</td>
<td>10,4</td>
<td>1,5</td>
</tr>
<tr>
<td>Melenhorst et al [215]</td>
<td>2008</td>
<td>A†=20</td>
<td>29,2</td>
<td>8,9</td>
<td>4,2</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>B††=20</td>
<td>22,6</td>
<td>8,3</td>
<td>1,4</td>
</tr>
</tbody>
</table>

**DISTINCT CONDITIONS**

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Incontinent episodes per week</th>
<th>Incontinence-score (CCIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before SNS (baseline)</td>
<td>After SNS (last FU)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before SNS (baseline)</td>
<td>After SNS (last FU)</td>
</tr>
<tr>
<td>Jarrett et al [216]</td>
<td>2005</td>
<td>2</td>
<td>12</td>
<td>9,8</td>
<td>1</td>
</tr>
<tr>
<td>Jarrett et al [217]</td>
<td>2005</td>
<td>12</td>
<td>12*</td>
<td>9,2</td>
<td>2,4</td>
</tr>
<tr>
<td>Jarrett et al [218]</td>
<td>2005</td>
<td>4</td>
<td>12</td>
<td>12,2</td>
<td>2</td>
</tr>
<tr>
<td>Ratto et al [186]</td>
<td>2005</td>
<td>4</td>
<td>19,5</td>
<td>12</td>
<td>2,5</td>
</tr>
<tr>
<td>Vitton et al [219]</td>
<td>2008</td>
<td>5</td>
<td>14*</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Jarrett et al [220]</td>
<td>2008</td>
<td>8</td>
<td>26,5*</td>
<td>5,5*</td>
<td>1,5*</td>
</tr>
</tbody>
</table>

* median, otherwise all data presented at mean
† A: after sphincter repair, †† B: with sphincter gap 17-33% of circumference, without repair.
An increasing body of evidence indicates that SNS may also be a treatment option for patients with sphincter defects, un repaired or after attempted anatomic reconstruction. The presence of an internal anal sphincter defect on anal sonography is reportedly unrelated to the success of permanent SNS [190]. Three of five patients with ultrasound evidence of sphincter disruption measuring 25%–33% of the circumference benefited from chronic SNS [222]. In 20 patients with unrepaired obstetric trauma, SNS resulted in significant improvement of the Cleveland Clinic score (CCS; from 16 to 3) in 19, and of the numbers of incontinent episodes per week (from 10–1) with a minimum follow-up of 4 years [223]. In patients with an unrepaired external or internal anal sphincter or both, the frequency of incontinent episodes per week decreased from 1.3 to 0.3 and the CCS improved (from 15 to 3.5) with a follow-up of 12–97 months [224]. Melenhorst et al. showed that the primary use of SNS in patients with a sphincter gap 17–33% of the circumference appeared to result in an outcome similar to its use after failed sphincter repair [215].

SNS in 6 of 8 patients presenting with faecal incontinence related to obstetric full thickness anal sphincter lesions ranging from >30-150 degree resulted at a median follow-up of 26.5 months in improved frequency of incontinent episodes per week from 5.5 to 1.5 clinical function [220], improved ability to postpone bowel emptying and improved ASCRS quality of life scores. A further cohort study [225] reports on the effect of permanent SNS in 53 patients presenting with either an intact external anal sphincter (N=32 [37.5% after sphincter repair]) or an external anal sphincter lesion (N=21 [81% after prior sphincter repair]) of ≤90° (N=11) or 90–120° (N=10). Improvement of symptoms and quality of life was achieved in all groups. Outcome after 12 months was statistically not significantly different between those patients with an intact sphincter complex and those without. Chan & Tjandra [226] reviewed 53 consecutive patients who underwent SNS for faecal incontinence. There was no significant difference in outcomes between those with and without an external sphincter defect. [LEVEL OF EVIDENCE: 3]

In a randomized controlled trial Tjandra et al [225] compared the effect of sacral neurostimulation for severe faecal incontinence with supervised optimal medical therapy that comprised pelvic floor exercises, bulking agents, and dietary manipulation. Permanent SNS in 53 patients was significantly better than conservative treatment in 60 patients: Cleveland Clinic Continence Score 1.2 vs. 14.1; incontinent episodes/week: 3.1 vs 9.4, days with incontinence/week: 1 vs. 9.4, lifestyle: 3.31 vs. 2.31, coping/behavior: 2.68 vs. 1.86, depression/self-perception: 3.25 vs. 2.64, embarrassment: 2.76 vs. 1.78. [LEVEL OF EVIDENCE: 2]

5. QUALITY OF LIFE

As with indications, outcome assessment has also evolved and aspects of quality of life were added to the evaluation of outcome (Cleveland Clinic Continence Scoring System, SF36 and FIQL Score.) The therapeutic impact of SNS is most evident when a disease-specific quality-of-life instruments ASCRS FIQL scale is applied.

In the multicenter clinical trial by Matzel et al [208], ASCRS FIQL was significantly increased in all 4 scales, SF-36 scores improved in 7 of 8 scales, the greatest being social functioning and mental health; but only social functioning reached statistical significance. A similar result was published by Leroi et al [210] using the French version of the ASCRS QOL (FIQL): at the final follow-up visit improvements in lifestyle, coping and behavior, depression and self-perception and embarrassment were significantly improved. Hetzer et al [213] demonstrated a significant improvement of the median Gastrointestinal Quality of Life Index score with permanent from a baseline score of 96 (range 47–128) to 107 (range: 36–128) at 6 months post-implantation. [LEVEL OF EVIDENCE: 2]

6. COST BENEFIT / ROLE IN THE TREATMENT ALGORITHM

Permanent SNS is expensive. Hetzer et al [227] conducted a comparative cost analysis of SNS with conservative treatment, anterior sphincteroplasty, dynamic graciloplasty and creation of a stoma in 34 consecutive patients. The 5-year cumulative costs for SNS is €19333, compared with €35965 for stoma with annual costs of €5339, and €34953 for dynamic graciloplasty with annual costs of €1659. The equivalent cost for conservative treatment was €3895. The overall median real cost for an anterior sphincteroplasty was €5327. [LEVEL OF EVIDENCE: 4]

7. SAFETY

SNS is a safe procedure. The rate of complications is relatively low [187, 188]. In only approximately 5% of the patients has discontinuation of treatment with device removal been necessary because of loss of effect, deterioration of symptoms, pain lead dislocation, or infection. When infection has necessitated removal, re-implantation at a later date has been successful [204]. [LEVEL OF EVIDENCE: 3]

VIII. POSTERIOR TIBIAL NERVE STIMULATION

For peripheral stimulation the tibial nerve is temporarily stimulated with surface or needle electrodes at the level of the malleolus. Scattered preliminary data from short term studies with temporary posterior tibial nerve
stimulation [228] indicate a therapeutic effect in idiopathic faecal incontinence [229] and incontinence due to partial spinal trauma [230] on frequency of incontinence episodes, incontinence scores and QoL. Larger patient studies are awaited. [LEVEL OF EVIDENCE: 4]

IX. INJECTABLE BIOMATERIALS

Injection of bulk-enhancing agents into the anal canal to treat faecal incontinence was a natural consideration after its successful use in urinary incontinence. The use of injectable agents to increase urethral resistance at the level of the bladder neck has had variable success; however the benefit of performing an outpatient procedure without anesthesia has resulted in its continued use [231]. The ideal agent for injection should be biocompatible, non-allergenic, non-immunogenic, easy to inject and not migrate within the tissues. No agent currently has all these properties. Agents that have a diameter of 80 µm are felt to be less prone to migration; however larger agents require a larger bore needle to inject, which put them at a higher risk for leakage from the injection site. The results of injectable biomaterials are shown in Table 6 [232-242].

The history of using injectable agents for faecal incontinence began in 1993 when Shafik [232] treated 11 patients (7 of whom had internal sphincterotomy and 4 idiopathic incontinence) with injections of polytetrafluoroethylene paste into the anal submucosa. After an 18-24 month follow-up, 64% reported complete cure and 36% had partial improvement. Shafik [233] subsequently treated 14 patients with autologous fat injections. All patients became continent after repeat injections. There were no complications using either agent. However, subsequent reports of autologous fat injection have resulted in serious complications including death, stroke and pulmonary embolism and thus at the present time is not used for faecal incontinence [243].

Other agents used for injection thus far include micro balloons, glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen), PTQ implants (Bioplastique), Pyrolytic carbon-coated zirconium oxide beads (DuraspHERE), dextranomer- hyaluronic acid co-polymer (Zuidex), cross-linked porcine dermal collagen (Permacol), and polyacrylamide hydrogel (BulkaKam). A small series of six patients injected with self-detaching cross-linked silicone micro balloons with a biocompatible filler material demonstrated fairly good results with Browning-Parks incontinence scores for the group decreasing from 16 to 5 (range 0-20) [234]. However, sterilization issues have prevented the ongoing use of this product.

The first reported injections of glutaraldehyde cross-
linked collagen for faecal incontinence included 17 patients [235]. Following injection, with a mean follow-up of 8 months, 11 patients showed marked symptomatic improvement. A much larger series was recently reported by Stojkovic et al [236]. Patients were injected with 1.7 ml of collagen transanally into the submucosa in three separate areas just proximal to the anal canal. Of the 73 patients, 63% reported an improvement in their incontinence. The 49 patients with idiopathic incontinence (no sphincter defect and no pudendal neuropathy) had a significant decrease in their Cleveland Clinic Florida Incontinence Score (CCFIS). The disadvantages of using synthetic collagen are its potential to be allergenic and degradation over time. Furthermore, its success in urinary incontinence has been limited [231].

Injectable silicone biomaterial, also previously known as macroplastique and bioplastique, has been used extensively for urinary incontinence. It consists of polydimethylsiloxane particles suspended in a bioexcretable carrier hydrogel of polyvinylpyrrolidone. Two pilot studies in 2001 and 2002 [237, 244] led to increased use of this product in Europe and it has been renamed PTQ implants (PTP implants in Australia). Malouf et al [237] studied 10 patients with passive incontinence injected circumferentially or at a single site with Bioplastique. At six weeks, 6 of 10 patients showed either marked improvement or complete cessation of leakage. However, after six months, only 2 of 7 had maintained marked improvement. Complications included anal pain and ulceration at the injection site.

Tjandra et al [238] randomized 82 patients with severe faecal incontinence to receive PTP implants either with or without endoanal ultrasound guidance for injection. All patients had a significant improvement in their Cleveland Clinic Continence scores (range 0-20). The ultrasound guided group had a decrease in score from 14.5 to 3 and the non-guided group had a decrease from 14.5 to 11 at 12 months. Six patients, two from the ultrasound guided group complained of pain at the injection sites. There were no other complications. The ultrasound guided group was also found to have a more significant improvement in resting pressures and quality of life scores. The same group injected PTQ in 7 patients with passive incontinence after hemorrhoidectomy and found significant improvement of Cleveland Clinic Continence scores and quality of life scores in all patients [245].

Only one report exists of long-term results for injectable agents and this was using Bioplastique. Maeda et al [246] reported the 5 year outcome of 6 patients injected with Bioplastique in 1999. The median St. Mark's incontinence score was essentially unchanged from 11 to 13 (range 9-20) and one patient had undergone a colostomy. However, four of the remaining five patients reported subjective improvement in their incontinence and quality of life scores.

The largest series of patients injected with silicone biomaterial included 20 patients with passive faecal incontinence of liquid or solid stool who had failed conventional therapy [239]. Ten patients had disruption of the internal anal sphincter; nine had degeneration of the sphincter. Patients were injected trans-sphincterically using an 18-gauge needle in the skin 2 cm from the anal margin and a finger in the anal canal to direct the injection above the dentate line in the submucosal plane. Three areas were injected with 2.5 ml of product. The Cleveland Clinic Continence score (0-20) decreased significantly from 13.5 to 4.5 at one month and slowly increased to 9.4 at two years, which was a still a significant improvement from the baseline score. Quality of life scores also improved, but there was no effect on resting and squeeze pressures measured at baseline and 3 months after injection. Of note, 70% of patients experienced pruritus ani and one patient developed an infection at an injection site. Post procedure endoanal ultrasounds found no evidence of migration of the product in 19 patients.

Pyrolytic carbon-coated zirconium oxide beads (Duraphsphere) are non-reactive and are not biodegradable. However, they are known to migrate within the tissues and require a large bore needle to inject the substance. Davis et al [240] assessed the short and long-term efficacy in 18 patients with an internal anal sphincter defect refractory to conservative management. It was injected in the submucosal plane at the site of the defect until adequate anal sphincter symmetry was restored. At 12 months, incontinence scores and patient satisfaction scores were significantly improved. Fifteen of eighteen patients reported improvement in their incontinence. An abstract presented by Weiss et al [247] demonstrated improvement in ten patients who were only followed for 3 months. Altomare et al [241] recently published a study of 33 patients with minor or medium severity faecal incontinence (Cleveland Clinic Continence score \( \leq 14 \) and/or American Medical Systems score \( \leq 89 \)) were injected with a mean of 8.8 ml (range 2-19 ml) of Duraphsphere into the submucosa at the level of the dentate line using an 18-gauge needle. After a mean follow-up of 21 months, the incontinence severity scores for the group decreased significantly but the faecal incontinence specific quality of life did not change. Resting and squeeze pressures were also increased 12 months after injection. Adverse events included anal pain in two patients, asymptomatic leakage of material in one patient, and distal migration of product in two patients.

Dextranomer-hyaluronic acid co-polymer (Zuidex) has been used to treat urinary incontinence [248] and a randomized placebo controlled trial is underway to assess its efficacy for faecal incontinence. Dextranomer microspheres are suspended in non-animal stabilized hyaluronic acid. There are no published reports of its use in faecal incontinence to date.
Another study of injectable agents for faecal incontinence involves two other products, cross-linked porcine dermal collagen (Permacol), and polyacrylamide hydrogel (Bulkamid) [242]. Ten patients with passive faecal incontinence to liquid or solid stool who had failed conventional treatments received either of the two products. Injection was performed transsphincterically after injecting the skin 2 cm from the anal margin. The median volume to achieve closure of the anal canal under direct vision was 9 ml for Bulkamid and 15 ml for Permacol. There was a decrease in the St Mark’s incontinence score at 6 weeks for both groups and only a sustained decrease in the score for the Bulkamid group at 6 months. As this was a pilot study, there was inadequate power to assess the different in these treatments for faecal incontinence.

In summary, the data for injectable biomaterials incontinence involves two other products, cross-linked porcine dermal collagen (Permacol), and polyacrylamide hydrogel (Bulkamid) [242]. Ten patients with passive faecal incontinence to liquid or solid stool who had failed conventional treatments received either of the two products. Injection was performed transsphincterically after injecting the skin 2 cm from the anal margin. The median volume to achieve closure of the anal canal under direct vision was 9 ml for Bulkamid and 15 ml for Permacol. There was a decrease in the St Mark’s incontinence score at 6 weeks for both groups and only a sustained decrease in the score for the Bulkamid group at 6 months. As this was a pilot study, there was inadequate power to assess the different in these treatments for faecal incontinence.

In summary, the data for injectable biomaterials comprises several small case series that in general show short term efficacy. [LEVEL OF EVIDENCE: 3]

**X. COLOSTOMY**

A permanent colostomy is usually formed as a last resort for severe faecal incontinence when all other interventions have failed. Because colostomy is generally regarded as a failure of treatment, its effectiveness, perioperative complications, and impact on the quality of life have never been properly evaluated except for patients with functional bowel disorders after spinal cord injury [249, 250]. For a specific role of colostomy for these patients, please refer to the specific chapter. Not only for patients with spinal cord injury, but also for the general population with severe faecal incontinence, colostomy is a frequently successful management strategy that restores dignity and allows them to regain social function.

No systematic reviews, randomized controlled trials or non-randomized cohort studies have been reported regarding colostomy for faecal incontinence, and only one case control study [251], two case series [252, 253], and one systematic review [146] were identified. [LEVEL OF EVIDENCE: 4]

Colquhoun et al [251] conducted a cross-sectional postal survey, comparing quality of life between 71 patients with faecal incontinence and 39 with a colostomy created for rectal cancer, complicated colonic diverticular disease or faecal incontinence. Analysis of the Short Form 36 General Quality of Life Assessment revealed significantly higher social function score in the colostomy group than in the faecal incontinence group (0 vs. -0.6, p=0.022). An age- and gender-adjusted regression analysis of the Faecal Incontinence Quality of Life score revealed significantly higher scores in the coping (2.7 vs. 2.0, p=0.005), embarrassment (2.7 vs. 2.2, p=0.014), and lifestyle scales (3.2 vs. 2.7, p=0.14) in the colostomy group compared to the faecal incontinence group.

The authors concluded that a colostomy is a good option for patients who suffer from severe faecal incontinence and offers a definitive cure with improved quality of life.

Tan et al [146] performed a systematic review specifically comparing the cost-effectiveness between end stoma (ES), artificial anal sphincter (AAS) and dynamic graciloplasty (DG). The quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) were compared between the three procedures, by obtaining the probability estimates for patients with faecal incontinence from published data supplemented by expert opinion. The end stoma was the most cost-effective therapy at 5 years, with a QALY gain of 3.45 for 16,280 GBE and an ICER of £4,719/QALY, compared to AAS (4.38 for £23,569; £5,387/QALY) and DG (4.00 for £25,035; £6,257/QALY). After 10 years, AAS became the most cost-effective surgical intervention, with a QALY gain of 8.384 for £32,397 and an ICER of £3,864/QALY, compared to ES (6.9 for £27,910; £4,046/QALY) and DG (7.678 for £35,165; £4,580/QALY). The results of this study, however, must be interpreted with great caution, because it is not an intervention study but a systematic review with a rather complicated methodology and a variety of possible biases.

Norton et al [252] examined patients’ view of a colostomy by conducting a questionnaire study of patients who had a colostomy created to manage their faecal incontinence. Sixty-nine people (58 women) responded. When patients were asked to rate their ability to live with their stoma now on a scale of 0-10, the median score was 8 (range 0 – 10). The majority (83%) felt that the stoma, within the past month, restricted their life “a little” or “not at all”. Eighty-four percent answered that they would “probably” or “definitely” choose to have the stoma again. When they were asked the question “compared to when you were continent, how much change has having a stoma made to your overall quality of life?” on the scale of -5 (much worse) to +5 (much better), the median rating was +4.5 (range -5 to +5). The authors concluded that health care professionals should discuss the option of a stoma with incontinent patients because of the overwhelmingly positive outcomes.

An end sigmoid colostomy without proctectomy is usually recommended as a procedure of choice for patients who elect colostomy for the management of their refractory faecal incontinence. Creating such a colostomy, however, does not always solve all the problems of patients with faecal incontinence. Catena et al [253] reported a retrospective chart review of 44 patients (35 women) who underwent elective end sigmoid colostomy for faecal incontinence of various
etiolgies. After colostomy formation 19 patients (43%) were asymptomatic, while the other 25 experienced such problems with their rectal stump as diversion colitis and mucus leakage. Of the 25 patients, 12 (27% of the total) underwent a secondary proctectomy due to the rectal stump problems sufficient to warrant the operation. Histological examination revealed diversion colitis in 6 patients. The factor associated with proctectomy was age, with younger patients being more likely to require rectal excision. The authors concluded that data are insufficient to recommend primary proctectomy in patients with severe faecal incontinence warranting permanent end sigmoid colostomy.

### XI. ANTEGRADE CONTINENCE ENEMA

The concept of irrigation is to ensure emptying of the colon and/or rectum to prevent seepage of stool. It has been used for patients with neurogenic bowel dysfunction and those with symptoms of incontinence [254, 255].

Antegrade irrigation involves operative construction of an appendicostomy, cecostomy, or sigmoidostomy which will serve as a continent conduit for colonic enemas [254, 256-258]. The operation can also be done laparoscopically. There is a reported 65 to 78% subjective improvement in patients, but some studies have included patients with concurrent difficulty with defecation [259-261]. [LEVEL OF EVIDENCE: 3] The disadvantages of the procedure have been documented; the most common has been wound infection in up to 45% of patients [259]. This seems to be reduced by creating a so-called ‘neo-appendicostomy’ with a part of ileum [262, 263].

### B. SURGERY FOR PEDIATRIC FAECAL INCONTINENCE

Faecal incontinence is common in children who have anorectal malformations, Hirschsprung’s disease and spinal problems. Despite advances in technique for anatomic corrective surgery, many patients continue to suffer from persistent incontinence. This guideline mainly focuses on anorectal malformations and corrective surgeries along with their results and subsequent management in case of persistent incontinence. The latter is also applicable for treatment of patients suffering from incontinence after surgery for Hirschsprung’s disease and those with spinal problems. Other surgical interventions used less frequently were also reviewed.

Anorectal malformations occur one in 3000-5000 live births. Although the severity of malformation varies, it is invariably associated with defecatory problems including incontinence. The surgical advances have been most prominent in last few decades, particularly with the advent of posterior sagittal approach. [LEVEL OF EVIDENCE: 3] This technique has enabled surgeons to visualize the anatomy under direct vision and perform corrective surgeries more accurately [264, 265]. In brief, a mid-sagittal incision is performed and the sphincter mechanism is completely divided in the midline. The rectum is separated from the genitourinary tract and moved down to the perineum. The most challenging aspect of the operation is the separation of the rectum from the vaginal or urinary tract, which effectively requires creating two walls out of one septum without damaging each structure. This approach can also be used for reoperation in anorectal malformations [266] and can also be applied for reconstruction of severe perineal trauma [267].

For both male and female babies, urethral-perineal fistula is the simplest fistula to correct. These require the so-called ‘minimal posterior sagittal approach,’ which enlarges the stenotic orifice and relocates the rectal orifice posteriorly within the limits of the sphincter complex. For males with recto-urethral-bulbar fistula or recto-urethral-prostatic fistula and females with recto-vestibular fistula or cloaca with short (less than 3 cm) common channel, posterior sagittal approach is the main operation performed. For males with higher fistulas such as recto-bladder neck fistula and other complex and unusual defects and females with cloaca with long (greater than 3 cm) common channel and complex defects, the posterior sagittal approach needs to be coupled with abdominal access which can be either laparoscopy or laparotomy.

Cloacal repair is the most challenging amongst the corrective surgeries for anorectal malformations. A recent operative advance in cloacal repair is a maneuver called total urogenital mobilization, whereby the rectum is separated from the vagina and both vagina and urethra are then mobilized together. The advantage of this technique is to avoid separating rectum, vagina and urethra completely, which is not feasible all the time and risks damaging these structures during the procedure. This technique avoids the risk of urethrovaginal fistula and vaginal stricture (previously reported as complications in 10% of cloacal repairs) and also gives enough mobilization to allow more than 50% of all cloacal repairs without opening the abdomen [268, 269].

Functional outcomes depend on the severity of the malformations. A review of more than 1000 anorectal malformation cases showed 100% of babies who had perineal fistula repair achieved continence. Approximately 55% of patients who had been operated
for recto-vestibular fistula had bowel control. Any malformations more complicated resulted in only up to 30% achieving continence. All patients who had recto-bladder neck fistula repair were incontinent. In cloacal repair the length of common channel shorter or longer than 3 cm appears to be the distinct prognostic factor in terms of functional outcome [270]. Overall it is estimated that nearly 40% will have voluntary bowel movement and no soiling, but some of them may still lose bowel control in case of severe diarrhea, and 25% of all repairs will result in total incontinence [271].

For the group of patients with persistent incontinence following the corrective surgery, the next aim will be to keep the colon clean to avoid unpleasant accidents and improve their quality of life. A good option is implementation of a bowel management program whereby the patient and family are instructed in the use of daily enema, manipulation of diet, and medication to remain clean [272]. This is also a good treatment for constipation, which is the most common difficulty after corrective surgery [273].

Although most young children accept their parents administering enemas, when they get older they want privacy and rectal enemas on a daily basis becomes an unpleasant routine. In such cases, continent appendicostomy is a feasible option, whereby a conduit for the administration of an antegrade continence enema (ACE) is created. First described by Malone [274], it has become an important option in pediatric surgery for functional bowel disorders.

According to the initial description by Malone, appendicostomy was created by dividing the appendix at its base and reimplanting by a reverse manner into the cecum, which was then exteriorized through the right lower quadrant. Malone later revised it and the reimplantation of appendix is no longer considered necessary [275]. Levitt et al introduced utilizing the appendix in situ and added cecal plication to prevent reflux of stool and exteriorizing through umbilicus fold rendering it less noticeable [276]. This appears to yield good long-term results [277], though a recent study has shown that cecal fixation and wrap may be unnecessary for appendicostomy (44 patients, consecutive) [278]. The benefit of a variation called orthotopic continent appendicostomy stoma is not clear [279]. However, construction of appendicostomy with the cecum, which was then exteriorized through the right lower quadrant and reimplanting by a reverse manner into at its base and subsequently lead to overflow incontinence due to incomplete evacuation [299]. Once the rectum is dilated impaction, which can lead to development of a dilated segment of bowel called ‘megarectosigmoid’. This can subsequently lead to overflow incontinence due to incomplete evacuation [299]. Once the rectum is dilated it is refractory to conservative management, and resection of megarectum or megasigmoid has been associated with improvement [299-301]. A small minority of patients (5%) who fail these options may need colostomy [272].

### II. OTHER CAUSES OF Faecal INCONTINENCE

Some children with Hirschsprung’s disease following pull-through operations and severe constipation may also present with symptoms of incontinence [297]. Patients with spinal problems often lack bowel control due to paralysis and absence of sensation; 50% of children with spina bifida suffer from incontinence [298]. The majority of these cases can be successfully managed with the above mentioned bowel management program including appendicostomy, although wheelchair-bound children with spinal neuropathy is a predictive factor for poorer outcome with ACE [287].

The mechanism of incontinence after an operation for Hirschsprung’s disease, anorectal malformations and severe constipation is thought to be due to impaired bowel motility. Impaired bowel motility causes faecal impaction, which can lead to development of a dilated segment of bowel called ‘megarectosigmoid’. This can subsequently lead to overflow incontinence due to incomplete evacuation [299]. Once the rectum is dilated it is refractory to conservative management, and resection of megarectum or megasigmoid has been associated with improvement [299-301]. A small minority of patients (5%) who fail these options may need colostomy [272].

### III. OTHER SURGERIES

Sphincter augmentation by either palmaris longus transposition, gluteus muscle transposition, graciloplasty or levatorplasty has been used for children with faecal incontinence, albeit in small series[110, 302-309]. Dynamic graciloplasty has also been piloted and 50% of patients achieved complete continence, though the study only contained four patients [310]. [LEVEL OF EVIDENCE: 4]
Data regarding the surgical treatment of faecal incontinence are generally weak. Randomized, controlled studies are few, and practical considerations make the likelihood of such studies improbable. The quality of data reported in older studies was often poor. Problems included heterogeneous patient populations; variable definitions of "continence," "incontinence," "success," and "failure"; non-standardized and non-validated continence scales; underreporting of validated symptom-specific quality of life measures; variable patient follow up and lack of independent assessment of continence outcomes. However, there has been a notable improvement in the quality of studies reported in the past decade. The spectrum of surgery for faecal incontinence is broad and expanding. Interventions range from simple outpatient procedures to major reconstructive surgery. As the reported outcomes of these various operations are often similar, a sound general principle is to proceed first with the simplest and least invasive procedure. Major operations associated with more profound morbidity should be restricted to patients who have failed simpler measures.

1. Sphincter Repair (Grade B)
Sphincter repair is indicated for patients with acute traumatic sphincter disruption, such as following obstetrical injury, but many patients experience persisting symptoms.

2. Sphincteroplasty (Grade B)
Overlapping sphincteroplasty can be offered to patients with significant faecal incontinence and a documented sphincter defect. Most patients improve after sphincteroplasty, but outcomes deteriorate over time.

3. Postanal Repair (Grade C)
Postanal repair can be performed with modest success in carefully selected patients. However, this procedure is now rarely performed due to the advent of newer treatments.

4. Non-Stimulated Muscle Transposition (Grade C)
Non-stimulated muscle transposition repair can be performed with modest success in carefully selected patients, notably in children. However, this procedure is now rarely performed due to the advent of newer treatments.

5. Stimulated Muscle Transposition (Grade C)
Stimulated muscle transposition has been shown to have reasonable success but is associated with significant morbidity. It remains a useful technique in selected patients with significant perineal tissue loss or in those who have failed other treatments.

6. Artificial Anal Sphincter (Grade B)
Artificial anal sphincter has been shown to have reasonable success but is associated with significant morbidity. It remains a useful technique in carefully selected patients, particularly those who have failed other treatments.

7. Sacral Nerve Stimulation (Grade B)
SNS is an effective therapy for most patients with clinically significant incontinence who fail conservative management. The technique is safe, minimally invasive, and has the unique advantage of allowing a therapeutic trial prior to permanent stimulator implantation.

8. Posterior tibial nerve stimulation (Grade D)
Posterior tibial nerve stimulation is an investigational technique with few available data regarding efficacy and outcome.

9. Injectable Biomaterials (Grade C)
Most series of injectable biomaterials report reasonable success rates. However, the optimal injectable bulking agent and the technique for its insertion have not been established.

10. Colostomy (Grade C)
Formation of an end colostomy is a reasonable treatment option for patients with refractory faecal incontinence who are able to accept the associated alteration in body image. Colostomy provides restoration of a more normal lifestyle and improves quality of life. It also could be the most cost-effective in the short to medium term, compared to more complicated surgical procedures such as artificial anal sphincter and dynamic graciloplasty. Colostomy should not be regarded as a treatment failure but rather a reasonable treatment option for patients whose lives are restricted by faecal incontinence that is not amenable to other therapies. An end sigmoid colostomy alone, without proctectomy, is recommended. The minority of patients who develop significant symptoms from their retained rectal stump may eventually require proctectomy as a secondary procedure.

11. Antegrade Continence Enema (Grade C)
Antegrade continence enema is a useful technique to ameliorate faecal incontinence refractory to more conventional therapies. Patients must accept placement of a small stoma and be willing to adhere to a regular irrigation program.

12. Surgery for Pediatric Faecal Incontinence (Grade C)
Anorectal malformations should undergo surgical repair, most commonly by a posterior sagittal repair. An antegrade continence enema procedure can be considered for children with persistent or refractory faecal incontinence.
REFERENCES


Habr-Gama A, Alves PA, da Silva e Souza AH, Femenia


Guelinckx PJ, Sinsel NK, Gruwez JA. Anal sphincter reconstruction with the gracilis maximus muscle: anatomical and physiologic considerations concerning conventional


224. Ratto C. Sacral nerve stimulation in fecal incontinence due to anal sphincter lesions. Paper presented at: European Society of Coloproctology 2nd Annual Scientific Meeting; September 27, 2007; Malta.


267. Applebaum H, Atkinson JB. The posterior sagittal approach

266. Brain AJ, Kiely EM. Posterior sagittal anorectoplasty for

265. Pena A, Devries PA. Posterior sagittal anorectoplasty:

263. Christensen P, Buntzen S, Krogh K, Laurberg S. Ileal


258. Pena A. Total urogenital mobilization—an easier way to

257. Rintala RJ. Are cecal wrap and

256. Pena A, Guardino K, Tovilla JM, Levitt MA, Rodriguez G,


Committee 18

Fistulas in the Developing World

Chairman

D. De Ridder (Belgium)

Members

G. H. Badlani (USA),
A. Browning (Ethiopia),
P. Singh (India),
I. Sombie (Burkina Faso),
L. L. Wall (USA)
## CONTENTS

<table>
<thead>
<tr>
<th>Background</th>
<th>IV. Classification Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature Searching Strategy</td>
<td>V. Conservative Management</td>
</tr>
<tr>
<td><strong>I. Aetiology and Epidemiology of Vaginal Fistulas in the Developing World</strong></td>
<td></td>
</tr>
<tr>
<td>1. Geographical Distribution of Obstetric Fistulas</td>
<td>VI. Surgical Management</td>
</tr>
<tr>
<td>2. Development of an Obstetric Fistula</td>
<td>1. The Simple Fistula</td>
</tr>
<tr>
<td>3. Epidemiology of Fistulas</td>
<td>2. The Complex Fistula</td>
</tr>
<tr>
<td>5. Physical, Social and Psychological Consequences</td>
<td>4. Complications</td>
</tr>
<tr>
<td><strong>II. Diagnosis</strong></td>
<td>VII. Organisation of Fistula Care in the Developing World</td>
</tr>
<tr>
<td>1. Signs and Symptoms</td>
<td>1. Local Hospital or a Specialist Fistula Centre?</td>
</tr>
<tr>
<td>2. Clinical Evaluation</td>
<td>2. Ethical Considerations</td>
</tr>
<tr>
<td>3. Evaluation with Advanced Technology</td>
<td><strong>VIII. Summary and Goals for Future Research</strong></td>
</tr>
<tr>
<td><strong>III. Fistula Prevention</strong></td>
<td>IX. Recommendations</td>
</tr>
<tr>
<td>1. Patient Factors</td>
<td><strong>References</strong></td>
</tr>
<tr>
<td>2. Quality of Care Factors</td>
<td></td>
</tr>
</tbody>
</table>
Fistulas in the Developing World

D. De RIDDER,
G. H. BADLANI, A. BROWNING, P. SINGH, I. SOMBIE, L. L. WALL

BACKGROUND

Obstetric fistulas destroy the lives of many young women in the developing world. While obstetric vesicovaginal fistulas have vanished from the industrialized world, despite the efforts of many charitable organizations, they continue to occur in epidemic numbers in developing countries. The national and local governments of these countries do not have either the resources or the political will to address this problem and help these outcast women. The number of vesicovaginal fistulas in a region reflects the quality and the level of perinatal care delivered by the local health systems. In regions where health care (particularly maternal health care) is poor or absent, the number of obstetric fistulas is likely to be high. Although the treatment of women with obstetric fistulas is a worthy endeavour, the ultimate goal should be to eliminate fistulas entirely by providing adequate maternal health services and perinatal care. As some Africans say: “Treating obstetric fistulas is like taking a serpent by the tail—you can only control the snake by taking it by the head.” The ultimate goal must be fistula prevention.

Only rough estimates can be given on the incidence and prevalence of fistulas and reliable data on cure rates and surgical complications are available only from a few authors. There is no internationally-accepted classification system for fistulas and the development of such a system has been hampered by the absence of prospective clinical research that could establish a relationship between fistula classification and surgical outcome.

LITERATURE SEARCHING STRATEGY

From the standpoint of evidence-based medicine, the literature on fistulas is disappointing. A total of 515 articles were identified using search engines such as Pubmed and Sumsearch, of which 149 were published during the last 5 years. Out of this literature, only 8 trials could be identified involving fistulas. Most of the published articles were simple observational studies. There are no evidence-based guidelines or well-designed randomized controlled trials. The major large-scale literature review is the last report of this committee [1].

Data are scarce on health economic issues as well. While there has been a gradual improvement in the number and quality of papers published on obstetric fistulas in the developing world over the last few years, none of these papers rises higher than “level 3” evidence. There is still a generalized lack of reliable data on obstetric fistulas. If the fistula problem is to be tackled successfully, this must change. The academic communities of both the industrialized and the developing worlds must work together to change this situation, thereby improving both maternal health care and the quality of services provided to women with obstetric fistulas.
A fistula is an abnormal communication between the vagina and the bladder (or rectum) of a woman that results in a constant leakage of urine and/or faeces. Most commonly fistulas develop as a result of obstetric trauma, hence the term “obstetric fistulas.” Obstetric fistulas have emerged as an international public health problem which is attracting increasing international attention [2, 3]. The aetiology and epidemiology of obstetric fistulas is reviewed in this section, along with the physical, psychological and social consequences suffered by those affected. This summary is based on recent literature reviews on the subject.

1. GEOGRAPHICAL DISTRIBUTION OF OBSTETRIC FISTULAS

Today, obstetric fistulas have vanished from the developed world and occur almost exclusively in the non-industrialized countries of Africa and Asia, where access to quality medical care is lacking for many (perhaps most) women. The disappearance of this condition from the developed countries is largely the result of universal access to emergency obstetric care. As will be seen later in this chapter, it is not possible at present to give a reliable estimate of the total number of obstetric fistulas in the developing world. Perhaps the most useful comparative health statistic in these countries is the maternal mortality ratio, which appears to be a reasonably accurate surrogate marker for obstetric fistulas. Obstetric fistulas are invariably found in regions where maternal mortality is high because both statistics reflect absence of effectively-functioning emergency obstetric services. Recent (2005) maternal mortality estimates by the World Health Organization indicate that there are half a million maternal deaths worldwide each year, and that 99% of those deaths occur in developing countries, with slightly more than half of those deaths occurring in sub-Saharan Africa, followed by South Asia. Maternal mortality in these two regions accounted for 88% of the world’s maternal deaths [4] (Figure 1).

2. DEVELOPMENT OF AN OBSTETRIC FISTULA

Obstetric fistulas usually develop from prolonged obstructed labour that occurs as the result of foeto-maternal disproportion during the course of delivery. The foetal head (or other presenting part) becomes wedged into the pelvis, through which it cannot pass, trapping the woman’s soft tissues between two bony plates. This in turn occludes the blood supply to the affected tissues, which then slough away to create the abnormal communication between the vagina and the bladder and/or rectum, leading to a fistula (figure 2). The foeto-maternal disproportion that causes obstructed labour is due either to a small pelvis (particularly in young, teenage primiparas who have become pregnant before they have reached their full adult pelvic growth), reduced pelvic proportions due to disease or injury, an abnormal foetal presentation (transverse lie, shoulder, breech, etc), or foetal macrosomia. AbouZahr has estimated that foeto-pelvic disproportion of this kind arises in 0.5% to 6.5% of deliveries [5], but no publications have been found to suggest what proportion of such deliveries actually result in the formation of a fistula. Harrison reported on 22,774 deliveries at the Amhadu Bello University Teaching Hospital in Zara, Nigeria [6]. He reported 70 cases of fistula in this series, giving a ratio of one fistula per 288 deliveries. In cases of obstructed labour, preventing the formation of a fistula depends on timely access to emergency caesarean delivery. In the needs-assessment carried out in 20 countries as part of UNFPA’s Campaign to End Fistula, caesarean section rate ranged from 0.1% to 3% [7], well below the absolute minimum rate of 5% recommended by WHO to meet maternal health needs. An analysis of data from Demographic and Health Surveys (DHS) has demonstrated that access to caesarean delivery is directly linked to the poverty level based on household goods, the poor having substantially less access to care than do the rich. Using DHS data, Ronsmans and colleagues [8] have shown substantial differences in caesarean rates between urban and rural areas. Not surprisingly women living in rural areas have less access to caesarean delivery than women who live in urban areas [9]. Additional factors including cultural beliefs, perceptions of disease severity, transportation issues, and restrictions on women’s social mobility may also reduce the access to caesarean section and other emergency obstetric services [10,11]. Thaddeus and Maine have suggested that there are three “stages of delay” which interact to produce maternal death and serious maternal morbidity: 1) delay in deciding to seek care; 2) delay in arriving at a health care facility, and 3) delay in receiving adequate care at that facility [12]. The cultural and biological elements that lead to obstetric fistula formation are summarized in figure 3 [3].

A second cause of fistula formation is iatrogenic injury sustained during the course of delivery such as at the time of laparotomy, caesarean section, or through the use of forceps. In many cases the relationship between the intervention and the fistula cannot be determined. Many fistulas develop in women who, after labouring for several days in a remote village, finally present for care at a medical facility. There the woman undergoes a very difficult caesarean delivery, often performed under less-than-ideal circumstances, with delivery of a stillborn baby and subsequent development of a fistula. There are many cases of this type reported in the literature [13-18]. In some cases the fistula is the result of direct injury
Figure 1: Maternal mortality map 2005

Figure 2: The foetal head is forced into the pelvis, trapping the bladder, urethra, and other soft tissues between the foetal head and the pelvic bones. This unrelenting pressure leads first to tissue ischemia and the to tissue necrosis with fistula formation. In most cases the bladder will not have been emptied as suggested by this picture, but will be markedly overdistended. The progressive thinning of the bladder wall from overdistention increases the likelihood of ischemic injury. The level at which labour becomes obstructed is directly related to the level at which the fistula occurs, as shown in the drawing on the right. (adapted from Elkins 1994)
under these difficult circumstances; in other cases the tissues involved were already avascular from obstructed labour. There is no doubt that a proportion of fistulas developing in these circumstances will be dependent on the qualifications of the persons performing the obstetric intervention and the nature of the facility where delivery takes place, but there are few data which would allow an accurate analysis of the proportion of fistulas that are the result of surgical misadventure. Because of the lack of trained gynaecologists and general surgeons in Africa, general medical doctors, nurses and midwives have been trained to perform caesarean sections in some areas, and some success has been reported with these programs [19-22]. The long-term success of such programs is uncertain and maintenance of adequate quality of care will depend upon close and continuing supervision of such programs by trained surgeons. This is an area that requires further study.

A third group of factors causing fistulas includes accidents, sexual abuse and rape [23]. A recent review on the subject of traumatic fistulas caused by violence against women documents the presence of such cases in war-torn areas of Africa such as the Democratic Republic of Congo, Sierra Leon, Sudan, and Somalia [24]. However, the prevalence of traumatic fistulas in these areas is sometimes difficult to determine with accuracy as the authors report that many women with fistulas claim a history of sexual abuse even when this does not appear to be the case. Two articles published in the Congo Medical Journal and included in the Acquire Project review demonstrate the importance of fistulas resulting from sexual violence [24]. The study by Kalume et al revealed that 17 of the 100 female victims of sexual violence developed a fistula as a result of their injuries [25]. At the Maternity Hospital in Kindu, 36 of the 2010 female victims of sexual violence developed a fistula as the result of sexual assault (28 vesicovaginal fistulas, 2 rectovaginal fistulas and 6 combinations of both fistula types) [26]. In a study in Ethiopia, Muleta et al [27] reported on 91 girls and women with fistulas resulting from sexual violence. A study in Kenya, Nduati and Muita [28] identified two cases of fistula (one rectovaginal, one vesicovaginal) among 21 sexual abused children. These data demonstrate both the variability in the prevalence of post-violence fistulas as well as the importance of this problem in war-torn parts of Africa. More detailed studies are needed in this area.

The last group of causes involved in fistula formation includes traditional cutting practices based on erroneous assumptions of disease aetiology or other cultural values. In northern Nigeria, a harmful practice called gishiri-cutting accounts for between 2-13% of vesicovaginal fistulas. Gishiri is the Hausa word for “salt.” It also refers to a disease state in the Hausa ethnomedical system. The belief exists that ingestion of too much salt, sugar or similar substances (especially during pregnancy) will result in the vagina becoming “encrusted,” narrowed, or “covered with a filmy membrane” that will prevent the child from being born. When this condition is diagnosed (obstructed labour) a traditional healer (barber, midwife) is consulted who makes a series of gishiri cuts in the vagina to “relieve” this obstruction. This often results in direct trauma to the urethra or bladder, causing a fistula.

The cut is usually made on the anterior vaginal wall. Repeated cutting over a period of time may extend the incision area to the posterior vaginal wall. Wall et al [29] identified among 932 cases of fistula 21 (2.3%) that might be caused by this practice. Tahzib found that gishiri-cutting was carried out in 12 of the 80 children (15%) with fistulas [30] and in 13% of the 1443 fistula patients treated at the University Hospital Ahmadu Bello between 1969 and 1980 [31].

Severe forms of female genital cutting such as like infilubations are often said to be possible contributors to the development of fistulas although there is little evidence in the world literature to support this belief. Direct injury to the urinary tract can, of course, occur at the time of “deinfibulation” or anterior episiotomy at the time of delivery (Andrew Browning, personal communication). There is evidence that women who have been subjected to female genital cutting have worse obstetric outcomes than women who have not had these procedures done. A recent study by the World Health Organization looking at the relationship between female genital cutting and obstetric outcome found that “deliveries to women who have undergone FGM are significantly more likely to be complicated by caesarean section, postpartum haemorrhage, episiotomy, extended maternal hospital stay, resuscitation of the infant, and inpatient perinatal death, than deliveries to women who have not had FGM ”[32]. The authors were unable to describe any clear mechanism to explain these findings, and the study was not able to look at long-term obstetric outcomes, including fistula formation. If genital cutting practices predispose women to fistulas, the most likely explanations would be direct injury to the genitourinary system at the time of the procedure as already noted, or scarring at the vaginal outlet that leads to prolonged labour. Since most cases of obstructed labour occur higher up in the pelvis than at the outlet, it seems unlikely that female genital cutting by itself is the sole cause of the obstruction that leads to a fistula. One study from Sweden—a highly industrialized country—compared the duration of the second stage of labour in “circumcised” immigrant and “nincircumcised” nulliparous women and found that those who had undergone female genital cutting actually had a shorter second stage than those who had not been “circumcised.” The authors concluded that prolonged labour does not seem to be associated with female genital cutting in an affluent society with high standards.
of obstetric care [33]. Similarly, an unpublished series of 2000 patients from Ethiopia compared those with and without female genital mutilation. There was no difference between the groups with respect to classification of fistula, length of labour, parity, age and outcomes implying that female genital cutting has little or no influence on the development of obstetric fistulas (A Browning, personal communication).

3. EPIDEMIOLOGY OF FISTULAS

a) Availability and quality of data

Two major shortcomings are present in the published papers on obstetric fistulas. The first is the overall paucity of reliable data on obstetric fistulas. The second is the fact that almost all studies have been done in a hospitals where fistula repair is carried out. Such studies are subject to considerable selection bias and do not provide reliable estimates of the true incidence of fistulas worldwide [34, 35].

b) Indicators for monitoring programs in the struggle against fistulas

In 2006 the WHO proposed indicators for monitoring and evaluating fistula treatment and prevention programs (table 1), [36, 37]. These indicators can be subdivided in four groups: epidemiologic indicators, service delivery indicators, training indicators, and markers of the quality of care provided. There is very little information on programmatic indicators of success in the social reintegration of fistula patients [38].

c) Population-based incidence and prevalence of fistulas

A review of the recent epidemiologic literature by Stanton et al [34] has demonstrated that our knowledge of the incidence (new cases) and prevalence (already-existing cases) of obstetric fistula is based on poor quality data. These authors organized the existing population-based estimates of obstetric fistula into three categories. The first category consisted of estimates reported in the scientific literature that did not specify the methods used to obtain the estimate. The most commonly quoted number was 2 million cases of obstetric fistula worldwide, with 50,000 to 100,000 new cases each year. The second group of estimates is those made by surgeons, again with no methodology clearly specified. Examples include estimates of fistula prevalence in northern Nigeria, the number of new cases each year in Ethiopia and Tanzania, the proportion of pregnant women with fistulas in Pakistan or other developing countries, and the proportion of married women with fistulas seen in Bangladesh. Although interesting, these estimates have low reliability when applied across national populations. The third group of estimates is those originating in population-based surveys where there is an adequate description of the methods used to obtain the estimates. Only four such papers could be

<table>
<thead>
<tr>
<th>Table 1. Proposed indicators for monitoring and evaluating fistula prevention and treatment WHO, 2006 [115].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiologic</strong></td>
</tr>
<tr>
<td>• Prevalence: the estimated number of women living with obstetric fistulas</td>
</tr>
<tr>
<td>• Incidence: the estimated number of new cases of obstetric fistulas per year</td>
</tr>
<tr>
<td>• Estimated rate of obstetric fistulas per 1000 deliveries</td>
</tr>
<tr>
<td>• Number of women treated for obstetric fistula per year</td>
</tr>
<tr>
<td>• Estimate of unmet need for fistula repair</td>
</tr>
<tr>
<td><strong>Service delivery</strong></td>
</tr>
<tr>
<td>• Number of midwives, nurses, and physicians with midwifery skills per 1000 births</td>
</tr>
<tr>
<td>• Number of physicians or midlevel providers able to perform a caesarean delivery per 1000 births</td>
</tr>
<tr>
<td>• Proportion of births managed with a partograph</td>
</tr>
<tr>
<td>• Number of facilities providing simple fistula treatment services</td>
</tr>
<tr>
<td>• Number of centres providing specialist fistula services</td>
</tr>
<tr>
<td>• Number of fistula treatment services which include social reintegration activities</td>
</tr>
<tr>
<td>• Number of surgeons able to undertake simple repairs</td>
</tr>
<tr>
<td>• Number of surgeons able to undertake complex repairs Training</td>
</tr>
<tr>
<td>• Number of training facilities (pre-service and in-service including obstetric fistula prevention and treatment as part of the core syllabus</td>
</tr>
<tr>
<td>• Number of surgeons who undergo simple fistula repair training per year</td>
</tr>
<tr>
<td>• Number of in country surgeons who undergo specialist fistula training (either in country or elsewhere) per year</td>
</tr>
<tr>
<td><strong>Quality of care</strong></td>
</tr>
<tr>
<td>• Proportion of women who have a successful first repair at each facility. Ideally, the closure rate should be 85%, with continence achieved in 90% of women with a closed fistula (this success rate can also be disaggregated into different types of fistulas)</td>
</tr>
<tr>
<td>• Proportion of women who have had 2 or more unsuccessful repairs</td>
</tr>
<tr>
<td>• Percentage of women successfully reintegrated in their community following treatment</td>
</tr>
</tbody>
</table>
identified. The estimates were based on a cohort of pregnant women in western Africa, interviews of women concerning loss of urine or faeces one month after delivery in Bangladesh, model-based estimates of regional and age-specific fistula prevalence and incidence, and the lifetime prevalence of obstetric fistula from the 2005 Demographic and Health Survey (DHS) in Malawi. The cohort study of pregnant women identified only 2 fistula cases. Based solely on these 2 cases, the authors of this study reported an estimated incidence of 10.3 cases of obstetric fistula per 100,000 deliveries. The sample size of this study was clearly inadequate to generate meaningful estimates. In the study of post-partum incontinence in Bangladesh, all 3 women who responded “Yes” to the question on urinary/faecal leakage were examined by a female physician and none were found to have a fistula [34]. In 2007, Muleta and co-workers [39] found a prevalence of 1.5 non-treated fistulas per 1,000 women of reproductive age, based on interviews with 26,819 such women in Ethiopia. Since these reports of urinary and/or faecal incontinence were not confirmed by physical examination, these data are unreliable as incontinence may be due to factors other than a fistula.

The literature review by Stanton et al. suggests only 2 estimates of fistula incidence and 2 of fistula prevalence adequately describe the methods by which these estimates were obtained. These estimates vary from an empirical estimate of 124 obstetric fistulas per 100,000 deliveries for rural sub-Saharan Africa reported by Vangeenderhuyzen et al [40] to a model-based estimate of 18.8 fistulas per 100,000 women of reproductive age for all of sub-Saharan Africa reported by AbouZahr [5]. This latter estimate was only for rectovaginal fistulas and did not include vesicovaginal fistulas, which are more common than rectovaginal fistulas in all reported case series of obstetric fistulas. AbouZahr also estimated the global prevalence of obstetric rectovaginal fistulas at 654,000 cases in 1990, with 262,000 of these in sub-Saharan Africa. The only empirical estimate of the lifetime prevalence of obstetric fistula is the DHS estimate from Malawi [41], which suggested that 1 in 20 women of reproductive age were affected. The authors recommend the usefulness of the figures from the model-based estimate even when those date from 1990 because they result from a well-defined method based on the complete literature review and taking into account the age and the causes of women’s death [34]. None of these data are very convincing.

d) The estimated number of obstetric fistulas per 1000 deliveries

The estimated number of obstetric fistulas per 1,000 deliveries is a way of attempting to assess a woman’s risk of developing a fistula after any given delivery. Danso et al have reported the evolving trends in the number of cases of obstetric fistula per 1000 deliveries at Komfo Ankoye Teaching Hospital in Ghana, calculated over 5-year periods from 1977 to 2004. [42]. This indicator ranged from 0.78 for the years 1977-1981 to 0.66 for the years 2002-2004 and peaked between 1987-1991 at 1.46.

e) The number of women treated for obstetric fistulas per year

The number of women treated for obstetric fistulas per year is an indicator that takes into account the capacity of the health system to care for women with fistulas. Figure 4 demonstrates the impact of the presence of external funding to pay for the treatment of fistula patients in a rehabilitation centre in Nigeria between 1999 and 2006 [43]. Initially (1999-2002) this project (FORWARD) was funded by the UK Department of International Development. From 2003 onwards the project was funded by donations and by the government. The dependence on external funding is clearly shown by drop in cases treated when financial support was withdrawn.

f) Unmet need

This indicator takes into account the number of patients needing treatment who cannot get care. This would be the most useful information for policymakers to use in strategic planning, but this requires accurate information on the total number of fistula cases that exist in any given area. These data simply do not exist.

4. FACTORS PREDISPONING TO THE DEVELOPMENT OF FISTULAS

A woman’s obstetric history is the most salient element in the development of an obstetric fistula. It is often stated that fistula patients tend to be young women with small, immature pelves (most commonly primiparas), with an antecedent history of obstructed labour, prolonged delay in receiving emergency obstetric care, sometimes having undergone late caesarean delivery [44-51]. Creanga and Genardy [35] analysed the role of 5 socio-medical factors in the development of fistulas: age, parity, duration of labour, the place of delivery, and whether the delivery was attended by a qualified person along with the proportion of caesarean sections. The authors identified only 5 studies that included data on all these 5 factors, 7 other studies that reported data on 4 of these factors, and an additional 7 that reported data on only 3 of these factors. We have updated their work by including articles published in 2007 that reported data on these 5 socio-medical factors [52, 53]. The results of this enhanced review are presented in table 2. The proportions of young women, primiparas and caesarean deliveries are higher than in the general population. Moreover, the duration of labour in these cases is greater than 2 days, strongly suggesting that fistulas develop most commonly in young women with obstructed labour. Such predisposing factors were confirmed in a case-control study from Gombe Hospital.
Figure 3: The obstetric fistula pathway

( Worldwide Fistula Fund, used by permission )
Figure 4: Evolution of the number of fistula patients receiving treatment Residential Centre of Dambatta, Nigeria [43]

Table 2. Socio-medical risk factors associated with obstetric fistulas

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>No of cases</th>
<th>Obstetric causes,%</th>
<th>Mean age, years (patients younger than 16, 18 or 20 years, %)</th>
<th>Mean, duration of labor, days</th>
<th>Primiparas (mean parity) %</th>
<th>Place of delivery, %</th>
<th>Cesarean delivery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilton and Ward (1998)</td>
<td>2484</td>
<td>92.2</td>
<td>28.0 (13.0&lt;16, 32.0&lt;20)</td>
<td>2.5</td>
<td>31.4 (3.5)</td>
<td>Home, 27.0 Hospital, 73.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Tahzib (1983)</td>
<td>1443</td>
<td>83.8</td>
<td>21.0 (32.9&lt;16, 54.8&lt;20)</td>
<td>3.0</td>
<td>52.0 (1.6)</td>
<td>Home, 64.4 Hospital, 35.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Wall et al (2004)</td>
<td>932</td>
<td>96.5</td>
<td>27.0</td>
<td>2.4</td>
<td>45.8</td>
<td>Home, 23.5 Hospital, 76.5</td>
<td>40.3</td>
</tr>
<tr>
<td>Kelly and Kwast (1993)</td>
<td>309</td>
<td>97.4</td>
<td>22.4 (7.0&lt;16, 42.0&lt;20)</td>
<td>3.9</td>
<td>62.7</td>
<td>Home, alone or with an unskilled attendant, 60.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Ibrahim et al. (2000)</td>
<td>31</td>
<td>100.0</td>
<td>(60.0, 13-15) 90.0 &lt; 18)</td>
<td>4.0</td>
<td>81.0</td>
<td>Home, 16.0 Hospital, 84.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Rijken and Chilopora (2007)</td>
<td>407</td>
<td>92.3</td>
<td>22.8 (32.8&lt;20)</td>
<td>49.8</td>
<td>36.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafiou et al (2007)</td>
<td>111</td>
<td>100</td>
<td>22.5 (25.0&lt;20)</td>
<td>3.0</td>
<td>44.0</td>
<td>Home, 35.1 en route, 5.4 Hospital, 59.5</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Adapted from Creanga and Genadry, 2007 and completed with two new references
in Nigeria which compared 80 women with fistulas to 80 inpatients without fistulas who were recruited randomly as a control group. Major risk factors for the development of a fistula included early age at first marriage (average 14 years), short stature (average height of 146.2 cm), illiteracy, rural residence and living at more than 3.0 km from the nearest health care facility [54].

5. PHYSICAL, SOCIAL AND PSYCHOLOGICAL CONSEQUENCES

Recent publications [29, 55-61] and a review by Ahmed and Holtz [62] have documented the physical, social, economic, emotional and psychological consequences of fistulas in affected women. A meta-analysis of the literature published between 1985 and 2005 showed that 36% (95% CI: 27%-46%) of women afflicted with fistulas were divorced or separated and foetal loss occurred in 85% of cases in which a fistula developed. Low self-esteem, feelings of rejection, depression, stress, anxiety, loss of libido and loss of sexual pleasure were commonly reported by these women. It also appears that the rates of separation or divorce increases the longer a woman lives with a fistula, particularly if she remains childless [63]. Not surprisingly, successful fistula repair reduces the prevalence of these psychosocial pathologies [62].

Three recent articles further document the presence of these problems in women with fistulas. In their 2007 article on the health and social problems of women with fistulas in Ethiopia, Muleta et al [39] reported 69.2% of fistula victims were divorced, only 19.2% were members of a local community association, and 44.2% ate separately from other family members. Forty-eight of 52 women felt listless and 28 had suicidal thoughts. Goh et al [56] conducted a prospective observational study to screen women in Bangladesh and Ethiopia with fistulas for mental health dysfunction.

Of the 68 women with fistulas screened, 66 were at risk for mental dysfunction as measured by the General Health Questionnaire (GHQ-28) compared with only 9 of 28 controls. In a prospective interventional study, 51 women with fistulas in the north of Ethiopia were screened for mental health issues before and 2 weeks after surgery using the GHQ-28.

Prior to surgery, all women had signs of mental dysfunction, but two weeks after fistula surgery, only 36% still had signs of mental distress. Among the 45 women who were cured of their incontinence, only 27% had signs of mental dysfunction two weeks after surgery, whereas all of the six patients who remained incontinent continued to screen positive for mental distress on the GHQ-28 [55]. These studies highlight the importance of attending to mental health issues among women who have sustained an obstetric fistula.

II. DIAGNOSIS

1. SIGNS AND SYMPTOMS

Obstetric fistulas may develop early, either after vaginal delivery or after an emergency caesarean section. Even though these women may be under medical supervision, these early fistulas may not be detected by the local staff. Many of these women leave the hospital without a baby but with a fistula [64]. Once the fistula is established, the continuous leakage of urine will lead to a foul odour, skin deterioration, and a cascade of hygienic and social problems. In most cases these women will be poor. Women may present early or late after a fistula appears.

2. CLINICAL EVALUATION

A fistula patient often has more than just a fistula. When examining and treating a woman in whom a fistula is suspected, the clinician should look for evidence of the entire ‘obstetric labour injury complex’ [65]. Clinical evaluation should include the assessment not only of urologic and gynaecologic injury, but also for evidence of the presence of rectovaginal fistulas, orthopaedic trauma, neurologic and dermatologic injury as well. The psychological impact of the fistula should never be underestimated. (table 3)

After admission, fistula patients should undergo a thorough evaluation through the taking of a detailed history, general physical examination as well as a careful pelvic examination. The site of the fistula, the condition of the surrounding tissues, and the feasibility of a vaginal surgical approach should all be assessed. In many countries the absence of advanced technology will mean that careful clinical examination will be the only tool available to the surgeon in planning a repair.

a) Urologic injury

1. BLADDER

The loss of bladder tissue from pelvic ischemia during obstructed labour affects both the technique needed for, as well as the functional outcome of, fistula repair. Loss of bladder tissue is one of the main reasons why obstetric fistula repair is technically difficult. The surgeon must try to close large defects in the bladder often with only small remnants of residual bladder tissue with which to work. Although there are as yet no basic histological studies of the tissue surrounding obstetric fistulas, it seems clear that these tissues have themselves sustained significant damage during obstructed labour. The fistula itself develops in an area which becomes necrotic; but the tissues surrounding the fistula have also suffered varying degrees of ischemia. In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 - 50 ml) bladder that
remains virtually functionless. Because most of the innervation of the bladder runs through the base and trigone, ischemic injury to these areas probably also produces an element of neuropathic bladder dysfunction. Basic scientific studies confirming this hypothesis have yet to be undertaken.

Clinically it will be important to assess the number and size of the fistulas, their location, the amount of fibrosis present, and any involvement of the ureters and or the urethra.

Clinical experience also suggests that bladder compliance may be altered by the extensive fibrotic changes that often take place. To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure [66, 67]. In the former study bladder compliance was not measured. In the latter study by Carey et al., of 22 women with severe urinary incontinence after fistula closure, 9 had urodynamic stress incontinence with normal bladder compliance, 3 had urodynamic stress incontinence with poor bladder compliance, 9 had mixed incontinence, and one had voiding difficulty with incomplete bladder emptying and overflow. There is a great need for further investigation of these issues; unfortunately, those hospitals most likely to see large numbers of patients with obstetric fistulas also usually lack the resources for more advanced urologic investigation.

A number of patients with vesicovaginal fistulas develop vesical calculi [68, 69]. Often these bladder stones develop in association with a foreign body in the vagina. In some cases a foreign body may have been the original cause of the fistula (such as an object used for masturbation or a container filled with traditional herbal medicines, placed in the vagina for an ostensibly therapeutic purpose). In other cases, the stone may form in association with an object that was placed into the vagina in an attempt to plug the fistula and prevent urine loss, which subsequently became stuck, eventually became calcified, and ultimately increased the overall misery of the afflicted woman. In other cases, no foreign body can be found. Frequently in these cases it is the increasing pain associated with stone formation that causes the suffering patient to present for care. In fistula cases complicated by the presence of vesical calculi, the stone is often located supratrigonally and the bladder may be able to hold at least a small amount of urine in the vicinity of the calculus (which allows for its continued growth) [69].

Removal of the stone (usually at a separate operation) is a prerequisite for successful fistula closure in such cases. After stone removal, the bladder should be allowed to heal prior to attempted fistula closure. If this is not done, there is substantial risk of post-operative infection and breakdown of the repair.

2. URETHRA

The ischemic changes produced by obstructed labour often have a devastating impact on urethral function. Complete urethral loss occurs in about 5% of fistula patients, with about 30% of fistula patients sustaining partial urethral injury. Goh et al. found that up to 63% of fistula patient have sustained some injury to the urethra [70]. The great Egyptian fistula surgeon Naguib Mahfouz was well aware of this problem [71].

Mahfouz stated [71] that fistulas “in which the whole urethra has sloughed” are “the most troublesome of
The experience of subsequent surgeons seems to bear this out. In a 1980 series of 1,789 fistula patients, Sister Ann Ward reported that only 26 cases were inoperable; but in all 26 urethral loss was present [72]. There are no comparative surgical studies that evaluate differing techniques of urethral reconstruction in patients with obstetric fistulas. There are no data on post-operative urethral function. Work of this kind is badly needed.

3. Ureters

Ureterovaginal fistulas from direct injury to the distal ureter during obstructed labour are uncommon, comprising only about 1% of fistula cases. Depending on the amount of tissue that is lost at the bladder base, the ureteral orifices can be found in bizarre locations, ranging from the lateral vaginal walls all the way up to the level of the vesico-urethral junction and the pubic arch (Figure 5).

Aberrant ureteral locations of this kind can easily be missed on clinical examination and are one cause of persistent incontinence after otherwise “successful” fistula closure. Standard urological tools such as ureteral stents are usually not always available in hospitals in the developing world, and most of the surgeons who work in such hospitals are not trained in “urologic” techniques such as ureteral reimplantation [73].

![Figure 5: Complex fistula with intravaginal ureters](image)

4. Kidneys

The incidence of secondary injury to the upper urinary tract in fistula patients has received little study, but this phenomenon appears to be clinically important. Clinical experience suggests that renal failure is a common cause of death in women with obstetric fistulas.

Upper tract damage could result from chronic ascending infection, obstruction from distal ureteral scarring, or even from reflux in very young patients. Lagundoye et al [74] found that 49% of fistula patients had some abnormality of the kidneys when intravenous urograms were performed. Most of the pathology that was detected consisted of minor calyceal blunting, but 34% of patients had hydro-ureter, 9.7% had ureteral deviation, four patients had bladder stones, and 10 patients had a non-functioning kidney. More research is needed in this field. Iatrogenic causes of hydronephrosis and renal insufficiency may also exist. Injury of the ureters during the surgery or scarring in the post-operative phase might play a role, but data to support this are currently missing.

b) Gynecologic injury

1. Vagina

An impaction of the foetal head serious enough to cause ischemic injury to the bladder will also cause ischemic injury to the vagina, which is likewise trapped between the two bony surfaces. These injured areas heal with varying degrees of scarring. A small sonographic study by Adetiloye and Dare [75] detected fibrotic changes in 32% of fistula patients and minor vaginal wall fibrosis in another 36%. Vaginal injuries in fistula patients exist along a spectrum that includes only small focal bands of scar tissue on one end all the way to virtual obliteration of the vaginal cavity on the other. Roughly 30% of fistula patients require some form of vaginoplasty at the time of fistula repair. The degree of vaginal injury has several important implications. In the first instance, severe vaginal injury results in loss of substantial portions of the vagina. In many instances the scarring is such that vaginal intercourse is simply not possible. There is very little information available on the sexual functioning of fistula patients, yet this is obviously an important concern in healthy marital relationships and undoubtedly contributes to the high rates of separation and divorce that appear common among these women. Browning et al. noted that among 240 fistula patients only 7.1% were having sexual intercourse prior to surgery and of those who were sexually active, 17.6% had dyspareunia. Six months after surgery 35% of patients were sexually active. Of those, 10.0% had dyspareunia. The main reasons for lack of sexual relations were divorce, anxiety about damaging the repair, widowhood or a scarred vagina [63].

Surgical repair of fistulas in women with extensive vaginal scarring often requires the use of flaps and tissue grafts in order to close the fistula. Little work has been done to assess whether or not sexual function normalizes in women who have had such operations. The presence of scarring that requires the use of plastic surgical techniques of this kind markedly reduces the effectiveness of surgical repair when fistula closure is attempted by surgeons who lack experience in reconstructive gynaecologic surgery. Although several papers have described various techniques for vaginoplasty that may be required in fistula patients [76-78], there is a pressing need to
investigate the role of vaginal plastic surgery at the
time of fistula repair and to evaluate subsequent
sexual functioning in patients who require surgery of
this kind [79].

Vaginal scarring impacts on more than just sexual
functioning. The presence of vaginal scarring appears
to be an important prognostic factor in determining the
likelihood both of successful fistula closure, and also
for the development of debilitating urinary stress
incontinence after otherwise successful fistula repair.
In one unpublished series of 26 fistula patients with
severe vaginal scarring, 57.7 percent suffered from
stress incontinence after fistula repair and 23.5 percent
had a persistent or recurrent fistula. This would
compare to an expected stress incontinence rate of
around 26% and a failed fistula closure rate of about
7% in the overall population of fistula patients
(Arrowsmith, personal communication). Kelly and
Kwast have also reported worsening surgical outcome
in fistula patients who have vaginal scarring than in
those without such findings [80].

2. CERVIX, UTERUS, AND FUTURE REPRODUCTIVE
PERFORMANCE

From an obstetric point of view, timely termination of
obstructed labour requires operative intervention,
most often by caesarean delivery. When timely access
to caesarean section is not available, prolonged
obstructed labour results in a high rate of uterine
rupture, usually with catastrophic consequences for
both mother and child. For example, Ekele and co-
workers reported one uterine rupture for every 79
deliveries in Sokoto, Nigeria, an impoverished rural
area with poor obstetric services [81]. Caesarean
delivery in such cases is often lifesaving, but in some
cases it may also be implicated in the formation of a
vesico-uterine fistula [82-84]. Vesico-uterine fistulas
can present in different ways, depending on their
location, size, and the degree of patency of the
endocervical canal. The least troublesome vesico-
uterine fistulas do not result in incontinence, but are
characterized by the absence of vaginal menstruation
in the presence of cyclic haematuria (“menouria” or
“Youssef’s syndrome”), whereby the menstrual flow
exits exclusively through the urinary tract [85-87].
Other vesico-uterine fistulas may be associated with
various combinations of altered menstruation and
either periodic or continuous incontinence. The finding
most characteristic of an uterovesical fistula is
a demonstrable loss of urine through the cervix (a
finding that also occurs with vesicocervical fistulas). In
the absence of operative intervention, uterovesical and
vesicocervical fistulas are relatively rare.

Many patients sustain severe cervical damage as well
as vaginal injury during the course of obstructed
labour. It is rare to see a completely normal cervix
when examining a fistula patient. In the worst cases,
prolonged obstructed labour may result in complete
cervical destruction, leaving the patient with no
identifiable cervical tissue at all. Unfortunately, detailed
descriptions of the condition of the cervix have not been
included in the case series of fistulas published to
date. Since cervical competence is such an important
factor in future reproductive performance, this is yet
another clinical area that demands further study. Other
studies have shown amenorrhea rates from 25% to
44% [88-90]. Many of these patients undoubtedly
have hypothalamic or pituitary dysfunction [89]. A
follow up study by Browning et al. showed that while
the amenorrhea rate was 58% pre-operatively, this rate
improved to 29% at 6 months after surgery, suggesting
a recovery of ovulation in a proportion of operated
women [63]. While the high incidence of amenorrhea
in vesicovaginal fistula patients is widely recognized,
only one unpublished study has been done to date
looking specifically at uterine pathology in the
vesicovaginal fistula population. Dosu Ojengbede of
the University of Ibadan (personal communication)
performed hysteroscopy on fistula patients in Nigeria
and found that intrauterine scarring and Asherman’s
syndrome were common in these women. The
combination of widespread amenorrhea, vaginal
scarring, and cervical destruction leads to a tremen-
dous problem of secondary infertility among these
patients. To date, there have been no serious scientific
efforts to explore treatment of cervical and uterine
damage in vesicovaginal fistula patients.

Subsequent reproductive performance of women who
have had an obstetric vesicovaginal fistula has been
analyzed in a few articles [88, 90-92]. Emembolu
analyzed the subsequent reproductive performance
of 155 fistula patients delivered at Ahmadu Bello
University Teaching Hospital in Zaria, Nigeria, between
January 1986 and December, 1990 [92]. This series
included pregnancies in 75 women who became
pregnant after successful fistula closure and 80 women
who became pregnant while still afflicted with an
unrepaired fistula that had occurred in a previous
pregnancy. The data presented do not allow one to
determine the subsequent fertility rates of women
who develop a fistula, but clearly indicate that women
can, and do, become pregnant after sustaining an
obstetric fistula. The proportion of booked pregnancies
receiving antenatal care was higher in the repaired
group (73%) than in the unrepaired group (51%),
and reproductive performance was better (but still dismal)
in those patients who had had a fistula repair. Of the
69 patients whose fistulas had been repaired, there
was a recurrence of the fistula in 8 (11.6%), and
among those undergoing a trial of vaginal delivery, the
fistula recurrence rate was nearly 27%. In women
with pre-existing, unrepaired fistulas who became
pregnant but who did not register for prenatal care in
the subsequent pregnancy, maternal mortality and
morbidity in those pregnancies was high, reflecting
continuation of the conditions that led to fistula
formation in the first place [92].
The commonest maternal morbidity, excluding recurrence of vesicovaginal fistulas, was haemorrhage requiring blood transfusion in 35 patients (27.3%). Others included ruptured uterus in 3 unbooked patients whose fistula had not been repaired, bladder injury at caesarean section in 1.6% and acute renal failure in 0.8%. Maternal complications occurred more frequently in the patients whose fistula had not been repaired and who were also unbooked.

The largest series is that of Aimakhu, who analyzed subsequent reproductive performance in 246 women who underwent successful fistula closure at University College Hospital in Ibadan, Nigeria, between 1957 and 1966 [88]. Only 48 patients became pregnant following fistula repair with a total of 65 pregnancies. All but 6 of these were managed at University College Hospital. Five patients aborted prior to the 16th week of gestation, leaving only 60 viable pregnancies. The plan was to perform elective caesarean section on all patients who became pregnant after fistula repair, but only 49 caesarean operations were carried out. The results of the vaginal deliveries were not encouraging. Patients who underwent caesarean delivery fared better. There were 49 babies delivered and 47 survived. There was no recurrent fistula among women previously repaired who became pregnant and had a subsequent caesarean section. There was one maternal death from pulmonary embolism in a woman who underwent an emergency delivery at 32 weeks gestation due to a prolapsed fetal umbilical cord.

c) The rectovaginal fistula

Rectovaginal fistulas appear to be significantly less common than vesicovaginal fistulas. In case series of patients presenting with vesicovaginal fistulas, between 6% and 24% have a combined rectovaginal and vesicovaginal fistula (Figure 6) [29-31, 49, 93-102]. In most series, isolated rectovaginal fistulas are less common than combined fistulas. Indeed, most series do not even mention isolated rectovaginal fistulas as a clinical phenomenon. In a series of patients from Turkey reported by Yenen and Babuna [103], 7.1% had rectovaginal fistulas and 6.5% had “combined” fistulas. From the report it is not clear if this latter figure was comprised solely of rectovaginal and vesicovaginal fistulas, or if it included other combinations of urinary tract fistulas as well (vesicocervicovaginal, urethrovaginal, etc.). Kelly and Kwast [80] reporting data from the Addis Ababa Fistula Hospital, noted a 15.2% pre-valence of combined fistulas, and a 6.8% prevalence of isolated rectovaginal fistulas in that population. Ethiopia appears to have one of the highest rates of rectovaginal fistulas reported in the literature. Whether this relates to specific obstetric characteristics of the Ethiopian population or whether this relates to other social factors — such as the cases of rape and sexual abuse of young Ethiopian girls reported by Muleta and Williams [27] — is unclear.

Figure 6 : rectovaginal fistula

Since the pubic symphysis poses an obstruction to delivery through the anterior pelvis, in normal birth mechanics the foetal head is normally forced posteriorly towards the rectum, anus, and perineum at the end of the second stage of labour. In non-obstructed labour, direct laceration of the perineum is not uncommon, occasionally resulting in a complete perineal tear with complete disruption of the anal sphincter. If this is not repaired, a complete perineal tear with sphincter disruption can create a rectovaginal fistula at the anal outlet [104]. This mechanism of fistula formation seems more likely to account for low rectovaginal fistulas, whereas rectovaginal fistulas higher in the pelvis would seem more likely to be caused by direct tissue compression from obstructed labour.

d) Orthopaedic trauma

Ischemic injury from obstructed labour not only affects pelvic organs, but also the pelvis itself. These changes are most pronounced in the pubic symphysis. The normal radiography of the symphysis pubis has been described in detail by Vix and Ryu [105]. In obstructed labour, the pubic bones are often directly involved as they form one side of the bony vice in which the vulnerable soft tissues are trapped. In fistulas where large amounts of bladder tissue are lost, the periosteum of the pubic arch can often be palpated directly through the fistula defect. It is these cases in which ischemic damage to the pubic bones is most likely to be demonstrable. In a study of 312 Nigerian women with obstetric vesicovaginal fistulas Cockshott [106] detected bony abnormalities in plain pelvic radiographs in 32 percent of these patients. The findings included bone resorption, marginal fractures and bone spurs, bony obliteration of the symphysis, and wide (>1 cm) symphyseal separation. Most of these changes appear to be the result of avascular
necrosis of the pubic symphysis. Their long-term significance remains uncertain and further study is required.

e) Neurologic injury

Another tragic injury associated with obstetric fistula formation is footdrop [107]. The relationship between difficult labour and neurological injury has been known for centuries, and the condition was traditionally called “obstetric palsy” [108]. Women with this condition are unable to dorsiflex the foot and therefore walk with a serious limp, dragging their injured foot, and using a stick for support (Figure 7). Sinclair’s paper on maternal obstetric palsy in South Africa [108], made the comment that “There are no records of this lesion associated with vaginal fistulas, where there has been prolonged pressure by the foetal skull in the lower part of the pelvis.” This statement is clearly wrong. In Waaldijk and Elkins’ review of 947 fistula patients, nearly 65% of those studied prospectively had evidence of peroneal injury either by history or physical examination [107]. The prevalence of clinical footdrop among patients seen at the Addis Ababa Fistula Hospital is about 20% [65].

Various theories have been proposed for the aetiology of this condition. In general clinical series of peroneal nerve palsy, the most common aetiologies appear to be direct trauma from ankle inversion, fractures of the hip, femur, fibula or tibia; knee injuries, alcoholic neuropathies, and a variety of miscellaneous or idiopathic causes. In obstetric patients the lesion most likely develops from one of three causes: prolapse of an intravertebral disk, pressure from the foetal head on the lumbo-sacral nerve trunk in the pelvis leading to direct compression of the peroneal nerve, or direct trauma to the peroneal nerve from prolonged squatting and pushing in the second stage of labour [108-110]. There is very limited experience with the performance of electromyography on fistula patients. Bademosi and colleagues performed EMG studies on 34 Nigerian women with obstetric neuropaxia at the University of Ibadan and found that 88% of the lesions were due to lumbosacral plexus injury high in the pelvis [111].

Footdrop has also been associated with trauma sustained in difficult forceps deliveries, particularly mid-pelvic rotations, but again, as others have emphasized “The peripheral nerve lesion following instrumental delivery may have developed in any case and forceps were but incidental or at the most a precipitating factor in border-line cases” (Sinclair 1952). The prognosis for recovery from this injury is unclear, as there are no proper prospective studies of women who have developed this condition. Waaldijk and Elkins suggest that most patients recover some or all of their nerve function spontaneously within two years of the injury [107]; however 13% showed persistent signs of nerve trauma. In some cases the affected women are almost completely crippled from bilateral lesions and suffer tremendously from the additional burden imposed by immobility on someone who already suffers from intractable urinary incontinence.

Physiotherapy and the use of posterior splints improve the condition of some patients. Others may require surgical intervention: the use of posterior tibialis tendon transfer is a well-established procedure for patients with footdrop from other causes (such as leprosy), and it may be that this method will be useful in treating women with unresponsive obstetric palsy as well [112, 113].

f) Dermatologic injury

Skin lesions can be variable, depending on the importance of the leakage, the duration of the leakage and the level of hygiene. The condition of the skin, which is in constant contact with a stream of urine and/or faeces, is one of the most bothersome problems for the fistula patient (Figure 8). In some women minimal skin damage will be noted, while in other extreme causes, the vulvar skin might be covered with uric acid crystals and salts or might be superinfected.

g) Psychological injury

The consequences of isolation, divorce etc… have been described in II.5. Depression has a high prevalence in patients with obstetric fistula. Care must be taken to acknowledge these factors. A significant improvement can be expected after successful surgery in many patients.

Figure 7 : Neurological injury

Figure 7 : Neurological injury
3. EVALUATION WITH ADVANCED TECHNOLOGY

The use of technology beyond simple physical diagnostic techniques in women with fistulas will depend entirely on the local availability of such resources. Cystoscopy, ureteral catheterisation, ultrasound or radiographic examination and urodynamic testing facilities are not always present. Utilization of modern diagnostic techniques might be especially useful in the evaluation of the upper urinary tract and in developing strategies for long-term follow-up of fistula patients. The ability to obtain some basic or advanced laboratory tests, would also be useful in many cases. At a minimum, it is desirable to have basic haematology and electrolyte testing available, if the data can be trusted. HIV testing is optional.

III. FISTULA PREVENTION

Preventing obstetric fistulas is an enormous task that will depend largely on continuous improvements in the maternal healthcare infrastructure of the countries where fistulas are prevalent. The magnitude of the needs in this part of the world is staggering. Waaldijk has stated that at least 75,000 new obstetric units should be built across Africa to deliver adequate perinatal care and to prevent new cases of fistulas [114].

Historical experience from Western countries suggests that fistula prevention can only be accomplished by providing good antenatal screening and surveillance of ongoing pregnancies, delivery in the presence of trained birth attendants, and prompt access to emergency obstetric services when problems arise during labour. In fistula-prevalent areas, basic emergency obstetric care is usually inaccessible due to problems with transportation and referral centres for advanced care are usually far away for women living in rural areas. A recent survey by UNFPA and UNICEF showed that each African country assessed had only one emergency obstetric unit per 500 000 inhabitants and none had the recommended number of facilities for the provision of basic emergency obstetric care. The unmet obstetrical needs were huge: only 8.2-35% of women with complications during labour received care at an appropriate facility [115]. Even when a woman with a complication arrives at such a facility, the receipt of good care is not guaranteed. In most countries the patient must pay for emergency care, including caesarean section and many families simply cannot afford the cost involved or are left in debt afterwards for many years [116].

In addition to creating centres for emergency obstetric care, adequate training for health care professionals has to be provided, financing mechanisms have to be established and access to these facilities has to be guaranteed for all patients who need these services. This is an enormous task and most governments in the developing world do not have the necessary resources for it (or the political will to carry such projects out). Western aid organizations are often more interested in funding the treatment of women with fistulas than with doing the hard work of constructing primary care obstetric units or funding the provision of emergency obstetric services [117]. What is clear is that perinatal care is grossly inadequate due to the large number of vesicovaginal fistulas that is being reported in many developing countries. It is also clear that there are multiple reasons that young mothers at risk of obstructed labour do not attend medical facilities, most of which have already been described. Even when patients in need arrive at a healthcare facility, they may not receive the care they need. This situation is described eloquently by Sundari in his paper on how health care systems in the developing countries contribute to maternal mortality [11]. The same problems are applicable to the prevention of fistulas. Thaddeus and Maine (1994) have elaborated on the three causes of delay that contribute to maternal mortality. These same causes of delay contribute to obstetric fistula formation once labour becomes obstructed.

1. PATIENT FACTORS
   - Delay in arriving at a healthcare facility
   - Non-use or non-availability of prenatal care
   - Transportation problems
   - Financial problems
   - Lack of women’s authority over decision-making regarding healthcare
   - Lack of information about risk factors, health problems, availability of services
2. QUALITY OF CARE FACTORS

- Shortage of trained personnel
- Lack of equipment
- Poor patient management

The lack of decent training is prevalent and is the result of the interaction of many different factors. There is wide high variability in the quality of training and in the curricula at many African universities and teaching hospitals. Once trained, local doctors may experience difficulties in maintaining their skills because of political issues, lack of equipment, and administrative decisions by local health authorities. In many developing countries poor staff training is compounded by the fact that only a ‘survival health economy’ exists, meaning that elective surgery is usually delayed until an emergency exists. Many pregnant women will have been warned about the risk of obstructed labour and its consequences, but simply do not have the money to undergo elective caesarean section even when it is advisable. Many local doctors depend on private income in order to survive in difficult economic situations. Inappropriate operations may compound the healthcare delivery problems that already exist. In India, where industrialisation is more advanced and the healthcare system is better than that of most African countries, caesarean sections are being misused for profit in the private sector of some of the states [118].

Ideally, therefore, fistula centres should be developed in collaboration with other maternal healthcare initiatives and they should also be prepared to provide services dealing with the entire obstructed labour injury complex and its consequences. A comprehensive approach that combines a curative setting with prevention is being advocated by many [119]. Doing this effectively will require the establishment of incentives at multiple levels throughout the healthcare system.

a) At the level of the patient

- Prenatal care is important because it plugs patients into the healthcare system and helps them access care when emergencies arise.
- “Maternity waiting homes” can be established for women at high risk of obstetric complications [120-123]. They then stay in the vicinity of the hospital until labour begins, at which time they are transferred to the hospital for monitoring and intervention. The success of such programs depends on multiple factors operating at the local level (D. De Ridder, personal observation, RD Congo 1987).
- Local radio or television shows involving former fistula patients can help create awareness about these problems and provide social mobilization.
- Young women and men should be educated about the risks of bearing children at too young an age.

Changing traditional customs of early marriage will require steady and prolonged pressure over time, but is one of the most important social interventions.

- These measures should be incorporated in a wider program that emphasizes education for girls and women. This is an extremely effective means of promoting maternal health [124] [7].

b) Professional level

Local midwives and doctors should be trained to screen for injuries associated with obstructed labour. It is not uncommon for a patient to undergo an emergency caesarean and to leave hospital later with a vesicovaginal fistula without any of the medical staff being aware of this problem (D. De Ridder, personal observation, Kisantu RD Congo 2007).

Several challenges are present:

- Continuing education on perinatal care
- Screening patients for risk factors
- Adequate and improved technical obstetrical skills
- Appropriate postoperative care
- Early detection of fistula formation
- Staff accountability for the quality of care provided
- Hospital level
- Careful record keeping
- Social accountability

c) Community level

At the community the level, awareness about the availability of antenatal care and the risk of obstetric fistula formation ought to be increased. Some fistula centres note that up to 30% of their patients are being referred by former patients who are now cured. Ways should be explored to use former patients as a mechanism to increase awareness of the problem and to organize prevention strategies, perhaps by monitoring women at the village level to detect prolonged labour early in its course.

Community-wide associations to promote maternal health should be encouraged, linking local farmers’ unions, women’s organisations, and religious associations, for example.

Patients often depend on their own finances or those of their relatives to be able to pay for health services. This is one of the main reasons for not undergoing timely caesarean sections in many countries. Local communities should be encouraged to embark on microfinance projects and revolving community credit schemes to help finance promote prompt access to emergency obstetric services when problems arise. Such projects could be facilitated within their catchment areas by fistula centres. Research in this area should be encouraged [125-130].
d) The Indian example

A national family health survey in India revealed that 65% of the births in rural areas took place in the homes of the women’s parents and that only one in seven deliveries was attended by trained health practitioners. According to the Indian government’s annual report in 2001-2002, maternal morbidity and mortality had not changed in the last four decades [131]. In the three years preceding the India’s National Family Health Survey 1998-1999 (NFHS-2), 35% of pregnant women received no antenatal care. This is only marginally better than the 36% in the 1992-1993 NFHS [132]. The government shifted its focus during the 1990s from contraceptive and fertility reduction targets and incentives for population control toward a broader system of performance goals and measures designed to encourage a wider range of reproductive and child health services. This approach seeks to address issues such as safe motherhood, safe abortion, and the quality of health services. Under this broader approach, the government initiated the Child Survival and Safe Motherhood Programme in 1992 in partnership with the World Bank and the United Nations Children’s Fund (UNICEF). In spite of such measures vesicovaginal fistulas and other urinary fistulas are still common. In rural areas, the majority of women with fistulas are not getting proper treatment. The results of surgery by surgeons who operate on these problems only rarely are so poor that many of them have abandoned the treatment of such cases altogether. Although the surgical results are good in hands of experienced surgeons, such practitioners are often more interested in procedures that have the potential for high financial gain, such as endo-urology and laparoscopy. Consequently, the majority of fistula patients are neglected. In urban areas where more surgeons are available, early caesarean delivery in cases of prolonged labour has reduced the obstetric causes of fistulas but there has been a concurrent increase in the number of fistulas resulting from gynaecological surgery (vesicovaginal fistulas, ureterovaginal fistulas, and uterovaginal fistulas).

In Kerala, one of the states of India that has achieved universal literacy, institutional deliveries have been made compulsory. This has resulted in a drastic reduction in maternal morbidity, and particularly in a reduction of obstetric fistulas [133]. In Kerala there is a more equitable distribution of health facilities and consequently better utilisation. Improved education has increase access to such services and there is also a higher degree of political awareness among the people in rural Kerala. Nag concluded that governments should give higher priority to social equity than to economic equity. In that state a rising trend in caesarean rates is seen and up to 28% of the first live births occurred by caesarean section [134]. The availability of these services is much appreciated by the local women and the use of the services was excellent (99% of a cohort of women participating in a survey visited a doctor at least 3 times during the pregnancy [135].

IV. CLASSIFICATION SYSTEMS

There is currently no uniform system for classifying fistulas and a wide variety of different systems have been proposed. Classification of fistulas is important only to the extent that the classification has a meaningful relationship to the prognosis of the injury. In recent attempts at fistula classification the size of the fistula and involvement of the urethral closing mechanism are taken into account. Some systems attempt to classify fistulas according to the anticipated degree of difficulty of the repair, while others classify them according to the type of surgical intervention that will be needed [36]. Systems based on the anatomical appearance of the fistula do not necessarily predict the difficulty of repair nor the post-operative prognosis [136]. Table 4 lists the most common classification systems in current use. Recently a large international multicenter study has started in an attempt to develop a prospectively-validated system for classifying fistulas (R. Genadry, personal communication 2008).

V. CONSERVATIVE MANAGEMENT

Little is known about the conservative treatment of vesico-vaginal fistula. As mentioned above, the diagnosis of a fistula is often missed by medical staff in the early phase after its development. This may be due to neglect by the staff or due to a patient who is eager to return home as soon as possible after delivery who simply thinks the initial urinary leakage is a normal consequence of her difficult delivery. Waaldijk published his personal experience with the conservative approach to fresh obstetric fistula [137-139]. He reported a series of 1716 patients with fresh obstetric fistulas, of whom 265 were treated conservatively with a CH 18 indwelling catheter. If there was no sign of healing after 4 weeks, a surgical approach was utilized. All but one of these women were cured by catheter drainage alone. Unfortunately, he provided no data on fistula size or location in this subgroup.

A recent evidence-based review by Bazi T. on the spontaneous closure of vesicovaginal fistula after bladder drainage alone came to the following conclusions [140]:

- It was not possible to correlate the aetiology of the fistula (obstetric or gynaecologic) with the likelihood of success
<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Size</th>
</tr>
</thead>
</table>
| Marion Sims (1852)             | 1) Urethrovaginal  
2) Bladder neck  
3) Body and floor of bladder  
4) Utero-vesical               |                           |
| Mc Connachie (1958)            | Grade 1: normal healthy tissue  
Grade 2: mild scarring  
Grade 3: more scarring, poor vaginal access  
Grade 4: repeat repair  
Grade 5: inoperable per vagina | Type A: <1cm  
Type B: >1 but <2cm  
Type C: >2cm  
Type D: A, B or C with rectovaginal fistula |
| Lawson (1968)                  | 1) Juxta-urethral  
2) Mid-vaginal  
3) Juxta-cervical  
4) Vault  
5) Massive combination fistula |                           |
| Hamlin (1969)                  | 1) Simple vesico-vaginal  
2) Simple recto-vaginal  
3) Simple urethra-vaginal  
4) Vesico-uterine  
5) High rectovaginal fistula  
6) Complex fistula            |                           |
| Waaldijk (1995)                | Type 1: not involving closing mechanism  
Type 2: involving closing mechanism  
A) Without (sub)total urethral involvement  
B) With (sub)total urethral involvement  
a) No circumferential defect  
b) Circumferential defect  
Type 3: ureteric and exceptional fistula |                           |
| Arrowsmith (2007)              | Scarring score:  
1 mild  
2 moderate  
3 severe  
Urethral status score:  
0 intact.  
2 partial damage  
3 complete loss |                           |
| Goh (2004)                     | Location of fistula:  
Type 1: distal edge >3,5cm from urethral meatus  
Type 2: distal edge 2,5-3,5 cm from urethral meatus  
Type 3: distal edge 1,5-2,5cm from urethral meatus  
Type 4: distal edge <1,5cm from urethral meatus  
Fibrosis:  
i. None or mild  
ii. Moderate or severe  
iii. Special consideration | a) <1,5cm diameter  
b) 1,5-3cm diameter  
c) >3cm diameter |
| WHO (2006)                     | Good prognosis/simple:  
Single fistula  
Vesicovaginal fistula  
Closing mechanism not involved  
No scarring  
No circumferential defect  
Minimal tissue loss  
Ureters not involved  
First attempt to repair | <4cm |
| Complicated/uncertain prognosis: | Multiple fistula  
Rectovaginal, mixed fistula, cervical fistula  
Closing mechanism involved  
Scarring  
Circumferential defect  
Extensive tissue loss  
Intravaginal ureters or bladder stones  
Failed previous repair | > 4cm |
- Most fistulas reported cured by catheter drainage alone are small, usually less than 1 cm in diameter.
- It was not possible to establish a relationship between fistula size and outcome, although a 5mm diameter has been set as an arbitrary cut-off limit.
- Duration of drainage utilized varies between 10 days and six weeks, but has not been studied properly.
- No data are available on which type of catheter drainage yields the best results.
- Fresh fistulas are more likely to close than those of longstanding duration.

The conclusion reached was that conservative management of a fresh fistula may be an option in small fistulas, but if healing has not taken place within a few weeks, surgical repair will likely be required for cure.

VI. SURGICAL MANAGEMENT

Fistula surgery requires some form of anaesthesia. The position used during fistula surgery depends on the nature and location of the fistula to be repaired. For the vast majority of fistulas a high lithotomy position with the buttocks pulled well over the edge of the operating table (in steep Trendelenburg position), with or without episiotomies provides excellent exposure (Figure 9). Surgery in this position can safely be performed under spinal anaesthesia, which is the cheapest and easiest form of anaesthesia for "low technology" settings in developing countries. Spinal anaesthesia can be administered by the surgeon which is an advantage over general anaesthesia [141].

Vaginal surgery for small fistulas can be attempted under local anaesthesia [142]. Larger or more complex fistulas can be treated under spinal anaesthesia, which is to be preferred over epidural or general anaesthesia [143]. Spinal anaesthesia will yield a better pain control than epidural anaesthesia in rural settings [144].

Alternative positions are the knee-chest position, which is uncomfortable for the patient and generally requires intubation. Operating by the abdominal route increases the cost and time of the operation, but is still often performed for some high fistulas where surgical access is problematic. Experienced fistula surgeons may be able to repair such defects vaginally. A retrospective study by Chigbu compared the outcome of juxtacervical fistula through the vaginal or abdominal approach [145].

Both approaches had similar cure rates and hospital stays, but the abdominal route was associated with a significantly higher need for blood transfusion. General anaesthesia is also more expensive, more complicated to administer, carries more risks, and should therefore be reserved for those patients who need an abdominal approach.

1. THE SIMPLE FISTULA

In practiced hands, skilled fistula surgeons routinely achieve a closure rate of over 80% for simple fistulas at the time of first operation. Multiple papers reporting large case series support this contention [29, 49, 71, 94-103, 146-161].

A fairly general consensus concerning the basic principles of fistula repair was reached at the first ‘Fistula Surgeons Experts Meeting’ at the WHO in Geneva 2004. These principles can be summarized as follows:

- The best chance for successful fistula closure is at the first operation and closure rates tend to diminish with each subsequent attempt at operative repair. In their large series of 2,484 obstetric fistula patients, Hilton and Ward (1998) reported successful fistula closure in 82.8% of patients at the first attempt. Successful closure was achieved in only 65% of those patients who required two or more operations. Another unpublished series of 400 patients from the Addis Ababa Fistula Hospital reported a successful closure rate of 92% and urethral incontinence of 33% at the first operation, a closure rate of 73% and urethral incontinence rate of 50% at the second operation and a closure rate of only 52% and urethral incontinence of 75% at the third operation (Browning, personal communication).
- The ureters should be identified and protected to ensure they are not cut or ligated during the fistula repair (if the site and size of the fistula puts them in proximity to the operative field).
- The fistula should be widely mobilized from the surrounding tissues at the time of repair.
• The fistula should be closed without tension on the site of repair.
• The repair must be ‘water-tight’. To ensure this, a dye test is performed intra-operatively and if there is still leakage, the repair is sutured again. There is one very experienced fistula surgeon who does not do this, preferring to drain the bladder continuously for up to 4 weeks postoperatively.
• After fistula repair the bladder should be kept on free drainage for 10-14 days. There is some weak evidence that 10 days of drainage is just as effective at six months follow up (for fistulas of less than 3 cm diameter with mild to moderate scarring) [162]. This change in catheter management could make a significant impact on the resources of hospitals where these operations are performed. If the time needed for postoperative bladder drainage could be reduced by 4 days, the capacity of the hospital to care for fistula patients would increase by 30% just from this gain in efficiency.
• There is debate as to whether or not a Martius bulbo cavernous flap or other graft should be used in fistula repair. The argument has always been that such practices bring in a new blood supply to help nourish the injured tissues surrounding the fistula. One retrospective paper compared the surgical outcomes of operations involving similar fistulas repaired with and without use of the Martius flap and demonstrated a higher successful closure rate when such a flap was employed [163]. Another more recent retrospective analysis evaluated 400 patients in which comparable fistulas were repaired with and without use of the Martius flap and demonstrated a higher successful closure rate when such a flap was employed [162].

What constitutes a “simple case?” This is a case that has a high chance of cure and is suitable for those without expensive experience in fistula surgery. Only about 20% of obstetric fistulas can be defined as simple. Simple fistulas are less than 3 cm in diameter, with no or only mild scarring and do not involve the urethra. The first pre-requisite for successful fistula repair is meticulous attention to detail. As Abbott aptly (if somewhat quaintly) noted [149], “There must be no attempt to operate on these cases with one eye on the clock and the other on the tea wagon”. In fact, the operator upon vesicovaginal fistulas should combine traits of daintiness, gentleness, neatness and dexterity of the English bulldog.”

After positioning the patient on the table the surgeon must obtain adequate exposure of the operative field. Figure 11 depicts a typically narrow, scarred vagina of the type that often develops after obstructed labour (Figure 11). For simple cases without scarring, the use of a weighted Auvard speculum should be sufficient. Sometimes an episiotomy is required to increase the exposure. The ureters should then be identified and catheterized. This can usually be done by passing the catheters through the fistula under direct vision (Figure 12). Note that for very small fistulas in the midline or for urethrovaginal fistulas well away from the ureters, this step may not be needed. Once the ureters have been catheterized, the ureteral catheters can be brought out of the bladder through the urethra, keeping them away from the operative field. Although some fistula surgeons leave the catheters in place for up to 14 days after surgery, most can be removed at the end of the operation or a few days afterwards.

Once the fistula is exposed and the ureters protected, the next step is to mobilize the bladder/urethra from their surrounding structures (Figures 13-17). The proximal margins of the fistula are incised and the incision is then extended laterally from the angles either side. Using traction and counter-traction the tissues planes are developed. The distal margins of the fistula are also incised. Two flaps are then developed, again using traction and counter-traction and sutured away to the labia. The fistula edges should now be fully exposed and mobilized. The mobilization should be adequate to be able to bring the margins of the bladder defect together under no tension. Often the angles of the fistula are adherent to the inferior pubic ramus either side. Releasing these attachments close to the bone gains much more mobility (Figure 17). This dissection can extend into the space of Retzius. It is also noted that the majority of the mobilization comes from the proximal dissection, not from the distal dissection and the amount of dissection reflects this. The distal dissection should really be only enough to secure a suture. It is best not to over dissect here and merely create scarring around the urethra.
Figure 10: a simple fistula

Figure 11: Exposure of the fistula. The illustration to the left shows a vagina that has been narrowed considerably by scarring, thus making the fistula difficult to see. Because adequate exposure of the operative field is the most important criterion for successful surgery, exposure must be improved in such cases. This is done by cutting a generous lateral episiotomy through the scar tissue on either side of the vagina. Although this is unavoidable in some case, the surgeon must remember that such incisions may bleed significantly and increase intraoperative blood loss. (Copyright Worldwide Fistula Fund, used by permission).

Figure 12: Catheterisation of the ureters. Knowledge of where the ureters are located is extremely important in fistula surgery, as closure of the fistula may inadvertently lead to ureteral injury. Particularly if the fistula is large, the surgeon should look for the location of the ureters in relation to the edges of the fistula. Giving the patient intravenous furosemide or indigo carmine dye, may help locate the ureteral orifices. When the fistula has been closed and the operation is over, the ureteral catheters may simply be removed. There is no benefit to keeping them in longer post-operatively, unless there are special circumstances. (Copyright Worldwide Fistula Fund, used by permission).

Figure 13: The initial incision. The initial incision should be made directly along the vesico-vaginal junction on the posterior edge of the fistula (see previous figure). The incision should be extended well out onto the lateral vaginal sidewalls. The purpose of the large incision is to allow wide mobilization of all tissues surrounding the fistula so that the fistula may be closed without any tension on the suture line. Very broad mobilization of tissues is especially important in more complicated fistulas and fistulas with extensive scarring. (Copyright Worldwide Fistula Fund, used by permission).
Figure 14: Extension of the initial incision. Once the incision has been made, it should be extended posteriorly, freeing the vagina from the underlying bladder. The initial opening of the incision is often facilitated using Thorek scissors, which have right-angled blades. Once the initial incision has been opened, the spaces can be widened using the Potts-Smith dissecting scissors. Blunt dissection with a finger to open these tissue planes is to be encouraged. (Copyright Worldwide Fistula Fund, used by permission).

Figure 15: Anterior extension of the incision around the fistula and into the anterior vagina. Again, the purpose of dissecting the fistula out from the surrounding tissues is to gain mobility so that the fistula can be closed with minimal tension. This involves mobilization of large areas of the vagina. (Copyright Worldwide Fistula Fund, used by permission).

Figure 16: Creation of anterior vaginal flaps. Once the initial incision around the fistula has been extended anteriorly, the dissection is carried out laterally to separate the vaginal skin from the underlying bladder. (Copyright Worldwide Fistula Fund, used by permission).

Figure 17: Entering Retzius' space. Mobility is further increased by penetrating the endopelvic fascia underneath the pubic rami and opening the space of Retzius. This further increases lateral mobility of the bladder and vagina. (Copyright Worldwide Fistula Fund, used by permission).
Once the fistula is adequately mobilized, it is closed. Traditionally, fistula closure was done by closing the bladder in two layers. Many surgeons now close the bladder in one layer using interrupted dissolvable sutures placed approximately 4 mm apart (Figures 18, 19, 20). The adage for the trainee is that a good tension-free closure with adequate good healthy tissue has no reason to fail.

The repair is then examined to ensure that ‘water-tight’ closure has been achieved by filling the bladder with 60-120 ml of coloured dye (dye test). Occasionally during this test a second fistula previously unknown will be found. If present, this, too, must be closed.

Once the fistula has been closed, the vagina is next repaired. When this has been finished, a vaginal pack is placed, and the urinary catheter is left in situ. The following day, the vaginal pack is removed and the patient is encouraged to mobilize and eat.

The bladder is left on continuous free drainage for 10-14 days. Each day the ‘3-Ds’ of post-operative fistula repair are checked. These are whether the patient is dry, drinking and the catheter is draining. The patient has to be dry; that is the fistula repair must be intact; drinking to ensure adequate irrigation of the bladder; and draining, that is, the catheter is not blocked. If the catheter does become blocked and the bladder fills, the repair is at risk of breaking from

Figure 18 : Placement of supporting stitches. Particularly in cases where the bladder neck and urethra are poorly supported, improved anterior vaginal support can be obtained by placing anchoring sutures into the tissues lateral to the edge of the fistula and then passing such sutures through the periosteum of the pubic arch (as shown in the inset). These sutures help decrease tension along the line of bladder closure. (Copyright Worldwide Fistula Fund, used by permission)

Figure 19 : Initial closure of the fistula. The defect in the bladder is closed using absorbable suture. Many surgeons prefer to close the bladder in two layers, so that the initial closure is reinforced; however, others do not do this. If any tension is encountered during bladder closure, this indicates that the initial dissection of the tissues around the fistula was inadequate and should be revised. (Copyright Worldwide Fistula Fund, used by permission).

Figure 20 : Closure of the fistula, second layer (if needed). A second set of sutures is placed to imbricate the second line of closure over the initial line of closure. This can be done either with interrupted sutures (shown here) or with a continuous running suture. When this line of closure is completed, the fistula should be “water tight.” Closure of the fistula can be tested by placing a trans-urethral Foley catheter and then filling the bladder with 100 – 200 mL of either colored water (indigo carmine, methylene blue, Gentian violet) or sterile infant feeding formula to check for the presence of leaks. If any leakage is noted, the repair should be reinforced with additional sutures until no leakage is demonstrated. If such leaks are not easily fixed it is better to take down the entire repair and start over rather than to struggle with repeated attempts to place additional sutures here and there. (Copyright Worldwide Fistula Fund, used by permission).
increasing tension on the repair site. If the catheter does become blocked and the repair ruptures, this may often be rectified by continuous prolonged catheter drainage. By ensuring an empty and relaxed bladder, the sides of the defect may come together and close, but this can take as long as 4 weeks to occur. The success rate is about 70% in such cases, less if the defect involves the urethra.

Following these principles in the repair of simple fistulas, the surgeon can anticipate successful closure in 90% of the patients and a postoperative urethral incontinence rate (“closed but still wet”) of 10%.

2. THE COMPLEX FISTULA

A complex obstetric fistula can be described being larger than 3 cm, involving the

- urethra, and associated with reduced vaginal capacity from significant scarring and/or a reduced bladder volume. Sometimes the defect may be urethrovaginal, but more commonly both the urethra and bladder are involved and therefore the fistula is called an urethrovesicovaginal fistula.

- Virtually all authors with extensive experience in the management of obstetric fistulas comment on the great difficulty in achieving postoperative continence in patients who have had extensive damage to the urethra, even if the defect itself has been closed successfully. Rates of postoperative urethral incontinence range between 6-50% (165) [37, 67]. Often the diagnosis of postoperative incontinence is given only if the patient suffers from severe incontinence while walking. If rigorous questioning is used to exclude any leakage with coughing or other exertion, the rate of postoperative incontinence increases dramatically.

- The four risk factors that lead to a high rate of incontinence following fistula repair are:
  - Urethral involvement. (Odds Ratio 8.4 for developing urethral incontinence post operatively.)
  - Large size of the fistula. (Odds ratio 1.34 for each cm increase in size of the defect.)
  - Severe vaginal scarring. (Odds Ratio 2.4 if the scarring is significant enough to prevent the introduction of a Sims speculum without relaxing episiotomies.)
  - Small bladder size. (Odds ratio 4.1 if the bladder capacity is less than 120 ml.) [166].

- In repairing complex obstetric fistulas, the principles for simple fistula repair still apply, but with the following additions:
  - Exposure is more difficult. In complex cases the fistula may be obscured from view due to the presence of severe vaginal scarring. Such scarring often consists of a thick band of scar tissue on the posterior vaginal wall. Occasionally, the vagina has been completely occluded. Wide bilateral episiotomies may be required and where possible the scar should be released from the lateral pelvic sidewalls. This will enable the fistula to be seen more clearly.
  - The ureters should be identified and protected against possible injury, as in the case of a simple repair.
  - The bladder and urethra should again be carefully mobilized. The tissues are often thin, scarred, and fragile in such cases. The mobilization often has to be extended along the lateral pelvic side walls and even on to the posterior aspect of the pubic symphysis in order to free the lateral and anterior bladder.
  - The mobilization of tissues should be wide to ensure a tension-free closure.
  - The utility of tissue flaps remains controversial.
  - Often destruction to the vagina has been so extensive that rotational flaps are required in order to cover the defect [167].

If these principles are applied, the success rate in fistula closure is high, but many women remain incontinent despite successful closure. In patients in whom all of the risk factors mentioned above are present, the postoperative incontinence rate may approach 100% [160]. In light of this dismal success rate, some surgeons now suggest that two further principles of repair be maintained:

Maintain the urethral length. It has been noted that post-repair fistula patients returning for further treatment of persistent urinary incontinence often have a shortened urethra. An unpublished series of 72 patients with post fistula repair incontinence found an average urethral length of 1.4 cm in these women. This suggests that continence might be improved if normal urethral length can be restored at the time of fistula closure. Vertical (as opposed to horizontal) repair of urethrovaginal fistulas has therefore been suggested. This appears to be possible in approximately 20% of such cases. In cases in which there is an urethrovesicovaginal defect, vertical repair of the urethral defect may improve success, while the vesical defect can be repaired either vertically or horizontally.

Support the urethra. For all urethral defects larger than 4 mm with a urethral remnant less than 2.5 cm, many fistula surgeons use an ‘anti-incontinence’ procedure during the initial repair. Currently there are two widely used procedures. The first sutures the urethra/bladder neck to the periosteum of the pubic ramus in a type of suspension operation. The fascia or muscle of the bladder is sutured on either side of the bladder neck area to the posterior aspect of the symphysis pubis or the arcus tendineus [141].
second procedure creates a sling of tissue to support the urethra. A pedicle of tissue is created on either side of the urethra from the lateral pelvic side wall. In theory this involves use of the pubococcygeus muscle, but more often it is simply a pedicle of fibromuscular tissue or scar that can be harvested. The pedicles created on either side are then sutured together in the midline [160, 166].

If either of these two extra steps are used, the incontinence rate after closure of complex fistulas can be reduced from 100% to 50% [160]. If all simple and complex fistulas are treated according to these extra principles, the postoperative incontinence rate can decrease from 33% to 18%.

a) The circumferential fistula

J. Chassar Moir, referred to the worst of obstetric fistula cases as “circumferential” fistula, which “involve a destruction of the bladder neck not only on the vaginal side, but in many instances, on the pubic side as well. The result is a circumferential sloughing with subsequent discontinuity of the urethra and bladder; the intervening tissue is merely the epithelium that has grown over, and become adherent to the periosteum of the back of the pubic bone.” [153]. This type of injury seems to occur more frequently in primiparous women, who tend to be younger. Such defects are more likely to be associated with severe vaginal scarring, the presence of a recto-vaginal defect, larger defects, and urethral involvement in 96% of cases [168].

In repairing these injuries, some fistula surgeons ignore the anterior defect in the bladder and merely repair the posterior section by suturing the bladder along the periosteum of the posterior symphysis pubis and then to the urethra. The anterior portion of the urethra will thus be pubic bone. These patients invariably suffer severe post-operative urethral incontinence, and the shorter the urethral remnant is to begin with, the more severe their incontinence is likely to be [169].

According to Moir, the three great problems involved in dealing with this type of fistula are: 1) extremely difficult exposure; 2) technical difficulty in dissecting the tissue remnants from the pubic bone; and 3) difficulty in joining the bladder neck to the urethral remnant or stump, if, indeed, any portion of the urethra is still intact. In order to deal with this type of injury, the bladder must be completely mobilized so that it can be drawn down low enough to create a tension free anastomosis with the urethral remnant. Freeing the urethral remnants and bladder from their adherence to the pubic bone may even require a suprapubic incision with the dissection from above in order to accomplish this. In such cases Moir took care to reinforce the bladder neck with buttressing sutures and generally brought in a Martius graft for support and a renewed blood supply. Today many experienced surgeon perform this operation entirely through the vagina and rarely use the Martius graft, but employ the continence saving steps to the procedure as described previously. The basic principles still apply, but emphasis is placed on completely releasing the bladder from any attachments to the posterior symphysis pubis. Once the bladder has been released, it is drawn down posteriorly to expose the plane of dissection between the bladder and pubic bone.

Once the bladder is mobilized circumferentially it is anastomosed to the urethra anteriorly with sutures at 12, 9 and 3 o'clock around the proximal section of the urethral remnant, usually anchoring it to the periosteum of the posterior pubic symphysis for stability. Often the distal defect in the bladder/urethra is much larger than the proximal defect in the bladder. To perform the anastomosis with this discrepancy in size, the bladder is pulled around the proximal part of the urethra and sutured. The remaining defect in the bladder is repaired vertically, again in an attempt to maintain the length of the urethra. (Figure 21).

The urethra is then suspended or supported with a sling as an anti-incontinence procedure. Despite these measures, post-operative incontinence is still high, with up to 45% of patients still incontinent in the immediate post-operative period [169].

The most difficult injury to repair is when the entire urethra has been sloughed. This may happen in up to 5% of cases [101]. If the urethra is only injured in its posterior aspect, the remaining urethral tissue can be mobilized and repaired vertically over an indwelling catheter with adequate results. More often, however, the whole circumference of the urethra is sloughed. To reconstruct a functional urethra is nearly impossible in such cases.

Figure 21: A circumferential fistula
(by courtesy of A. Browning)
In cases of complete destruction of the urethra and the anterior bladder neck, Hamlin and Nicholson recommended constructing a new urethra by creating a new "inner" urethra using the skin and fibrous connective tissue covering the pubic bones and the inferior border of the pubic symphysis. The neourethra thus created is then reinforced using a gracilis muscle flap taken from the thigh, preserving its neurovascular pedicle. Once this has been accomplished, additional grafting is necessary using a Martius flap which is then covered with skin flaps. Using this technique, the authors reported no deaths and only one ‘complete failure’ in 50 operations in which the blood supply to the gracilis flap failed. In some cases small urethrovaginal fistulas remained which were repaired at a subsequent operation. Surprisingly, only 8 women (16%) developed “severe” stress incontinence after this reconstruction, four of whom regained “satisfactory” continence over time, and four of whom required a subsequent operation for stress incontinence. In these latter four patients, only two operations were completely successful. Six patients (12%) developed a urethral stricture, three of whom were successfully treated by the passage of a sound and three of whom required surgical correction. The remaining 35 patients (70%) were discharged within six weeks of surgery cured or with mild residual stress incontinence which did not appear to be clinically bothersome [170]. There is no long-term follow-up on these patients, but anecdotally many patients who have had this procedure have returned for further care years after the operation with incontinence and complete stenosis of the neo-urethra.

Various authors have described neourethral reconstruction using bladder flaps [171, 172]. All of these operations are based upon transabdominal techniques such as that described by Elkins et al. [173]. In this technique, a neo-urethra is created by mobilizing a flap from the anterior bladder, which is then rolled into a tube. The anterior and lateral edges of the fistula are freed up and the space of Retzius is entered transvaginally beneath the pubic bone. The anterior bladder is pulled down into the vagina and mobilised. A 3cm incision is made into the bladder and the anterior bladder wall is then rolled around a 16 Fr. Foley catheter, creating a tube. The anterior surface of the neourethra is then sutured in two layers and the posterior edge of the fistula is closed transversely, also in two layers. The neourethra is reattached to the posterior edge of the pubic symphysis, and a Martius graft is placed before reapproximating the vaginal epithelium. In 18 of 20 cases, this technique resulted in fistula closure, but four women had severe stress incontinence post-operatively. It is not known how many had mild incontinence.

Neither of these surgical methods is ideal. Although they may create an anatomic urethra, often that urethra does not function normally. A further option in such cases is to create a ‘tube’ using either technique and then attempt to render the patient continent with the use of a urethral plug [24].

b) Additional advanced surgical techniques

Fistula centres in India tend to have more resources available to them than do fistula centres in Africa. In these situations it may be feasible to use more advanced surgical techniques on patients with fistulas. For example, the fistula centre at the Banaras Hindu University (Varanasi) has a substantial experience in managing more than 800 genito-urinary fistulas over a 15 year period. Fistula is common here: it was the most common diagnosis (40.5%) in female patients admitted for surgery in the past five years, followed by urinary stone disease (25.2%) and malignancy (14.6%). Vesicovaginal fistulas were the most common fistula encountered (66.6%) and vesico-uterine fistulas were the least common (5%) (174). Obstructed labour was the most common aetiology of fistulas (72.2%), followed by hysterectomy. Conservative management was successful in only 1-3% of the patients with vesicovaginal fistulas and the remaining cases were managed surgically with excellent results. A transabdominal approach was used for large, supravaginal vesicovaginal fistulas, associated ureterovesical fistulas or if bladder augmentation and bladder neck reconstruction was required. The transvaginal route was preferred for small sub-trigonal fistulas. A combined abdominal and vaginal approach was used for large fistulas involving the trigone or the bladder neck. The surgical approach varied in each patient. Interposition grafts or flaps were used when required [175]. The overall surgical failure rate was 4.3%. The average operative time for layered closure was 72 minutes (45-130 minutes) and that for graft or interposition tissue repair 100 minutes (90-165 minutes). The mean hospital stay was 9 days (6-17 days). There were no reported intra-operative complications. Postoperative complications were urinary tract infection, haematuria, wound infection and fever. None of the patients required blood transfusion. For the repair of small fistulas, surgeons did not use interpositional flaps but rather used the layered closure technique with a success rate of 97.1%. Complicated fistulas required repair by graft or tissue interposition and had a success rate of 94.8% which is similar to the experience of other Indian centres [176]. Risk factors for the failure of vesicovaginal surgery included previous failed repair, large-sized fistulas, fistulas involving the trigone or ureteral orifices, a small bladder capacity and unhealthy vesical urothelium at the time of surgery. Several techniques were used in addition to the standard layered closure:

1. **VESICAL AUTOPLASTY:** If the longitudinal diameter of the fistula was too large to allow simple layered closure and would put the bladder closure under
tension, a vesical autoplasty was performed based on the advancement flap technique used frequently by plastic surgeons. The initial steps are as in the layered closure technique. The vaginal layer is closed with interrupted 3/0 polygalactin sutures. Two incisions are made from either end of the proximal margin of the bladder defect and are extended proximally and laterally to make a wider based bladder flap. This flap is advanced over the vaginal layer and is sutured as in performing a layered closure. This technique avoids overlapping the suture line and also avoids tension [177].

2. O’Connor Repair. The majority of the large-sized fistulas were successfully repaired using the trans-abdominal technique described by O’Connor, with interposition of an omental flap (178). This technique works well except when the fistula extends up to the bladder neck or when its transverse diameter is too large to allow tension-free approximation.

3. Ileal Segment Interposition. This technique is used for fistulas which involve the entire posterior bladder wall or fistulas with a wide transverse diameter that extend up to the bladder neck, cases in which obtaining tension-free closure is difficult. Approximately 15-20 cm of the small bowel is isolated on its pedicle and opened at the anti-mesenteric border. The bladder wall is dissected away from the vagina, which is closed with interrupted sutures. This segment of small bowel is interposed posteriorly, along with an omental flap. This technique has yielded satisfactory results in complicated fistulas, and also augments bladder capacity (175, 179).

4. Bladder Mucosal Graft: This technique is an alternative to layered closure in cases where closure of the bladder may result in tension along the suture line. If sufficient pliable bladder wall is available, a vesical autoplasty may be performed. In a small-capacity fibrotic bladder, the fistula may be repaired using a free-graft taken from a healthy area in the dome of the bladder, as described by Vyas et al (180). A bladder mucosal graft is also a good alternative in fistulas where the ureteral orifices are close to the fistulous margin and might otherwise require ureteral reimplantation.

5. Combined Abdominal and Vaginal Approach. This technique may be required in complicated fistulas involving the bladder neck. In cases where urethral continuity is disrupted due to a fistula, a combined approach may be preferable. The fistula is repaired by the abdominal route and continuity of the urethra is established by anastomosing the urethra through the vaginal route.

c) Rectovaginal Fistula

Rectovaginal fistulas (RVF) are less common than vesicovaginal fistulas in developing countries. In one (unpublished) series of 75 obstetric fistula cases from Ethiopia, only 6.7% were isolated obstetric rectovaginal fistulas and 84% were associated with significant vaginal scarring. Two of the 75 required a temporary diverting colostomy prior to repair; both were high fistulas adherent to the sacral promontory. This compares to 15% needing a diverting colostomy prior to RVF repair in Addis Ababa [165].

The basic principles of vesico-vaginal fistula repair also apply to the repair of rectovaginal fistulas: wide mobilization of the fistula and a tension-free closure. The vaginal epithelium is incised around the circumference of the fistula and laterally from either angle. The vagina is reflected away and the bowel is mobilized, paying special attention to release of any lateral attachments. Severe bleeding can occur along the lateral aspect of the bowel. The bowel muscularis is repaired in 2 layers preferably in a horizontal plane to avoid creating strictures within the bowel lumen. The vagina is then repaired.

3. Urinary Diversion in the Developing World

Urinary diversion in developing countries is usually not a viable option since stoma appliances and catheters (in the case of continent urinary diversions) are often unavailable or are too expensive [79]. In such cases performing a diversion procedure merely moves the fistula to another part of the body and the end result of such surgery may be more stigmatizing in the local culture than the original injury!

Uretero-sigmoidostomy has been used as a surgical option in developing countries for many years. Long-term follow-up of a series of 65 Swiss oncology patients over a 20-year period showed early complications in 25 patients (pyelonephritis, anastomotic complications, wound problems) and late complications in 36 patients (pyelonephritis, electrolyte disturbances, ureteral stenosis, incontinence and colon tumour (3)). At 5 years 25 patients had survived: 23 of these (88%) were continent during daytime and 14 (54%) were continent at night as well [181]. These data show that both short- and long-term complications will arise and that surgeons must be prepared to treat them. This requires access to adequate diagnostic equipment. A series of 9 Tanzanian patients undergoing diversion found that results were acceptable and that patients had a marked improvement in their quality of life [182]. The Mainz II pouch or Sigma-rectum pouch was introduced by Fisch et al. to create a detubularized, low pressure, high capacity pouch that would protect the upper urinary tract and improve continence [183]. This technique has also been used in patients with vesico-vaginal fistulas. A series of 62 such patients was reported by Arrowsmith (184), 89% of whom were dry during the day and 66% were also dry during the night. Twenty-six patients had major complications, 35 had minor complications, and 6 patients died. The author does not mention the type of complications that occurred.
Urinary diversion with the creation of a sigmoid or rectal pouch is feasible in selected patients. Long-term data on outcome are not yet available. The risk of complications is rather high and managing complications adequately often requires diagnostic capabilities that are absent in developing countries. This situation requires that patients should be counselled extensively before they are offered this kind of surgery [185]. The risk of cancer has to be discussed as well. These discussions must take current life expectancy into account and balance the risk of complications (such as late occurrence of colon cancers) against any improvement in the quality of life. Current life expectancy in Africa is estimated to be 52.8 years, but such numbers vary substantially from country to country due to differing experiences with AIDS, poverty, malnutrition and war [186]. The decision to proceed with urinary diversion must be made jointly by the patient in consultation with the operating surgeon; it is not the surgeon’s choice alone. If a diverting operation is performed, it must be performed in a setting in which adequate post-operative follow-up is available. It is inappropriate for a visiting surgeon to perform a complicated operation of this kind and to leave the country without insuring that the patient has competent on-going care should complications arise.

4. COMPLICATIONS

4a) Urinary incontinence post fistula repair

1. The continence gap and urethral loss

Fistulas can be closed successfully in 72% to 92% of cases [187]. The definition of success, however, is often different when the perspectives of the patient and the surgeon are compared. “Success” to a fistula patient means complete restoration of urinary continence and control, whereas many surgeons define “success” as simply closing the fistula. It is essential to establish defined criteria that will allow meaningful comparison of treatment outcomes. The patient-oriented criterion of continence restoration should be the goal when the outcomes of various fistula treatments are compared. Persistent incontinence despite successful closure of the fistula has been termed “the continence gap” [188]. A patient whose fistula is closed but who remains incontinent may be just as wet as a patient whose fistula closure operation failed. The estimates of persistent urinary incontinence after a successful closure of the fistula come from case series, ranging from 16.3% in a large retrospective review of patients by Wall et al [29] to 33% in a small series of complex fistulas in which the proximal urethra was lost [189]. Adequate epidemiologic studies on the prevalence of fistula and its sequelae are scarce, and because long-term data on surgical outcomes are difficult to obtain, the prevalence of persistent incontinence after surgery appears to be severely underestimated. Techniques that are used in reconstructive urology in industrialized countries are seldom mentioned in the fistula literature [59, 190]. More research and training is needed in this field.

Persistent urinary incontinence in patients after fistula repair is due to multiple factors including scarring and location of the fistula as well as failure to perform a sling operation at the time of repair in patients likely to require such intervention. The goal of fistula surgery should be restoration of continence and resumption of a full and active life on the part of the patient, not just closing the fistula.

2. Pathophysiology of persistent urinary incontinence after fistula repair

Several possible etiological factors can be postulated in women who remain incontinent after successful fistula closure: massive damage to the mid-urethral continence mechanism, damage to the bladder neck, levator ani dysfunction, damage to the lateral attachments of the urethra, fibrosis and loss of compliance, neuropathy, etc. . . .

Although persistent incontinence tends to be blamed on urethral dysfunction, a few urodynamic studies suggest that bladder dysfunction may play a role as well [67, 191]. A small study of 22 women who underwent urodynamic studies to analyze post-repair incontinence revealed that 41% suffered from urodynamic stress incontinence, 41% had combined urodynamic stress incontinence and detrusor overactivity, 14% had a small non-compliant bladder, and 4% had a voiding disorder and overflow incontinence. In these cases the incontinence may be so severe that the urethra functions only as an open ‘drain pipe’ through which urine passes in a nearly-continuous stream. The result is little different from the leakage that occurred through the original fistula [67].

3. Assessment of urinary incontinence

A complaint of persistent leakage by the patient needs to be evaluated. The first step is to assure that the fistula has been closed successfully. This can be done by placing a balloon catheter into the bladder, occluding the bladder neck, and filling the bladder with a solution of water coloured with indigo carmine or another type of dye. If the fistula has not been closed successfully, the leakage should be readily apparent. If deflating the balloon or moving it away from the bladder neck produces incontinence, the question may be differentiating transurethral incontinence from a urethra-vaginal fistula. Where more advanced technological capabilities are available, diagnosing the presence of an urethrovaginal fistula may be facilitated by the use of a double-balloon catheter that allows occlusion of the urethra at each end and perfusion of the urethra through an opening between the two balloons. Most commonly, however, the diagnosis will have to be made on the basis of simple...
clinical testing by occluding the urethral meatus, asking the patient to strain, and seeing if there is leakage. Limited data from urodynamic studies by Hilton [191] and by Carey, Goh et al [67] suggest that detrusor overactivity and changes in bladder compliance are frequent causes of urinary incontinence in fistula patients with post-repair incontinence, in addition to the leakage resulting from successful closure but persistent intrinsic sphincter deficiency.

4. Management of urinary incontinence

1) Preventive management.

Assessment of host factors causing urinary incontinence following fistula repair:
The best approach to this problem is preventive and this starts with the assessment of host factors. The most important concept is the recognition of the differences between simple and complex fistulas.

Surgical techniques at the time of primary fistula repair to prevent urinary incontinence:
When the fistula involves the continence mechanism and is associated with moderate to severe scarring of the urethrovaginal junction, a sling procedure may be advisable to improve urethral closure. Several techniques have been used, including a sling or graft made of labial fat incorporating the bulbocavernous muscle, remnants of the pubococcygeus muscle, or a gracilis muscle flap [160, 189], as well as fascial grafting. The results obtained with this relatively simple low-cost operative procedure have not been replicated in other centres, nor are there long-term data on outcomes.

2) Initial management of urinary incontinence after fistula repair.

Pelvic floor muscle exercises have been proposed as a first step in the treatment of persistent incontinence after otherwise successful fistula closure. Some patients on a muscle exercise regimen improve after six months of therapy. A novel system for grading urinary incontinence has been proposed in an effort to predict which patients are likely to benefit from this type of therapy and which will not. This system is currently in use in only a handful of centres and prospective data are not yet available as to its general applicability.

Continence status after fistula closure can be graded as follows:

1. Cured, no incontinence leaks
2. Wet with exertion (coughing or physical exertion)
3. Wet when walking, but dry when sitting or lying down
4. Wet when walking, sitting, or lying down, but able to void some urine from the bladder
5. Wet all the time, no urine to void

After six months of physical therapy, in 50% of cases women with continence grades 2 or 3 were cured of their leakage, but only 18% of women with continence grades 4 or 5 were cured. Women in this latter group therefore seem likely to require further surgical treatment.

3) Secondary management for urinary incontinence after fistula repair.

If a patient with transurethral incontinence is still complaining of the leakage at follow-up, the treatment proposed must be cheap, effective and not dependent on expensive synthetic materials that are unlikely to be available in countries where obstetric fistulas are prevalent. Treating persistent incontinence after successful fistula closure requires good surgical skills. Some kind of bladder evaluation is essential prior to considering urethral support surgery. The type of repair proposed is based largely on analogies with other urethral operations such as those carried out to repair a urethral diverticulum, to attempt to achieve continence after radiation therapy, or the kinds of reconstructive operations carried out in patients who have extrophy or epispadias [79]. In these cases the use of tissue transposition techniques such as the Martius graft and various forms of sling operations are the mainstays of treatment. The traditional dissection required to place a sling may be difficult and may result in recurrence of the fistula and/or breakdown of the entire urethra. Thus, some authors have recommended using an in situ vaginal sling. Fascial slings are preferred; there is no place for a synthetic sling in these cases due to the levels of scarring found, the lack of vascularity in the surgical field, the high likelihood of infection, and the problems of sling erosion with little or no access to follow-up.

Several surgical methods have been described for treating fistula patients with post-closure stress incontinence; few have been successful and data are quite limited. A standard Burch-type retropubic bladder neck suspension operation combined with urethrolysis and tissue plication, may work in a few patients [141], but in general the results of this approach have been disappointing. Carey and co-workers reported a small series of patients who had undergone previous fistula closure and who later underwent re-operation for stress incontinence. After urodynamic testing, 9 women with severe urodynamic stress incontinence underwent a retropubic urethrolysis and pubovaginal sling procedure combined with placement of an omental J-flap. Four weeks after surgery, 78% were continent; however this fell to 67% at 14 months follow-up [67]. An operation described by Waaldijk involves urethralisation of the bladder neck as a neourethra in patients with a markedly shortened bladder neck. Following this, a fasciocolposuspension to the arcus tendineus is performed. Cure rates of 60-70% have been reported, but these results have not been replicated in other fistula centres [141].
An alternative approach for those patients who fail a surgical procedure or who are deemed unsuitable for an attempt at surgical repair is to use a urethral plug [24]. Although successful use of urethral plugs and various injectable materials has been reported, these technologies are not usually available in areas where obstetric fistulas are common. However, if an ongoing supply link can be arranged, urethral plugs seem to work well for many women with a high degree of patient satisfaction.

Urge-related bladder dysfunction can often be treated with low-cost antimuscarinic drugs. In cases where there has been extensive loss of bladder tissue or marked reduction in bladder compliance due to fibrosis, augmentation cystoplasty can be performed, usually using by interposing a segment of bowel. In some case, urinary diversion may be indicated, but only after careful discussion of the issues involved with the patient.

CONCLUSION

The vast majority of obstetric fistulas can be successfully closed using appropriate “low technology” surgical techniques; however, making these women completely continent and restoring their lives to normal functioning is the ultimate, but more difficult to achieve, goal. Persistent incontinence after fistula repair remains an underappreciated condition that requires further attention if overall outcomes are to be improved. There is a need for further research using clearly-defined outcomes and standardized data collection in this area.

VII. ORGANISATION OF FISTULA CARE IN THE DEVELOPING WORLD

1. LOCAL HOSPITAL OR A SPECIALIST FISTULA CENTER?

At the present time the care of fistula patients is not well-structured. Fistula centres are not networked with one another and most places where fistula surgery is performed carry out their work without much reference to the activities of other centres. Most fistula care is provided by individuals working alone, and by various charities and non-governmental organizations who largely “march to the sound of their own drums.” Funding for fistula initiatives is haphazard and frequently insecure. Around the world, the voices of women with fistulas are still not heard by most of the national healthcare systems that should be responsible for providing care to them. Wall has suggested that a fistula centre can survive and flourish only if three prerequisites are in place [192]. A fistula centre must have:

a) Adequate long-term funding

This funding usually must come from foreign donors, as local authorities often do not consider the care of fistula patients to be an important priority. Because fistula patients are largely destitute, they can rarely pay for the costs of care. This means that fistula surgery must be heavily subsidized in order to reach the maximum number of patients and this may breed resentment in hospitals where other patients are routinely charged for their care.

b) A dedicated fistula surgeon

A surgical program will only succeed if it is staffed by competent, responsible surgeons. Ideally the surgeon in charge of a fistula repair program should be someone who can treat both simple and complex fistulas, as well as with the complications of surgery (e.g., vaginal stenosis, persistent incontinence, etc). Surgeons must understand both their own limitations as well as the limitations placed on them by the environment in which they must operate. Maintenance of skills and improvements in data collection and research are likely to be improved by enabling the formation of networks of fistula surgeons who face similar problems in different parts of the world.

c) Adequate operating theatre time and adequate supplies

Surgical programs can only be successful if there is adequate time and adequate supplies to perform the necessary operations. General hospitals (especially rural hospitals) tasked with taking care of the entire range of medical and surgical problems—particularly obstetric emergencies and acute trauma—often lack the resources need to carry out large numbers of fistula repairs. Elective scheduled cases such as fistula repair are always in jeopardy of being bumped from the operating theatre schedule due to the arrival of victims of a road traffic accident, orthopaedic trauma or obstetric haemorrhage.

For these reasons many advocate that fistula programs be organized around a specialized fistula centre that focuses on these patients as its highest priority. Such a centre is optimized to deliver high quality specialized care for these women. Focused programs of this kind will be more difficult to operate in regions where transportation is difficult, making it difficult for people from remote areas to reach the centre.

It is also obvious that the small number of specialist centres that currently exist in Africa will never be able to treat all of the women currently living with fistulas. Whatever strategy is proposed, it must be based on a realistic assessment of local circumstances [193] [194]. Further research in this area is recommended.

Wherever possible, fistula care should be integrated into a broader preventive perinatal care program. A recent systematic review of inequalities in maternal health care in 23 developing countries showed a wide...
variation in the use of antenatal care [195]. In addition to factors related to the availability of health care services (distances travelled, clinic availability), user-related factors such as patient age, education, medical insurance, and clinical risk factors played a role in determining utilization. The interactions among these factors are also influenced by funding, organization, the structure of the local social system, and local cultural variations. The authors concluded that context-specific causes of variations in the use of maternal health care services need further investigation.

One overarching concern must be the standard of care provided in such programs: Poor quality antenatal care will almost certainly decrease the utilization of the services provided [196]. How fistula care should be organized must be seen within this larger context (Figure 22).

2. ETHICAL CONSIDERATIONS

There are many ethical issues intertwined with the epidemic of obstetric fistulas in developing countries. These issues range from the broadest human rights concerns arising from a devastating problem that only affects women to the most intimate issues involved in the responsibilities of individual surgeons for the care of individual patients to complex issues regarding clinical research. Everyone involved in caring for women with obstetric fistulas must realize the vulnerable nature of this patient population and the special needs they present for those entrusted with their care. Recently a code of ethics for the fistula surgeon was published with the aim of fostering common goals and a common ethical perspective as to how the campaign to eradicate fistulas ought to proceed [197]. This code of ethics emphasizes the following basic points: [197].

- The fistula surgeon should be dedicated above all else to providing the best possible care for women with obstetric fistulas permitted by the resources available and the local circumstances in which care is rendered.
- The surgeon must recognize the vulnerable nature of this population of patients, treat them with respect, and involve them in decision-making regarding important aspects of their care. Such patients should not be subjected to experimentation without their consent and research on fistula patients should be overseen by an appropriate ethical review board.
- The fistula surgeon must assume direct personal responsibility for the care of those patients on whom he or she operates and must provide them with access to competent ongoing care, particularly in the immediate post-operative period.
- The fistula surgeon should limit his or her practice to that which he or she is competent to deliver by education, training, experience, and available resources, and should not hesitate to refer complicated patients to a higher level of care.

Figure 22: The organisation of a fistula centre
The fistula surgeon should strive to improve his or her clinical skills through the regular collection and review of objective data on treatment outcomes.

The fistula surgeon should never take advantage of a patient for his or her own personal benefit or allow such patients to be abused by others.

Fistula surgeons must acknowledge the fundamental social inequalities that promote the development of obstetric fistulas and must help work to eradicate these injustices. They should actively support initiatives that seek to prevent fistulas and should work to remove barriers that hinder access to emergency obstetric care.

VIII. SUMMARY AND GOALS FOR FUTURE RESEARCH

The number of patients with obstetric fistulas in Africa cannot be estimated accurately at this time, but all authors agree that the number is high and that several million women may be affected by this terrible condition. Lack of adequate facilities for fistula repair prevents reduction of the backlog of women currently suffering with fistulas. Lack of adequate access to emergency obstetric services prevents the elimination of new fistula cases.

There is much that still needs to be learned about the optimal care for women with obstetric fistula. There is a great need for further research on both the best treatment of fistulas as well as on the types of programs that will be most effective in preventing fistulas from developing in the first place. There is almost no reliable data on how to develop and implement programs to rehabilitate women who have sustained a fistula and how to reintegrate them into their societies.

Repair of simple fistulas has a high success rate if the operation is performed by a trained surgeon. In cases of this kind, use of a Martius flap may not be required.

Complex fistulas remain challenging, sometimes daunting. A high proportion of women with complex fistulas will have persistent incontinence despite successful fistula closure. The number of women who will suffer from stress incontinence after successful fistula closure can probably be reduced by performing some type of autologous sling operation at the time of fistula repair. Exact protocols for doing this need to be developed.

In addition to their fistula, many patients also suffer from other components of the obstructed labour injury complex involving urological, gynaecological, gastrointestinal, musculoskeletal, psychological and social injuries. These comorbidities must also be taken into account during treatment planning.

The literature on fistulas in the developing world consists primarily of retrospective observational studies. Many fistula surgeons work for charitable organisations whose ultimate goal is the care of patients. Many surgeons are involved in fistula surgery only during short-term trips and leave without having any good idea about patient follow-up or the outcome of surgery. The organization of research in this field is therefore often complicated.

The development of partnerships between charitable organizations and academic institutions could help alleviate this problem. Joint programs between Western academic centres and local African hospitals would not only have a positive influence on the training and scientific expertise of the local staff, but would also be likely to improve the standard of care provided to patients. Several areas for future research can be suggested:

- Health economic studies
- Health organisation studies
- Studies on techniques for fistula closure and related surgical issues
- Urodynamic studies of patients following successful fistula closure
- Studies on long-term outcome, social reintegration, and the effect of fistulas on family life and child health

IX. RECOMMENDATIONS

All recommendations are based on articles with level of evidence 3 or 4. Hence all recommendations have grade C.

- Patients with vesicovaginal fistula should be treated as a person, and they deserve the right to adequate counselling and consent to the treatment they will eventually undergo, despite language and cultural barriers that may exist.
- Surgeons embarking on fistula surgery in the developing world should have appropriate training in that setting and should be willing to take a long-term commitment.
- Prevention of fistula is the ultimate goal. Collaboration between fistula initiatives and maternal health initiatives must be stimulated.
COMPLEX FISTULA

- Simple fistula, which have a less favourable outcome.
- Careful clinical examination will allow the distinction between both types of fistula, although no generally accepted classification system is available. Key items are the size and location of the fistula, the eventual involvement of the urethra and the urethral closure mechanism and the amount of vaginal scarring.
- Associated pathologies should be actively searched for and should be taken into account in the treatment plan: all components of the ‘obstructed labour injury complex’ should be examined.

TREATMENT

- The treatment for vesicovaginal fistula is surgical.

SIMPLE FISTULA

- A vaginal approach is preferred, since a single fistula can be reached vaginally and since spinal anaesthesia carries less risk than general anaesthesia needed for an abdominal approach necessitating. A trained surgeon should be able to manage these simple fistulas.
- After wide dissection a tension-free single layer closure of the bladder wall and closure of the vaginal wall in a separate layer are advocated. A Martius flap in primary simple obstetric fistula repair is not recommended.
- A care program for failed repairs and for persisting incontinence after a successful repair needs to be installed.

COMPLEX FISTULA

- Complex fistula should be referred to a fistula expert in a fistula centre.
- In principle most complex fistula can be dealt with by vaginal approach, but an abdominal approach can be useful in some cases (e.g. concomitant reconstructive procedures). Advanced training and surgical skills are prerequisites for treating this type of fistula.
- If the urethra and/or the urethral closure mechanism is involved a sling procedure, using an autologous sling, should be performed at the same time as the fistula correction. There is no place for synthetic sling material in that setting.

ASSESSMENT

- The majority of patients with as simple fistula will be cured after the repair. A proportion of them and an even larger proportion of the patients after complex fistula repair will remain incontinent. Depending on the local possibilities an after-care program should be installed.

REFERENCES


168. Browning A. The circumferential obstetric fistula: characteristics, management and outcomes. BJOG. 2007 Sep;114(9):1172-6.


Committee 19

Bladder Pain Syndrome
International Consultation on Incontinence

Chairman
P. HANNO (USA)

Members
A. LIN (Taiwan),
J. NORDLING (Denamark),
L. NYBERG (USA),
A. VAN OPHOVEN (Germany),
T.UEDA (Japon)
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
</tr>
<tr>
<td>I. NOMENCLATURE/ HISTORY/ TAXONOMY</td>
</tr>
<tr>
<td>II. EPIDEMIOLOGY</td>
</tr>
<tr>
<td>III. AETIOLOGY</td>
</tr>
<tr>
<td>IV. PATHOLOGY</td>
</tr>
<tr>
<td>V. DIAGNOSIS</td>
</tr>
<tr>
<td>VI. CLASSIFICATION</td>
</tr>
<tr>
<td>VII. CONSERVATIVE TREATMENT</td>
</tr>
<tr>
<td>VIII. ORAL THERAPY</td>
</tr>
<tr>
<td>IX. INTRAVESICAL / INTRAMURAL THERAPY (Table 5)</td>
</tr>
</tbody>
</table>
Bladder Pain Syndrome
International Consultation on
Incontinence

P. HANNÓ,
A. LIN, J. NORDLING, L. NYBERG, A. VAN OPHOVEN, T. UEDA

INTRODUCTION

1. EVIDENCE ACQUISITION

The unrestricted, fully exploded Medical Subject Heading (MeSH) “interstitial cystitis” (including all related terms as “painful bladder syndrome,” “bladder pain syndrome”, or different terms such as “chronic interstitial cystitis,” etc.) were used to thoroughly search the PubMed database (http://www.ncbi.nlm.nih.gov/PubMed/) of the US National Library of Medicine of the National Institutes of Health; 1795 hits were retrieved. After exclusion of uncommon languages (other than English, French, German, Italian, Japanese, Spanish, Swedish) and by limiting the publications to the time period January 2004 to May 2008, 512 publications resulted.

Abstracts if available and titles of the 512 hits were reviewed, focusing on (but not limited to) clinical trials, randomised controlled trials, meta-analyses, scientific guidelines, and core clinical journals. The literature update thus achieved was added to the pre-existing database, covering the time period before and during 2004 (generated for the 2004 ICI Incontinence guideline, published 2005) that was established according to the same protocol.

Rating of the level of evidence and grade of recommendation was performed according to the Oxford Scale.

The committee believes that the Oxford system for categorizing levels of evidence is primarily relevant only for the sections on treatment, which follow. While the committee’s opinions will be expressed, where applicable, regarding evidence and conclusions for other areas, including diagnosis, aetiology, and pathophysiology, use of the Oxford system in this context is more open to interpretation.

2. DEFINITION

Bladder Pain Syndrome (BPS) is a clinical diagnosis that relies on symptoms of pain in the bladder and or pelvis and other urinary symptoms like urgency and frequency. Based on the evolving consensus that BPS probably is strongly related to other pain syndromes like Irritable Bowel Syndrome, Fibromyalgia and Chronic Fatigue Syndrome, the European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis (ESSIC) recently published a comprehensive paper on definition and diagnosis of BPS [1].

BPS was defined as chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional, and sexual symptoms should be addressed.

This definition has been broadly accepted although actual wording differs somewhat [2]. Because omitting the name “Interstitial Cystitis” might cause serious problems in different health systems by affecting reimbursement, the possibility of patients gaining disability benefits, and so forth, the name Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) could be used in parallel with BPS for the time being. In this chapter the term Bladder Pain Syndrome largely replaces the older Interstitial Cystitis term, but the two are essentially interchangeable as there is no accepted definition that clearly delineates the interstitial cystitis syndrome from bladder pain syndrome. The Consultation believes the latter term more appropriately describes the disorder.
Historically, definitions of IC have moved from a severe inflammatory bladder disease to a condition described primarily by symptoms (Table 1) [2].

The International Continence Society [9] (ICS) used the term Painful Bladder Syndrome (PBS) defined as “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology”. ICS reserved the diagnosis Interstitial Cystitis (IC) to patients with “typical cystoscopic and histological features”, without further specifying these. It has however been shown, that only a fraction of patients believed by experts to have BPS fulfil this definition [10].

The condition will therefore in the remainder of this chapter be referred to as BPS. As the terminology is in flux, some of the older literature may be discussed using the original terminology in the interests of clarity. Logically “interstitial cystitis” should include some form of demonstrable inflammation in the bladder wall, while “bladder pain syndrome” should include pain in the region of the bladder. The diagnosis of BPS is based on exclusion of other diseases in the bladder, urethra, and other pelvic organs including the musculoskeletal system. As with other diseases without clear objective diagnostic criteria or pathophysiological explanation, countless theories have been put forward without adding much to the delineation or understanding of the disease.

In practice, patients with symptoms of BPS are screened to exclude other relevant diagnoses or confusable diseases [1], and a focused evaluation is performed at the discretion of the physician or centre. This evaluation might include cystoscopy under local or general anaesthesia, bladder distension with registration of bladder capacity and/or the presence of glomerulations and Hunner’s lesion. Bladder wall biopsies might be obtained and evaluated for inflammation, ulcer, fibrosis, mast cells etc. The evaluation might also include urodynamics with registration of bladder capacity, compliance and bladder stability [11]. One view of the relationship of BPS with OAB is graphically depicted in Figure 1 [12]. The 14% incidence of urodynamic detrusor overactivity in the BPS [13] patients is probably close to what one might expect in the general population if studied urodynamically [14].

In the end, these investigations might prove to be normal and the patients are identified as having BPS as a diagnosis of exclusion. The relevance of urodynamic, cystoscopic and histological findings is further obscured, because the methodology by which these results is obtained is rarely comparable and it is therefore recommended to use the standardisations described by ESSIC [1].

### Table 1. Historical definitions of interstitial cystitis

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1887</td>
<td>Skene [3]: An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.</td>
</tr>
<tr>
<td>1915</td>
<td>Hunner [4]: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).</td>
</tr>
<tr>
<td>1951</td>
<td>Bourque [5]: Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all moments of the day and of the night suffering pains every time they void.</td>
</tr>
<tr>
<td>1978</td>
<td>Messing and Stamey [6]: Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia.</td>
</tr>
<tr>
<td>1990</td>
<td>Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner’s ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc [7].</td>
</tr>
<tr>
<td>1997</td>
<td>NIDDK Interstitial Cystitis Database Entry Criteria: Unexplained urgency or frequency (7 or more voids per day), OR pelvic pain of at least 6 months duration in the absence of other definable etiologies [8].</td>
</tr>
</tbody>
</table>

### 1. HISTORICAL NOTES

Recent historical reviews confirm that interstitial cystitis was recognized as a pathologic entity during the 19th century [15,16]. In his textbook Practical Observations on Strangulated Hernia and Some Diseases of the Urinary Organs, Joseph Parrish, a Philadelphia surgeon, described 3 problematic cases of recurrent, severe lower urinary tract symptoms in which he made repeated attempts to locate a bladder stone, which was the most common source for these symptoms in early 19th century America [17]. As Teichman et al have convincingly argued, these patients displayed all of the clinical hallmarks of IC including chronic frequency, urgency, dysuria and pelvic pain in the absence of demonstrable pathology [18]. Although he used the term repeatedly in his manuscript, Parrish did not elaborate upon the clinical definition of “tic doloureux,” likely because contemporaneous physicians would have been familiar with the concept. However, Parrish attributed the term Tic doloreux to his mentor, Dr. Phillip Syng Physick, who had applied it to patients with severe lower urinary tract symptoms with no discernible etiology, with the most common etiology during the 19th century being bladder stones.
A review of archival material from the Philadelphia College of Physicians indicates that by 1808 Physick had developed a concept of bladder inflammation, a “bladder ulcer,” that produced lower urinary tract symptoms in the absence of bladder stone [15]. Tic doloureux at its time represented a neurological irritation, most often associated with the trigeminal nerve but applicable to other sensory distributions as well, which produced pain and discomfort in the absence of injury or other specific physical findings. In applying the concept of tic doloureux to bladder sensation Parrish was ascribing the paroxysmal lower urinary tract symptoms occurring in patients to an idiopathic process affecting the nerves of the bladder. This sophisticated concept continues to be a prominent component of modern theories of BPS pathogenesis. Furthermore, Tic doloureux allowed him to formulate a diagnosis for those patients who chronically manifested the symptoms caused by a stone (severe frequency, urgency, dysuria and pelvic pain) but had no stone that could be detected. That is, he considered a neuropathic etiology in the absence of any other tangible causes of bladder pain. Clearly, this experience strongly resonates with the contemporary diagnosis of BPS.

50 years after Parrish’s first publication on the condition, Skene used the term interstitial cystitis to describe an inflammation that has “destroyed the mucous membrane partly or wholly and extended to the muscular parietes” [3]. Early in the 20th century, at a New England Section meeting of the American Urological Association, Guy Hunner reported on 8 women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years [4,19]. He drew attention to the disease, and the red, bleeding areas he described on the bladder wall came to have the pseudonym “Hunner’s ulcer”. As Walsh observed, this has proven to be unfortunate [20]. In the early part of the 20th century, the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall, he thought they were ulcers. For the next 60 years, urologists would look for ulcers and fail to make the diagnosis in their absence. The disease was thought to be a focal, rather than a pancystitis.

Hand authored the first comprehensive review about the disease, reporting 223 cases [21]. Many of his epidemiologic findings have held up to this day. His description of the clinical findings bears repeating. “I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distension”. He notes, “small, discrete, submucosal hemorrhages, showing variations in form...dot-like bleeding points...little or no restriction to bladder capacity.” He portrays three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients were grade 1 and only 13% were grade 3. Walsh later coined the term “glomerulations” to describe the petechial haemorrhages that Hand had described [20]. But it was not until Messing and Stamey discussed the “early diagnosis” of IC that attention turned from looking for an ulcer to make the diagnosis to the concepts that 1) symptoms and glomerulations at the time of bladder distention under...
anesthesia were the disease hallmarks, and 2) the diagnosis was primarily one of exclusion [6,20]. However, this description was not suitable for defining this disease in a manner that would help physicians make the diagnosis and set up research protocols.

The National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) held a major meeting in 1987 with researchers and clinicians from around the world [22]. This ultimately resulted in the 1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner’s ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc [7].

In order to validate the criteria, which were designed not for clinical diagnosis, but rather to ensure that patients enrolled in research trials could be agreed upon to have the disease, a database with broad entry criteria was created. The 1997 NIDDK Interstitial Cystitis Database Entry Criteria: unexplained urgency or frequency (7 or more voids per day), OR pelvic pain of at least 6 months duration in the absence of other definable etiologies [23]. Urgency was not defined in the protocol. Participants were given a 10 point scale, and those who scored 2 or higher on self report satisfied the urgency criteria. The protocol was written in 1992, a time when the definition of “urgency” was not a particularly controversial topic. When a comparison of the NIDDK revised criteria with the database entry criteria was performed, it was apparent that up to 60% of patients clinically believed to have interstitial cystitis by experienced clinicians were being missed when the NIDDK research criteria were used as a definition of the disease [24]. The last decade has been an active one from an international standpoint in terms of wrestling with the issues of diagnosis and definition [25-27].

2. NOMENCLATURE AND TAXONOMICAL CONSIDERATIONS

There is currently no agreement how this complex syndrome should be referred to. The literature over the last 170 years has seen numerous changes in description and nomenclature of the disease. The syndrome has variously been referred to as tic doloureux of the bladder, interstitial cystitis, cystitis parenchymatosa, Hunner’s ulcer, panmural ulcerative cystitis, urethral syndrome, and painful bladder syndrome [3,5,16,18,19,28,29]. The term “interstitial cystitis,” which Skene is credited with coining and Hunner for bringing it in to common usage, is a misnomer; in many cases not only is there no interstitial inflammation, but also, histopathologically, there may be no inflammation at all [30-33].

By literally focussing exclusively on the urinary bladder, the term interstitial cystitis furthermore does not do justice to the condition from both the physician’s and the patient’s perspective. The textual exclusiveness ignores the high co-morbidity with various pelvic, extra-pelvic and non-urological symptoms [34] that frequently precede the onset of the bladder condition [35].

With the formal definition of the term “painful bladder syndrome” by the ICS in 2002, the terminology discussion became an intense international focal point [9].

- In Kyoto at the ICICJ in March 2003, it was agreed that the term “interstitial cystitis” should be expanded to “interstitial cystitis/chronic pelvic pain syndrome” when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology [36].

- The European Society for the Study of Interstitial Cystitis (ESSIC) held its first meeting in Copenhagen soon after Kyoto. Nomenclature was discussed, but no decision was reached, as the meeting concentrated on how to evaluate patients for diagnosis [11].

- At the 2003 meeting of the NIDDK titled, “Research Insights into Interstitial Cystitis,” it was concluded that “interstitial cystitis” will inexorably be replaced as a sole name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as “interstitial cystitis/painful bladder syndrome” in keeping with International Continence Society nomenclature [37].

- At the 2004 inaugural meeting of the Multinational Interstitial Cystitis Association in Rome, it was concluded that the syndrome should be referred to as “painful bladder syndrome/interstitial cystitis” or “PBS/IC” to indicate an intellectual and taxonomical hierarchy within the acronym [37].

- The International Consultation on Incontinence in 2004, cosponsored by the ICS and Societe Internationale d’Urologie in association with the World Health Organization, included the syndrome as a part of its consultation. The chapter in the report was titled, “painful bladder syndrome (including interstitial cystitis),” suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, co-authored by nine committee members and five consultants from four continents, it was referred to as PBS/IC (one inclusive entity) [38].

- In June 2006 Abrams and colleagues published an editorial focussing on the nomenclature problem [39]. They noted that: “It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain
syndromes suffered by patients seen at most pain, gynecological, and urological clinics. For the most part these “diagnoses” describe syndromes that do not have recognized standard definitions, yet infer knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous. The editorial went on to note that a single pathologic descriptive term (interstitial cystitis) for a spectrum of symptom combinations ill serves patients.

The umbrella term “painful bladder syndrome” was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of chronic pelvic pain syndrome. Sufferers would be identified according to the primary organ that appears to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms.

One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research, and that removes the automatic presumption that the end-organ in the name of the disease should necessarily be the sole or primary target of such research.

• At the major biannual IC research conference in the fall of 2006, held by the National Institute of Diabetes, Digestive, and Kidney Disorders (Frontiers in Painful Bladder Syndrome/Interstitial Cystitis), the ESSIC group was given a block of time with which to present their thoughts and conclusions. Because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations, ESSIC suggested that Painful Bladder Syndrome be redesignated as Bladder Pain Syndrome (BPS), followed by a type designation. BPS is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3, indicating increasing grade of severity) and the second to biopsy (A, B, and C, indicating increasing grade of severity of biopsy findings) (Table 2). Although neither cystoscopy with hydrodistention nor bladder biopsy was prescribed as an essential part of the evaluation, by categorizing patients as to whether either procedure was done, and if so, the results, it is possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy [40].

As Baranowski et al. conceived it in early 2008, BPS is thus defined as a pain syndrome with a collection of symptoms, the most important of which is pain perceived to be in the bladder [41]. IC is distinguished

---

**Table 2.**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Cystoscopy with Hydrodistention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not done</td>
</tr>
<tr>
<td>not done</td>
<td>XX</td>
</tr>
<tr>
<td>normal</td>
<td>XA</td>
</tr>
<tr>
<td>inconclusive</td>
<td>XB</td>
</tr>
<tr>
<td>positive⁵</td>
<td>XC</td>
</tr>
</tbody>
</table>

⁴ cystoscopy: glomerulations grade II-III
⁵ with or without glomerulations

---


1465
as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neuro-visceral (myopathic) mechanisms. In IC, one expects end-organ primary pathology. This is not necessarily the case in the broader BPS.

A didactically very demonstrative way to conceptualize the dawning shift in conception of the condition is with the drawing of a target (Figure 2). There may be many causes of chronic pelvic pain. When an aetiology cannot be determined, it is characterized as pelvic pain syndrome. To the extent that it can be distinguished as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC, or simply categorized by ESSIC criteria. Patient groups have expressed their concerns with regard to any nomenclature change that potentially drops the term “interstitial cystitis” because the U.S. Social Security Administration and private insurances recognize IC but not the term BPS, and benefits potentially could be adversely affected. Whether the term “interstitial cystitis”, as difficult as it is to define and as potentially misleading as it is with regard to aetiology and end-organ involvement, should be maintained, is a subject of ongoing controversy.

II. EPIDEMIOLOGY

Figure 2: Conceptual Diagram of Pelvic Pain

It has been estimated that the prevalence of chronic pain due to benign causes in the population is at least 10% [42]. Numerous case series have, until recently, formed the basis of epidemiologic information regarding BPS. Farkas and associates [43] discussed IC in adolescent girls. Hanash and Pool [44] reviewed their experience with IC in men. Geist and Antolak [45] reviewed and added to reports of disease occurring in childhood. A childhood presentation is extremely rare and must be differentiated from the much more common and benign-behaving extraordinary urinary frequency syndrome of childhood, a self-limited condition of unknown etiology [46,47]. Nevertheless, there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of BPS. In Close and colleagues’ review of 20 such children [48], the median age of onset was younger than 5 years, and the vast majority of patients had long-term remissions with bladder distention.

A study conducted at the Scripps Research Institute [49] included 374 patients at Scripps as well as some members of theInterstitial Cystitis Association, the large patient support organization. A more recent, but similar study in England [50] concurred with the Scripps findings of urgency, frequency, and pain in the vast majority of these patients, devastating effects on quality of life, and often unsuccessful attempts at therapy with a variety of treatments. Although such reviews provide some information, they would seem to be necessarily biased by virtue of their design.

Epidemiology studies of BPS are hampered by many problems [51]. The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. Overlapping patterns of lower urinary tract symptoms and pelvic pain are common and present challenges for clinical practice and research [52]. This is most apparent when one looks at the variation in incidence reports in the United States and around the world. These range from 1.2 per 100,000 population and 4.5 per 100,000 females in Japan [53], to a questionnaire based study that suggests a figure in American women of 20,000 per 100,000 [54]. Certainly, bladder pain symptoms are more common than suggested by coded physician diagnoses [55].

Several population-based studies have been reported in the literature, and these studies tend to support the reviews of selected patients or from individual clinics and the comprehensive follow-up case-control study by Koziol [56]. The first population-based study [57] included “almost all the patients with interstitial cystitis in the city of Helsinki”. This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new female cases was 1.2 per 100,000. Severe cases accounted for about 10% of the total. Ten per cent of cases were in men. The disease onset was generally subacute rather than insidious, and full development of the classic symptom complex occurred over a relatively short
time. IC does not progress continuously, but usually reaches its final stage rapidly (within 5 years in the Koziol study [49]) and then continues without significant change in symptomatology. Subsequent major deterioration was found by Oravisto to be unusual. The duration of symptoms before diagnosis was 3-5 years in the Finnish study. Analogous figures in a classic American paper a quarter of a century earlier were 7-12 years [21].

Another early population study, this in the United States, first demonstrated the potential extent of what had been considered a very rare disease [58]. The following population groups were surveyed: 1) random survey of 127 board-certified urologists 2) 64 IC patients selected by the surveyed urologists and divided among the last patient with IC seen, and the last patient with IC diagnosed 3)904 female patients belonging to the Interstitial Cystitis Association 4) random phone survey of 119 persons from the US population. This 1987 study reached the following conclusions:

1. 43,500 to 90,000 diagnosed cases of IC in the USA (twice the Finnish prevalence)
2. Up to a five-fold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half million possible cases in the USA
3. Median age of onset 40 years
4. Late deterioration in symptoms unusual
5. 50% temporary spontaneous remission rate, mean duration 8 months
6. 10 times higher incidence of childhood bladder problems in IC patients vs controls
7. 2 times the incidence of a history of urinary tract infection vs. controls
8. Lower quality of life than dialysis patients
9. Costs including lost economic production in 1987 of $427 million

Other population studies followed. Jones et al [59] obtained their data from self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. The survey estimated that 0.5% of the population, or >1,000,000 people in the United States reported having a diagnosis of IC. There was no verification of this self-report by medical records. Bade et al [60] used a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8-16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. This prevalence in females compares to 4.5 per 100,00, in Japan [53]. The Nurses Health Study I and II [61] showed a prevalence of IC between 52 and 67 per 100,000 in the USA, twice the prevalence in the Held study [58] and three-fold greater than the Netherlands [60]. It improved on previous studies by using a large sample derived from a general population and careful ascertainment of the diagnosis. If the 6.4% confirmation rate of their study were applied to the Jones et al National Health Interview Survey data, the prevalence estimates of the two studies would be nearly identical. Ibrahim and colleagues [62] studied prevalence among community-dwelling women in Michigan, comparing survey responses from 215 established BPS cases with 823 age-matched controls of 3.7% to 4.4%., a figure that corresponds with other symptom-based assessments around the world [63-65].

1. POPULATION BASED STUDIES AND THE NEED FOR A BETTER QUESTIONNAIRE: (Figure 3)

Increasingly epidemiological studies of BPS are being conducted on large populations. This is the best way to evaluate risk factors, as well as obtain more accurate measures of disease prevalence. However, in population based studies, disease assessment is done by symptom-based questionnaires. Warren, et al [66] combined a mail-in survey with randomly selected telephone surveys to determine the prevalence of BPS amongst first degree relatives in comparison to that of the general population. They concluded that adult female first degree relatives of patients with BPS may have a prevalence of BPS 17 times that found in the general population. This suggests but does not prove a genetic susceptibility to BPS. The O'Leary Sant (OLS) and the Pelvic Pain and Urgency/Frequency (PUF) questionnaires were compared by Rosenberg and Hazard [67] in the same general practice population of 1218 patients. The prevalence of BPS with the OLS was determined to be 0.57%, with the PUF the prevalence was determined to be 12.6%. This indicated the need for a more accurate screening tool/questionnaire to be used with population based studies. When Nickel, et al [68] utilized the OLS in outpatient urology practice populations of 65 urologists, the prevalence of IC was determined to be 2.8%. This is strikingly similar to studies using the OLS in Finland, Austria, and Taiwan [63-65]. Again this demonstrates the need for a more refined symptom based questionnaire which can be used by epidemiologists and non-urologists to get an accurate determination of prevalence in population studies.

Leppilahti, et al [64,69] studied a general population of women, in Finland, using the OLS. These urologists estimated the prevalence of BPS in the general Population of Finland to be 6.8%. However, when a sample of those women was examined by one of the urologists, the more accurate prevalence approached that reported by Nickel, et al: 3.0%. This demonstrates the variability of the OLS questionnaire, and how the
estimates can differ when confirmed by clinical examination.

The need for a more general symptom based questionnaire specific for epidemiological studies was again demonstrated by Clemens et al. [70]. They administered the OLS questionnaire to 5000 women and men that a clinician had determined not to have IC. Their results demonstrated that the OLS questionnaire, when utilized as a screening tool in a general population estimated IC to be 30 to 50 fold higher in women than the prevalence of a coded physician diagnosis. These findings suggest that the current population based studies conducted using either the OLS or PUF questionnaires tend to report a much higher prevalence of BPS than confirmed by physical exam. This increasingly becomes a problem as population based studies are conducted by epidemiologists and findings are not confirmed by clinical examination. It indicates the pressing need for development of a validated symptom based questionnaire with documented sensitivity and specificity to identify not only prevalence, but also risk factors and associated disorders.

An estimation of the prevalence at this time, recognizing that a consistent definition of the condition has not been used in epidemiologic studies, appears to be about 300 per 100,000 women, and a male prevalence of 10% to 20% of the female estimate. Level of Evidence: 1 Grade of Recommendation: A

2. OTHER CONSIDERATIONS

The Interstitial Cystitis Database Cohort (ICDB) of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys [71]. Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. Although all symptoms fluctuated, there was no evidence of significant long-term change in overall disease severity. The data suggest that BPS is a chronic disease and no current treatments have a significant impact on symptoms over time in the majority of patients. Quality of life studies suggest that BPS patients are 6 times more likely than individuals in the general population to cut down on work time owing to health problems, but only half as likely to do so as patients with arthritis [72]. There is an associated high incidence of comorbidity including depression, chronic pain, and anxiety and overall mental health [38, 73, 74]. There seems to be no effect on pregnancy outcomes [75].

Most studies show a female to male preponderance of 5:1 or greater [38, 76]. In the absence of a validated marker, it is often difficult to distinguish BPS from the chronic pelvic pain syndrome (nonbacterial prostatitis, prostatodynia) that affects males [77], and the percentage of men with BPS may actually be higher [78-80]. Men tend to be diagnosed at an older age and have a higher percentage of Hunner's lesion in the case series reported [80, 81].

3. ASSOCIATED / OVERLAPPING DISORDERS

Until recently bladder pain syndrome was investigated by urologists and urological scientists focusing predominantly on the bladder. This can be attributed at least in part to the fact that the NIDDK Diagnostic Criteria, and other BPS definitions focused almost entirely on the bladder symptomatology. In 1994, a biostatistician at the Scripps Research Institute [56] reported that there was a significant association of IC with irritable bowel syndrome, as well as sinusitis, allergies and other inflammatory and autoimmune disorders. In the following year Dan Clauw, a rheumatologist, [82] published a novel unifying hypothesis which linked many chronic pain disorders such as BPS, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and others, to a common central pathogenesis and pathophysiology. Dr. Clauw concluded that “a multidisciplinary approach which examines a number of symptoms and systems concurrently is likely to be much more effective than examining one aspect at a single point in time”. In 1997, Clauw, et al [83] reported on the symptom overlap between two cohorts of patients, one with fibromyalgia and one with IC. In the same year an analysis of a survey by Alagiri, et al [84] of over 6,700 persons who had a physician diagnosis of Interstitial Cystitis reported that individuals with BPS were 100 times more likely to have inflammatory bowel disease, and that allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia also have an increased association with IC. The investigators concluded that “IC, which at present has neither a specific nor a curative treatment, has an increased association with certain chronic disease and pain syndromes, and raises the question of whether these dysfunction syndromes should be investigated for a common
biochemical defect”. Unfortunately over a decade has passed and these concluding statements remain relevant, and the investigation of associated symptoms has not been a significant focus of investigation by BPS treating physicians.

Erickson, et al [85] reconfirmed the data reported by Clauw, et al 4 years earlier, in which BPS and fibromyalgia cohorts were compared. The Erickson group concluded that BPS patients had significant occurrence of symptoms of aches in joints, abdominal cramps, headache, other pelvic discomfort, etc. They concluded that the pathophysiology that affects BPS symptoms may affect other organ systems besides the bladder. An analysis of a co-twin control study in Seattle, Washington assessed the association of numerous chronic pain disorders including BPS, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, etc. and concluded that there was a high rate of association between these disorders [86,87]. It went on to suggest that treating physicians should examine affected patients for comorbid clinical conditions. They concluded that this multisystem assessment will help in determining a temporal relationship between the disorders as well as develop strategies for early intervention.

Peeker, et al [88] sub-classified BPS into classic (with ulcer) and non-ulcer and then evaluated for concurrent systemic and autoimmune disorders. Their findings supported the co-occurrence of associated disorders but did not see any significant differences between findings in the two categories of BPS patients. Weissman, et al [89] reported from a case-control and family history study the association of panic disorder with confirmed BPS and suggested there might be a subset of BPS patients with a genetic linkage to a possible syndrome associated with panic disorder, thyroid disorder and other disorders of autonomic or neuromuscular control.

There are very few studies reported by urologists using a patient sample. The study reported by Erickson, et al [85] is, perhaps, the most complete patient centered investigation reported by a urologist. Clemens, et al [90] reported a medical record survey at Kaiser Permanente Northwest in Portland, Oregon. They confirmed that BPS is associated with multiple other unexplained physical symptoms. They also confirmed previous findings of Peters, et al [91] that BPS is also associated with a history of child abuse.

Recent literature strongly suggests that these associated symptoms must be assessed in both BPS patients as well as patients with related disorders.. Brand, et al [92] have published “The Fibromyalgia Bladder Index” which is a validated fibromyalgia-specific instrument that captures information about the sensory bladder symptoms in a patient with fibromyalgia. Aaron and Buchwald [93] developed a series of multidisciplinary screening questions which address the more common associated/overlapping conditions. This is an excellent start to a complex problem.

The study of the associated symptoms and disorders must be continued and expanded utilizing cohorts of BPS diagnosed patients. A screening questionnaire must be developed by a multidisciplinary team of clinical specialists so that IC and its co-morbidities can be more effectively evaluated and treated by urologists, gynecologists, rheumatologists, general practice physicians and other clinical providers.

### III. AETIOLOGY

The aetiology of BPS is still an enigma. Hypotheses abound with sparse evidence to support them. Studies on all aspects of BPS are hampered significantly because there is no general consensus on how to define and classify this condition.

#### 1. INFLAMMATION

Inflammation is a non-disputable feature only in the classic or ulcerative form of BPS. Histological examination of bladder lesions has revealed pancystitis and perineural inflammatory infiltrates of lymphocytes and plasma cells [94,95]. **Level of Evidence: 1 Grade of Recommendation: A**

#### 2. MAST CELL ACTIVATION

Mast cells are thought to have a role in the etiology and/or pathogenesis of BPS. They are multifunctional immune cells that contain highly potent inflammatory mediators such as histamine, leukotrienes, serotonin, and cytokines [96]. These cells are the repositories of many potent inflammatory factors. Many of the symptoms and findings in ulcerative BPS such as pain, frequency, oedema, fibrosis, and the production of new vessels in the lamina propria, could possibly be ascribed to the release of mast cell-derived factors. Hence, the mast cell-IgE system and its interaction with other inflammatory cells and the nervous system[97] seems to be of importance when it comes to pathogenesis.

There is a ten-fold increase in mast cell count in bladder tissue from patients with ulcerative BPS as compared to controls. In non-ulcer BPS, however, the mast cell count is normal or only slightly increased [96,98,99].

Other mechanisms have also been put forward. Bouchelouche [100] compared the urinary excretion of leukotrienes E4 and eosinophil protein X in patients in IC and noted detrusor mastocytosis and increased urinary leukotrienes E4 and eosinophil protein X. **Level of Evidence: 1 Grade of Recommendation: A**
3. UROTHELIAL DYSFUNCTION/GAG-LAYER DEFECTS

A defect in the glycosaminoglycan (GAG) layer has been proposed by Parsons and co-workers [101]. With such a defect the sub-mucosal nerve filaments might become accessible to noxious substances in the urine and this might explain bladder pain and urinary frequency. In ulcerative BPS there is granulation tissue indicating a reparative process following repeated disruption of the mucosa [102]. Widened tight junctions and increased permeability have been demonstrated by scanning electron microscopy and other techniques [103,104].

A more recent study by Parsons et al [105] has shown that Tamm-Horsfall protein is quantitatively different in BPS patients as compared to controls. Tamm-Horsfall protein is synthesized in the kidney and excreted into the urine. It has been suggested to have a role in immune defense and in preventing damage to the urothelial cells by injurious urinary constituents. Level of Evidence: 2 Grade of Recommendation: B

4. INHIBITION OF UROTHELIAL BLADDER CELL PROLIFERATION

One explanation of the bladder epithelial dysfunction might be the fact that the cells produce an inhibitor of heparin-binding epidermal growth factor-like production in BPS [106]. It was shown that explanted urothelial cells from BPS patients differ from controls not only as to production of epithelial growth factors but also in the rate of proliferation and the production of an antiproliferative factor (APF). Keay and co-workers [107] studied gene expression patterns in normal bladder urothelial cells treated with APF and with mock APF as compared to patterns expressed by BPS urothelial cells. The results indicate that the mechanism of APF inhibition of urothelial cells may involve both down-regulation of genes that stimulate cell proliferation along with up-regulation of genes that inhibit cell growth. The same group of researchers has indicated that APF seems to be specifically elevated in the urine of patients with BPS but not in persons with no or other conditions. These findings might open up new avenues for identification and development of urine markers for BPS [108]. Level of Evidence: 2 Grade of Recommendation: B

5. AUTOIMMUNE MECHANISMS

There are numerous reports on autoantibodies in patients with BPS [109-112]. The precise identity of these autoantibodies has yet to be determined. Some of the common clinical and histopathological characteristics present in BPS patients show certain similarities with other known autoimmune disturbances. Studies on autoantibodies in BPS have shown that these mainly consist of antinuclear antibodies [111] and these findings are in turn similar to the autoantibody profiles in some systemic diseases like Sjögren syndrome, which is known to be of autoimmune origin [88,113,114]. Only a portion of BPS patients have auto-antibodies. It has been proposed that the presence of auto-antibodies in these patients could be a reflection of disease severity [115].

Vascular immunopathology with immune deposits in the bladder wall was found by Mattila [116]. Further studies also suggest activation of complement [117]. By means of immunophenotyping and flow cytometric analyses of the bladder mucosa and peripheral blood, differences between ulcerative and non-ulcer BPS patients have been demonstrated. In the former group intense T-cell infiltrates and B-cell nodules were seen, compared to far less T-cell infiltrates in non-ulcer BPS [118]. Involvement of the immune system is one feature found in some individuals with BPS, but findings are conflicting and have not been helpful in explaining the aetiology. The lack of thorough descriptions of patients in many published studies has made classification and comparison between series impossible. Level of Evidence: 2 Grade of Recommendation: C

6. INFECTION

No microorganism has ever been revealed as the cause of BPS. Lynnes and coworkers did not find any evidence of recent or remote Gram negative or Gram positive infections in patients with BPS, nor did they find increased urinary IgA and IgG elevation [119]. This makes infection by an untested organism unlikely. Warren et al [120] in a case control study of women with recent onset of BPS symptoms, reported that documented evidence of UTI at symptom onset was found in only a minority of patients. Polymerase chain reaction techniques to amplify bacterial 16S rRNA genes that would be present if there were bacteria in bladder tissue or urine in BPS patients despite negative cultures have been without success [121]. Contrary to what was demonstrated for chronic gastritis, there is no evidence for helicobacter in BPS patients [122]. The possibility of a microbial contribution to the etiology of BPS remains an open question. Level of Evidence: 1 Grade of Recommendation: A

7. NEUROBIOLOGY/PELVIC CROSS-TALK

Several authors have described autonomic nerve changes [123-125], but the findings are far from uniform. An increase of sympathetic innervation and activation of purinergic neurotransmission has been reported. The S-100 family of proteins appear in Schwann cells of the peripheral nervous system [126,127]. Decreased levels of S-100 protein in the non-ulcer group as compared to controls has been found [128], which is consistent with a decreased nerve content in patients with non-ulcer BPS, a finding conflicting with the results of Hohenfellner [124] who used polyclonal antihuman protein gene product 9.5 antibody and found the overall nerve content increased.
in BPS patients as compared to controls. However, their study did not include subtyping of the disease into ulcerative and non-ulcer type. A distinctive ultrastructural appearance of specimens from patients with non-ulcer BPS prompted Elbadawi and Light to propose neurogenic inflammation as a trigger to a cascade of events taking place in this disease [129]. In this context it should be noted that afferent nerves release transmitters like substance P which could activate immune cells, or vasoactive intestinal polypeptide. These events may constitute a link to the immune cell system and promote a decrease of lymphocyte proliferation.

A prominent increase of tyrosine hydroxylase immunoreactivity in bladder tissue of BPS patients, as compared to controls, has been described [130]. This can presumably be interpreted as a sign of generally increased sympathetic outflow. This lends support to the notion of a neurogenic etiology and or pathogenesis.

Malykhina and others [131-135] have demonstrated in innovative animal studies that there is a bidirectional neural cross-sensitization of the colon and lower urinary tract. Acute colitis sensitized lumbosacral spinal neurons receiving input from the urinary bladder result in spinal neuronal hyperexcitability that may be involved in central cross-organ sensitization of visceral nociception between the colon and urinary bladder. This provides information which not only supports a neurogenic etiology but also may account for the substantial overlap of BPS with other chronic pelvic pain disorders, especially the inflammatory bowel disorders [84]. Rudick and Colleagues have shown in a murine model organ cross talk in pelvic pain and modulation of pain responses by visceral inputs distinct from the inflamed site [136]. Level of Evidence: 2 Grade of Recommendation: B

8. NITRIC OXIDE METABOLISM

Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunologic responses in BPS. The oral administration of L-arginine, the substrate for nitric oxide production [137] has been shown to increase nitric oxide related enzymes and metabolites in the urine of patients with BPS [138].

It has been reported that differences in NO evaporation between ulcerative and non-ulcer BPS allows for subtyping of cases meeting the NIDDK criteria. This could negate the need for cystoscopy [139]. Level of Evidence: 2 Grade of Recommendation: C

9. TOXIC AGENTS

There are a few publications which have suggested that toxic substances in the urine may cause injury to the bladder resulting in symptoms consistent with BPS. One published hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect [140]. Another group of investigators has suggested that defective constituent cytokine production may decrease mucosal defense to toxic agents [141]. Level of Evidence: 3 Grade of Recommendation: D

10. HYPOXIA

Decreased microvascular density has been reported to be a feature of bladders from some individuals with BPS [142] One group of investigators has reported that bladder perfusion decreased with bladder distension in some PBS patients compared to the opposite effect in control subjects [143] Despite these observations, the investigators have noted that bladder ischemia alone would not account for the symptoms associated with BPS. Level of Evidence: 4 Grade of Recommendation: D

11. THE ROLE OF GENETICS IN BPS

Warren et al [144] report findings from a small cohort of twins which demonstrated a greater concordance of BPS among monozygotic that among dizygotic twins. This finding suggested that there could be a genetic susceptibility to BPS. A later study by the same research group [66] suggested that adult female first-degree relatives of patients with BPS may have a prevalence of IC 17 times that found in the general population. This coupled with the previously reported twin data suggests, but does not prove, a genetic component adds to the susceptibility for BPS.

The report by Weissman et al [89] of the increased frequency of BPS in patients and their first degree relatives with panic disorder and other seemingly disparate disorders, has suggested that there is a familial syndrome consisting of BPS and other disorders of possible autonomic or neuromuscular dysfunction. More recent studies by the same group [145] from a case control study, suggested that this syndrome might include other anxiety disorders as well, and that families with and without this collection of symptoms were genetically distinguishable on chromosome 13. Level of Evidence: 1 Grade of Recommendation: B

CONCLUSIONS

There have been no significant conclusive advances made in understanding either the etiology or pathogenesis of BPS. It is now believed that the aetiology of BPS is more complex than has been previously envisioned [84,86,90,146-148]. The consideration of BPS as a part of a generalized somatic disorder should open new pathways to the study of BPS. Investigators should continue to explore central neurological mechanisms of pathogenesis, as well as genetic/familial, immunological and infectious etiologies of this puzzling, complex disorder.

An algorithm that attempts to illustrate an etiologic schema is presented below (Figure 4).
Figure 4: Proposed Pathogenesis of Bladder Pain Syndrome
IV. PATHOLOGY

One can have pathology consistent with the diagnosis of BPS, but there is no histology pathognomonic of this syndrome. The role of histopathology in the diagnosis of BPS is primarily one of excluding other possible diagnoses. One must rule out carcinoma and carcinoma-in-situ, eosinophilic cystitis, tuberculous cystitis, as well as any other entities with a specific tissue diagnosis [102,149,150].

Level of Evidence: 1 Grade of Recommendation: A

While earlier reports described a chronic, edematous pancytisitis with mast cell infiltration, submucosal ulcerations and involvement of the bladder wall and chronic lymphocytic infiltrate [151,152], these were cases culled from patients with severe disease and not representative of the majority of cases currently diagnosed. The pathologic findings in BPS are not consistent. There has been a great variation in the reported histologic appearance of biopsies from BPS patients, and even variation among biopsies taken from the same patients over time [22].

Lepinard and colleagues [153] reported a pancytisitis affecting the 3 layers of bladder wall. In nonulcerative disease the vesical wall was never normal, epithelium being thinned and muscle being affected. Johansson and Fall [102] looked at 64 patients with ulcerative disease and 44 with nonulcerative IC. The former group had mucosal ulceration and hemorrhage, granulation tissue, intense inflammatory infiltrate, elevated mast cell counts and perineural infiltrates. The nonulcer group, despite the same severe symptoms, had a relatively unaltered mucosa with a sparse inflammatory response, the main feature being multiple, small, mucosal ruptures and suburothelial hemorrhages that were noted in a high proportion of patients. As these specimens were almost all taken immediately after hydrodistention, how much of the admittedly minimal findings in the nonulcer group were purely iatrogenic is a matter of speculation.

One can see completely normal biopsies in the nonulcerative BPS group [154]. Transition from nonulcerative to ulcerative BPS is a rare event [98], and pathologically the two types of IC may be completely separate entities. While mast cells are more commonly seen in the detrusor in ulcerative BPS[155], they are also common in patients with idiopathic bladder instability [156]. Mastocytosis in BPS is best documented by tryptase immunocytochemical staining [157]. Larsen and colleagues recommend taking biopsies from the detrusor of patients with suspected BPS and examining them with tryptase-stained 3 micron thick sections, with every seventh section used for quantification. They consider 27 mast cells/mm² indicative of mastocytosis [158]. Despite attempts to develop a diagnostic algorithm based on the detrusor to mucosa mast cell ratio and nerve fiber proliferation [97], mast cell counts per se have no place in the differential diagnosis of this clinical syndrome.

Mast cells could be valuable in clinical phenotyping, but as yet that is unproven. Mast cells trigger inflammation that is associated with local pain, but the mechanisms mediating pain are unclear. In a murine model of neurogenic cystitis, Rudick and colleagues [159] demonstrated that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor respectively. Therefore, pain is independent of pathology and inflammation, and histamine receptors may represent direct therapeutic targets for the pain of BPS and other chronic pain conditions.

Lynes and coworkers [32] concluded that biopsy specimens are often not helpful in confirming the diagnosis. Although BPS patients in his study had a higher incidence and degree of denuded epithelium, ulceration, and submucosal inflammation, none of these findings was pathognomonic. In addition, these “typical” findings occurred only in BPS patients with pyuria or small bladder capacity. Epithelial and basement membrane thickness, submucosal edema, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis were not significantly different in the BPS and control patients.

Attempts to definitively diagnose BPS by electron microscopy have also been unsuccessful. Collan’s group [160], in the first such study, wrote that the similarity of the ultrastructure of epithelial cells in controls and IC patients makes it improbable that the disease process originates in the epithelium. Other investigators found no differences in the morphologic appearances of the glycocalyx and of urothelial cells in patients with IC when compared with controls [161]. Anderstrom and colleagues [104] saw no surface characteristics specific for IC, but believed that the mucin layer covering the urothelial cells seemed reduced in IC compared with controls, a fact disputed by Nickel in a very elegant paper [162]. Elbadawi and Light [129] observed ultrastructural changes sufficiently distinctive to be diagnostic in specimens submitted for pathologic confirmation of nonulcerative interstitial cystitis. Marked edema of various tissue elements and cells appeared to be a common denominator of many observed changes. The wide-ranging discussion of the etiology of IC in his paper is fascinating, but the pathological findings are potentially marred by the methodology, in that specimens were obtained after diagnostic hydrodistention [163].

So what is the place of pathologic examination of tissue in BPS? Attempts to classify the painful bladder by the pathoanatomical criteria described by Holm-Bentzen [164] are of questionable value. There is a
group of patients with what she describes as “nonobstructive detrusor myopathy” [165]. In her series, these patients with degenerative changes in the detrusor muscle often had residual urine, a history of urinary retention, and an absence of sensory urgency on cystometry with bladder capacities over 400cc. Most would not be clinically confused with BPS. A similar English series [166], however, included patients who met NIDDK research criteria and associated detrusor myopathy with diminished detrusor compliance and ultimate bladder contrac-

The Interstitial Cystitis Database (ICDB) study worked backwards from symptoms to pathology, and concluded that certain symptoms are predictive of specific pathologic findings [30,167]. Denson et. al. [33] analyzed forceps biopsies from 65 females and 4 males with BPS. Ten per cent of specimens showed vasodilatation or submucosal edema. Inflammation was absent in 30% of patients, and mild in another 41%. Cystoscopic changes did not correlate with degree of inflammation. Hanus and colleagues [168] studied 84 biopsies from 112 BPS patients and reported a linear relationship between the mean bladder capacity under anesthesia and severity of glomerulations. They did not find a correlation between severity of symptoms and histopathological changes observed by light or electron microscopy.

Rosamilia reviewed the pathology literature pertaining to BPS in 2 recent publications and presented her own data [31,38]. She compared forceps biopsies from 35 control and 34 PBS/IC patients, 6 with bladder capacities less than 400cc under anesthesia. Epithelial denudation, submucosal edema, congestion and inflammatory infiltrate were increased in the BPS group. Submucosal hemorrhage did not differentiate the groups, but denuded epithelium was unique to the BPS group and more common in those with severe disease. The most remarkable finding in her study was that histological parameters were normal and indistinguishable from control subjects in 55% of BPS subjects. Method of biopsy can be important in interpreting findings, as transurethral resection biopsies tend to show mucosal ruptures, submucosal hemorrhage and mild inflammation [102], while histology is normal approximately half the time with cold-cup forceps biopsies [31,32,169].

Histopathology plays a supportive diagnostic role at best [170]. Major reconstructive procedures appear to have better outcomes in patients with pathology consistent with Hunner’s lesions [171]. Inflammatory features can be seen in 24% to 76% of patients without a visible Hunner’s lesion [172]. While recent studies suggest that a severely abnormal pathology may be associated with poor prognosis [173,174], this is not necessarily the case [175]. At this point in time, excluding other diseases that are pathologically identifiable is the primary utility of bladder biopsy in this group of patients.

V. DIAGNOSIS

Much work has been put into the attempt to define objective diagnostic criteria based on, among other factors, cystoscopy under local or general anesthesia, bladder distention with registration of bladder capacity and/or possible presence of glomerulations and Hunner’s lesion, bladder wall biopsies evaluated for inflammation, ulcer, fibrosis, mast cells, etc. and urodynamics with registration of bladder capacity, compliance and bladder stability. Results have, however, been frustrating. It is more fruitful to establish a broad clinical diagnosis, mainly on the basis of symptoms and exclusion of other diseases, and then stratify patients by urodynamic, cystoscopic, histological, and other tests on the basis of the significance of these findings for results of treatment and prognosis of disease. Current efforts to phenotype the disorder by the presence or absence of associated syndromes and diseases may also prove useful in the same way.

What follows is based solely on expert opinion. Level of Evidence:4 Grade of Recommendation:C

It is hoped that future Consultations will have the data to base such suggestions on more a more firm foundation.

1. HISTORY

A general thorough medical history should be taken. Special emphasis should be given to:

- Previous pelvic operations
- Previous UTI
- Bladder history/urological diseases
- Location of pelvic pain (referred pain) and relation to bladder filling/emptying.
- Characteristics of pain: onset, correlation with other events, description of pain
- Previous pelvic radiation treatment
- Autoimmune diseases
- Physical examination

A common physical examination should be performed including palpation of the lower abdomen for bladder fullness and tenderness:

- Standing: kyphosis, scars, hernia
- Supine: abduction/adduction of the hips, hyper-aesthetic areas

In females physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe.
2. PAIN MAPPING

Inspection:
- Vulva
  - exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
  - evaluation of introital area (endometriosis)
  - tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or finger tip)
- Vagina
  - tenderness during insertion and opening of speculum
  - cervical pathology
  - vaginal fornices (endometriosis)
- Bimanual physical examination
  - tenderness of urethra, trigone and bladder
  - superficial/deep vaginal tenderness
  - tenderness of pelvic floor muscles (levator, adductor)
  - tenderness in adnexal areas

In males digital rectal examination (DRE) should be performed with pain mapping of the scrotal–anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

3. LABORATORY TESTING

- Urine dipstick (ABS, pH, leucocytes, nitrate), urine culture in all. If sterile pyuria culture for tuberculosis.
- Urine cytology in risk groups.
- Investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional.

4. SYMPTOM EVALUATION

- Voiding diary with volume intake and output for 3 days at initial evaluation. Patient sensation at voiding might be recorded (see chapter outcome assessment, Hanno).
- At follow-up only number of voidings during day and night time is necessary. Morning volume might be recorded as a help to monitor highest functional capacity.
- The O’Leary–Sant Symptom Score supplemented should be used as basic symptom score supplemented with the Quality of Life Score from the International Prostate Symptom Score (see chapter symptom scales, Hanno3).
- Pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to fit with the voiding diary). Separate scores for the average, mildest and worst pain should be obtained (see symptom scales)

5. URODYNAMICS

Level of Evidence: 4 Grade of Recommendation: C

The NIDDK criteria excluded patients with detrusor overactivity at filling cystometry in order not to confuse the picture in clinical trials [22]. This does not however mean that detrusor overactivity can not coexist with bladder pain syndrome. In the interstitial cystitis database approximately 14% of BPS patients had overactive bladders [13]. Whether these patients respond better to antimuscarinics than BPS patients with stable bladders has never been systematically investigated. If so, a rationale for routinely employing urodynamics as a part of the evaluation would follow. In males, infravesical obstruction might be a differential diagnosis [176], and it is recommended to do flowmetry in all males and pressure-flow studies in men with a peak flow rate below 20ml/seconds.

There are no data to support the following recommendations:

In females, flowmetry, post void residual urine volume and pressure- flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rate <20 ml/s a pressure-flow study and measure of residual urine volume should be done. It is recommended to perform filling cystometry with a filling rate of 50 ml/s (to comply with the revised Potassium Test - see below) to look for overactivity, volume at first desire to void and cystometric capacity.

6. POTASSIUM TESTING

Level of Evidence: 1 Grade of Recommendation: -A (not recommended)

Parsons has championed an intravesical potassium chloride challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4 M potassium chloride solution. The test has proved controversial [177]. Pain and provocation of symptoms constitutes a positive test. Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients, or hypersensitivity of the sensory nerves is unclear. Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small [178]. The concentration of potassium used is 400meq per liter, far exceeding the physiologic urinary concentrations of 20-80meq/liter depending upon dietary intake [179]. Healthy controls can distinguish KCl from sodium chloride, though they don’t experience severe pain [180]. The hope is that this test may stratify patients into those who will respond to certain treatments (perhaps those designed to fortify the glycosami-noglycan layer), but to date this information is lacking [181].

Used as a diagnostic test for interstitial cystitis, the potassium chloride test is not valid [182]. The gold standard in defining BPS for research purposes has been the NIDDK criteria. These criteria are recognized
to constitute a set of patients that virtually all researchers can agree have BPS, though they are far too restrictive to be used in clinical practice [24]. Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test [183]. In the group it should perform the best in, it is lacking in sensitivity. When we look at the specificity side of the equation, in the universe of asymptomatic persons, it performs relatively well and is rarely positive, although a recent study reported a 36% false positive rate in asymptomatic men [184]. It is in the patient population with confounding conditions for which we would want help in sorting out BPS from other disorders. Twenty-five percent of patients with overactive bladder test positive and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive [183,185]. The results with chronic prostatitis / chronic pelvic pain syndrome in men are variable, but 50-84% of men have been reported to test positive [184,186,187]. In women with pelvic pain results are similar [188], and based on these findings, Parsons has expressed the view that BPS may affect over 20% of the female population of the United States [189]. Others have reported prevalence in unselected female textile workers in Turkey using similar methods at 32.8% [190]. Another way to interpret the findings would be that the KCl test is very nonspecific, missing a significant number of BPS patients and over-diagnosing much of the population.

Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of BPS have found no benefit of the test in comparison with standard techniques of diagnosis [182,191,192]. A recent modification of the test using 0.3 molar potassium chloride for potential differentiation between patients with IC and detrusor overactivity (DO) showed that the 0.3 M KCl reduces maximum cystometric capacity in BPS and DO, the effect being more pronounced in DO. Urothelial hyperpermeability was not specific to IC. Comparative cystometry using NS and 0.3 M KCl does not help to differentiate BPS from DO [193,194].

The development of a painless modification of the potassium chloride test [195] using cystometric capacity and a 0.2M solution may improve acceptability among patients. The so-called revised or Comparative Potassium Test has shown prognostic value in bladder irrigation studies, [196] but is considered optional by ESSIC. If performed it should be performed according to Daha et al. [195]: A Foley balloon catheter (14F) is inserted and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50 ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference. A difference in bladder capacity > 30% is considered positive. Besides reduction of bladder capacity with 0.2 M KCl there is a stronger feeling of urgency in IC patients compared to the saline filling, which is also clinically relevant.

7. CYSTOSCOPY

Level of Evidence:2 Grade of Recommendation:B

The classic cystoscopic picture of BPS as an “elusive” bladder ulcer with a corresponding cystoscopic appearance of patches of red mucosa exhibiting small vessels radiating to a central pale scar was described by Hunner in 1914 [4]. Since then, glomerulations, described as punctuate petechial hemorrhages and observed after hydrodistention, have become the primary cystoscopic feature of BPS [6]. But not all patients with symptoms of BPS have glomerulations, [24,33,197] and not all patients with glomerulations have symptoms of BPS [198-200]. Neither presence nor severity of glomerulations correlate with any of the primary symptoms of BPS, [30] although the presence of a Hunner’s lesion is significantly associated with bodily pain and urinary urgency [199]. The finding of a Hunner’s lesion or glomerulations has been somewhat subjective. Some researchers find a Hunner’s lesion in 50% of their BPS patients, while others rarely see one [201].

No study comparing individual perceptions and variations in reporting or classifying glomerulations has ever been reported. Bladder capacity during hydrodistention has not drawn much attention, although it is strongly associated with increased urgency [199].

Because considerable variation in the duration of distension, repetition of distension, the pressure used for distension, and the measurement of bladder capacity have been described [202], the ESSIC has suggested a standardized procedure for cystoscopy and hydrodistention [11]:

A rigid cystoscope is preferred to facilitate taking of adequate biopsies. Glycine or corresponding filling fluid should be used to allow for coagulation after biopsies. Infusion height should be approximately 80 cm above the Symphysis Pubis. A dripping chamber is used and the bladder is filled until fluid dribbling stops. If necessary, a digital block is applied around the urethra to prevent leakage. Pre-distension inspection includes observation for radiating vessels, coagulum or fibrine deposits, white spots, hyperaemia, oedema, cracks, scars or any other mucosal changes. Continuous inspection while filling the bladder is advised. When maximum capacity is reached, the distension is maintained for 3 minutes. The bladder is emptied and the colour of the fluid checked for the
degree of bleeding. The total volume drained is the measured maximum bladder capacity. During a second filling, the bladder is filled to approximately 1/3rd to 2/3rd of the bladder capacity to achieve optimal vision for inspection and biopsies. The bladder should not be filled to maximum capacity or distended again to avoid further provocation of changes with doubtful reproducibility.

a) Inspection

Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

b) Classification

Grade 0 = normal mucosa  
Grade I = petechiae in at least two quadrants  
Grade II = large submucosal bleeding (ecchymosis)  
Grade III = diffuse global mucosal bleeding  
Grade IV = mucosal disruption, with or without bleeding/oedema

c) How useful is hydrodistention?

Hydrodistension results fail to identify any statistically significant differences in post-distention objective findings (anesthetic capacity, glomerulations) or therapeutic benefits when patients are categorized according to presenting symptoms [203]. Cystoscopy with hydrodistention may provide little useful information above and beyond the history and physical examination findings. In one study, 56% of 84 patients reported symptom improvement, but the duration was short lived with a mean of 2 months [204].

Damerau and colleagues examined the relationships between symptoms and cystoscopic findings in 12 women newly diagnosed with BPS who had not previously received treatment. Pain symptoms had consistent positive correlations with the cystoscopic findings. An increase in pain with bladder filling was associated with inflammation (P = 0.011), ulceration, and smaller bladder capacity. Pain relief after voiding correlated with smaller bladder capacity (P = 0.019), hematuria, and total cystoscopic score. Pain intensity in the urethra was related to ulceration and hematuria, and pain in the lower abdomen was related to a smaller bladder capacity (P = 0.047), glomerulations, and a larger total cystoscopic score. Daytime frequency correlated negatively with most cystoscopic findings, and nocturnal frequency had a positive relationship with most cystoscopic findings and was significantly associated with a smaller bladder capacity (P = 0.010). Urgency showed no strong associations with any cystoscopic findings. The results of this study contradict those of previous studies that found no relationship between symptom reports and cystoscopic findings suggesting possible effects of treatment on pain perception and therapeutic influence on cystoscopic findings [205].

It is important to keep in mind that the cystoscopic appearance of the bladder wall after hydrodistention may not be constant over time, and the absence of initial findings of glomerulations or terminal hematuria does not preclude further development of these hallmarks of the disease on subsequent evaluation [206]. Rare cases of hydrodistension induced bladder necrosis have been described [207].

d) Morphology

Pathological changes in light microscopic and electron microscopic features in patients with BPS have been described including infiltration with inflammatory cells in all or specific parts of the bladder wall. Although these findings are important in our attempt to understand the disease and perhaps as an aid to stratification of patients, there are at this time no pathognomonic findings on biopsy in terms of diagnosis [30]. Expert opinion as per the ESSIC suggests the following procedures when biopsy is planned for BPS evaluation:[11]

1. Biopsies

During cystoscopy the bladder is distended to full capacity. After draining the bladder, bladder biopsies are taken at roughly half full bladder capacity: Biopsy procedures should be performed by using large forceps and include detrusor muscle; alternatively double punch biopsies or resections of lesions can be used.

2. Number of Biopsies

At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from visually abnormal areas. The biopsies are to be immediately fixed in neutral buffered 4% formalin.

3. Biopsy Handling

Biopsies are treated conventionally. Six adjacent 3 mm sections are cut and placed with 3 specimens on each of two specimen slides. The first slide is stained with H&E, the next with a connective tissue stain suitable for the individual institute. Twenty-four 10 mm sections are then cut and every third section is mounted on a specimen slide for mast cell counting. The specimens are stained by Lederstain (naphthol-lesterase) according to routine procedures. Finally, a 3mm section is obtained to ensure the presence of detrusor muscle in the specimens.

4. Mast Cell Counting

The use of a measuring grid (e.g. Leitz periplan 6F 10_N ocular containing a standardized grid) is necessary. Only mast cells containing nucleus are included. When counting the cells those covering or touching the bottom should be excluded whereas those covering the upper and left line are included. At least 3 biopsies must be the subject of mast cell counting and if possible one including a lesional area.
Biopsies for mast cell counting should contain detrusor muscle.

5. The Pathology Report

- Epithelium
- Not present
- Present
- Dysplasia with grading
- Abnormal but no dysplasia: description is mandatory.
- Propria
- Normal
- Inflammation: description with a grading
- Other findings are described
- Detrusor muscle. Abnormal muscle cells: describe
- Intrafascicular fibrosis
- Not present
- Present
- Mast cell count: At least three biopsies should be included in the counting. Only the biopsy with the highest number of mast cells per mm2 should be reported.

Larsen recommends examining the detrusor biopsies with tryptase-stained 3 micron thick sections, with every seventh section used for quantification. 27 mast cells/mm2 is considered indicative of mastocytosis [158].

e) Biomarkers

The lack of universally accepted clinical diagnostic criteria for BPS affects all aspects of making progress in understanding this disease. Insights into risk factors, pathogenesis, trials for effective therapy, prognosis, and outcome criteria for treatment are all affected by this lack of diagnostic criteria. A major factor affecting the controversy over accepted clinical diagnostic criteria is that the current criteria are predominantly symptom specific. An objective biomarker would advance the establishment of reproducible diagnostic criteria for BPS and also aid in monitoring effects of treatment.

A biomarker for any disease needs to demonstrate high sensitivity and high specificity. In addition, the marker assay needs to be reproducible in many laboratories and should be suitable for use in a clinical diagnostic laboratory.

Many of the published studies on biomarkers for BPS have been on biomarkers isolated from urine. Erickson et al has published excellent reviews of urine markers for BPS [08,209]. The most thoroughly investigated marker is antiproliferative factor (APF). This factor has been identified and characterized by Dr. Susan Keay and her colleagues at the University of Maryland [210,211].

APF seems an ideal candidate for a biomarker for symptomatic BPS. There need to be additional studies to determine if it can serve as a BPS marker for patients in remission or for those who have not yet become symptomatic. As of 2008, the findings on asymptomatic patients have yet to be replicated by laboratories around the world, and the biologic assay has not proven suitable for commercial development as it currently exists.

GP-51 is a glycoprotein present in both the transitional epithelium and urine of humans and other mammals. Moskowitz et al have shown that bladder biopsies of BPS patients had decreased staining for GP-51 [221]. The same laboratory also demonstrated that although GP-51 demonstrates a high specificity for BPS, it is not as sensitive as APF [222].

There have also been many published studies on heparin-binding epidermal growth factor-like growth factor (HB-EGF) [107,213,214,223,224]. HB-EGF is a growth factor found in normal urine. It has been shown that APF inhibits the production of HB-EGF. There have been no large population studies focusing solely on HB-EGF as a biomarker for BPS.
f) Confusable Diseases

Criteria for a diagnosis are needed only if the target disease may be confused with other diseases (confusable diseases) because of overlapping features [225]. For a diagnosis, the target disease has to be recognized in a pool of confusable diseases in one of two ways: by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases. For the diagnosis of BPS both methods might be used because:

- Confusable diseases are more common than BPS, so recognition is mandatory because many can be treated.
- Failure to diagnose a confusable disease would automatically incorrectly yield a diagnosis of BPS.
- Patients may have a confusable disease plus BPS. The diagnosis of BPS can thus be made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis is possible. Symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the specific feature and diagnostic criteria would not be necessary.

In evidence-based medicine, diagnoses are based on medical history, physical examination, and appropriate clinical investigations to eliminate diseases from a list of differential diagnoses (confusable diseases) and to confirm the final diagnosis. BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. Cystoscopy with hydrodistension and biopsies might in this situation document positive signs of BPS thereby making a double diagnosis more probable. For therapeutic studies it makes sense to exclude patients who also have a confusable disease because symptoms and signs may be caused by BPS, the confusable disease, or both. For prevalence studies of BPS, on the other hand, all cases with BPS should be included, also those with a confusable disease. This approach eliminates the need for separate diagnostic criteria for clinical practice and scientific studies. Table 3 summarizes confusable diseases related to BPS and their mode of exclusion based upon the aforementioned diagnostic proposals and procedures [11,40].

Table 3. Differential Diagnosis of Bladder Pain Syndrome.

<table>
<thead>
<tr>
<th>Confusable disease</th>
<th>Excluded or diagnosed by*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma and carcinoma in situ</td>
<td>Cystoscopy and biopsy</td>
</tr>
<tr>
<td>Infection with</td>
<td>Routine bacterial culture</td>
</tr>
<tr>
<td>Common intestinal bacteria</td>
<td>Special cultures</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Exostick; if “sterile” pyuria culture for M. tuberculosis</td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td>Physical examination</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>Medical history</td>
</tr>
<tr>
<td>Mycoplasma genitalium</td>
<td>Medical history</td>
</tr>
<tr>
<td>Corynebacterium urealyticum</td>
<td>Medical history</td>
</tr>
<tr>
<td>Candida species</td>
<td>Urolithiometry and ultrasound imaging or cystoscopy</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Medical history and/or hematuria: upper urinary tract</td>
</tr>
<tr>
<td>Herpes simplex and human papilloma virus</td>
<td>imaging such CT or IVP</td>
</tr>
<tr>
<td>Radiation</td>
<td>Medical history</td>
</tr>
<tr>
<td>Chemotherapy, including immunotherapy with cyclophosphamide</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Anti-inflammatory therapy with tigecycline acid</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Bladder neck obstruction and neurogenic outlet obstruction</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Bladder stone</td>
<td>Physical examination</td>
</tr>
<tr>
<td>Lower ureteric stone</td>
<td>Postvoid residual urine volume measured by ultrasound scanning</td>
</tr>
<tr>
<td>Urethral diverticulum</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Ureteral prolapse</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>Physical examination</td>
</tr>
<tr>
<td>Cervical, uterine, and ovarian cancer</td>
<td>Postvoid residual urine volume measured by ultrasound scanning</td>
</tr>
<tr>
<td>Incomplete bladder emptying (retention)</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Overactive bladder</td>
<td>Medical history and physical examination</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Pelvic floor muscle-related pain</td>
</tr>
<tr>
<td>Benign prostatic obstruction</td>
<td>Pelvic floor muscle-related pain</td>
</tr>
<tr>
<td>Chronic prostatic prostateitis</td>
<td>Pelvic floor muscle-related pain</td>
</tr>
<tr>
<td>Chronic non-bacterial prostatitis</td>
<td>Pelvic floor muscle-related pain</td>
</tr>
<tr>
<td>Pelvic floor nerve entrapment</td>
<td>Pelvic floor muscle-related pain</td>
</tr>
</tbody>
</table>

CT = computed tomography; IVF = intravenous pyelogram; PSA = prostate-specific antigen.

* The diagnosis of a confusable disease does not necessarily exclude a diagnosis of BPS.

VI. CLASSIFICATION

Interstitial cystitis was originally described as bladder disease with severe inflammation of the bladder wall described by Hunner as an ulcer [4]. The lesion is however not an ulcer but a vulnus (weakness) that can ulcerate on upon distention, and the name of the bladder lesion has consequently been changed to “Hunner’s lesion” [1]. The finding of a Hunner’s lesion could therefore originally be regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations as another typical finding for IC and this was included in the NIDDK criteria [7]. Magnus Fall proposed, that patients with Hunner’s lesion (classic IC) and patients with glomerulations (non-ulcer type) represented two different subtypes [98] with different clinical pictures, different outcomes, and different responses to treatment [226] meaning that patients fulfilling the NIDDK criteria represents at least two different patient populations. Moreover up to 60% of patients clinically believed to have BPS by experienced clinicians do not fulfil the NIDDK criteria [24] and whether or not these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally Japanese urologists consider that “interstitial cystitis” should be preserved as a disease name for patients with urinary symptoms and cystoscopic findings of glomerulations or Hunner’s lesion as outlined in the NIDDK criteria [227].

In an attempt to unite these different philosophies into a coherent schema, ESSIC proposed a classification of BPS based on findings during cystoscopy with hydrodistension and morphological findings in bladder biopsies [1]. (Table 2) The classification includes groups not having had cystoscopy with hydrodistension (group X) as well as groups not having had morphological investigation of bladder biopsies (group XX). By using this classification future research will be able to identify if findings of glomerulations and/or Hunner’s lesion as well as morphological changes in bladder biopsies does have significant importance for disease prognosis and/or treatment outcome.

VII. CONSERVATIVE TREATMENT

1. BEHAVIORAL MODIFICATION

A PubMed search (performed in June, 2008) using the keywords, “interstitial cystitis” and “behavioral therapy” identified 6 articles. One English-language article focused on behavioral therapy [1] has been summarized with two additional articles [2,3]. Level of evidence: 3 Grade of recommendation: C

Despite a low level of evidence, behavioral therapy has become the cornerstone of treatment for patients with BPS. Some efficacy has been reported in the treatment of motivated patients with urinary frequency and urgency. No problematic side effects have been identified.

Behavioral therapy includes timed voiding (scheduled voiding time and interval), controlled fluid intake, pelvic floor muscle training and bladder training (gradually extending voiding interval).

Chaiken et al [228] reported that when they conducted behavioral therapy consisting of frequency-volume chart, timed voiding, controlled fluid intake and pelvic floor muscle training for the treatment of 24 female patients, 50% of the patients showed improvement in the number of urinations and bladder capacity. At the same time, they considered that as the data was collected from 12 weeks’ intensive therapy conducted by skilled therapists for selected patients whose main symptom was urinary frequency, it should not be generalized.

Parsons and Koprowski [229] reported that when 21 patients with the main symptom of urinary frequency underwent bladder training using a frequency-volume chart, 15 patients showed improvement. In 15 patients, the mean voided volume after one month increased by 65cc, whereas a persistent sensation of bladder fullness remained unchanged.

2. PHYSICAL THERAPY

A PubMed search (performed in June, 2008) using the keywords, “interstitial cystitis” and “physical therapy” identified 60 articles. Three usable English-language articles [230-232] focused on physical therapy were examined with 4 additional articles [233-236]. Level of evidence: 3 Grade of recommendation: C

Some efficacy has been reported in the treatment of motivated patients with urinary frequency, urinary urgency and coital pain. No problematic side effects are reported.

Physical therapy for the pelvic floor is said to be effective for genitourinary and anorectal disorders [235]. Biofeedback and soft tissue massage may stimulate the relaxation of the pelvic floor muscles [233,234].

Lukban et al conducted a direct myofascial release treatment on 16 BPS patients with high-tone pelvic floor dysfunction and sacroiliac dysfunction. The treatment was effective for urinary frequency and suprapubic pain. Fifteen patients (94%) showed improvement in the O’Leary & Sant symptom score. Coital pain relief was observed in 15 of 16 patients, with 9 patients becoming able to resume sexual intercourse [231,236]. Transvaginal Theile massage was also reported to be effective for 9 of 10 patients of the same group [232]. Mendelowitz showed a 69% success rate when treating 16 patients using electromyographic biofeedback [233]. However, it was suggested that a placebo effect may have occurred because the effect did not correlate with the improvement in patient’s...
awareness of the pelvic floor muscle movement and position before and after the therapy. Weiss [230] reported that 70% of 10 patients with IC showed symptomatic improvement, rating from “effective” to “remarkably effective”. ??

3. STRESS REDUCTION

A PubMed search (performed in June, 2008) using the keywords, “interstitial cystitis” and “mental health” identified 7 articles. Four articles [73,74,237,238] which are focused on interstitial cystitis have been summarized with 5 additional articles [49,239-242 here. Level of evidence: 4 Grade of recommendation: C

Stress reduction is believed to contribute to an overall improvement in quality of life. No problematic side effects are reported.

It is known that mental stress is one of the factors which aggravate the symptoms of BPS. Kozol et al [49] reported, in a survey of 374 patients, that more than half of the patients experienced intensified pain due to stress. Rothrock et al [241] reported that when comparing patients with BPS and healthy people, increased pain and urgency caused by stress were observed only in patients with BPS.

It is believed that exercise and bathing favorably influence the quality of life by reducing stress, [242] however, behavioral therapies may not provide sufficient effect [49]. It can be beneficial, when possible, to shorten working hours, choose a job with less stress or create a less stressful home environment. At the same time, involvement in patient education programs and patient support groups are considered to be beneficial [239,243].

World-wide patient support groups, including the Interstitial Cystitis Association (ICA) [240], http://www.ichelp.com/welcome.htm, are important sources of information for patients with IC. In Japan, there is an IC patient support group, “TOMONOKI” http://www.tomonoki.org/. Another good source of information is the International Painful Bladder Foundation http://www.painful-bladder.org/. Psychiatric support is important because IC patients often suffer depression, which may negatively impact upon the quality of life. Effective self-care strategies taught by psychiatric nurses are considered to be useful [73,74,238,244].

4. DIETARY MANIPULATION

A PubMed search (performed in June, 2008) using the keywords “interstitial cystitis” and “diet” identified 17 articles. Nine English-language articles [245-253] which are mostly focused on dietary manipulation have been summarized with additional 5 articles [49,56,242,254,255] here. Level of evidence: 4 Grade of recommendation: C

No problematic side effects have been reported. Acidic beverages, coffee, spicy food, and alcohol may aggravate the symptoms of most patients with BPS [49,56,242,247]. The symptoms of the majority of BPS patients can be improved by dietary manipulation [242,246,247,249,255]. On the other hand, Nguan et al [256] reported that there was no statistically significant difference in pain and other symptoms, when they evaluated the influence of the changes in urinary pH on the symptoms of 26 patients with BPS by instilling pH5.0 and pH7.5 saline solutions into the bladder.

Although dietary manipulation has no proven scientific basis, it was ranked in the top five frequently used treatments in a cohort study of the Interstitial Cystitis Data Base (ICDB) [251]. As the influence of diet is variable with regard to food, beverage, and patient, there is no reason for patients to be uniformly on a strict diet. It is advised that each patient experiment to find out the foods that tend to aggravate their symptoms and avoid them. The ICA home page, (http://www.ichelp.com/welcome.htm) introduces the foods often avoided by patients with IC.

VIII. ORAL THERAPY

Several categories of medication have been used in the management of patients with bladder pain syndrome including analgesics, antidepressants, antihistamines, immunosuppressants, and glycosaminoglycans. Many of these drugs are used empirically. Only a few of them have been studied in randomized controlled trials and none have a grade A recommendation (Table 4).

1. ANALGESICS

The long-term, appropriate use of pain medications is indispensible in the treatment of bladder pain syndrome. Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents [257] have a place in pain therapy. Patients with more severe symptoms can often be helped with medical pain management using medications commonly used for chronic neuropathic pain syndromes including antidepressants, anticonvulsants, and opioids.

Gabapentin, introduced as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy [258] and postherpetic neuralgia [259]. It demonstrates synergism with morphine in neuropathic pain [260]. Sasaki et al reported that 10 of 21 male and female patients with refractory genitourinary pain had subjective improvement of their pain following treatment with gabapentin [261].

Pregabalin has similar structure as gabapentin and also has been shown to reduce the pain of diabetic neuropathy [262]. Prebabalin was proved effective for treating pain associated with fibromyalgia [263].
Pregabalin might be worthwhile to try for bladder pain syndrome, particularly for those with concurrent fibromyalgia, though studies are lacking.

Opioids are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed [264]. Chronic opioid therapy can be considered as a last resort in selected patients, who have disabling pain and often receive inadequate doses of short-acting pain medications, which put them on cycles of short-term relief, anxiety, and pain.

The major impediment to the proper use of opioids when they are prescribed for long-term nonmalignant pain is the fear of addiction. Some studies suggest the risk is low [265], but not zero [266]. Using opiates is a difficult decision that requires much thought and discussion between patient and urologist, and a pain specialist. They are best administered in a pain clinic setting, requiring frequent reassessment by both patient and physician [267].

In addition to narcotics, concurrent usage of nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, acetaminophen, and tricyclic antidepressants may provide better pain control [268]. The common side effects of opioids include sedation, nausea, mild confusion, and pruritis. These are generally transient and easily managed. Respiratory depression is extremely rare if they are used as prescribed. Constipation is common and a mild laxative is generally necessary. The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

### 2. ANTIDEPRESSANTS

#### a) Amitriptyline

Amitriptyline is a tricyclic antidepressant with the
property of blocking H1-histaminergic receptors [269]. It stabilizes mast cells and inhibits mediator stimulated vascular leakage. It inhibits synaptic reuptake of serotonin and norepinephrine, thus inhibiting painful nociception from the bladder at the level of the central nervous system. Its nighttime sedation can be therapeautic in the BPS population and its purported beta-adrenergic receptor stimulation in the bladder may facilitate urine storage [270].

Using a dose titration of up to 75mg taken before bed, Hanno and Wein reported success in about half of 20 patients who could tolerate the medication. Twenty percent of the initial 25 patients dropped out because of fatigue, weight-gain, or dry mouth. In a follow-up report [271], 18 of 28 patients who could tolerate the drug had major relief of symptoms within 3 to 6 weeks of onset of therapy with a mean follow-up of 14.4 months. However, about one-third of patients initially placed on the drug could not continue on it because of side effects. Kirkemo et. al [272] treated 30 patients and 90% had subjective improvement in 8 weeks. Pranikoff and Constantino [273] reported improvement in 16 of 22 patients with urinary frequency and pain who did not have a diagnosis of interstitial cystitis, noting that 5 of the 22 could not tolerate the drug.

van Ophoven et al performed the only reported prospective, double-blind, placebo-controlled study of amitriptyline. Fifty patients were randomized to placebo or a titrated dose of amitriptyline up to 100mg daily. Forty-two percent of patients initially placed on the drug could not continue on it because of side effects. Wammack et al used the combination of doxepin and piroxicam, a cox-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms [276]. One study reported satisfactory outcome with desipramine [277]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor has also been tried but without therapeutic effects [278].

b) DOXEPIN, DESIPRAMINE, DULOXETINE

Other tricyclic antidepressants that have been used for bladder pain syndrome are doxepin and desipramine. Wammack et al used the combination of doxepin and piroxicam, a cox-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms [276]. One study reported satisfactory outcome with desipramine [277]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor has also been tried but without therapeutic effects [278].

3. ANTIHISTAMINES

Simmons first proposed use of antihistamines in 1955 [279]. His findings of mast cells in the wall of a normal bladder and the edema and increased vascularity seen in the IC bladder suggested that histamine may be responsible for the development of interstitial cystitis. He reported on 6 patients who had some improvement with pyribenzamine for limited periods [280].

a) Hydroxyzine

Hydroxyzine is the most widely used antihistamine for bladder pain syndrome. Its ability as an H-1 receptor antagonist, to inhibit bladder mast cell activation, along with its anticholinergic and anxiolytic properties and good safety profile, have made it a reasonable candidate for use as a therapeutic agent for bladder pain syndrome [281]. In 1933, Theoharides first reported significant benefits of hydroxyzine in reducing pain and urinary symptoms [282]. His two subsequent reports of uncontrolled series further suggested the therapeutic effects of hydroxyzine [283 284]. However, in an NIDDK randomized controlled trial, the global response rate for hydroxyzine was only 31% compared to a 20% response to those not treated with hydroxyzine. When looked at by itself the response was 23% vs. 13% on placebo. None of the results in this under-powered trial reached statistical significance [285].

a) Cimetidine

Cimetidine, a H2 histamine receptor antagonist, has been explored for treatment of bladder pain syndrome. In a pilot study [286], 9 patients were treated with a dose of 300mg orally twice daily for one month. At follow-up 26 to 42 months later, 4 patients had complete relief of urinary symptoms and suprapubic pain. Lewi [287] reported 31 patients given 200mg three times daily with mean followup of 6.6 months. Seventy-one per cent experienced varying degrees of symptomatic relief, 45% were pain free, and 26% went into remission of all symptoms. In a later report [288] of 69 patients treated over a 4 year period, 67% of patients had complete relief of all symptoms. A small, prospective, placebo-controlled RCT studied 36 patients who either received oral cimetidine or placebo [289]. Median suprapubic pain and frequency scores improved significantly, but the publication does not state exactly how many patients in each group improved.

4. IMMUNOSUPPRESSANT

a) Cyclosporine

Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of a novel bladder pain syndrome trial [290]. Eleven patients received cyclosporine for 3-6 months at an initial dose of 2.5-5 mg/kg daily and a maintenance dose of 1.5 to 3mg/kg daily. Micturition frequency decreased, and mean and maximum voided volumes increased significantly. Bladder pain decreased or disappeared in 10 patients. After cessation of treatment, symptoms recurred in the majority of patients.

In a longer-term follow-up study, 20 of 23 refractory IC patients on cyclosporine therapy followed for a mean of 60.8 months became free of bladder pain. Bladder capacity more than doubled. Eleven patients
subsequently stopped therapy, and in 9, symptoms recurred within months, but responded to reinitiating cyclosporine [291]. Sairanen et al further found that cyclosporine A was far superior to sodium pentosanpolysulfate in all clinical outcome parameters measured at 6 months [292]. Patients who responded to cyclosporine A had a significant reduction of urinary levels of epidermal growth factor (EGF) [293].

b) Suplatast Tosilate

Suplatast Tosilate (IPD-1151T) is an immunoregulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce IL-4 and 5. It is used in Japan to treat allergic disorders including asthma, atopic dermatitis, and rhinitis. Ueda et al reported a small study in 14 women with interstitial cystitis [294]. Treatment for one year resulted in a significantly increased bladder capacity and decreased urinary urgency, frequency, and lower abdominal pain in 10 women. Concomitant changes occurred in blood and urine markers suggesting an immune system response. Larger, multicenter, randomized controlled trials in the United States and Japan are planned.

c) Azathioprine and Chloroquine derivatives

In a single report in 1976, Oravisto et al used azathioprine or chloroquine derivatives for BPS patients not responding to other treatments [295]. About 50% patients responded.

5. SODIUM PENTOSANPOLYSULFATE

Sodium pentosanpolysulfate (PPS), a synthetic sulfated polysaccharide, is available in an oral formulation, 3-6% of which is excreted into the urine and theoretically may replenished the damaged glycosaminoglycan (GAG) layer overlying transitional epithelium of the urinary bladder of BPS patients. An intact urothelial GAG layer has been proposed to be essential to keep the urothelium impermeable to urinary components. A defective bladder GAG layer is hypothesized to be one important cause for BPS [296].

PPS’s mechanism of action has been attributed not only to correction of a putative defect in the GAG layer, but also its ability to inhibit histamine release from mast cells, [297] and a possible effect mediated by nonspecific binding of the molecule with the inflammatory stimulants of urothelial activation, an action that would occur in the urine rather than at the mucosal membrane [298].

PPS is the most intensively studied treatment ever proposed for BPS. It is the only medication approved by the Food and Drug Administration for the pain of interstitial cystitis. Parsons initially administered the drug at a dosage of 50mg 4 times daily or 150mg twice daily in an open trial involving 24 patients [299]. Twenty-two of 24 patients experienced a good or excellent response within 8 weeks. In a subsequent randomized, placebo-controlled trial using a dose of 100mg three times daily in 62 patients, pain and urgency improved in 44% vs. a placebo response of 15%. Urgency improved by 38% vs. 18% on placebo. The average number of daily voids was unchanged [300].

Five randomized controlled trials for pentosan polysulfate have yielded conflicting results of efficacy. Holm-bentzen et. al [301] reported the first multicenter double-blind placebo controlled trial in 1987 looking at 115 patients with bladder pain syndrome. Patients were randomized to a dose of 200mg twice daily vs. placebo for 4 months. The results showed no difference between pre and post trial values with regard to symptoms, urodynamic parameters, cystoscopic appearance, or mast cell counts in the two groups. The study concluded that the drug had no clinically significant effect.

The first of two pivotal studies for the FDA was performed in the United States in 1990 [302] A total of 110 patients in 5 medical centers were studied for 3 months on a dosage of 100mg three times daily. Twenty-eight per cent of patients on PPS reported “more than slight improvement” versus 13% of those on placebo. Pain and pressure to urinate were the main parameters to show benefit with PPS.

The FDA asked for a second study which was reported 3 years later [303]. In a multicenter, placebo-controlled RCT 148 patients were randomized to 100mg three times daily of pentosanpolysulfate vs. placebo. In the primary endpoint of patient self-evaluation of global improvement, 32% of those on PPS reported 50% or more overall improvement vs. 16% on placebo at 3 months. Pain, urgency, and pressure showed significant improvement with drug. Frequency, nocturia, and volume voided showed no significant changes between study groups.

The NIDDK performed their own 2 X 2 factorial study to evaluate PPS and hydroxyzine [285]. Each drug was used alone and in combination and compared to a placebo group. Patients were treated for 6 months. There were 121 participants in 7 centers. No statistically significant response to these medications was documented. A non-significant trend was seen in the PPS treatment groups (34%) compared to non-PPS groups (18%). Of the 29 patients on PPS alone, 28% had global response (primary endpoint) of moderately or markedly improved vs. 13% on placebo, very similar in this 6-month study to improvement rates in the 3-month pivotal studies, though not reaching statistical significance in the longer study.

In summary, of 5 RCTs 2 had unfavorable and 3 had favorable results for PPS. Such conflicting results might suggest that a minority of patients do respond to PPS, but currently there is no reliable method to identify such patients.
Long-term, open-label studies with PPS have been reported. Populations of patients receiving extended treatment for up to 90 months or more in the compassionate use program showed no further improvement in symptoms after 1-2 years, though there seemed to be little tachyphylaxis [305,304]. A total of 2809 patients had begun treatment with a 3 month supply of PPS and 21% continued with treatment beyond this point and reordered medication. This seems to correlate with the 28-32% improvement rate previously reported. The dropout rate in the first 6 months was extraordinarily high with only 178 active patients out of 1742 who initially ordered the drug. There was an overall improvement in symptoms in 62% of the patients who did remain in treatment for 6-35 months.

PPS appears to be a very well-tolerated medication [304] with no common central nervous system side effects, and appears to be beneficial with regard to improving the pain associated with interstitial cystitis in up to one-third of patients, a standard often expected with a placebo. A 3-6 month course is required to see an effect in most patients. Claims suggesting greater efficacy and claims urging its use in patients who do not meet the standard definition of bladder pain syndrome should be regarded with caution.

6. OTHER ORAL MEDICATION THAT HAVE BEEN USED FOR BPS

a) L-Arginine

Foster and Weiss were the original proponents of L-arginine in the therapy of interstitial cystitis [305]. Eight patients with IC were given 500mg of L-arginine 3 times daily. After one month, urinary nitric oxide synthase activity increased 8-fold and 7 of the 8 patients noticed improvement in IC symptoms. An open-label study of 11 patients showed improvement in all 10 of the patients who remained on L-arginine for 6 months [306].

An open-label study of 9 women in Sweden failed to find any change in symptom scores or in nitric oxide production in the bladder [307]. A placebo-controlled randomized controlled trial of 53 IC patients could find no difference on an intention to treat analysis between drug and placebo-treated patients [308]. A smaller randomized placebo-controlled crossover trial of 16 IC patients found no clinically significant improvement with L-arginine and concluded that it could not be recommended for IC treatment [309].

Data does not support the use of L-arginine for the relief of symptoms of interstitial cystitis.

b) Quercetin

Quercetin, a bioflavanoid available in many over-the-counter products, may have the anti-inflammatory effects of other members of this class of compounds found in fruits, vegetables, and some spices. Katske et. al [310] administered 500mg twice daily to 22 BPS patients for 4 weeks. All but one patient had some improvement in the O’Leary/Sant symptom and problem scores as well as in a global assessment score. Further studies are necessary to determine efficacy.

c) Antibiotics

Warren et. al [311] randomized 50 patients to receive 18 weeks of placebo or antibiotics including rifampin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for 3 weeks each. Intent to treat analysis demonstrated that 12 of 25 patients in the antibiotic and 6 of 25 patients in the placebo group reported overall improvement while 10 and 5 respectively noticed improvement in pain and urgency. The study was complicated by the fact that 16 of the patients in the antibiotic group underwent new BPS therapy during the study as did 13 of the placebo patients. There was no statistical significance reached. What was statistically significant were adverse events in 80% of participants who received antibiotic compared to 40% in the placebo group. Nausea and/or vomiting and diarrhea were the predominant side effects. Most patients on antibiotics correctly guessed what treatment arm they were in, and those that guessed correctly were significantly more likely to note improvement after the study. No duration in improvement after completion of the trial of antibiotics was reported.

Burkhard et. al [312] reported a 71% success in 103 women presenting with a history of urinary urgency and frequency and chronic urethral and/or pelvic pain often associated with dyspareunia and/or a history of recurrent urinary tract infection. This was a large, inclusive group and one that is probably broader than the bladder pain syndrome we are focusing on. Nevertheless, he recommended empiric doxycycline in this group. The overwhelming majority of BPS patients have been treated with empiric antibiotics prior to diagnosis.

At this time there is no evidence to suggest that antibiotics have a place in the therapy of BPS in the absence of a culture-documented infection [313].

d) Methotrexate

Low dose oral methotrexate significantly improved bladder pain in 4 of 9 women with BPS, but did not change urinary frequency, maximum voided volume, or mean voided volume [314]. No placebo-controlled, RCT has been done with this agent.

e) Montelukast

 Mast cell triggering releases 2 types of proinflamma-tory mediators, including granule stored pre-formed types such as heparin and histamine, and newly syn-
thesized prostaglandins, and leukotriene B4 and C4. Classic antagonists, such as montelukast, zafirlukast and pranlukast, block cysteinyl leukotriene 1 receptors. In a pilot study, [315] 10 women with IC and detrusor mastocytosis received 10mg of montelukast daily for 3 months. Frequency, nocturia, and pain improved dramatically in 8 of the patients. Further study would seem to be warranted, especially in patients with detrusor mastocytosis, defined as > 28 per mm².

e) Nifedipine

The calcium channel antagonist nifedipine inhibits smooth muscle contraction and cell-mediated immunity. In a pilot study, [316] 30mg of an extended release preparation was administered to 10 female patients and titrated to 60mg daily in 4 of the patients who did not get symptom relief. Within 4 months five patients showed at least a 50% decrease in symptom scores, and 3 of the 5 were asymptomatic. No further studies have been reported.

f) Misoprostol

The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 micrograms daily [317]. At 3 months 14 patients were significantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urinary bladder was postulated.

IX. INTRAVESICAL / INTRAMURAL THERAPY (Table 5)

Intravesical therapies form one of the staples of BPS therapy, though regulatory approvals and availability throughout the world differ from nation to nation. What follows are treatments that have been reported in the recent literature, some of which are commonly used. Older therapies that are rarely used now include silver nitrate [44,330-333] and chlorpactin WCS90 [6,334-338]. These have not been included in this current edition of the Consultation, but have level 3 evidence to support a grade C recommendation based on original reports.

1. DMSO (Dimethyl sulfoxide)

Grade of Recommendation: B
Level of evidence 2

• A small number of significant side effects.

Not approved in Japan.

DMSO is believed to reduce inflammation, relax muscles, eliminate pain, dissolve collagen, and degranulate mast cells. It has long been used as a therapeutic agent for BPS. Its mechanism of action, however, has not been clarified. Ten articles on DMSO for the treatment of IC were retrieved. Peekar et al [339] reported that in a randomized study, frequency and pain were improved in ulcer-type IC patients, although no improvement was observed in maximum bladder capacity. Perez-Marrero et al [340] reported that in a non-randomized controlled study, 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%). Around an 80% improvement rate has been reported in case series and retrospective studies [341-348].

With regard to side effects after instillation of DMSO, most patients recognize a garlic-like odor, which disappears within a day, and about 10% of patients report bladder irritative symptoms which resolve with or without symptomatic treatment [349]. It is hypothesized that these transient exacerbations occur as the result of mast cell degranulation. The number of significant side effects is considered to be small [348]. Cataracts have been reported in animal studies, [350,351] though not in humans. Negative effects on bladder compliance have been noted in rat detrusor [352]. DMSO may accelerate the absorption of other drugs instilled simultaneously, which could be a source of side effects.

Table 5. Intravesical therapy for BPS; assessments according to Oxford System

<table>
<thead>
<tr>
<th>Intravesical Agent</th>
<th>Level of Evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Heparin</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
<td>1</td>
<td>D</td>
</tr>
<tr>
<td>Chondroitin Sulfate</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Pentosan Polysulfate</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Capsaicin / Resiniferatoxin</td>
<td>1</td>
<td>-A (ineffective)</td>
</tr>
<tr>
<td>Bacillus Calmette-Guerin (BCG)</td>
<td>1</td>
<td>-A (ineffective)</td>
</tr>
<tr>
<td>Oxybutinin</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Botulinum Toxin</td>
<td>4</td>
<td>D</td>
</tr>
</tbody>
</table>
The instillation method has not been standardized. Generally, 50cc of a solution of medical grade 50% DMSO is instilled into the bladder. If pain occurs immediately following instillation, local anesthesia (e.g. 20ml of 2% lidocaine solution) may be instilled. Average retention time is considered to be 10 to 20 minutes [349]. The instillation is performed weekly for 6-8 weeks. After an initial course, treatment is suspended until symptoms recur. If a good result was obtained, another 6 week course (often followed by monthly maintenance) can be initiated. The long-term effect is unknown, although there is no upper limit for the duration of the treatment. DMSO is medically approved in the US, while it has not been approved yet in Japan.

2. HEPARIN
Grade of Recommendation: C
Level of Evidence: 3

Side effects primarily related to effects intravesical catheterization and slight chance of bladder hemorrhage.

The glycosaminoglycan (GAG) layer on the bladder urothelium is a kind of muco-polysaccharide, working as a non-specific defense mechanism. It is believed that a deficiency or abnormality of GAG secondarily causes inflammation of the bladder by increasing the permeability of the bladder mucosa, leading to the pathologic cascade of BPS. Heparin has similarities to the GAG layer of the bladder. When instilled into the bladder, theoretically it might replace the damaged GAG layer. Kuo [353] reported that the International Prostate Symptom Score, as well as bladder capacity at initial desire to void and maximum bladder capacity, improved significantly. According to the report by Parsons et al [354] symptoms were reduced in 56% of patients treated 3 times weekly for 12 weeks. These reports suggest the efficacy of heparin, however, there is no randomized comparative study to give conclusive evidence. One study indicated that intravesical heparin instillations may prolong the response to dimethyl sulfoxide treatment [355].

No significant side effects have been reported, as it does not affect systemic coagulation parameters. In the case of patients with hematuria, however, it may exacerbate local hemorrhage.

The instillation method has not been standardized. Generally, 10,000-40,000 units of heparin are instilled. It is unusual to have pain or irritation as a result of instillation, and retention times can be 30 minutes or more. Instillation frequency can be up to every other day and is often administered at home by the patient. Parsons et al [356] recently reported that when 40,000 units of heparin combined with 1 to 2% lidocaine was instilled 3 times a week for 2 weeks, about 80% efficacy was obtained. There is no upper limit for the duration of the treatment, but a long-term effect is unknown.

A bleeding tendency may occur. Heparin for intravesical use is not approved by drug regulatory authorities.

3. HYALURONIC ACID
Grade of Recommendation : D
Level of Evidence: 1

- No significant side effects.

Hyaluronic acid, like heparin, is a mucopolysaccharide, that could theoretically repair a damaged GAG layer of the bladder mucosa. Six reports have indicated efficacy [357-362]. In the summer of 2003 Bioniche Life Science Inc http://www.medicalnewstoday.com/articles/112053.php and in the spring of 2004 Seikagaku Corporation reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40mg or 200mg per cc respectively) and neither showed significant efficacy of sodium hyaluronate compared to placebo. These negative studies have not been published in peer reviewed literature. Neither preparation has been approved for use for BPS in the United States. At the same time, no significant side effects were observed.

4. CHONDROITIN SULFATE
Grade of Recommendation: D
Level of Evidence: 4

- No significant side effects.

Chondroitin sulfate is another mucopolysaccharide. Its efficacy was suggested in one article when used alone [363] and in another trial when used in combination with hyaluronic acid [364]. A randomized comparative study has not been reported.

5. PENTOSAN POLYSUFATE
Grade of Recommendation: D
Level of evidence: 4

- No significant side effects are considered to be present.

Pentosan polysulfate (PPS) is a mucopolysaccharide similar to heparin, with a similar postulated mode of action when used locally. Like other mucopolysaccharides, it has not been well-studied clinically. Bade et al in a randomized controlled trial found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo [365]. A more recent placebo-controlled study of 41 patients found the addition of a 6 week course of intravesical PPS to a regimen of oral PPS significantly improved results [366].

6. CAPSAICIN, RESINIFERATOXIN
Grade of Recommendation: -A (ineffective)
Level of Evidence: 1

- Significant side effects: local irritation possible.

It would seem reasonable that capsaicin, a C-fiber
afferent neurotoxin, could alleviate the pain of BPS by desensitizing bladder afferents. Resiniferatoxin (RTX) is considered to have a stronger action than capsaicin, by desensitizing C-fibers more quickly, and causing less initial irritation. Efficacy was indicated in five relatively small clinical trials [367-371]. No severe side effects were reported. A randomized multicenter placebo-controlled clinical trial of RTX failed to demonstrate benefit over placebo [372].

7. BACILLUS CALMETTE-GUERIN (BCG)
Grade of Recommendation: -A (ineffective)
Level of Evidence: 1

• Potential serious complications

Seven articles reported on a BCG instillation therapy. Zeidman et al first reported that 5 patients who did not respond to other therapies showed symptomatic improvement [373]. Peters et al conducted a randomized double blind study showing a 60% improvement compared to 27% [374] placebo response with good long-term results at 27 months [375]. Sixty-five percent of the patients experienced burning sensation, 41% irritation of the bladder, and 35% pelvic pain. One patient was reported to have dropped out due to joint pain.

Peeker et al conducted a randomized double blind study comparing intravesical BCG and DMSO and failed to find any efficacy with BCG [339]. A very large, multicenter randomized placebo controlled trial conducted by the National Institute of Diabetes, Digestive, and Kidney Disorders failed to identify benefit from BCG, although the side-effect profile was surprisingly similar to that of placebo [376].

8. OXYBUTYNIN
Grade of Recommendation: D
Level of Evidence: 4

• Side effect profile is unknown

Barbalias et al observed significant improvement when combining intravesical instillation of oxybutynin with bladder training [377]. Randomized trials are lacking.

9. LIDOCAINE
Grade of Recommendation: C
Level of Evidence: 2

• No significant side effects.

Lidocaine is a local anesthetic that relieves pain by blocking sensory nerves in the bladder. Four articles [378-381] reported on the electromotive drug administration (EDMA) of lidocaine. Using EDM, ionized lidocaine is actively introduced into the bladder using an electrical current. Three articles reported that lidocaine and dexamethasone were instilled following hydrodistention. According to the report by Rosamilia et al [381], 85% of the patients had a good result, with the effect persisting for 6 months in 25%.

There are two other case reports [382,383]. A report on a pharmacokinetic effect, demonstrated safe levels of lidocaine absorption into the bladder [384]. Randomized, placebo-controlled trials are needed to ascertain efficacy, optimal treatment parameters, and length of response to intravesical lidocaine preparations [385]. Advantages seem to be immediate response, low-cost of generic medication, and ability of patients to self-administer at home.

10. BOTULINUM TOXIN
Grade of Recommendation: D
Level of Evidence: 4

• Side effects include dysuria, incomplete bladder emptying

In a study using rats, botulinum toxin inhibited pain response induced by acetic acid and calcitonin gene related peptide release from afferent nerves, which indicates the possibility of relieving pain and other symptoms of BPS [386]. Smith et al observed symptom improvement in 9 of 13 BPS patients treated with 100-200 units of botulinum toxin injected into 20 to 30 sites under general anesthesia [387]. Giannantoni and colleagues [388] noted improvement in 13 of 15 patients at 1 and 3 months after injection of 200units diluted in 20cc injected into the lateral bladder walls and trigone. By the 5 month mark only 26.6% of patients had any benefit, and at 12 months all patients had baseline symptoms. Dysuria occurred in a majority of patients and persisted in a minority for several months after initial injection. Three patients required clean intermittent catheterization for 2-3 months following therapy. Further studies will be needed to obtain conclusive evidence for its efficacy, duration of effect, and side-effect profile.

X. NEUROMODULATION

Level of Evidence: 3
Grade of Recommendation: C

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. As early as 1989, Tanago et al showed that stimulation of S3 may modulate detrusor and urethral sphincter function [389]. FDA approved the usage of sacral neuromodulation for treating refractory detrusor overactivity in 1997 and for urinary urgency and frequency in 1999. Although the effectiveness of SNS for detrusor overactivity is largely confirmed by a good number of papers, only a few papers report the effect of SNS in treating BPS.

Zerman et al reported significant improvement in a 60-year-old woman treated for severe BPS pain using sacral nerve stimulation implant. Pain and accompanying bladder dysfunction were improved by temporary and permanent sacral nerve stimulation for up to six months [390].
Maher et al showed that temporary stimulation was effective in 73% of 15 women with refractory BPS [391]. Mean voided volume during treatment increased and mean daytime frequency, nocturia and pain decreased significantly. As indicated by the Short Urinary Distress Inventory and SF-36 Health Survey, the quality of life parameters of social functioning, bodily pain and general health significantly improved during the stimulation period.

Chai et al found that percutaneous S3 nerve root stimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with BPS [213]. In their report in 2003, Comiter et al prospectively investigated the effect of SNS on a series of 17 patients with refractory BPS. At an average of 14 months follow-up mean daytime frequency, nocturia and mean voided volume improved significantly.

The average pain decreased from 5.8 to 1.6 points on a scale of 0 to 10 and Interstitial Cystitis Symptom and Problem Index scores (ICSI and ICPI) decreased from 16.5 to 6.8 and 14.5 to 5.4, respectively. Of the 17 patients 16 (94%) with a permanent stimulator demonstrated sustained improvement in all parameters at the last postoperative visit [392].

Whitmore et al applied percutaneous sacral nerve root stimulation on 33 patients with refractory interstitial cystitis. Statistically significant improvements were seen in pain and urinary symptoms.

Significant improvements were also seen in ICSI and ICPI scores [393]. Peters et al reported a reduction of narcotic usage in 18 BPS patients following SNS for a mean of 15.4 months, although the dose reduction was modest (36%) and only 4 of 18 discontinued the narcotics [394]. However, Elhilali and colleagues found that both of two patients with interstitial cystitis reported no improvement following sacral neuromodulation [395].

Zabihi et al more extensively stimulate S2-S4 by implanting electrodes into epidural space through sacral hiatus. 23 of 30 (77%) patients had successful trial stimulation and were permanently implanted. Among these patients, the symptom score was improved by 35% (p=0.005). The pain score improved by 40% (p=0.04). Patients reported an average of 42% improvement in their symptoms [396].

Sacral nerve modulation is still considered an investigational procedure for BPS by the Consultation. Its therapeutic benefits appear to be significant in selected cases.

Strict patient selection and detailed discussion with patients prior to surgery is mandatory. Long-term results should be collected and reported, and trial results discussed with patients before employing this treatment modality.

**XI. PAIN EVALUATION AND TREATMENT**

**Level of Evidence:** 4  
**Recommendation:** C

As is evident in the information presented in this section, studies on the use of analgesics for bladder pain syndrome are sparse, and the majority of data is inferred from non-BPS types of pain and expert opinion

Health professionals should ask about pain, and the patient’s self report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales and should document the efficacy of pain relief at regular intervals after starting or changing treatment. Systematic evaluation of the pain involves the following:

- Evaluation of severity
- Detailed history of the pain including assessment of pain intensity and character
- Evaluation of the psychological state of the patient, including assessment of mood and coping responses
- Physical examination emphasizing the neurologic examination
- Diagnostic workup to determine the cause of the pain
- Re-evaluation of therapeutic strategy and response.

The initial evaluation of pain should include a description of the pain, PQRST characteristics serve well for this purpose:

- **P:** Palliative or Provocative factors, ‘what makes it less intense?’
- **Q:** Quality, ‘what is it like?’
- **R:** Radiation, ‘does it spread anywhere else?’
- **S:** Severity, ‘how severe is it?’
- **T:** Temporal factors, ‘is it there all the time, or does it come and go?’

**1. PAIN MEASUREMENT**

A number of different rating scales have been devised to attempt to methodically measure pain and to allow patient follow-up. These have been used in research, audit and in clinical practice. They all rely on a subjective assessment of the pain and therefore make inter-individual comparisons difficult. Additionally, pain is a multidimensional complex phenomenon and is not adequately described by unidimensional scales, however there is value in making some sort of an assessment to aid clinical practice.
• Categorical scales e.g., verbal rating scales: mild, moderate, severe pain
• Visual analogue scale (VAS)
• Complex pain assessment compendiums e.g., Brief Pain Inventory (BPI), McGill Pain Questionnaire [397-399].

The BPI consists of several visual analogue scales grouped together assessing pain at rest, on movement, and other aspects of the pain including interference with function and effect on work.

2. BASICS OF CHRONIC PELVIC PAIN MANAGEMENT

a) Analgesia

1. NON-ACIDIC ANTIPYRETIC ANALGESICS

Paracetamol (acetaminophen) is the main representative of this group. It has antipyretic activity and is a simple analgesic. There is very little evidence about its role in chronic pelvic pain. Further studies need to be considered. Paracetamol should be considered for mild pain.

2. ACIDIC ANTIpyRETIC ANALGESICS

The classical non-steroidal anti-inflammatory drugs (NSAIDs) fall into this group and include salicylic acid. They are known to act on the cyclooxygenase (COX) enzyme. The early NSAIDs tended to have little selectivity for COX2 over COX1, and are therefore said to be associated with more side effects than the newer COX2 selective inhibitors. The COX1 enzyme is mainly involved in normal ‘housekeeping’ functions, such as mediating gastric mucosal integrity, and renal and platelet function. Blocking the COX1 enzyme is the cause of the platelet, gastric and renal complications that can occur with NSAIDs. It has been suggested that the COX2 enzyme is inducible as a result of tissue damage, and that it is the main enzyme involved in inflammation and peripheral sensitization of nociceptors. As a result, the analgesic efficacy of COX2 selective drugs should be as good as that of the nonselective drugs. This, however, has been disputed [402-405]. The selective COX2 agents should be used with caution as an alternative to the non-selective drugs where there is an increased risk of gastric complications. They should be avoided in patients with known cardiovascular disease. NSAIDs should be taken with food and consideration must be given to the use of gastric protective agents. The benefits of the NSAIDs must be demonstrated to outweigh the risks. All NSAIDs are contraindicated in active gastrointestinal ulceration/bleeding and renal disease. They may seriously exacerbate asthma and produce fluid retention. Even if stronger analgesics such as opioids are added, the NSAIDs can be continued as they are likely to have a synergistic action improving pain control above and beyond that obtained with opioids alone [409].

b) Opioids

There is now a general acceptance that opioids have a role in the management of chronic non-malignant pain [410]. The use of opioids in urogenital pain is poorly defined. The following guidelines are suggested by the European Association of Urology [408].

General guidelines for the use of opioids in chronic/non-acute urogenital pain

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient’s family doctor).
3. Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The patient should undergo a trial of opioids [410]
5. The dose required needs to be calculated by careful titration.
6. The patient should be made aware (and possibly give written consent):
   I. that opioids are strong drugs and associated with addiction and dependency
   II. the opioids will normally only be prescribed from one source
III. the drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period

IV. the patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken

V. inappropriate aggressive behaviour associated with demanding the drug will not be accepted

VI. hospital specialist review will normally occur at least once a year

VII. the patient may be requested to attend a psychiatric/psychology review

VIII. failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.

7. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow release/modified release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral dosing is undesirable and should be avoided where possible.

1) Morphine. There is no compelling evidence that one opiate is better than another [410]. Morphine is the traditional gold standard. In an acute situation, the daily morphine requirement may be calculated by titration of the drug with progressively increasing doses of 4-hourly rapid-release morphine. However, in most cases, starting with a low dose of slow-release morphine and confining the increments to occur at intervals of no less than 3 days to 1 week is adequate.

2) Diamorphine is not generally available orally, because of its high first-pass metabolism within the liver. It should not be used routinely for long-term pain because of its high first-pass metabolism within the liver. It should not be used for long-term pain because of its high first-pass metabolism within the liver.

3) A fentanyl patch is used when oral absorption is restricted or when the patient suffers with nausea and vomiting. Patches are generally changed every 72 hours. The problem with the currently available patches is that the dosing increments between patches are large. Care needs to be exercised when increments in dose are undertaken.

4) Methadone is a strong analgesic which has a long track record [411]. It may have a useful role in the management of urogenital pain, though there is very little science to support this. Methadone has the tendency to accumulate with repeated dosing and cause delayed respiratory arrest. Therefore, whereas it may be a very useful drug, it should only be prescribed by a practitioner familiar with its use as an analgesic. Methadone as an analgesic is usually prescribed 6 hourly as its analgesic action is relatively short-lived compared with the longer benefits seen from using the drug in drug addiction.

5) Pethidine 100 mg intramuscular (i.m.) is about as effective as tramadol 100 mg i.m [412] or morphine 10 mg i.m. Its oral bioavailability is, however, poor. Pethidine has a short duration of action and is therefore not an ideal drug for use in chronic/non-acute pain.

6) Other opioids. Oxycodone and hydromorphone are now both available as slow/modification-release preparations. They may be useful for opiate rotation if side effects or tolerance is a problem. They are powerful opioids. Phenazocine is effective in severe pain. It may be administered sublingually if nausea and vomiting are a problem. Buprenorphine and pentazocine both have agonist and antagonist properties and can induce withdrawal symptoms in patients used to opioids. Naloxone may only partly reverse respiratory depression. Buprenorphine topical patches are now available. Codeine and dihydrocodeine are effective for the relief of mild-to-moderate pain. However, dihydrocodeine is a drug that is frequently abused.

7) Opioid-like agents. Tramadol produces analgesia by two mechanisms: an opioid effect; and an enhancement of serotoninergic and adrenergic pathways [413,414]. It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential).

c) Neuropathic analgesics

- Tricyclic antidepressants. Tricyclics have a definite analgesic effect on neuropathic pain compared with placebo [415]: 30% of patients should obtain more than 50% pain relief; 30% will have minor adverse effects; and 4% will have to stop treatment because of side effects. Tricyclics are said to work in doses that are too low to affect mood. They may work by increasing levels of norepinephrine and/or serotonin. They also have actions at sodium channels. They are extensively used for pelvic pain and good evidence exists to justify their usage (see oral therapy) [416,417].

- Serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors appear to be less effective for the management of pelvic pain [418]. Fluoxetine can increase plasma levels of amitriptyline and induce toxicity, and therefore care must be exercised if the drugs are combined.

- Anticonvulsants have been used in the management of pain for many years. Gabapentin and pregabalin have recently been introduced for pain management. There is evidence to show that both compounds are effective in neuropathic pain [419]. There is limited evidence to show that gabapentin is effective in acute pain [420]. Whereas there is little evidence to support the use of anticonvulsants in the management of genitourinary pain, they should be considered if there
is a suggestion of neuropathic pain or central sensitization [421,422].

- **N-methyl-D-aspartate (NMDA) antagonists.** The NMDA receptor channel complex is known to be an important channel for the development and maintenance of chronic pain. It is felt to be particularly important when there is evidence of central sensitization and opioid tolerance [423]. Ketamine has been used as a general anaesthetic for over 30 years. It has also been used as an intravenous analgesic in burn units, and accident and emergency units. Ketamine is thought to act primarily at the NMDA receptor, though it may also have actions at sodium channels, as well as opioid (kappa and mu) receptors [424]. Ketamine has been shown in both human and animal models of neuropathic pain to reduce central sensitization and wind-up [424-426]. These phenomena alter signal transmission within the nervous system so that non-painful stimuli may become painful (allodynia) and pain from a painful stimulus is magnified (hyperalgesia). Ketamine has been found to be useful in a number of chronic pain states including: peripheral neuropathies with allodynia, stump and phantom pain, central pain, and cancer-related pain with and without a neurological component [427]. Difficult urogenital pains may therefore be helped by ketamine if there is evidence of nerve injury or central sensitization [428-431]. Ketamine may be useful in opioid-resistant pain in which it may restore the opioid dose-response curve towards normal [428,432]. Oral ketamine has a bioavailability of about 17%. A test dose given by intravenous infusion is a quick way of establishing whether oral ketamine may be viable. Ketamine is a street drug of addiction and great care must be exercised if a patient is to be managed at home on parenteral ketamine. Ketamine should only be used by an experienced practitioner trained in its use.

### XII. SURGICAL THERAPY

**Bladder Pain Syndrome (BPS) is a chronic and debilitating disease. Major surgical options should be considered only when all conservative treatment has failed.** The patient should be informed of all aspects of surgery and understand consequences and potential side effects of surgical intervention. An experienced surgeon familiar with the particular surgical technique should perform the procedure.

#### 1. HYDRODISTENTION

Bladder distention has been used for many years [433] not only as a diagnostic/ classification tool but also for treatment of BPS. In 1957 Franksson reported on a retrospective series of 33 patients, with symptom improvement in all, and lasting up to 1 year in 7 patients [434]. Reports from the seventies were contradictory. Using the Helmstein method [435], Dunn reported complete absence of symptoms in 16 of 25 patients [436], while Badenoch found no improvement in 44 of 56 patients [437]. More recent literature reports poor results with only a minority of patients reporting a small improvement in symptoms for a relatively short period of time [203,204,215,438]. Most studies are retrospective and uncontrolled. **Level of evidence 3; recommendation C**

#### 2. TRANSURETHRAL RESSECTION

In his first papers Hunner described open resection of the bladder ulcer in the treatment of patients with IC[4]. He later abandoned this treatment due to operative morbidity and recurrence of symptoms. Results of transurethral resection were originally reported by Greenberg et al. [439] and Fall [440]. The retrospective results of this treatment in 116 patients with Hunner’s lesion from Fall’s Swedish clinic was later reported by Peek et al [441]. Hunner’s lesion was first recognized by bladder distension under general anesthesia. All lesions were then resected including at least half of the underlying muscular coat. Large areas of the bladder might be treated to resect all diseased tissue. Ninety-two of the 116 patients experienced amelioration of their symptoms. Average duration of symptom alleviation was 23 months ranging from 0-180 months. Up to 16 re-resections were performed if symptoms recurred. This is the only center having reported a large clinical series of patients with BPS treated in this manner. Shanberg and Malloy reported in 1987 on laser fulguration of 39 patients with BPS [442]. Nineteen of 39 had Hunner’s lesion. Of the 19 patients with Hunner’s lesion 17 reported good pain relief lasting between 6 and 18 months. In the 20 patients without Hunner’s lesion, reddened areas in the bladder were photoagulated with the Neodymium:Yag laser.

Thirteen felt marked improvement of symptoms but time to symptom recurrence was not reported. Small bowel perforation in 2 patients was the most important complication in this series. This series was extended to 76 patients [443] where 21 of 27 patients with Hunner’s lesion (BPS ESSIC type 3X) experienced symptom improvement; 12 had relapse within 18 months. Of patients with BPS ESSIC type 1 or 2, 20 of 49 improved but 10 required further therapy within 1 year. Rofeim et al [444], reported on Nd:YAG laser ablation of Hunner’s lesion in 24 patients with BPS type 3X. All had symptom improvement within days without complications. Pain, urgency, nocturia, and frequency were improved after 23 months, but relapse in 11 patients required up to four additional treatments. **Transurethral resection, coagulation, or laser ablation of Hunner’s lesions is a recommended treatment for patients with BPS type 3X.** **Level of Evidence: 3** **Grade of Recommendation: C**
3. CYSTOLYSIS – PERIPHERAL DENERVATION

Hunner [4] simply dissected bladder from surrounding tissue. Initial results were encouraging, however after 3 years of follow-up, symptoms recurred. Worth and Turner-Warwick [445] attempted to do more formal cystolysis and were more successful with regard to symptoms. Worth [446] followed patients up to 7 years and found bladder areflexia to be a significant complication of this procedure. Patients had to use Credé technique or even be on intermittent self-catheterisation. Albers & Geyer [447] reported symptom recurrence after 4 years in most of the patients.

- Cystolysis – peripheral denervation is not indicated for BPS; Level of Evidence: 3 Grade of Recommendation: -A (not recommended)

4. SYMPATHETIC DENERVATION

Visceral pain is transmitted in most cases by the sympathetic nervous system. Gino Pieri [448] applied this principle to the bladder pathology and suggested resection of the superior hypogastric plexus (presacral nerves), paravertebral sympathetic chain, and gray rami from S1-3 ganglia (Level 4). This was repeated by Douglass [449] a few years later. Immediate results were very good; however Nesbit [450] showed that the long term results were short lived.

- Sympathetic denervation is not indicated for BPS
  Level of Evidence: 4
  Grade of Recommendation: -A (not recommended)

5. PARASYMPATHETIC DENERVATION

Based on the contribution of S2-S4 segments to bladder innervation, Moulder and Meirowsky [451] used S3 neurectomy in 3 patients with good long term follow-up. Larger series were reported by Milner [452] and Mason [453] but results after five years were not encouraging. To improve results selective dorsal sacral root neurectomy, unilateral or bilateral, was introduced encouraging. To improve results selective dorsal sacral root neurectomy, unilateral or bilateral, was introduced by Douglass [449] a few years later. Immediate results were very good; however Nesbit [450] showed that the long term results were short lived.

- Parasympathetic denervation is not indicated for BPS
  Level of Evidence: 4
  Grade of Recommendation: -A (not recommended)

6. BOWEL SURGERY

a) Bladder augmentation-cystoplasty has been commonly used for refractory BPS for 50 years. First reports of ileocystoplasty from 1958 were very promising [455]. Later publications were less sanguine with good results varying from up to 100% 456,457 to 25% [458,459]. Cystoplasty is usually done with or without bladder resection.

Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken [460], advocating augmentation with removal of the diseased tissue. Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy [457,461-463]. These were all retrospective studies and conclusions should be taken with reservation. Cystoplasty with partial or total removal of the bladder requires bowel tissue substitution. Different bowel segments are used to enlarge the bladder. It is the general consensus that the intestine segment used for bladder augmentation should be detubularized [464]. Experiences with different bowel segments have been reported in numerous articles with level 4 evidence:

- ileum [456-458,463,465-469]
- ileocecum [330,457,459,461,470,471]
- cecum [456,472,472]
- right colon [457,458,473]
- sigmoid colon [461,463,466,470]
- gastric segments [474,475]

There is no significant different between different bowels segments with regard to outcome except for gastric tissue substitution which is associated dysuria and persistent pain due to production of acids

b) Cystoplasty with Supratrigonal Resection

(i.e. trigone-sparing) has been reported in various studies. Von Garrelts [456] described excellent results in eight of 13 patients with a follow-up of 12-72 months. Bruce et. al [463] reported satisfactory relief of BPS symptoms by ileocystoplasty and colocystoplasty in eight patients. Dounis and Gow [476] reported improvement in pain and frequency in seven BPS patients after supratrigonal cystectomy with ileocecal augmentation. Kontturi et. al [461] used segments of colon and sigmoid colon in 12 cases with 100% symptom-free outcome in five patients augmented with sigmoid colon over 4.7 years of follow-up. Two of seven cases augmented with colon required ileal conduit and cystectomy. Linn et. al [477] followed six BPS patients for 30 months, and reported that all were symptom-free and voided spontaneously. The report by Nielsen et. al [459] was less favorable. Six out of eight patients had good results. Van Ophoven et. al [478] reported the long-term (mean 5 years) results of orthotopic substitution enteroplasty in 18 women with BPS, using ileocecal (n = 10) or ileal (n = 8) segments with only two failures. In the group [479] augmented with ileum, three patients required self-catheterization and one a suprapubic catheter. Peeker et. al [480] found that patients with end-stage ulcerative BPS had excellent results following ileocystoplasty but not so the patients with non-ulcer disease. A follow up on this paper was recently published [171] with the same conclusion for the
patients with end stage BPS ESSIC type 3C, while both continent diversion and iliocystoplasty were unrewarding in patients with type 2X BPS. Patients with low cystoscopic capacity (<200 ml) under general anaesthetic have achieved better results [6, 21, 481,482].

**c) Cystoplasty with Subtrigonal Cystectomy** — orthotopic continent bladder augmentation (i.e. with trigone removal but preservation of the bladder neck) in the management of BPS has been reported less often [479,483-485]. Because of the need of ureteral reimplantation, it is associated with some risks of urine leakage, urethral stricture and reflux [484]. Linn et. al [477] had three failures in 17 patients and half of the patients with good symptomatic response required self catheterization. Nielsen et. al [459] had better results following orthotopic substitution with low bladder capacity (200 mL versus 525 mL, respectively). Orthotopic continent bladder augmentation, particularly when removing the trigone, may cause incomplete voiding requiring intermittent self catheterization. Therefore patients considering such procedures should be advised accordingly and must be considered capable of performing, accepting and tolerating self catheterization. Nurse suggested that the decision on whether to due a subtrigonal or supratrigonal cystectomy be based on the results of trigonal biopsy, with the former procedure indicated in the patient with trigonal inflammation [486].

There is no compelling evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy but it tends to be associated with more complications and poorer functional bladder rehabilitation. Level of evidence: 3; Grade of Recommendation: C

**d) Urinary Diversion with or without Total Cystectomy and Urethrectomy**

This is the ultimate, final and most invasive option. It should be used as a last therapeutic resort in selected patients. Techniques include simple or continent urinary diversion. Continent diversion may be preferable for cosmetic reasons in younger patients.

Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for BPS/IC [487]. Initially, diversion can be done without cystectomy and only when bladder pain is persistent, cystectomy may be considered. Bladder de-functionalization alone produced symptom-relief in several reports [6,21,458,488,488,489]. Often diversion is performed as a next step after unsuccessful bladder augmentation. To avoid further bowel resection, a bowel segment used for cystoplasty can often be converted to a conduit [490]. In some patients chronic inflammatory changes have been seen in the cystoplasty pouch resembling interstitial cystitis [6,458,491,492], preventing one from using this technique. Similar bowel changes however have been described when cystoplasty is performed for pathology other than interstitial cystitis, suggesting that these pathologic findings are not a direct result of the exposure of bowel to BPS urine [493]. Relatively good responses to diversion with or without cystectomy have been reported in small series [459,494].

Urinary diversion with and without cystectomy may be the ultimate option for refractory patients. Continent diversion may have better cosmetic and life style outcome but recurrence of pain in the pouch is a real possibility. Level of Evidence: 3; Grade of Recommendation: C

**XIII. CLINICAL SYMPTOM SCALES**

Symptom scales have enabled patients to be categorized by symptom severity and have also served to follow results of treatment in patients with bladder pain syndrome. Their future development may enable a presumptive diagnosis of the syndrome but at this time that is not possible. A brief survey that reliably segregates BPS from other urologic disorders would make the ability to diagnose the syndrome reliable, inexpensive, and available to all healthcare providers. It would aid in epidemiologic studies as well. Currently such work sponsored by NIDDK is ongoing (http://www.niddk.nih.gov/fund/other/niddkfrontiers/frontiers%20PBS%20Summary%20Report.pdf). The goals of the RAND Interstitial Cystitis Epidemiology (RICE) study are to: (1) develop a case definition for IC in women for patient screening and epidemiological studies; (2) develop and validate a symptom questionnaire to identify female IC patients through self-report; (3) develop IC specific self-report measures of functional status and disease burden; (4) conduct first and second stage screening for IC; and (5) describe the impact of IC on quality of life compared to other disease.

A process for development of a case definition for IC has been developed by adapting the RAND/University of California, Los Angeles Appropriateness Method. This involves a panel consisting of nine experts with experience in BPS and related diseases, literature review of case definitions of BPS, initial ratings of symptoms as indicators of the BPS diagnosis, and discussion and a second set of ratings to establish criteria for diagnosis through patient reports. Symptom questionnaire development, based on the results of the case definition exercise, and validation are the following steps to identify populations of women with
symptoms of BPS who do or do not meet NIDDK criteria, which allows determination of the specificity and sensitivity of the case definition for use in population screening.

Questionnaires and symptom scales are currently utilized to measure treatment outcome and are especially valuable in clinical research studies as well as for guiding therapy for individual patients.

There are 3 published BPS symptom questionnaires: the University of Wisconsin IC Scale (figure 5), the O'Leary-Sant IC Symptom Index (ICSI) and IC Problem Index (ICPI) (figure 6), and the Pelvic Pain and Urgency/Frequency (PUF) Scale (figure 7).

1. The University of Wisconsin IC Scale includes 7 BPS symptom items and has not been validated for identification or diagnosis of BPS. It captures severity of symptom expression [495,496]. Unlike the other two instruments, it addresses some quality-of-life issues, and this is an advantage when such issues are subject of investigation. Its most attractive aspects are its clinically apparent face validity and its ease of implementation.

2. The O'Leary-Sant indexes are validated questionnaires that were originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to BPS patients and asymptomatic controls [497,498]. The questionnaires center on 3 questions related to urgency/frequency and one on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. This is not because these questions were not considered in the formulation of the questionnaire.

Of 73 questions in the preliminary instrument covering domains of urinary symptoms, pain, sexual function, menstrual variability, and general health, only the four questions now in the instrument were needed to reliably and validly describe the illness experience of those with IC and distinguish these patients from those without the disorder [499].

3. The most recently published instrument is the Pelvic Pain, Urgency, Frequency (PUF) questionnaire [189].

It was specifically designed to include questions that directly reflect a wide variety of the symptoms experienced by patients who are affected by this disorder. One-third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum. A large study utilizing the PUF questionnaire has concluded that up to 23% of American females have BPS [189]. This makes one wary as to the utility and face-validity of the PUF [500]. A total score of 10-14 =74% likelihood of positive potassium test (PST); 15-19=76%; 20+=91%. To the extent that the PST is suspect, the reliability of PUF data comes into question.

4. Discussion

Neither the PUF nor O'Leary Sant questionnaires have been shown to be of value in diagnosis of the individual patient [501]. In an interesting epidemiologic study in Finland, Leppilahni and colleagues randomly selected 2000 participants from the Finnish population registry and administered the O'Leary Sant IC symptom and problem index [64]. Women with symptom scores 7 or higher with no history of urinary tract infection in the preceding month were invited to undergo clinical examination. Of these 32 women, 21 underwent examination of whom 3 had probable interstitial cystitis and 4 had possible interstitial cystitis. Based on this specificity, a population prevalence in Finnish women of 230/100,000 probable interstitial cystitis and 530/100,000 possible interstitial cystitis was calculated. Thus, one can get some idea as to O'Leary Sant specificity. For probable BPS it would be about 14% using a parameter of 7 or greater on the symptom index.

The O'Leary-Sant and University of Wisconsin instrument correlate strongly in a large population of patients with BPS [502]. Clemons and co-workers administered the ICSI to 45 patients scheduled to undergo laparoscopy for pelvic pain. Seventeen were diagnosed with BPS based on the finding of glomerulations on bladder distention associated with urgency, frequency, or nocturia. A score of 5 on the ICSI had a 94% sensitivity and a 93% negative predictive value in this enriched population of patients with pelvic pain [503]. However, Clemons and colleagues have found a high degree of overlap in International Prostate Symptom Scores, the O'Leary Sant Symptom Index, and the Chronic Prostatitis Symptom Index in a random sample of over 1400 men and women with urologic symptoms, underscoring that we should be cautious in using these questionnaires as a basis for diagnosis in epidemiologic studies [504].

Rosenberg and Hazzard [67] surveyed 1218 consecutive patients presenting to their primary care office and found 7 (0.6%) who had a 7 ICSI score. Likely BPS was noted in 12.6% of patients on the PUF scale, a figure 21 times higher, suggesting that either the PUF drastically overestimates BPS, or the ICSI lacks sensitivity. Based on the correlation of the potassium sensitivity test and the PUF questionnaire, Parsons [54] stated that 30.6% of 3rd year female medical students at his California institution had probable BPS. Sahinkanat and coworkers [190] in Turkey administered the PUF questionnaire to all 442 female textile workers in two local factories. Eighty-six per cent of those with a PUF score 7 or greater had an 86% positive rate of PST testing versus 9% positive in the group with PUF less than 7. They extrapolated that bladder epithelial permeability dysfunction was present in 32.8% of these unselected women. The ICSI estimate seems much more in line with current epidemiologic data.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score each symptom from 1-6 (0=not at all) (6=a lot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bladder discomfort</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>2. Bladder pain</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>3. Other pelvic discomfort</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>4. Headache</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>5. Backache</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>6. Dizziness</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>7. Feelings of suffocation</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>8. Chest pain</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>9. Ringing in ears</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>10. Getting up at night to go to the bathroom</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>11. Aches in joints</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>12. Swollen ankles</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>13. Nasal congestion</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>14. Flu</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>15. Abdominal cramps</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>16. Numbness or tingling in fingers or toes</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>17. Nausea</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>18. Going to the bathroom frequently during the day</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>19. Blind spots or blurred vision</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>20. Heart pounding</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>21. Difficulty sleeping because of bladder symptoms</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>22. Sore throat</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>23. Urgency to urinate</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>24. Coughing</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>25. Burning sensation in bladder</td>
<td>0 1 2 3 4 5</td>
</tr>
</tbody>
</table>

*Figure 5: University of Wisconsin Symptom Instrument (J. Urol. 173:835-840, 2005)*
**IC SYMPTOM INDEX**

During the past month …

Q1. … how often have you felt the strong need to urinate with little or no warning?
   0. Not at all
   1. Less than 1 time in 5
   2. Less than half the time
   3. About half the time
   4. More than half the time
   5. Almost always

Q2. … how often have you had to urinate less than 2 hours after you finished urinating?
   0. Not at all
   1. Less than 1 time in 5
   2. Less than half the time
   3. About half the time
   4. More than half the time
   5. Almost always

Q3. … how often did you most typically get up at night to urinate?
   0. Not at all
   2. A few times
   3. Almost always
   4. Fairly often
   5. Usually

Q4. … have you experienced pain or burning in your bladder?
   0. Not at all
   2. A few times
   3. Almost always
   4. Fairly often
   5. Usually

Add the numerical values of the checked entries.
Total Score: ___

---

**IC PROBLEM INDEX**

During the past month how much has each of the following been a problem for you:

Q1. Frequent urination during the day?
   0. No problem
   1. Very small problem
   2. Small problem
   3. Medium problem
   4. Big problem

Q2. Getting up at night to urinate?
   0. No problem
   1. Very small problem
   2. Small problem
   3. Medium problem
   4. Big problem

Q3. Need to urinate with little warning?
   0. No problem
   1. Very small problem
   2. Small problem
   3. Medium problem
   4. Big problem

Q4. Burning, pain, discomfort, or pressure in your bladder?
   0. No problem
   1. Very small problem
   2. Small problem
   3. Medium problem
   4. Big problem

Add the numerical values of the checked entries.
Total score: ___

---

*Figure 6: O’Leary Sant Symptom and Problem Indexes*
While perhaps not ideally suited for epidemiologic studies, these questionnaires can reveal important epidemiologic data. Porru and colleagues [505 compared University of Wisconsin scores including both urinary and non-urinary symptoms, for 30 BPS female patients and 30 female controls. While the IC group had significantly higher scores for the urinary symptoms, they did not appear to indiscriminately report higher scores than controls for different somatic and general complaints, as might be expected if this disease is a manifestation of a more generalized disorder. Diggs and colleagues [506] used the ICSI to investigate how interstitial cystitis patients interpret urgency. The ICSI question regarding: “the strong need to urinate with little or no warning” consistently underestimated the response to the International Continence Society definition of urgency: “the compelling urge to urinate that is difficult to postpone.

Treatment outcome studies have also used the Global Response Assessment (figure 8): a balanced patient self-report on overall response to therapy, developed for NIDDK sponsored multicenter therapeutic trials [285]. The O’Leary Sant and University of Wisconsin questionnaires are responsive to change over time in patients with BPS and have been recommended as secondary endpoints in future clinical trials of the disorder. Propert and colleagues in the Interstitial Cystitis Clinical Trials Group determined that a 1.2 point change in the O’Leary Sant indexes and a 3.1 point change in Wisconsin IC inventory corresponded to a one-category change in the GRA. Individual symptoms were also responsive [507].

Figure 7: Pelvic Pain, Urgency, Frequency Scale

Figure 8: Global Response Assessment (GRA)

1. THE PROBLEM

BPS/IC has been a difficult condition for which to assess therapeutic impact. There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months [58]. A somewhat surprising finding from the Interstitial Cystitis Database was that although there was initial improvement in symptoms partially due to regression to the mean [508] and the intervention effect, there was no evidence of a long-term change in average symptom severity over the four year course of follow-up [71]. In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, patients are desperate and often seem to respond to any new therapy. A
skeptical view of outcomes is essential (figure 9), as patients can be victims of unorthodox health care providers using unproven forms of therapy, some medical, some homeopathic, and some even surgical.

2. THE PLACEBO ISSUE

Where possible, the results of randomized controlled studies should be used for decision making. Placebo, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy.

Placebo effects influence patient outcomes after any treatment which the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects [71,509-511]. Unfortunately, few BPS treatments have been subjected to a placebo-controlled trial. This is not to say that what seems effective is not, but rather that a high index of skepticism is healthy, even in treatments tested in controlled trials [512].

While in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value [513], a good case for true placebo comparison can readily be made for BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that it is not life threatening, mean that there is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (though generally unproved) therapies. It has long been recognized in protocols that use subjective criteria for assessment that "improvement" may be expected in up to 35% of placebo-treated patients [514]. As the spontaneous remission rate (though temporary) for BPS is 11% [295] to 50% [58], combined with the placebo improvement it can be difficult to prove efficacy.

Even in placebo controlled trials, it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over placebo [515,516]. Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials [517]. When occurring late in a study after one would expect onset of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in BPS and any disorder where primary outcomes may be subject to patient-specific psychological and physiological factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also where delay in treatment has been shown to result in disease progression [518-520]. However, there are methodological concerns with equivalence and non-inferiority active agent comparison trials [521]. These include an inability to determine if the treatments are equally good or equally bad, and the possibility that successive non-inferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied [522].

The value of placebo-controlled trials is aptly illustrated by the recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for BPS [523,524] after placebo-controlled trials failed to establish efficacy. These include low concentration hyaluronic acid (Bioniche, Canada), high concentration hyaluronic acid (SKK, Tokyo), and resiniferatoxin (iCOS, Bothell, Washington, USA). Nalmefene, an initially promising oral therapy in the 1990's, [326] also failed phase 3 trials (iVAX, Miami). Placebo trials are impractical in surgery and it can be difficult to evaluate surgical reports. The many older medications currently used off-label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off-label often requires dependence on the largesse of government agencies like the National Institute of Health [285,376,525].

2. OUTCOME INTERPRETATION

As has been discussed with regard to rheumatologic disorders [526], the interpretation of measurements of physical functioning in clinical trials should consider the composition of the study sample, with attention to the stage of disease and the heterogeneity in disease duration. Patients with long-standing disease or compromised bladder capacity or central sensitization can be expected to be less responsive to treatments directed toward the bladder itself. Finally, when considering objective changes, the concept of statistical versus clinical significance is paramount. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement [527]. As Gertrude Stein reportedly stated, "A difference, to be a difference, must make a difference". An increase in bladder capacity of 30cc may be statistically significant but clinically irrelevant. Number needed to treat and number needed to harm data [528] may be particularly important in BPS and have not typically been included in efficacy analysis.
Figure 9: Selected reported treatment outcomes in uncontrolled studies in IC literature: Percentage of patients initially improved.
3. IMMPACT RECOMMENDATIONS

The core outcome domains for chronic pain clinical trials have been published [399,529]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations indicate that core outcome domains should be considered in all clinical trials of the efficacy and effectiveness of treatments for chronic pain. These domains include:
1. Pain
2. Physical functioning
3. Emotional functioning
4. Participant ratings of improvement and satisfaction with treatment
5. Symptoms and adverse effects, participant disposition

CONCLUSIONS

Currently for BPS/IC there are no accepted biologic disease markers that can be used for the assessment of response to therapy. The O’Leary Sant, University of Wisconsin, and Global Response Assessment are well-validated questionnaires to follow disease progression and response to therapy. The IMMPACT recommen-dations suggest that as well as symptoms scores, any future study on a pain syndrome must involve more general assessments of psycho-physical functioning. There is limited experience in BPS/IC for the use of well-validated measures available for the study of chronic pain. Future NIDDK research initiatives may help to rectify this. http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-07-003.html http://www.nih.gov/news/health/sep 2008/ niddk-05.htm.

International recognition of an agreed upon definition and inclusion and exclusion criteria of BPS/IC will help future studies to fulfill the highest standards available, and placebo-controlled, double-blind, randomized controlled trials, where possible, will provide the highest level of evidence to move the field forward.

XV. PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline. Different groups of “experts” would undoubtedly create different “best practices”. The compromise approach devised by an experienced cross-section of urologists and gynecologists from around the world at the International Consultation on Continence 2004 meeting in Monaco [38] has been reviewed and updated by the committee and allows for significant latitude to reflect varying individual practice patterns and to account for patient preference.

An underlying principle is that, where possible, treatment decisions of bladder pain syndrome should be evidence based. Unfortunately, high level evidence of efficacy is lacking for many common treatments, either because such studies have not been done, or were done and failed to demonstrate efficacy [530,531]. The previous Consultation reported that only oral amitriptyline and intravesical dimethyl sulfoxide had supporting evidence to have a B level of recommend-ation in the Oxford system [38]. A subsequent review by Karsenty and colleagues added oral cimetidine to that list [532].

Another principle is that we should be guided by patient perceived and driven outcomes for bladder pain syndrome, which is, after all, diagnosed on the basis of symptoms after exclusion of confusable diseases. Many patients prefer noninvasive therapies [533], and it would seem reasonable to start with oral therapies if conservative non-medical interventions fail to result in significant symptom amelioration. Use of surgical therapies should be approached with some caution. Ingber and coworkers reported that women with BPS have significantly more pelvic surgeries than controls, and the majority were performed prior to diagnosis of BPS, possibly for pain related to undiagnosed BPS [534].

1. HISTORY / INITIAL ASSESSMENT

Men or women with an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes [535] should be evaluated for bladder pain syndrome. The initial assessment consists of a frequency/volume chart, focused physical exam, urinalysis, and urine culture. Cytology and cystoscopy are recommended if clinically indicated.

Patients with infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and/or hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with BPS.

2. INITIAL TREATMENT

Patient education and support, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial management of BPS. It is important to address the patient’s pain, and understand that at some point in the progression of treatment, referral to a pain specialty clinic may be desirable.

When the conservative approach fails, or symptoms are severe and conservative mana-gement unlikely to succeed, oral medication, physical therapy, and/or intravesical treatment can be prescribed.
3. SECONDARY ASSESSMENT

If oral or intravesical therapy fails, or before beginning such therapy at the discretion of the clinician, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia. Laparoscopy may be indicated if there is a suspicion of gynecologic disease. Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner’s lesion suggest therapy with transurethral fulguration or resection of the ulcer. Distention itself can have therapeutic benefit in up to one-third of patients, though benefits rarely persist for longer than a few months.

4. REFRACTORY PBS/IC

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities, generally in the context of clinical trials. These might include neuromodulation, intravesical botulinum toxin, and/or experimental pharmacologic protocols of promising new treatments. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urine stream. Augmentation (substitution) cystoplasty and urinary diversion with or without cystectomy have been used with good results in very well selected patients.

It is the opinion of the committee that, because of the natural history of the disorder, it is best to cautiously progress through a variety of treatments. Whereas the shotgun approach, starting newly diagnosed patients on a variety of simultaneous medications, seems to have many adherents, employing one treatment at a time makes the natural history of the disease itself an ally in the treatment process. If a treatment has no efficacy, it should be stopped. It a treatment results in modest improvement, it should be continued and another treatment option employed in an attempt to further improve symptoms. The goal is to maximize quality of life and dispense with ineffective treatments in a somewhat controlled fashion. The patient and clinician must remember that “perfect is the enemy of good” and expectations should be realistic. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore, patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare. Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient. Level 4 Grade C

XVI. FUTURE DIRECTIONS IN RESEARCH

There are five major recommendations for future directions in research on BPS that the committee believes will lead to a greater understanding of the condition and will have a major impact on its management.

1. EPIDEMIOLOGICAL STUDY

1. Develop a reliable screening tool with adequate sensitivity and specificity to conduct epidemiologic research in the general population to study the incidence, prevalence and identify risk factors for the development of BPS.

2. Establish patient data bases in different regions and conduct longitudinal follow up to understand the natural history of the disease and to examine the differences in disease natural history among regions.

2. SUB-GROUPING/PHENOTYPING PATIENTS

Patients who have or develop additional pain syndromes, such as vulvodynia, temporomandibular disorder, irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome, or autoimmune diseases such as lupus erythematosus and Sjögren’s syndrome might have different pathophysiology, natural history and treatment response from those patients without co-morbidities. Sub-grouping patients not only allows us to develop better treatment strategy but also may answer the question: Is BPS an end-organ disease of the bladder or a systemic condition? However, to properly phenotype patients, it is necessary to develop an easy-to-use tool for non-specialists to identify those with co-morbidities. It is also important to validate the concept that categorizes all types of pelvic pain into one “chronic urological pelvic pain syndrome”, as some patients’ symptoms involve multiple pelvic organs, concurrently or sequentially along with other body systems.

3. DEVELOPING A SIMPLE, NON-INVASIVE DIAGNOSTIC TEST FOR BPS

This will most likely involve urinary markers. Urinary markers may help to sub-classify various types of BPS. This test will determine the diagnosis of BPS in the female population, as well as determine the subset of men currently diagnosed with non-bacterial chronic prostatitis/chronic pelvic pain syndrome who may actually have BPS.

4. COMPREHENSIVE STUDY ON HYDRODISTENTION

Hydrodistention is still a popular practice in many places around the world simply due to the limited effective therapeutic armamentarium that can be
offered to the patients. It is necessary to standardize the technique and conduct international cooperative studies to verify the true value of this treatment modality. Some important information can be gathered from these studies, such as identifying the patient variables that lead to a good therapeutic response.

5. DEVELOP A PRACTICAL MULTI-DISCIPLINARY CARE MODEL

In addition to physical morbidities (urinary frequency, pain), many BPS patients have associated psychological co-morbidities [537]. These can often be managed by psychological intervention. BPS patients also need help from dietitians and physiotherapists. A practical multi-disciplinary care model, which includes physicians, dietitians, physiotherapists, pain specialists, psychologists, psychiatrists and patient support groups, should be developed and tested in various settings.

XVII. SUMMARY (figure 10)

1. DEFINITION

Bladder Pain Syndrome (in the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis –ESSIC definition is given along with a slight modification made at a recent international meeting held by the Society for Urodynamics and Female Urology – SUFU

ESSIC: Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.

Consensus Definition from SUFU International Conference (Asia, Europe, North America) held in Miami, Florida February 2008: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.

2. BLADDER PAIN SYNDROME (BPS)

a) Nomenclature (Figure 11)

The scientific committee of the International Consultation voted to use the term “bladder pain syndrome” for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome. Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP), and focuses on the actual symptom complex rather than what appears to be long-held misconception of the underlying pathology.

b) History / Initial Assessment

Males or females with pain, pressure, or discomfort that they perceive to be related to the bladder with at least one urinary symptom, such as frequency not obviously related to high fluid intake, or a persistent urge to void should be evaluated for possible bladder pain syndrome. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

The initial assessment consists of a frequency/volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology and cystoscopy are recommended if clinically indicated. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS. Grade of recommendation: C

c) Initial Treatment

Patient education, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial treatment of BPS. The treatment of pain needs to be addressed directly, and in some instances referral to an anesthesia/pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome. When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed, oral medication, intravesical treatment, or physical therapy can be prescribed. It is recommended to initiate a single form of therapy and observe results, adding another modality or substituting another modality as indicated by degree of response or lack of response to treatment. Excellence can be the enemy of good. Grade of recommendation: C

d) Secondary Assessment

If initial oral or intravesical therapy fails, or before beginning such therapy, it is reasonable to consider further evaluation which can include Urodynamics, pelvic imaging, and cystoscopy with bladder distention...
**Bladder Pain Syndrome**

**Symptoms**
- Pain, pressure, or discomfort perceived to be related to the bladder with at least one other urinary symptom (e.g., frequency, nocturia, urgency)

**Basic Assessment**
- History
- Frequency/volume chart
- Focused physical examination
- Urinalysis, culture

**1st Line Rx**
- "Simple BPS" Conservative Therapy
- Patient Education
- Dietary Manipulation
- Nonprescription Analgesics
- Pelvic Floor Relaxation
- Address Treatment of Pain

**Complicated BPS**
- Urinary infection
- Incontinence
- Urinary infection
- Hematuria
- Gynecologic signs/symptoms

**Treatment**
- Consider:
  - Urine cytology
  - Further imaging
  - Endoscopy
  - Urodynamics
  - Laparoscopy

**Treat as indicated**

---

**Paradigm Change**

**Inflammatory Bladder Disorder**

**Interstitial Cystitis**

**Painful Bladder Syndrome**

**Chronic Pain Syndrome**

**Old Paradigm IC:**
- Identify marker
- Determine pathophysiology
- Modify pathophysiology

**New Paradigm: BPS**
- Chronic Pain Syndrome
- Treat the Pain
- Local causes in bladder
- Prevent Central Sensitization

---

*Figure 10: The new perspective of Bladder Pain Syndrome From Hanno, PM: Proceedings of the International Consultation on Interstitial Cystitis, Japan; Comfortable Urology Network, pages 2-9, 2008*

*Figure 11: The new perspective of Bladder Pain Syndrome From Hanno, PM: Proceedings of the International Consultation on Interstitial Cystitis, Japan; Comfortable Urology Network, pages 2-9, 2008*
and possible bladder biopsy under anesthesia. Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner’s lesion suggest therapy with transurethral resection or fulguration of the lesion. Distention itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. Grade of recommendation: C
e) Refractory BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include neuromodulation, intravesical botulinum toxin, or newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anesthesia pain clinic. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream. Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients. Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series. Grade of recommendation: C

REFERENCES

19. Hunner, G. L. A rare type of bladder ulcer. Further notes, with a report of eighteen cases. JAMA 70[4], 203-212. 1-26-1918. Ref Type: Journal (Full)


280. Indent


Committee 20

Management Using Continence Products

Chairman
A. COTTENDEN (U.K)

Members
D.Z.BLISS (USA),
B. BUCKLEY (Ireland),
M. FADER (U.K),
K. GETLIFFE (U.K),
J. PATERSON (Australia)
R. PIETERS (Belgium),
M. WILDE (USA)
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
</tr>
<tr>
<td>II. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS</td>
</tr>
<tr>
<td>III. PRODUCT EVALUATION METHODOLOGY</td>
</tr>
<tr>
<td>IV. HANDHELD URINALS</td>
</tr>
<tr>
<td>V. COMMODES AND BEDPANS</td>
</tr>
<tr>
<td>VI. ABSORBENT PRODUCTS</td>
</tr>
<tr>
<td>VII. SHEATHS</td>
</tr>
<tr>
<td>VIII. URINE DRAINAGE BAGS AND ACCESSORIES</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Not all incontinence can be cured completely and even those who are ultimately successfully treated may have to live with incontinence for a time, for example, whilst they wait for surgery or for pelvic floor muscle training to yield its benefits. Still others – depending on their frailty, severity of incontinence and personal priorities – may not be candidates for treatment or may choose management over attempted cure. For all such people, the challenge is to discover how to deal with their incontinence so as to minimise its impact on their quality of life. This usually involves using some kind of continence product(s) to control or contain leakage of urine and/or faeces, and/or to manage urinary retention. In short, the possible role of continence products should be considered at each stage of patient assessment and treatment and, if treatment is not available, appropriate, acceptable or (fully) successful – subsequent management. Managing incontinence successfully with products is often referred to as contained incontinence, managed incontinence or social continence, in recognition of the substantial benefits it can bring to quality of life even though cure has not been achieved [1].

This chapter is aimed primarily at healthcare professionals seeking to make informed decisions as they choose – or help their patients to choose - between continence product categories and then select a specific product within their chosen category. We have also aimed to make this information accessible to the user, particularly in the summary and recommendation sections. The chapter includes a section for each of the major product categories, each section reviewing published data and – where possible - identifying evidence-based recommendations for product selection and use. Products designed to deal with skin and odour problems caused by incontinence are also addressed.

The sections on the major product categories are preceded by two others. The first provides overall guidelines for product selection, describing the key elements of patient assessment and suggesting a classification of people with incontinence into a number of broad groups based on gender, age (adult or child) and the nature and severity of their incontinence. A table is provided for each group summarising the user characteristics, priorities and contexts which commonly favour or discourage the use of each of the major product categories available to them. Following these overall guidelines and preceding the sections on the major product categories, a review is provided of the methodological challenges of conducting continence product evaluations and interpreting the results.

Unfortunately, much of the evidence base for product selection and effective use is patchy and, where there is little published data to provide confident evidence-based advice on an issue commonly raised by patients and caregivers, an expert opinion is offered as the best advice available. The hope is that highlighting knowledge gaps in this way will help stimulate the research necessary to provide more robust evidence-based advice in the future.

The literature search strategy to identify material for this chapter additional to that reviewed for the third consultation [2] was conducted as follows. MEDLINE and CINAHL databases were searched from 2003 – 2008 for English language publications. Detailed search strategies were developed for each electronic database searched. Consideration was given to variations in terms used and spellings of terms in different countries so that studies were not missed. Relevant abstracts were examined and then pertinent articles were retrieved and reviewed, and the reference lists searched for further studies. For product categories associated with little or no research literature, analysis relied on expert opinion from clinical practice papers.

The following main search terms were used: incontinence AND device*, toilet* AND facilities, commode*, urinal*, bedpan*, urinary AND sheath*, condom AND catheter*, incontinence OR absorbent pad*, urinary AND catheter* (in title), urinary AND leg bag* OR legbag* OR drainage bag, faecal OR fecal AND incontinence AND plug OR pouch OR bag OR manage* system, flatus AND odour OR odor AND device, incontinence OR perineal AND dermatitis OR inflammation OR skin damage.
Selecting suitable continence products is critical for the well-being and quality of life of patients and carers. The ability to contain and conceal incontinence enables individuals to protect their public identity as a "continent person" and avoid the stigma associated with incontinence [3]. Failure to do so can result in limited social and professional opportunities, place relationships in jeopardy and detrimentally affect emotional and mental wellbeing [4]. The ability to contain and conceal incontinence enables carers to feel confident that the person(s) they care for will not be embarrassed publicly. It reduces the level of care required in relation to maintaining hygiene, skin care and laundry for the person who is dependant upon continence products [5].

Fortunately there is a diverse range of different products to choose from. However, without comprehensive and current information on the products available, this plethora of choice can be overwhelming and confusing [5]. Furthermore, the range of products actually accessible to users can vary enormously between and within countries, depending on the funding available, healthcare policy and the logistics of supply [5].

The choice of appropriate products for an individual with incontinence is influenced by the resources and care available and patient / carer preference, as well as assessment of specific client characteristics and needs [6,7].

The stigma associated with incontinence means that another measure by which the success of products is judged is their ability to conceal the problem [8]. Such concealment may involve compromises: for example, in order to prevent leakage from a product, those with a larger capacity than strictly necessary may be preferred but this can in itself introduce issues to do with discretion when the product is worn. The intimate and stigmatised nature of incontinence means that issues relating to self-image can affect some patients’ preferences. This may be especially marked in younger people for whom body-image may be particularly important and for whom disruption to normal social and interpersonal development may result in isolation or lack of access to normal experiences [9,10].

1. PRODUCT CATEGORIES

The continence products considered in this chapter may be divided into those that are intended to assist with toileting and those to manage urinary retention and / or contain incontinence (urinary and / or faecal) (Fig II-1).

II. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS

Selecting suitable continence products is critical for the well-being and quality of life of patients and carers. The ability to contain and conceal incontinence enables individuals to protect their public identity as a “continent person” and avoid the stigma associated with incontinence [3]. Failure to do so can result in limited social and professional opportunities, place relationships in jeopardy and detrimentally affect emotional and mental wellbeing [4]. The ability to contain and conceal incontinence enables carers to feel confident that the person(s) they care for will not be embarrassed publicly. It reduces the level of care required in relation to maintaining hygiene, skin care and laundry for the person who is dependant upon continence products [5].

Fortunately there is a diverse range of different products to choose from. However, without comprehensive and current information on the products available, this plethora of choice can be overwhelming and confusing [5]. Furthermore, the range of products actually accessible to users can vary enormously between and within countries, depending on the funding available, healthcare policy and the logistics of supply [5].

The choice of appropriate products for an individual with incontinence is influenced by the resources and care available and patient / carer preference, as well as assessment of specific client characteristics and needs [6,7].

The stigma associated with incontinence means that another measure by which the success of products is judged is their ability to conceal the problem [8]. Such concealment may involve compromises: for example, in order to prevent leakage from a product, those with a larger capacity than strictly necessary may be preferred but this can in itself introduce issues to do with discretion when the product is worn. The intimate and stigmatised nature of incontinence means that issues relating to self-image can affect some patients’ preferences. This may be especially marked in younger people for whom body-image may be particularly important and for whom disruption to normal social and interpersonal development may result in isolation or lack of access to normal experiences [9,10].

1. PRODUCT CATEGORIES

The continence products considered in this chapter may be divided into those that are intended to assist with toileting and those to manage urinary retention and / or contain incontinence (urinary and / or faecal) (Fig II-1).

2. IDENTIFYING THE NEEDS

The algorithms below (Figs II-2 and II-3) are designed to provide guidance for determining broadly which product(s) is likely to be of benefit to a particular patient. There are three main questions:

• Is there urinary retention (with or without incontinence)?
• Are there problems with toilet access (e.g. the proximity or design of the toilet; mobility or urgency problems for the patient)?
• Is there urinary incontinence or faecal incontinence or both?

Answers to these questions will determine which one (or both) of the algorithms is most appropriate for an individual and help identify the category(s) of products most likely to help.

Figure II-1: Products for toileting (top) and for managing incontinence and / or urinary retention (bottom). CIC = Clean intermittent catheterisation; IDC = Indwelling catheter.

All toileting products can be useful for dealing with urine and / or faeces except for handheld urinals which are just for urine. Containment / control products are subdivided into three overlapping classes: those for urinary retention, urinary incontinence, and faecal incontinence. So, for example, someone with urinary retention is most likely to benefit from one of the products in the red ellipse, while someone with urinary incontinence will most likely benefit from one in the blue ellipse. A patient experiencing both problems will need two products (one from each ellipse) or one product from the intersection of the two ellipses.
Figure II-2: Algorithm to help identify the category(s) of products most likely to help a patient with urinary incontinence and / or urinary retention. (Y = Yes; N = No; U = unsatisfactory ie considered and deemed unsuitable or tried and found not to work satisfactorily). * Consideration should be based on assessment of the patient’s physical characteristics, cognitive ability and personal preferences, as well as the nature of their incontinence. (CIC = Clean intermittent catheterisation; IDC = Indwelling catheter).

Figure II-3: Algorithm to help identify the category(s) of products most likely to help a patient with faecal incontinence. (Y = Yes; N = No; U = unsatisfactory ie considered and deemed inappropriate or tried and found not to work satisfactorily). * Consideration should be based on assessment of the patient’s physical characteristics, cognitive ability and personal preferences, as well as the nature of their incontinence.
3. PATIENT ASSESSMENT FACTORS

A careful patient assessment is an important part of the process of product selection and Table II-1 summarises the key elements to be considered.

The choice of appropriate products for an individual with incontinence is dependent upon the resources and care available. It must also be influenced by patient and carer preference as well as assessment of specific client characteristics and needs [6,7].

Assessment of physical characteristics such as anthropometrics, level of independence, mobility and dexterity, mental acuity and the nature of the incontinence will determine which products may be appropriate. In addition to these factors, successful product choice and effective use involves other practical and psychosocial considerations. Product effectiveness depends upon the same factors as any assistive device intended to address a disability or impairment: patient participation in device selection [11] provision of adequate instructions for use [12] and the need for products to fulfil their function reliably and not be difficult to use [9-12,13].

While Table II-1 provides general guidance on patient assessment relating to product selection, later sections in the chapter provide further discussion on assessment issues specifically related to the various product categories.

In addition to selection of appropriate and effective products following patient assessment, education and training of users or carers in the correct use of the devices is of importance if product use is to be optimal. This may be a simple matter of instruction in the effective fitting and changing of absorbent products, or may involve more in-depth training in the ongoing care of, for example, a suprapubic catheter.

Incontinence is often a long term condition and so monitoring and periodic reassessment is essential to maintain effective management with products.

4. MAIN USER GROUPS

Although needs, priorities and preferences vary between people with incontinence it is useful to divide patients into major user groups to help identify the category(s) of products most likely to benefit an individual. Seven primary groups are identified in this chapter:

- People with urinary retention.
- People who need help with toileting / toilet access.
- Females with light urinary incontinence.
- Males with light urinary incontinence.
- Females with moderate / heavy urinary incontinence.
- Males with moderate / heavy urinary incontinence.
- People with faecal incontinence.

An individual may belong to more than one group. Each group includes children and young people: the products available for them are broadly similar to those for adults.

5. CHOOSING BETWEEN PRODUCT CATEGORIES

Figs II-4 to II-9 summarise the user characteristics, priorities and contexts which favour or discourage the use of each of the categories of products available for six of the seven user groups identified in section II.4. Assistance with choosing appropriate products for the first group (people with urinary retention) is given in the section on catheters (Table XII-1) as all the product options for these people are in the same category (catheters).

The recommendations given in these charts are based on the evidence presented in the sections of the chapter dedicated to different product categories and they are intended to help identify which product category (categories) are most likely to help an individual. However, it should be remembered that the same product will not suit all people, even if they have very similar assessment outcomes on the factors summarised in Table II-1. Different people prefer different products and where possible patients should be given access to a range with which to experiment to determine the most satisfactory product(s). Similarly, the balance of priorities varies between users; for example, some pad users will opt for a bulky and, therefore, less discreet product to achieve an acceptably low risk of leakage while others will see the balance differently. It should also be noted that a mix of products from different categories may provide the best solution; for example, needs may vary between day / night and home / away. Once a product category of interest has been identified the corresponding chapter section should be consulted for further help.

6. SUMMARY

In conclusion continence products find an important role in enhancing the quality of life and reducing stigma of incontinence of those who: are awaiting treatment; are waiting for treatment to take effect; elect not to pursue cure options; are unable to be fully cured and are living with an ongoing bladder / bowel problem.

7. RECOMMENDATIONS

- Incontinence should be actively managed with products to minimise the impact of incontinence on quality of life (Grade of Recommendation C).
- Patients should be carefully assessed (and reassessed) to select the most appropriate products (Grade of Recommendation C).

1524
<table>
<thead>
<tr>
<th>Element</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of the continence problem</td>
<td>The frequency, volume and flow rate of the incontinence influences product suitability. Generally smaller, more discreet products should be tried before larger bulkier products. If catheterisation is necessary, intermittent catheterisation is a less invasive option than indwelling catheterisation.</td>
</tr>
<tr>
<td>Gender</td>
<td>Males may consider and prefer sheaths as a more masculine option to pads. Females may be attracted to products that are more feminine in design and presentation. Some ‘unisex’ products such absorbent pads have different designs that work better for men (or women).</td>
</tr>
<tr>
<td>Physical characteristics</td>
<td>Anthropometrics (e.g. height and waist, thigh, penile circumference) will influence the comfort and effectiveness of a product.</td>
</tr>
<tr>
<td>Mental acuity</td>
<td>Mental impairment can affect the person’s ability to manage the product. Products that resemble usual underwear (e.g. some absorbents) may be easiest to manage. Products which have health implications if used incorrectly (e.g. mechanical devices or catheter valves) should be avoided if mental impairment is present.</td>
</tr>
<tr>
<td>Mobility</td>
<td>Impaired mobility may make some product choices impractical or require toilet or clothing modification to allow effective use of the product.</td>
</tr>
<tr>
<td>Dexterity</td>
<td>Problems with hand or finger movement can make it difficult to use some products (e.g. taps on leg bags, straps with buttons).</td>
</tr>
<tr>
<td>Eyesight</td>
<td>Impaired eyesight limits effective application and management of some products.</td>
</tr>
<tr>
<td>Leg abduction problems</td>
<td>Difficulty with abduction can make the use of some products impractical or ineffective.</td>
</tr>
<tr>
<td>Lifestyle and environments</td>
<td>Daily activities and environments can influence the choice of product and a mixture of products may provide optimum management. Different products may be most satisfactory for daytime and going out (when discreetness may be a priority) and night-time or staying in (when comfort may be a priority), for holidays (when large quantities of disposables may be a problem) or for use at work. The proximity and accessibility of a toilet in the various environments may be a key factor.</td>
</tr>
<tr>
<td>Independence / assistance</td>
<td>If a carer is required to apply or change the product then it may be important to involve them in the selection of the product and to establish their willingness and ability to use it.</td>
</tr>
<tr>
<td>Laundry facilities</td>
<td>Washable pads and bed linen may be very heavy when wet and take a long time to dry. It is important to check that the person doing the laundry has the ability and facilities to cope.</td>
</tr>
<tr>
<td>Disposal facilities</td>
<td>Ability to appropriately, safely and discreetly dispose of the selected products needs to be considered.</td>
</tr>
<tr>
<td>Storage facilities</td>
<td>Some products – notably, pads for heavy incontinence – can be bulky. Adequate space to store supplies between deliveries / purchases needs to be available.</td>
</tr>
<tr>
<td>Personal preferences</td>
<td>Different people like different products and where possible patients should be given a choice of products with which to experiment to determine the most satisfactory product.</td>
</tr>
<tr>
<td>Personal priorities</td>
<td>Everyone wants to avoid leakage but other factors such as discreetness may be more or less important to individuals.</td>
</tr>
</tbody>
</table>
Figure II-4: Products for people who need assistance with toileting.
**Figure II-5: Products for females with light urinary incontinence**

<table>
<thead>
<tr>
<th>Product category</th>
<th>User characteristics / priorities / contexts which:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FAVOUR use</td>
<td>DISCOURAGE use</td>
</tr>
<tr>
<td><strong>Pads (Section VI.5)</strong></td>
<td>• In general (C)</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical devices (Section X)</strong></td>
<td>• Incontinence is predominantly stress (C)</td>
<td>• Incontinence has a significant urgency component (C)</td>
</tr>
<tr>
<td></td>
<td>• Manual dexterity is good (C)</td>
<td>• Concerns over risks of UTI are high (intra-urethral device) (C)</td>
</tr>
<tr>
<td></td>
<td>• Sound cognition (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Device concept is acceptable / preferrable (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Preventing leakage rather than containing it is attractive (C)</td>
<td></td>
</tr>
</tbody>
</table>
Figure II-6: Products for males with light urinary incontinence

<table>
<thead>
<tr>
<th>Product category</th>
<th>User characteristics / priorities / contexts which:</th>
<th>FAVOUR use</th>
<th>DISCOURAGE use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pads (Section VI.6)</td>
<td>• In general</td>
<td>• Device concept is acceptable / preferred (C)</td>
<td>• Unknown</td>
<td>• See Fig VI-17 for details.</td>
</tr>
<tr>
<td>Dribble containers (Section IX.2)</td>
<td>• Highly motivated (C) • Periodic / intermittent use (C) • Incontinence is predominantly stress (C) • Device concept is acceptable / preferred (C) • Preventing leakage rather than containing it is attractive (C)</td>
<td>• Incontinence has a significant urgency element (C) • Doubtful level of cognition (C) • Risk of skin / tissue damage (C) • Bladder sensation poor (C) • Poor dexterity (C)</td>
<td>• Skilled fitting by a professional is needed.</td>
<td></td>
</tr>
<tr>
<td>Mechanical devices (Section XI)</td>
<td>• Retention / voiding problem (if no alternative) (C) • Skin is severely damaged (C) • Pads (or other products) unsuccessful / inappropriate (C) • Unable to perform CIC (C)</td>
<td>• In general (A), but particularly if: • History of urethral trauma • Cognitive impairment (danger of interfering with catheter) • Avoidance of UTI is a priority</td>
<td>• See Table XII-1 for details.</td>
<td></td>
</tr>
</tbody>
</table>

Figure II-7: Products for females with moderate / heavy urinary incontinence.

<table>
<thead>
<tr>
<th>Product category</th>
<th>User characteristics / priorities / contexts which:</th>
<th>FAVOUR use</th>
<th>DISCOURAGE use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pads (Section VI.7)</td>
<td>• In general (C)</td>
<td>• Skin is severely damaged (C)</td>
<td>• See Fig VI-18 for details.</td>
<td>• CIC (C)</td>
</tr>
<tr>
<td>Indwelling Catheters (Section XII.2)</td>
<td>• Retention / voiding problem (if no alternative) (C) • Skin is severely damaged (C) • Pads (or other products) unsuccessful / inappropriate (C) • Unable to perform CIC (C)</td>
<td>• In general (A), but particularly if: • History of urethral trauma • Cognitive impairment (danger of interfering with catheter) • Avoidance of UTI is a priority</td>
<td>• See Table XII-1 for details.</td>
<td></td>
</tr>
</tbody>
</table>
Figure II-8: Products for males with moderate / heavy urinary incontinence.
Figure II-9: Products for people with faecal incontinence.
III. PRODUCT EVALUATION

METHODOLOGY

This section aims to assist those planning clinical trials of products. There have been relatively few large clinical trials of continence products (with the exception of urinary catheters) and for most product categories research evidence to guide the selection of individual products / designs / features is limited and in some cases absent.

Measuring the performance of continence products is methodologically challenging. Manufacturers modify and change their products regularly - in terms of both materials and designs - and this limits the long-term validity of research results. There are also complex issues regarding research questions, study design, product representation, blinding and sample size [14] which are discussed below.

It is common for practitioners to be asked (by their employers or by companies) to do a small evaluation or trial – sometimes to ‘test out’ a new product and sometimes to help choose between competing brands for bulk-buying. Such trials should be approached with caution; they can be very demanding but their results may be of very limited value even for local use. The methodological challenges identified below still apply but are compounded by small sample size and restricted product selection. These studies are likely to be helpful only for identifying gross product short-comings or benefits.

1. RESEARCH QUESTIONS

a) Comparisons

Part of the complexity of product evaluations is the sheer number and type of products which means that many different comparisons could be made. Table III-1 shows an example range of questions that may be asked about one particular product category (absorbent pads – following question 1) and many combinations and permutations of products / designs / feature are possible.

In the field of absorbent products the practitioner and / or patient wishes to know whether to use an underpad or a bodyworn product, a reusable or a disposable, a diaper or an insert (if they select a bodyworn), a diaper with internal elasticity (standing gathers) or without and, finally, which of the many diaper brands is likely to be most effective. Attempting to answer this final question is the most pertinent question for the practitioner (who may already have made decisions about questions 1-4) but is particularly problematic because of the high rate of product change. By the time the results of a clinical trial of product brands are known many of the test products will have been modified and the results will have limited value for product selection. However, these ‘single design’ studies do have value in demonstrating the range of performance within the group of product brands, and where objective measurements can be made (for example, of leakage performance) can allow for comparisons between groups of products. Single design studies are also helpful in promoting product improvement by revealing common problems experienced by patients and exposing particularly poor products or poor product features which are amenable to change by manufacturers.

Basic product designs, features and materials change much less frequently and attempting to answer questions 1-4 (Table III-1) is therefore likely to lead to more long-lasting results. Such studies have been attempted by many researchers, but these have frequently been confounded by problems with product representation.

b) Product representation

The single greatest (and most frequently overlooked) threat to the validity of clinical trials of products is the selection of the products entered into the study. Studies of single groups of similar product brands have shown that patient ‘overall opinion’ scores vary by as much as 70 percentage points [15] and the selection of products to represent the group of interest is therefore crucial. Studies that have purported to compare different designs or materials have often included a small number (most often just one) of arbitrarily selected product(s). Generalizing the results of such studies to whole product groups (e.g reusable underpads, or disposable bodyworns) is meaningless and misleading. It is perfectly possible to select (either by accident or design) a particularly ‘good’ product from one group and a particularly ‘poor’ product from another. A well-designed study will therefore be seriously flawed if there is no clear process or pilot study to determine and justify the choice of particular products. Even with a systematic process of product selection (or preferably a pilot study) it is unwise to select a single product to represent a whole group of products and selection of a small group of products (e.g, three) is preferable. This allows for any ‘within group’ differences to be detected and helps to demonstrate the ‘representativeness’ of the products selected.
The most controlled method of testing different designs, materials or features of products is to make up experimental batches which differ only in the aspect of interest (e.g. the material or the feature) and a small number of studies have attempted this [16,17]. However, experimentally made products are not usually identical to those available on the market which impairs the validity of such studies.

2. RESEARCH DESIGN

A randomized controlled trial is not possible for clinical trials of products in most categories simply because a ‘control’ product does not usually exist. Nor is there a ‘standard or reference’ product to act as a control and comparisons with ‘standard practice’ (i.e. the product currently in use) are prone to bias.

Although it is methodologically simpler (and more robust) to compare only two different product groups, it is more clinically relevant to compare several competing groups, using a multiple cross-over design, where there are valid comparisons. For example, there are four main design groups of disposable bodyworn pads for moderate / heavy incontinence (inserts, diapers, pull-ups and T-shaped). Evaluation of all four groups together is much faster (and therefore gives more long-lasting results) and more cost-effective than several serial studies. Cross-over trials are vulnerable to order effects and randomization of the order of testing should be carried out using Latin squares [18] to ensure balance.

It is important that clinical trials of single designs of products (which aim to enable selection of particular product brands) are comprehensive (i.e. cover all the available products) because otherwise manufacturers can justifiably claim that although their product may be similar to one of those tested even subtle distinctions may lead to clinically important differences.

A further problem with research design is the blinding of products. Different products have different appearances and it is impossible to blind subjects or staff to the product in use. Products can be repackaged to assist anonymising but this may have unwanted effects on the products and is expensive.

Previous product experience can also affect study results, particularly if a substantial proportion of subjects are currently using a product included in the study. It is therefore important to record which products are in current use in order to add this data to the model used in the analysis.

a) Sample size and study power

Studies that include more than two products (or two small groups of products) will need to be powered so that multiple comparisons can be made. As the number of products included in the study increases the number of possible comparisons of pairs of products rises. This requires a corresponding reduction in the significance level (e.g. by using the Bonferroni method) for each pair-wise comparison to retain the overall level of significance (usually p<0.05). Thus as the total number of pair-wise comparisons increases the likelihood of a type 2 error (accepting the null hypothesis when it is false) also increases.

Sample sizes therefore need to be calculated to allow for each pair-wise comparison. Sample size requirements rise rapidly if each subject does not test each product and the number of products entered into a study must therefore be limited by subject fatigue. As an example, a clinical trial of four product groups where the primary outcome variable will be binarised (e.g. satisfactory / unsatisfactory) will require a sample size of approximately 80 subjects with an alpha of < 0.05 and d (difference) of 20%.

b) Outcome variables

Studies of product performance have most frequently used self-report questionnaires at the end of the product test period to assess participant ratings of product performance. Diaries of product-related events such as leakage, laundry generation and product consumption are also commonly included. Subjects in some absorbent pad studies have been asked to identify and prioritise items of product performance [19, 21] to inform questionnaires and Table III-2 shows the most common items of high priority to women with light urinary incontinence identified by Getliffe and colleagues [20].

Outcome variables in studies designed to compare catheterisation strategies and / or catheter materials

<table>
<thead>
<tr>
<th>Table III-2. Most common items of high priority to women with light incontinence using absorbent products. Getliffe et al. [27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Hold urine without leaking</td>
</tr>
<tr>
<td>Contain smell</td>
</tr>
<tr>
<td>Stay in place</td>
</tr>
<tr>
<td>Discreetness</td>
</tr>
<tr>
<td>Comfort when wet</td>
</tr>
</tbody>
</table>
or other design features commonly encompass measures of urinary tract infection, tissue trauma and recurrent catheter encrustation leading to blockage (see Section XII-2).

Questionnaire items vary depending on the products being tested and for product groups where few studies have been carried out it is particularly important to tailor questionnaires to patient needs by asking study subjects to prioritise items and to assess final questionnaires for content and face validity. One study [22] has measured the test re-test reliability of a questionnaire to assess sheath performance and found moderately good Kappa scores (around 0.7) when assessing the same sheath twice with four weeks between measurement periods.

Skin health, urinary tract infection, pain or discomfort are the main physical health consequences of containment products and skin health (which can be rated by self-report or by skin inspection) has sometimes been used as the primary outcome variable (e.g.[23]). Urinary tract infection is an important outcome for invasive devices such as catheters. Although leakage performance is most frequently rated as the top priority for users, good leakage performance is not adequate as a sole measure of patient satisfaction with performance. A single (or multiple) fatal flaw such as poor comfort, bulkiness, or poor fit may cause a product that performs well for leakage to be unacceptable to the patient. For this reason aggregate measures - which assumes that the overall performance of a product can be calculated using a weighted sum of the scores for specific aspects of performance (like comfort and freedom from leakage) - are ill-advised. Patient overall opinion or satisfaction with the product should therefore be used as the primary outcome variable[14].

There are no quality of life measurement tools specifically designed for clinical trials of products, but there is a need for such tools to measure the impact that good or bad product performance has on people’s lives. Existing incontinence-specific quality of life tools are designed to measure change after interventions to improve incontinence and include urinary symptoms. These tools are therefore likely to be insensitive to changes in quality of life brought about by products which are designed to contain incontinence rather than reduce or prevent it. The first stage in the development of a quality of life tool for absorbent product users has been reported by Getliffe et al. [20] and a similar tool for catheter users is known to be under development.

3. SUMMARY AND RECOMMENDATIONS

- There is little published evidence on which to base summary and recommendations regarding methodology and so the following summary points / recommendations are all Level of Evidence 3 / Grade of Recommendation C.

- Evaluation of continence products is methodologically complex and many attempts at providing robust evidence for product selection have been hampered by methodological weaknesses.

- Product representation is critical to providing robust and generalisable data. Selection of products for inclusion in a study needs to be transparent and systematic and several products should preferably be included to represent a product group.

- Multiple crossover designs are likely to be more efficient than randomised controlled trials for many products (e.g. pads) and therefore sample sizes estimation needs to take into account the multiple comparisons that will be made.

- Outcome variables should include patient (or carer) questionnaire including items that have been established as important to patient users.

- Diary data should be included to determine leakage performance, skin health, laundry and product consumption.

- Incidence of urinary tract infection should be included when testing invasive devices such as catheters, but “significant” UTI/ bacteriuria needs to be carefully defined (see Section XII.2.8).

- The primary outcome variables should be patient overall opinion / satisfaction and patient preference.

- Health economics should be measured alongside product performance.

4. RESEARCH PRIORITIES

- The development of Quality of Life tools for users of continence products.

### IV. HANDHELD URINALS

Handheld urinals are portable devices designed to allow a person to empty their bladder when access to a toilet is not possible or convenient, often due to limited mobility, hip abduction or flexibility. They can be especially helpful for those suffering from frequency and / or urgency.

An effective hand held urinal must enable its user to empty his / her bladder in comfort and be confident of no spillage. It should not require excessive physical effort on their part and should be easy to empty without spillage.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of patient assessment particularly important for handheld urinals are user postures (in bed, on side of bed, back in
chair, on edge of chair, standing/crouching/kneeling), leg abduction, approach of urinal (from front, side, behind, above), ability to initiate void, dexterity and strength to position and remove urinal, level and availability of assistance, user preference.

There has only been one clinical trial [24] of female urinals and there are no published trials of male urinals. However, much helpful guidance and expert opinion has been published [25-28].

1. FEMALE HANDHELD URINALS

Female handheld urinals come in a variety of shapes and sizes (Fig IV-1). Most are moulded in plastic but they may be made from metal or (for single use items) cardboard. Some are designed for use in particular postures, like standing, sitting or lying down – (see below). Some have handles to facilitate grip and positioning. Some are intended to empty into a drainage bag during or after use.

![Figure IV-1: A variety of female handheld urinals.](image)

Although female handheld urinals are often described and discussed in general nursing articles on continence products they have only been the subject of one published (cross-over) evaluation. Fader et al. [24] carried out a multi-centre study in which each of 37 community-based women (age range 33-89y; mean age 61y) was invited to evaluate all 13 products on the UK market in 1997. No product suited everybody but each was successful for at least some subjects. The key requirements for success were that the user should be able to position the urinal easily and feel confident that it would catch urine without spilling (Level of Evidence 2). Many products were successful when used in the standing / crouching position or when sitting on the edge of a chair / bed / wheelchair. Fewer worked well for users sitting in a chair / wheelchair. Only one worked even reasonably well when users were lying / semi-lying (Subaseal). In general, subjects with higher levels of dependency found fewer urinals to be suitable for their needs.

Recently the development of a powered urinal designed to pump urine into a reservoir has been described [29]. The aim of the device was to provide active removal of urine without leakage and without the need for gravity-assisted drainage. The urinal was tested by 80 women from six countries. Although evaluated as ‘good’ or ‘okay’ by more than three-quarters of the women, nearly half the women found the device ‘poor’ for weight and size. Problems with reliability of the device were also common and the authors concluded that the current device needed further refinement but may have potential as an alternative to conventional urinals. Although this device is not currently on the market, at least one other powered device is available. However, there are no published reports on efficacy.

2. MALE HANDHELD URINALS

Most handheld urinals for men are somewhat similar, involving a narrowed neck opening into which the penis is placed. Some products come with a detachable or integral non-spill adaptor containing a flutter valve to impede back-flow of urine from the urinal. There are no published trials of such products.

A review paper by Vickerman [28] makes recommendations for selecting suitable urinals for men. A flat bottom urinal may be more stable (and less likely to spill) for those using a urinal in bed. Urinals made from soft plastic (jug-style or with a funnel) may be easier to grip for those with poor manual dexterity. Urinals designed to be attached to a drainage bag (for emptying the urinal) may also be helpful to men living at home with limited support.

Vickerman also suggests that home-made devices (such as empty wide-mouthed containers with a handle and lid (for example, those used for clothes-washing liquid or conditioner) may be a practical (and cheap) option for some men. For those with a retracted penis female urinals may be easier to use than male products.

3. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

The literature [25-28] suggests that successful use of urinals depends on many factors which are summarised below.

- Experimentation is often needed to find the optimum urinal for an individual. A ‘library’ of urinals (i.e. a collection of different types of urinals to be lent out to users for experimentation) has therefore been recommended [27] but rigorous cleaning methods are needed (see below).
- Clothing alterations can aid quick and easy use of a urinal. For men, extending the fly opening of trousers or replacing zips with Velcro can be helpful, as can boxer shorts. For women drop-front pants may be needed, particularly if mobility is limited.
- Disposable and reusable ‘travel’ hand-held urinals are available for both men and women. These
urinals fold away to fit into a pocket and may therefore be more discreetly portable than conventional urinals.

- Some disposable urinals include superabsorbent polymer in their reservoirs which turn urine into a gel and help to prevent spillage. Sachets of superabsorbent polymer may also be added to reusable urinals.

- Use of a urinal is not always free from leakage and provision of absorbent chair or bedpads to protect bedding, clothes and furniture (particularly when testing out urinals) may be necessary.

- The limited range of urinal options in acute settings, where often only bedpans are available, has been criticised and the process of introducing hand-held urinals to hospital services has been described and recommended [30].

- When used by one individual in the home, urinals can be cleaned with soap and water between uses. But where urinals are shared (i.e. cleaned and used by others), or if a library of urinals is used then robust methods are necessary. Some urinals can be cleaned in a bedpan washer but cleaning methods vary with different designs and materials and compliance with local infection control procedures will be needed.

4. RECOMMENDATIONS

- There is a wide range of female urinals and experimentation is likely to be necessary to identify the best one for an individual (dependent on their individual needs and abilities).

- A library of female urinals (used with robust cleaning methods) will help to facilitate experimentation (Grade of Recommendation B).

- Male urinals are less varied than female urinals, but may be supplemented by use of less conventional receptacles (e.g. jugs, home-made devices); experimentation will help to identify best options.

- Section IV.3 addresses other more general recommendations regarding urinal use.

5. PRIORITIES FOR RESEARCH

- Further development of female urinals is encouraged, particularly for supine users and those unable to move to the edge of a chair.

- The range of male and travel urinals need to be evaluated to provide guidance for users and carers.

V. COMMODES AND BEDPANS

Toilets can be difficult to use by people with mobility problems and other disabilities. Toilet adaptations such as raised toilet seats, padded seats, and grab rails can be very helpful in enabling individuals to access the toilet easily and comfortably. Bottom wipers and bidets can also be useful. However, if access to the toilet is impossible, commodes and other toileting receptacles should be considered.

Commodes are devices that comprise a frame supporting a toilet seat with a pan (disposable or washable) beneath to receive urine and faeces. They are used independently of a toilet and may be static or mobile. Mostly, they are used by people with reduced mobility who find it difficult to access a conventional toilet. Bedpans are portable receptacles that may be used for passing urine or faeces while in bed or chair. Some female urinals (see Section IV) may also be used to collect faeces.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding commodes and bedpans begin with appropriate indications for their use since Matsumoto and Inoue [31] reported that incontinent elderly persons or their caregivers misunderstand indications of commode use for incontinence. Other patient assessment elements include: a) physical characteristics of the person with incontinence (e.g. can an obese person fit on a commode and use its handrails?); b) mental acuity (e.g. will a person with dementia recognize a commode or bedpan as a device to be used for defecation?); c) need for supervision or foot supports whilst on the commode (what is the risk of falling?); d) mobility (e.g. does the person need a commode or bedpan?), ability to transfer and method of transfer to the commode (e.g. hoist, carer help, independent with transfer board), need for static or mobile commode (particularly when considering using commode over a toilet), postural stability and need for supportive commode, e) level of assistance needed and physical burden to caregiver involved; and f) personal preferences (e.g. comfort of bedpan type) including need for ‘non-commode-like’ appearance (e.g., particularly when used in own room, particularly the living room). Patient assessment findings need to be evaluated in terms of the safety and stability properties of a commode. The proximity of the area for waste disposal, storage facilities (i.e., the location / visibility of the commode in the household), the availability of privacy during defaecation, and length of time likely to remain on the commode (is there a need for a pressure-relieving commode cushion?), are additional factors to be considered.
Commodes (or better still toilets) are preferable to bedpans (which are relatively difficult to use and do not permit appropriate posture for passing urine/faeces). Bedpans are generally reserved for people who are confined to bed (e.g. post-operatively) and for whom safety (risk of falling) is an important assessment issue.

1. RESULTS

Fader [32] has reviewed the little work that has been done to evaluate existing commodes and bedpans and to identify the needs of users. An investigation of commode design by Nazarko [33] highlighted the problem of commodes providing poor trunk support for elderly and disabled people. Prolonged periods of sitting alone (for privacy) to enable defecation resulted in a risk of falls. Nazarko worked with a manufacturer to produce a design specification for a commode. Consultation with patients indicated that many would prefer to use a toilet. As a consequence, attention was focused in designing a shower chair which could also be used as a commode or could be wheeled over a toilet.

An evaluation of the four main types of commodes (standard; with adjustable height; with removable / drop-down arm; with adjustable height and removable / drop-down arm combination) was published by the UK Medical Devices Agency [34]. One third of the 150 commodes on the UK market at the time were found to have backwards instability, and most of them scored poorly for aesthetics and comfort. A discussion of the results of this evaluation and its application to nursing was subsequently published by Ballinger et al. [35].

The maintenance of hospital commodes can be a problem and Gillan [36] complained about the poor condition of commodes in wards for elderly people. Dassut [37] has recommended a commode cleaning and identification system, to help overcome this problem.

Naylor & Mulley [38] investigated the use of commodes in community-dwelling patients and the attitude of carers and users towards them (115 subjects and 105 carers). The main reasons for commode use were impaired mobility, difficulty climbing stairs and urinary incontinence. Main concerns were lack of privacy and embarrassment about using the commode, unpleasant smells and the poor physical appearance of the commode. Carers tended to view them negatively, particularly with regard to cleaning. Where commodes were used for defecation in a living area the authors highlighted the problem of odour that lingered even after a commode had been emptied, and recommended the use of a chemical toilet.

Thorough cleaning of commodes or bedpans after every use is necessary for hygienic purposes and to eliminate odours. Naylor & Mulley [38] report that typically a caregiver rather than the commode user empties and cleans a commode. No recommendations for cleaning a home commode or bedpan were found in the published literature. In institutional settings, large sinks with spray hoses or special sanitizing equipment are available. The size and shape of a bedpan or commode receptacle may be difficult to fit under a standard sink basin in the home. Whether certain commode cleaning products reduce any residual odour more than others is not known. Toilet bowl cleaning products are suitable for cleaning a commode or bedpan; many contain bleach or antibacterial ingredients but their effect on reducing odour of commodes or bedpans has not been studied. Gel formulations are advertised by manufacturers as being better able to cling to hard-to-reach surfaces than liquid agents. Use of a deodorizer can be considered (Level of evidence 4).

Nelson and colleagues [39] surveyed 147 spinal cord injured patients regarding their satisfaction and safety with the shower chairs (used for bowel care) used in the home. They found that around a half of patients were dissatisfied with their chairs and concerns expressed related to lack of hand access to the perianal area, difficulty in turning and rolling the chair and problems with keeping the chair clean. One third of patients experienced chair related falls and nearly a quarter reported pressure ulcers. Two-thirds of subjects felt that their safety was compromised.

The same group of researchers evaluated three shower chairs using video-taping, photography and questionnaires and produced performance criteria for the design of an optimal shower chair [40]. Pressure mapping devices were used to measure seat pressures on three subjects who tested all three bowel / shower chairs to inform seat design [41].

These researchers [42] then set about designing a more advanced commode-shower chair. It had lockable, swing-away armrests and lever activated brakes to facilitate transfers. To prevent pressure ulcers a chair frame and padding combination was designed to facilitate a seating position that distributed body weight and reduced pressure on pressure points. Cupped edgeless footrests were designed to reduce the risk of heel ulcers. An adapted version of this chair is now commercially available in the USA.

Matsumoto and Inoue [31] examined whether use of a commode in the home might prevent or delay nursing home admission of elderly people who were incontinent. A five-year follow-up of multiple predictors of institutionalization in elderly people in a rural town in Japan showed that 40% of incontinent men and only 17% of incontinent women used a commode. Use of a commode was not associated with institutionalization. The authors suggested several possible reasons: misunderstanding of appropriate indications for a commode based on the type of incontinence; physical
burden in assisting a care recipient to use a commode that seemed no different than for cleansing after an incontinence episode; and inadequate muscle strength of the elderly for using either a Japanese-style or Western commode.

Bedpans and other portable receptacles are not well described in the literature. Wells and Brink [43] describe three general shapes of bedpans: concave, cutaway, and shovel. The concave pan has a rounded triangle shape that slopes back to front and a curved seat. The cutaway has a rounded triangle shape with a flatter seat and rolled edges that allow for handgripping. The shovel shape, commonly called a “fracture pan” is a wedge or rectangle shape that has a flattened end that goes under the individual and a handle at the distal end. Generally bedpans are considered to be unsuitable for defecation for safety and acceptability reasons. However, for individuals with specific needs (e.g. frequency and urgency of defecation) a portable receptacle may be beneficial. Although many portable urinals are now available for both men and women, very few are recommended for defecation [44] and they have yet to be formally evaluated.

Privacy and dignity need to be given high priority when patients need to use a bedpan or commode, in particular in institutional settings. Care needs to be taken when transporting patients on a shower chair to maintain dignity and avoid revealing the patient’s bottom.

Bottom wiping and cleaning can be difficult for people with disabilities, particularly manual dexterity problems, or caregivers. Simple moist wipes may be helpful and are widely available. Devices designed to assist with bottom wiping problems are on the market and portable bidets are also available, however there are no published trials of these products. Bedpans have other disadvantages including difficulty removing the bedpan from under an individual without spilling (particularly if the individual is obese), risk of spilling and odour when transporting the contents for disposal since none have lids, and lack of privacy during use.

2. SUMMARY
• There are major defects in most of the current designs of commodes, especially: poor aesthetics; poor trunk support; instability (i.e. a tendency to tip over easily); poor comfort; difficult to clean; poor pressure relief (Level of Evidence 3).
• If direct transfer to a toilet is impossible or unsafe a sani-chair / shower chair is usually preferable to a commode (Level of Evidence 3).
• The main concerns of users about commodes and bedpans are: lack of privacy; embarrassment over use; odour; poor aesthetics; poor perineal cleansing accessibility; and inadequate facilities for cleaning the devices in the home (Level of Evidence 2).
• Defaecation on a bedpan or other portable receptacle presents problems of safety and unacceptability to users (Level of Evidence 2).

3. RECOMMENDATIONS
• If at all possible, access to a toilet should be made available for defaecation (Grade of Recommendation C).
• If direct transfer to a toilet is impossible or unsafe, a sani-chair / shower chair should be offered in preference to a commode wherever possible (Grade of Recommendation C).
• If a commode is used, care should be taken to ensure good trunk support; that the chair is stable; and that methods of reducing noise and odour are offered (Grade of Recommendation C).
• With commodes and sani-chairs / shower chairs, the user’s bottom should never be visible to others and transportation to the toilet and use of the toilet or commode should be carried out with due regard to privacy and dignity (Grade of Recommendation C).
• Bedpans and other portable receptacles should be avoided for defaecation purposes (Grade of Recommendation C).
• Patients vulnerable to pressure ulcers should not sit on a commode / sani-chair / shower chair for prolonged periods (Grade of Recommendation C).
• The person should be given a direct method of calling for assistance when left on the toilet / commode / sani-chair / shower chair (Grade of Recommendation C).
• Cleaning of bedpans and commodes should be carried out after each use following local infection control policies (in institutional settings) (Grade of Recommendation C).
• For individual’s at home there are no published guidelines regarding frequency of cleaning or type of cleaning product. However, thorough cleaning after bowel evacuation (to avoid odour and maintain aesthetics) is important, together with rinsing after urine has been passed. Cleaning needs may vary according to personal hygiene standards and offensiveness of urine/ faecal smells (Grade of Recommendation C).

4. PRIORITIES FOR RESEARCH
• Studies are needed to determine how to make toilets accessible to as many users as possible. These may lead to improved designs for toilets and associated equipment and / or strategies for toileting.
• Studies are needed to determine which commode / sani-chair / shower chair designs best meet performance and safety requirements.
• Development of better commodes designed to overcome the limitations identified.
VI. ABSORBENT PRODUCTS

1. INTRODUCTION

Absorbent products (commonly known as pads) are available in a wide range of sizes and absorbencies encompassing light through to very heavy incontinence. Most pads are bodyworn but some are used on the bed or chair (underpads, see Section VI.2); in this section the term ‘pad’ refers to bodyworn absorbent products. Broadly speaking, absorbent products can be divided into two main sub-groups: those suitable for light incontinence (usually smaller products) and those suitable for moderate-heavy incontinence (usually larger products). Manufacturers generally indicate the severity of incontinence that each product is designed to accommodate, but see the discussion in Section VI.4. Although absorbent pads are most commonly used for urinary incontinence they are also used by individuals for both faecal and urinary / faecal incontinence; however, there have been no published studies which specifically address this issue.

Incidental findings from evaluations of products indicate that absorption capacity alone does not determine whether a user will choose to use a product. Some users may have frequent, low flow-rate loss of small volumes of urine (“dribble”), whilst others may be dry for days but then have a higher volume, higher flow-rate incontinence incident (“gush” or “flooding”). Both may prefer to use pads for light incontinence. Mobile and independent community-dwelling women of all levels of incontinence are reported to generally prefer small pads and are often willing to change them frequently rather than use larger products and change them less often [45]. Conversely, dependent, immobile individuals may prefer the security of larger products despite relatively low urine volumes due to their dependence on others for pad changing.

Studies that have collected and weighed used pads to measure urine volume have found overlap between the quantities contained by pads from different sub-groups; thus in a study of insert pads for moderate-heavy incontinence used by older people in residential care around 15% of insert pads for moderate-heavy incontinence contained less than 100g of urine [46] and in a study of older women with light incontinence living in the community about 10% of insert pads for light incontinence were found to contain more than 100g of urine [47].

It is possible that a proportion of patients are simply provided with inappropriate products that exceed or fall short of the absorption capacity they require. One study investigated this issue [48] and found that patients were more satisfied with their products once their urine loss had been determined by pad weighing and appropriately absorbent products were provided. But many of these patients were using inadequate products to start with (such as pads comprising tissue paper) and firm conclusions could not be drawn. In practice, it is probably hard to justify the need for pad weighing to determine which absorbents should be provided and if there is doubt about which group a patient falls into then the patient should be offered small pads for light incontinence in the first instance and the size of pad titrated upwards as necessary.

General guidelines on patient assessment for product selection are discussed in Section II.

Aspects of assessment that are particularly important regarding absorbent pads are frequency / severity of leakage, day / night incontinence, gender (some products are designed for or are better for men / women than others), ability to change pad independently / need for carer, pad changing position (standing / lying), laundry / drying facilities, individual priorities (e.g. need for discreetness), personal preference for design / materials (washable / disposable), lifestyle (at home / travel / work etc).

Aspects of absorbent pad performance have been identified and prioritised (during interviews) by men and women taking part in a series of clinical trials of such products [20]. There was considerable consistency across patient groups (light / heavy, men / women) with the ability of a product to hold urine without leakage being the top priority, and the following aspects also being considered to be of high priority: discreetness, containment of smell, ability to stay in place, comfort when wet and ability to keep skin dry.

2. ABSORBENT PRODUCT CATEGORIES

Absorbent products may be classified into two broad categories - disposable (single-use) and washable (reusable) - with each category dividing into two sub-categories: bodyworn products (worn on the person) or underpads (placed under the person). Within each sub-category are different design groups such as diapers and pull-ups which are sub-divided by size (to fit users of different sizes) and / or absorbency (to cater for different severities of incontinence). Some designs are further subdivided into those intended for men, women or children. This classification is shown in Table VI-1.

- **Bodyworn** absorbent products can be divided into four main design groups:
  - **Inserts** (sometimes called liners or, in the case of small pads, shields) are held in place by close-fitting underwear or stretch mesh briefs (Fig VI-1). Some patients experience problems with keeping pads in place using the commonly supplied net pants. As a result, many use more robust stretch pants purchased privately (i.e. cotton / Lycra, etc). Many disposable inserts (Fig VI-2 and Fig VI-3) have an adhesive strip on the back to help secure them and may have an indicator that changes colour when the pad is wet to...
Figure VI-1: Mesh pants with (right) and without (left) legs, for securing incontinence pads in position.

Figure VI-2: Disposable inserts for light incontinence.

Figure VI-3: Disposable inserts with (right) and without (left) standing gathers, for moderate / heavy incontinence.
signal the need for a change. They may have longitudinal, elasticated standing gathers of hydrophobic material intended to impede lateral leakage of urine and faeces. They are sometimes rectangular but are more usually shaped to fit the body more snugly. Elastication at the legs may also be used to enhance fit. Washable inserts (Fig VI-4) are usually more simply designed than disposable inserts, with no elastication and are either shaped or a simple rectangle. Inserts are made in a wide range of sizes suitable for light through to very heavy urinary incontinence. For light faecal incontinence, the liner may be a small cotton gauze dressing placed against the anus and held in place by the cheeks of the buttocks (Fig VI-5).

- **Diapers** (sometimes called all-in-ones or briefs) are adult-size versions of babies’ diapers. Disposable diapers (Figs VI-6) usually have elasticated waist and legs and self-adhesive tabs (usually resealable), and often a wetness indicator and standing gathers. More recently modified diapers have been introduced that fasten round the waist before the front is pulled up pant and is either limited to the crotch area or as well as the designs described above. In particular terry-towelling squares may be used by those with heavy incontinence. These may be formed into briefs by folding into different configurations and fastening with pins and covered with plastic pants as a waterproof barrier. It is known that superabsorbers hold much more urine – weight for weight – than fluff pulp and retain it far more tenaciously under pressure. They are usually based on cross-linked salts of polyacrylic acid whose chemistry can be varied according to the balance of properties such as absorption capacity and absorption speed desired. Some thermoplastic fibres are also sometimes included in absorbent cores to reduce core break up and the collapse of the structure when wet. It is increasingly common for absorbent cores to comprise

### Table VI-1. Classification of absorbent continence products

<table>
<thead>
<tr>
<th>Categories:</th>
<th>Disposable (single use)</th>
<th>Washable (reusable)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sub-categories:</strong></td>
<td><strong>Bodyworns</strong></td>
<td><strong>Underpads</strong></td>
</tr>
<tr>
<td>Design groups*</td>
<td>Inserts</td>
<td>Bedpads</td>
</tr>
<tr>
<td></td>
<td>Diapers</td>
<td>Chairpads</td>
</tr>
<tr>
<td></td>
<td>Pull-ups</td>
<td>Pouches</td>
</tr>
<tr>
<td><strong>Sub-groups</strong></td>
<td>Groups sub-divide according to the severity of incontinence (light or moderate / heavy) and the gender of the intended users (M, F or unisex).</td>
<td></td>
</tr>
</tbody>
</table>

* The products within a given design group may vary considerably in their features and their constituent materials.
Figure VI-4: Reusable inserts for light (left) and moderate / heavy (right) incontinence.

Figure VI-5: Liner for light faecal incontinence. It is positioned against the anus and held in place by the cheeks of the buttocks.

Figure VI-6: Disposable diapers with (right) and without (left) standing gathers, for moderate / heavy incontinence. Diapers are shown open (top) and with the tabs secured (bottom).
Figure VI-7: A modified (T-shaped) diaper. The waist band (left) is secured first and then the front pulled up and secured in position (right).

Figure VI-8: A reusable diaper.

Figure VI-9: A disposable pull-up.

Figure VI-10: A reusable pull-up for heavy incontinence.

Figure VI-11: Reusable pull-up pant (also known as pants with integral pad) for lightly incontinent men (right) and women (left).
Figure VI-12: A disposable pouch for men.

Figure VI-13: Reusable pouches for men: side view (left) and front view (right).

Figure VI-14: A disposable underpad.

Figure VI-15: A reusable underpad.
two or more layers, each designed to perform a different function. For example, an upper layer might comprise low absorbency fibres engineered to receive and distribute urine efficiently and maintain a dry layer next to the skin, while lower layers provide absorption capacity. Some disposable products have ‘breathable’ plastic backings designed to reduce skin occlusion.

Washable absorbent cores are usually made from a needlefelt or knitted fabric comprising rayon and / or polyester fibres. A variety of polymers are used for the water-proofing. In general, the thicker, stiffer materials are more durable (the durability of the plastic backing often determines the lifetime of the product) but less comfortable. Topsheets are usually made from either cotton – which is hydrophilic and intended to have good dry comfort – or polyester – which is hydrophobic and intended to have good wet comfort.

Concern for the environment and also for controlling costs has led to an increase in the number of washable products available on the market. An important consideration in the comparison of washable and disposable designs is the relative environmental cost, particularly disposal (landfill) costs of disposable designs and energy costs associated with laundering the washables. A recent report on baby diapers concluded that there was no significant difference in environmental impact between three diaper systems

This means that, like pad performance, users' needs cannot be easily quantified. However, a number of studies have been published on work with pad users described as having moderate-heavy urinary incontinence have yielded corresponding figures of about 250ml and 600ml [51]. Accordingly, in this chapter the material is divided – somewhat simplistically – into that which relates to light incontinence and that which relates to moderate-heavy.

But the published work also makes it clear that some products work better for users whose incontinence is towards the lighter or the heavier end of the spectrum within each of these two groups and so, where necessary in the text and tables that follow, these distinctions are made by dividing light incontinence into “light LIGHT” and “heavy LIGHT”; and moderate-heavy incontinence into “light HEAVY” and heavy HEAVY”.

5. ABSORBENT PRODUCTS FOR WOMEN WITH LIGHT URINARY INCONTINENCE

There are four main product designs for women with light incontinence (Table VI-2). In addition menstrual pads are known to be frequently used for light urinary incontinence. The disposable pull-up group are relatively expensive, single-use items and are seldom used for light incontinence except as ‘emergency’ items. Underpads are not commonly used for light incontinence.

Aspects of assessment that are particularly important regarding pads for women with light incontinence include frequency / severity of leakage, day / night incontinence, individual priorities (e.g. need for discreetness), personal preference for washables / disposables, lifestyle (home / travel / work).

a) Quality of data

A small number of robust comparative evaluations of absorbent pads for lightly incontinent women have been published and there has been a Cochrane review [52]. A recent study has compared the most common designs: disposable inserts, menstrual pads, washable
inserts and washable pants with integral pad. One study has compared a range of disposable inserts and menstrual pads and there have been comprehensive single group studies of disposable inserts and washable pants with integral pads. A further study has compared specially made experimental products that have differed from one another in carefully controlled ways enabling more specific questions about product materials and design to be addressed.

b) Results

Using a crossover design, Fader et al [51] compared disposable inserts, menstrual pads, washable pants with integral pad, and washable inserts. Three products were selected (based on previous study results) to represent each design and each product was tested for one week (three weeks for each design block, total 12 weeks). Order was randomised. Product performance was characterised using a validated questionnaire to evaluate pad performance (leakage, discreetness etc) with a five point scale (very good – very poor) at the end of each week of product testing.

A pad change and leakage diary was used to record severity of leakage from pads (three-point scale: a lot, a little, or no leakage), and numbers of laundry items and pads used were recorded to estimate costs. Skin health changes were recorded weekly. At a final interview preferences were ranked (with and without costs), acceptability of the design recorded (highly acceptable – totally unacceptable) and overall opinion marked on a visual analogue scale (VAS) of 0-100 points (worst design – best design). This VAS score was used to estimate cost-effectiveness.

Eighty-five women (mean age 60) completed the study and 8691 used pads were weighed. The disposable insert was significantly better than the other designs on most variables except for discreetness. For leakage prevention, overall acceptability and preference, disposable inserts were found to be significantly better than menstrual pads, which were better than washable pants with integral pad, which were better than washable inserts. There was no clear benefit for skin health using either washable or disposable designs. Most women preferred the disposable insert pad but some preferred the other cheaper designs (6/85 preferred menstrual pads; 13/85 preferred washable pants), both of which were >50% cheaper to use than disposable inserts. Washable inserts were significantly worse than the other designs (72/85 found them unacceptable). Overall there were generally more practical problems with washables, particularly when away from the home (Level of Evidence 1).

The authors concluded that allowing women to choose their preferred design of absorbent product (or combination of different designs for different circumstances) would be more cost-effective and provide better patient satisfaction than provision of disposable insert pads (the most expensive product) alone.

Clarke-O’Neill et al. [19] compared the range (12 products) of disposable inserts for lightly incontinent women available in the UK in 2000. Products were tested by 60 community-based women aged 50 years or older who currently used products similar to those to be evaluated. Products were evaluated using a pad performance questionnaire and a pad leakage diary. As a group, the products performed well in terms of their ability to hold urine without leakage. However, the ‘overall opinion’ scores of the testers showed large differences between products with 88% of subjects scoring the most successful insert as Good or OK compared with 51% for the least successful product (p<0.001) (Level of Evidence 2).

A similar study by the same research group [53] compared all 10 washable pants with integral pad for lightly incontinent women available in the UK in 1999. Seventy-two community-based women who usually used absorbent products for light incontinence tested each product for one week each. Leakage performance was found to be disappointing with 69% (CI: 59-78) of the best performing product not leaking at all with 10g of urine, compared to 40% (CI: 29-51) for the least successful product. Again subjects’ ‘overall opinion’ scores showed wide differences between products with the best performing product scoring 85% Good or OK compared with 34% for the least successful product (Level of Evidence 2).

Baker and Norton [54] evaluated six small disposable inserts and two menstrual pads (available in the USA in 1991) with 65 community dwelling women. The products were rated using an evaluation questionnaire and daily diary of pad use. The two menstrual pads (which were the least expensive pads in the study)
scored significantly higher than many of the incontinence products although neither was the most popular pad. The authors concluded that women should try a ‘maxi’ menstrual pad first and then move onto a higher capacity (incontinence) pad if this was inadequate. However, this study was carried out more than 10 years ago and products have changed considerably since then (Level of Evidence 2).

Thornburn et al. [17] studied ‘wet comfort’ using small disposable pads that had been experimentally made using different combinations of materials in an attempt to reduce ‘wetback’ (the tendency of pads to allow urine to escape back on to the wearer’s skin). Twenty women tested the pads. Whenever differences in wet comfort, absorbency or overall performance were found they were in the expected order but differences were small and few reached statistical significance. The clinical value of including technically superior materials was not strongly supported. However this was a small study and may have had insufficient power to detect significant differences (Level of Evidence 2).

c) Summary

There is robust evidence that disposable inserts are more effective in terms of leakage and more acceptable than menstrual pads, washable pants and washable inserts (Level of Evidence 1). Menstrual pads are cheaper and washable pants cheaper still (on a per-use basis) and are acceptable to many, particularly those with lighter incontinence and particularly when used at home. Washable inserts are not acceptable to most women. The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in Fig VI-16.

d) Recommendations

- Disposable inserts are recommended as the most effective and preferred absorbent product for women with light incontinence (Grade of Recommendation B).
- Menstrual pads or washable pants may be sufficient for some patients with very light incontinence and are cheaper (Grade of Recommendation B).
- Washable inserts are not recommended (Grade of Recommendation B).
- Combinations of designs for different situations (e.g. disposable inserts for going out, washable pants with integral pad for staying at home) are likely to provide optimum management in terms of patient needs and cost-effectiveness, and product advice and provision (where purchased by institutions / services) should reflect this (Grade of Recommendation B).
- See also the general recommendations relating to pad selection in Section VI.11 and to washable pads in Section VI.12.

e) Research priorities

- Because the performance of washables was generally poor (particularly for leakage) compared to disposables, the development of better washable products is a priority.
- The use of combinations of designs for different situations needs to be evaluated.

6. ABSORBENT PRODUCTS FOR MEN WITH LIGHT URINARY INCONTINENCE

There are five main product designs for men with light urinary incontinence (Table VI-4). However, disposable and washable insert pads are often unappealing to men as they are frequently marketed specifically at women and bear a strong resemblance to menstrual pads. Anatomical differences are also likely to mean that they are less effective for men. Pouch, shield and leaf products (Figs VI-12 and VI-13) are designed to be more suitable for men by containing the penis or penis and scrotum.

Aspects of assessment that are particularly important regarding pads for men with light incontinence include frequency / severity of leakage, day / night incontinence, retraction of penis, individual priorities (e.g. need for discreetness), personal preference for washables / disposables, and lifestyle (home / travel / work).

Only one study has been published which has evaluated absorbent products for men with light urinary incontinence (55). It compared the four main absorbent designs of products available in the UK in 2003:

<table>
<thead>
<tr>
<th>Table VI-4. Bodyworn absorbent products for lightly incontinent men.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design groups</td>
</tr>
<tr>
<td>Inserts (Fig VI-2)</td>
</tr>
<tr>
<td>Pouch (Fig VI-12)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

1546
Figure VI-16: Designs of pads for women with light urinary incontinence. For definitions of light LIGHT and heavy LIGHT, see Section VI.4.
disposable insert pads, pouches and leaves and washable pants with integral pad. All six leaf products (five disposable and one washable) and all six pouches (all disposable) on the UK market in 2003 were evaluated, together with a selected disposable insert pad and a selected washable pant with integral pouch (chosen to represent their respective designs).

Seventy men with light urinary incontinence completed the 14 week study and filled out product performance questionnaires at the end of testing each product for a week. Products were supplied in random order within their design group and the design group order was also randomised. Pad leakage diaries were used to record product performance and used pad weight. At the end of testing each design a design performance questionnaire was completed.

‘Overall opinion’ was used as the primary outcome variable. Results showed that the pouch design performed significantly worse than the leaf and the insert design. The most common problems with the pouch were staying in place and difficulties re-inserting the penis in the pouch once the pouch was wet. The leaf designs had the best leakage scores, but one product was significantly better than the other leaves (Tena). The disposable insert was also effective for leakage prevention and was substantially cheaper than the leaf designs. The washable leaf was the least successful of the leaf designs. The washable pants with integral pad received polarised overall opinion scores (loved or hated) and scored well for staying place but poorly for leakage (Level of evidence 2). The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in Fig VI-17.

a) Recommendations

- Disposable leafs are recommended as the most acceptable and effective design for men with light incontinence, but some men prefer other designs which should be considered as alternatives (Grade of Recommendation B).
- Simple insert pads are cheaper and may be acceptable to some men (Grade of Recommendation B).
- Washable pants with integral pad are likely to be most suitable for men with very light incontinence who have difficulties keeping an insert or pouch in place (Grade of Recommendation B).
- See also the general recommendations relating to pad selection in Section 6.11 and to washable pads in Section VI.12.

b) Research priorities

Because the performance of washables was generally poor (particularly for leakage) compared to disposables, the development of better washable products is a priority.

7. ABSORBENT PRODUCTS FOR MEN AND WOMEN WITH MODERATE-HEAVY URINARY INCONTINENCE

There are 12 absorbent product designs for men and women with moderate-heavy urinary incontinence (Table VI-5). The most commonly used products are disposable bodyworn inserts and diapers (Figs VI-3 and VI-6). More recently, modified diapers (T-shaped diapers, Fig VI-7) have been introduced which can be applied by the wearer whilst standing. Pull-ups are also a relatively new innovation and comprise an absorbent pad integrated into a disposable elasticated pant (Fig VI-9). Washable counterparts to most disposable bodyworn designs are available but they have a much smaller market, where they are available. They are made from a variety of natural and synthetic materials. Disposable and washable bedpads are used on the bed at night with or without the support of a bodyworn product. Disposable and washable chairpads are used either without a bodyworn product (in which case the individual must sit directly on the pad with no underpant on) or in combination with bodyworn products to protect chairs from any leakage from the bodyworn. Both practices place an underpad on display and mark the individual as being incontinent and are therefore to be discouraged. Aspects of assessment that are particularly important regarding absorbent pads for moderate / heavy UI are frequency / severity of leakage, day / night incontinence, gender (some products are better for men/women than others), ability to change pad independently / need for carer, pad changing position (standing / lying), laundry / drying facilities, individual priorities (e.g. need for discreetness), personal preference for design / materials (washable / disposable) and lifestyle (at home / travel / work etc).

a) Quality of data

There have been two recent clinical trials comparing the main designs of disposable bodyworn pads (one also included washable designs). There have been no trials of underpads for the last 15 years. There have also been a large number of comparative studies of absorbent products for moderate-heavy incontinence but most are more than 10 years old and evaluated products that are no longer available. Furthermore, changes in materials and design features mean that it is impossible to generalise any particular findings to products of today. Brink (56) identified 30 studies of absorbent products published between 1965-1990. Some robust multi-centre international studies have examined the correlation between laboratory testing and the leakage performance of products clinically.
Figure VI-17: Designs of pads for men with light urinary incontinence. For definitions of light LIGHT and heavy LIGHT, see Section VI.4.

Table VI-5. Absorbent products for moderate-heavy adult incontinence

<table>
<thead>
<tr>
<th>Product category</th>
<th>User characteristics / priorities / contexts which:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposable pouches</td>
<td>- Discretion is a priority (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Using a specifically male product is important (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Penis is retracted (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Incontinence is heavy LIGHT (B/C)</td>
<td></td>
</tr>
<tr>
<td>Disposable leaves</td>
<td>- In general (B/C)</td>
<td></td>
</tr>
<tr>
<td>Disposable inserts</td>
<td>- Low cost is a priority (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Male specific product unimportant (C)</td>
<td></td>
</tr>
<tr>
<td>Washables</td>
<td>- Incontinence is light, LIGHT (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Low cost is a priority (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Design concept is acceptable / preferred (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- User is mobile and active (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Adequate laundry facilities are not available (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Design concept is unacceptable (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Carrying used pads when out is an issue (B/C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Incontinence is heavy LIGHT (B/C)</td>
<td></td>
</tr>
</tbody>
</table>

Table VI-5. Absorbent products for moderate-heavy adult incontinence

<table>
<thead>
<tr>
<th>Type</th>
<th>Disposable (single use)</th>
<th>Washable (reusable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inserts (Fig VI-5)</td>
<td>Bodyworns</td>
<td>Inserts (Fig VI-4)</td>
</tr>
<tr>
<td>Diapers (Fig VI-6)</td>
<td>Underpads</td>
<td>Diapers (Fig VI-8)</td>
</tr>
<tr>
<td>T shaped diapers</td>
<td>Bedpads</td>
<td>T shaped diapers</td>
</tr>
<tr>
<td>Pull-ups (Fig VI-9)</td>
<td>Bedpads, chairpads</td>
<td>Pull-ups</td>
</tr>
<tr>
<td></td>
<td>Disposable pouches</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disposable leaves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disposable inserts</td>
<td></td>
</tr>
<tr>
<td>Washables</td>
<td>Disposable pouches</td>
<td></td>
</tr>
</tbody>
</table>
b) Results

1. Evaluations comparing different designs of disposable and / or washable body worn absorbent products for urinary incontinence

Fader et al. [51] carried out two clinical trials of absorbent products for moderate-heavy incontinence; one involving subjects in the community and the other subjects in nursing homes. In the community-based trial 85 moderate / heavily incontinent adults (urinary or urinary / faecal) living in their own homes (49 men and 36 women) were enrolled, and tested three (or two) products from each of five design categories (total of 14 test products): disposable inserts (with mesh pants); disposable diapers; disposable pull-ups; disposable T-shape diapers; and washable diapers. All products were provided in a daytime and a (mostly more absorbent) night-time variant. Products were selected based on having similar scores for absorbency across the designs (Rothwell scores, (50) see below) and performance data from pilot studies. In the nursing-home-based trial 100 moderate / heavily incontinent adults (urinary or urinary / faecal) living in a total of 10 nursing homes (27 men and 73 women) evaluated one product from each of the four disposable design categories above. Products were selected on the basis of product performance from the community-based trial and, again, day and night-time variants were provided.

Product performance was characterised using validated questionnaires which asked the participants (in the community-based trial) or carers (in the nursing home based trial) to evaluate various aspects of pad performance (leakage, ease of putting on, discreetness etc) using a five point scale (very good – very poor) at the end of the week (or two weeks for the nursing-home-based trial) of product testing. In addition, participants / carers were asked to save individual used pads in bags for weighing and to indicate the severity of any leakage from them on a three-point scale (none, a little, a lot). These data were used to determine differences in leakage performance. Numbers of laundry items and pads used were recorded to estimate costs, and skin health changes were recorded by the participant or by the researchers. At the end of testing participants were interviewed and ranked their preferences (with and without costs), stated the acceptability of the design (highly acceptable – totally unacceptable) and recorded their overall opinion on a visual analogues scale (VAS) of 0-100 points (worst design – best design). A pad changing experiment was conducted with 12 women from the nursing home based trial to determine any differences between product designs. Under idealised conditions the different designs were applied (by the same carers) in random order for each patient and the speed of pad changing was timed using a stop-watch.

Findings from the community-based and nursing home trials were broadly similar. The leakage performance for the disposable inserts was worse than the other designs for day and night and disposable pull-ups were preferred over inserts for the daytime. The new T-shape diaper was not better overall than the traditional disposable diaper. But there were important differences in performance and preference findings between men and women from both trials and the men (in the community) had more severe urinary incontinence than the women - mean daytime urine mass 375 g for men and 215.g for women (difference148g, CI: 79.8, 217.7).

Pull-ups (the most expensive design) were better overall than the other designs for women during the day and for community-dwelling women during the night too. Although disposable diapers were better for leakage than disposable inserts (the cheapest), women did not prefer them, but for men (in the nursing homes and the community) the diapers were better both overall and for leakage and were the most cost-effective design. No firm conclusions could be drawn about the performance of designs for faecal incontinence and there was no firm evidence that there were differences in skin health problems between designs (Level of Evidence 1).

In the nursing home trial the carers found pull-ups and inserts significantly easier to apply (in the standing position) and significantly quicker in the pad change experiment (mean time 35.2 and 37.9 seconds for inserts and pull-ups respectively and 53.2 and 62 seconds for diapers and T-shaped diapers respectively) and ability to stand was associated with preference for pull-ups or inserts. Despite being designed for ease of changing the T-shape diaper was not found to be easier or quicker to change than the diaper.

The washable products (used in the community-based trial) gave diverse results. Two of the products were made from cotton terry-towelling (one a simple square, folded and pinned in a diaper shape; the other a shaped diaper-like design, both worn with plastic pants) while the third product had a felt absorbent core, with an integral plastic backing and was fixed by poppers. This third product performed significantly worse for leakage than the other two washables and was therefore excluded from the final data analysis. The terry-towelling washables were better for leakage at night than the other disposable designs, but were less popular overall for daytime use than the other disposable designs. Three quarters of the women (27/38) found them unacceptable, but nearly two thirds of men (31/49) found them highly acceptable at night.

Findings from the community-based trial showed that there were many practical problems dealing with washable products particularly when out of the house, but that they were more acceptable at home.

Macaulay et al, [21] carried out a pilot study of 19...
washable products with 14 community dwelling subjects. The products included a mixture of washable insert and brief designs and two disposable bodyworn products. Product performances varied widely: the most popular was rated as good (for overall performance) by 78% of testers, while the least popular scored 22%. Although most of the washable products performed poorly for leakage, one washable product made of cotton towelling (used with plastic pants), scored better than both the other washable and disposable products (Level of Evidence 3).

Seven older trials have compared disposable with washable bodyworn products for moderate-heavy incontinence [57-63]. The trials varied in size and design from a large controlled trial with 276 subjects [57] to a small trial of eleven subjects [60]. In addition some trials have compared disposable and washable bedpads and body-worns. Brown [23] [64] undertook a large trial of this kind. The fact that no systematic method of product selection was used for these studies limits the utility of the results since particularly good or poor products may have been selected to represent the disposable or washable groups.

Skin condition was used as an outcome measure in five of the above trials. However, only three used an experimental design and statistical methods of analysis. Beber [57] and Grant [58] both reported that they did not find statistically significant differences between their washable and disposable products in terms of an adverse change in skin condition. But Hu et al. [65] reported a statistically significant improvement in the skin condition of their disposable product users as compared to their users of washable products (See Section XIV).

Other parameters frequently investigated in these studies were staff preference, product leakage and laundry. Overall, the disposables in the studies were considered to have performed better than the washable products in terms of preventing leakage (often measured by quantity of laundry) and staff preference.

Four studies attempted to measure costs [58, 59, 64,66]. Of these, three used statistical methods of analysis. Hu et al. [66] and Brown [64] reported that although there were no statistically significantly differences in terms of per-day product costs of washable and disposable products, the laundry costs associated with the disposable product (ie for laundering soiled bed linen and clothes) were significantly lower than those associated with the washable product (ie for laundering the products as well as soiled bed linen and clothes). Brown [64] found no significant differences between daily costs of the washable and disposable products. However, statistically significant differences were found between the groups in terms of incontinence-related laundry, with the disposable group producing less laundry than the washable group. Grant [58] reported that the cost of washable products was significantly lower than that of disposables, but laundry costs were not taken into account. (see committee 22)

2. Disposable absorbent products for urinary incontinence: studies of single designs, laboratory tests and studies of materials

Clancy and Malone-Lee [67] compared versions of the same pad experimentally engineered to have different combinations of fluff pulp and topsheet materials. Forty-five heavily incontinent older adults participated. The main valuable finding from this study was that pads were more likely to leak if they were not held in place by pants (p<0.0001) and that, if there was any leakage from a pad, this tended to be less severe if the supplied mesh pants were worn than if normal pants were worn (p<0.05) (Level of Evidence 2). The mesh pants probably held pads more firmly to the body.

There have been two single design group studies of bodyworn products for moderate-heavy incontinence [68,69], both carried out in nursing homes. A study of shaped insert pads involved 228 subjects from 33 nursing / residential homes who tested 20 ranges of insert pads (74 products in total). A similar study of diapers involved 192 subjects from 37 nursing / residential homes who tested a total of 36 products. These studies showed the wide range of product performance that can exist within single product groups. For example, the least successful diaper (based on 'overall opinion') was found to be unacceptable to 100% of the test subjects while the most successful was unacceptable to only 6% (Level of Evidence 2).

In addition, there have been a number of studies on the impact of wet pads on skin health and these are reviewed in Section XIV.

Because clinical evaluations are expensive and time-consuming, laboratory evaluation procedures are in widespread use. Few have been clinically validated but there is a clinically-validated International Standard relating to the leakage performance of disposable bodyworn pads for moderate-heavily incontinent adults in institutions [50]. It describes a simple method for measuring the absorption capacity of pads in the laboratory that was shown to correlate well with the leakage performance of 18 different products evaluated in an international multi-centre clinical study involving 112 heavily incontinent adults [70] The strength of the correlation between technical and clinical data data depended on the exact parameters being compared, but typically r = 0.9 (Level of Evidence 2). This laboratory test (the Rothwell method) is now in common use in the UK, Sweden and other countries and provides a basis for selecting similar products with which to make direct comparisons (for cost purposes) or to select promising pads for inclusion in clinical trials.
The ability of ISO 11948-1 to predict the leakage performance of more recent bodyworn pads (138 diapers and inserts) for heavy incontinence was investigated by Cottenden et al. [71]. Correlations were poorer than in the original 1993 study (r<0.87 compared with r>0.95) but still strong enough to make the method useful. For a given Rothwell capacity, the leakage performance of diapers was far superior to inserts, but no evidence was found for any other design feature of the test products (inserts and diapers) having a significant impact on their leakage performance (Level of Evidence 2).

The repeatability and reproducibility of the ISO 11948-1 was investigated by Cottenden and co-workers [72] in three laboratories (UK, Spain and Sweden). Repeatability (precision between repeats in the same laboratory) was found to be very good with the coefficient of variation for five repeats rarely exceeding 5%. However, the reproducibility (precision between laboratories) was poorer, revealing systematic differences: results from the Swedish and Spanish laboratories typically exceeded those from the English laboratory by 13% and 8%, respectively. Efforts to identify the source(s) of this poor reproducibility have so far been unsuccessful but it seems likely that minor variations in interpretation of the standard when constructing the apparatus and/or executing the test are to blame (Level of Evidence 2).

c) Summary

Results from these studies indicate that there is no single best design (i.e. one design that is significantly better than all other designs for all users) (Level of Evidence 1). There is evidence that different designs are better for men and women, and that men leak substantially higher volumes of urine than women (Level of Evidence 1). Of the disposable designs, the more expensive pull-up and T-shaped diaper designs are not better overall than the cheaper diaper for men, indicating that the diaper is the most cost-effective design for men. For women pull-ups are better overall than the other designs (except for night-use in those living in nursing homes), but they are expensive (Level of Evidence 1). Unlike men, women in the community do not favour diapers over insert pads and of these cheaper designs, inserts may be preferred for women. There is also evidence that the leakage performance of inserts is worse than other designs, but that they leak significantly less if they are held in place by mesh pants than by ordinary pants, and using no pants at all is associated with significantly more leakage than if either kind of pant is worn (Level of Evidence 3). There is evidence that pads containing superabsorber leak less, are more comfortable, and keep the skin drier than those without (Level of Evidence 2). The leakage performance of inserts and diapers for heavy incontinence can be predicted with reasonable precision using an international standard laboratory tests (Level of evidence 2). This test has been shown to have very good repeatability and adequate reproducibility (Level of Evidence 2). Washable products are very varied in design and materials, and also in performance. There is evidence that terrycloth products (used with plastic pants) have good leakage performance, however they have limited acceptability - confined mainly to some men at night. There is no firm evidence regarding the performance of different designs for faecal incontinence and no firm evidence that any particular design or type of material (washable or disposable) is better or worse for skin health.

The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in Fig VI-18.

d) Recommendations

- **Gender** should be considered when products are prescribed/purchased for users. As men often have substantially higher incontinent urine volumes than women, men may require more products and/or more absorbent products than women (Grade of Recommendation B).

- **Gender** should also be considered when products are prescribed/purchased for users because men and women are likely to prefer different designs. Men generally prefer disposable diapers to inserts (Grade of Recommendation B).

- Women generally prefer disposable pull-ups to other designs, but these are expensive. Disposable inserts are a cost-effective alternative (Grade of Recommendation B).

- **Caution** is recommended if washable designs are being considered. Heavy bulk confines their use mainly to the night-time (where they may be particularly useful for users who lie on their side). They are unacceptable for most people during the daytime and for most women at any time and for this reason a blanket policy of health services providing washables alone is not recommended. If washables are being considered refer to points below (Grades of Recommendation B).

- **Freedom from leakage**: Where possible, international standard laboratory tests should be used to rank the likely leakage performance of different pads for heavy and light incontinence (Grade of Recommendation B). In general, diapers should be selected in preference to inserts to minimise leakage (Grade of Recommendation B).

- **Carer application**: When products are applied by a carer to a patient who can stand for pad changing, disposable inserts or pull-ups are
Figure VI-18: Designs of pads for adults with moderate-heavy urinary incontinence. For definitions of light HEAVY and heavy HEAVY, see Section VI.4.
e) Research priorities

- Comparison of absorbent products (disposable and washable) when used by carer-dependent users in the community.
- Development of more effective and aesthetically acceptable washable products, particularly for night-time use and for women.
- Development of more effective and acceptable disposable designs specifically for men.

8. DISPOSABLE UNDERPADS

There have been no published studies examining the use of bedpads during the last 15 years. This probably reflects the recognition of their limited role in long-term management of incontinence. Disposable underpads on chairs declare their user to be incontinent and require clothes to be pulled up (or absent) which is unacceptable for dignity. In the bed disposable underpads easily become displaced, folded and creased under the patient which inhibits their performance and comfort, and may potentially be a threat to skin health. Large disposable underpads with wings to tuck into the bed may have a role as bed protection ‘back-up’ to bodyworn pads. The main role of disposable underpads should be confined to temporary bed or chair protection such as during clinical procedures (e.g. enemas) or when using a urinal.

Published trials comparing different disposable bedpads are few [23] [73,74] and it is not possible to draw firm conclusions from them on the effectiveness of different product design features and materials. Some useful work has been done to highlight the risks of infection from disposable bedpads and to validate clinically some laboratory tests to assist with product selection by predicting pad leakage performance.

Bedpads are generally supplied as non-sterile items and Bradbury [75] has drawn attention to the risk of infection, particularly from products containing recycled paper. Leigh and Petch [76] and Sprott et al. [77] have conducted microbiological tests on a range of products. Both studies identified low levels of bacterial contamination but concluded that the risk to patients was minimal unless they were immunocompromised in some way. More recently, Stansfield and Caudle [78] reported an outbreak of wound colonization on a surgical orthopaedic hospital ward which they attributed to the use of disposable underpads containing virgin wood pulp.

Due to the paucity of published clinical data many technical tests have been devised to evaluate products in the laboratory. The only tests with published clinical validations are described by Cottenden et al. [70] who subjected six different bedpads to a variety of laboratory tests and to a multi-centre clinical evaluation in which 95 incontinent subjects tested each product in turn for a week, in random order. A combination of two laboratory tests (one to measure the absorption capacity and the other the absorption time of bedpads) gave a strong correlation with the percentage of subjects finding the leakage performance of a product acceptable when used as their sole protection (r = 0.94) and predicted the acceptability scores of all six products accurate to within ± eight percentage points. A different absorption capacity test produced a strong correlation for the leakage performance of bedpads used as back-up to bodyworn products (r = 0.96) and predicted the acceptability scores of all six products to within ± five percentage points.

a) Summary

No robust data are available on the effectiveness of current disposable bedpads or of their various design features or constituent materials. There is a risk of infection from bedpads made from recycled paper for immunocompromised users (Level of evidence 2). The leakage performance of bedpads (used alone or as back up to bodyworn pads) can be predicted with reasonable precision using clinically-validated laboratory tests (Level of Evidence 2).

b) Recommendations

- Disposable underpads should not be used for long-term management of incontinence, but have a useful role as temporary protection for chairs and beds during clinical procedures (Grade of Recommendation C).
- Immunocompromised people should not use bedpads made from recycled paper because of the risk of infection (Grade of Recommendation B).
- Where possible, clinically-validated laboratory tests should be used to rank the likely leakage performance of different products (Grade of Recommendation B).
c) Research priorities

Disposable underpads have a limited role in continence management but are known to be widely used. An exploration of patient views regarding their use may help demonstrate their limitations.

9. WASHABLE UNDERPADS

Aspects of assessment that are particularly important regarding washable underpads are patient acceptability and preference, particularly with regard to willingness to be naked below the waist (if sole use intended) and availability of laundry and drying facilities.

Cottenden [79] has reviewed comparative evaluations of different washable bedpads up to about 1990. Leiby and Shanahan [80] have since published a study. Some evaluations have found significant differences between products relating, for example, to leakage performance and impact on skin health but none of the products evaluated is still available in the variant tested. In addition, compared products always differed from one another in many respects making it impossible to draw reliable generic conclusions relating to the products now available. However, the choice of topsheet material and the presence or absence of features like tuck-in flaps and integral water-proofing appear to be, primarily, matters of personal preference.

In institutional settings washable bedpads are commonly used by multiple patients and questions are often asked about the risk of cross-infection. Cottenden et al. [81] assessed the risk by determining the microbial content of 145 bedpads of five different designs after a night’s use by incontinent adults, followed by laundering using a standard foul wash procedure which included heat disinfection at 71°C for three minutes. Laundering destroyed all known pathogenic organisms, although some commensal flora were isolated in small numbers. It was concluded that foul wash laundry had left bedpads safe for multiple patient reuse with no demonstrable risk of cross-infection.

a) Summary

The literature contains insufficient robust data on which to base guidelines for choosing between washable bedpads. Choice of topsheet material and the presence/absence of design features like tuck-in flaps and integral/separate water-proof backing appear to be, primarily, matters of personal preference (Level of evidence 3). Provided an approved foul wash procedure is used, the risk of cross-infection between different users of a bedpads is very low (Level of Evidence 2).

b) Recommendations

- If considering using washable underpads for sole use (ie without a bodyworn product) the patient will need to be naked below the waist.

Patient consultation and approval will therefore be needed (Grade of Recommendation C).

- Personal preferences of users with regard to topsheet material, tuck-in flaps and integral waterproof backing should be considered in making product selections (Grade of Recommendation C).

- Provided an adequate foul laundry wash cycle is used, the risk of cross-infection between successive users of washable bedpads is low and not a contra-indication for their use (Grade of Recommendation B).

c) Research priorities

Comparison of washable underpads with bodyworn products when used at night.

10. ABSORBENT PADS FOR CHILDREN WITH URINARY AND / OR FAECAL INCONTINENCE

Most children are expected to achieve daytime dryness by the age of three [82]. However, some children take longer to become dry and some (e.g. children with learning and physical disabilities) may never reach this goal. These children usually require absorbent products to contain leakage. (see committee 9)

Aspects of assessment that are particularly important regarding bodyworn products for children are presence of faecal incontinence, day / night incontinence, level of independence with toileting, and use of aids (e.g. callipers).

To date there has been only one study of absorbent products for children and this has compared the diaper design with the newer pull-up design (83). Sixty-one children with physical and / or learning disabilities tested five diaper products and five pull-up products, each testing each product for one week. The children were randomised to receive either the pull-up or diaper group first and individual products were tested in random order within each design arm. Parents completed a product performance questionnaire and a pad leakage diary to record wet weights and severity of leakage. Parents were asked to state their preference for a design for day and night use.

Findings indicated that generally, the diaper products performed similarly to each and so did the pull-up products, although there were some statistically significant differences between products within each of the two design groups. Overall diapers were preferred for night-time use by the majority of parents. By contrast, 40% of parents preferred pull-ups for daytime use and these were found to be particularly appropriate for older children and those who were attempting independent toileting, provided they did not have faecal incontinence and did not wear callipers or adapted footwear. Diapers were more suitable for
children who were dependent on carers and / or had faecal incontinence, and wore callipers or adapted footwear. The authors recommended that both diapers and pull-ups should be supplied for children, with pull-ups (which are about 50% more expensive than diapers) being provided for selected children during the daytime.

a) **Summary and recommendations**

Diapers and pull-ups meet different needs of children and both should be made available to children with disabilities, dependent on assessment (Level of Evidence 3 / Grade of Recommendation C).

b) **Research priorities**

Comparison of washable and disposable bodyworn products.

11. **PADS FOR FAECAL INCONTINENCE**

Most absorbent products are designed for urinary incontinence. No studies comparing available absorbent products for faecal incontinence were found. Bliss et al. [84] reported preliminary findings of a survey of the use and evaluation and suggested modifications of absorbent products for faecal incontinence by 188 community-living persons with the problem. Forty-five percent of persons used an absorbent product for FI. Ninety-eight percent of those with UI and FI used the same type of product for both. Suggested improvements in product designs included having better odour control, fit, and ability to stay in place; a clearer distinction between the front and back of a pantiliner or pad; adding wings for greater absorbency; and making them flushable, cooler feeling, wider and longer in the rear and more absorbent but less bulky. For mild faecal incontinence, especially when faeces remain between the buttocks without soiling underwear, persons have used a small disposable gauze surgical dressing placed between the buttocks. This product was more acceptable than a pantiliner or pad to some men [84] (Level of Evidence 2).

a) **Recommendations**

- A disposable gauze dressing that can be placed between the buttocks maybe acceptable for men with light faecal incontinence (Level of Recommendation C).

b) **Research priorities**

- Better designs of products are needed for light and moderate FI (with and without UI).

12. **GENERAL RECOMMENDATIONS ON PAD SELECTION**

- **Individuality:** No study has ever identified one product that worked best for all testers: needs and priorities vary. Accordingly, users are advised to try a variety of products when possible (Grade of Recommendation B).

- **Brand differences:** The individual product brands within a design group often exhibit a wide range of performance and acceptability for individuals, and it cannot therefore be assumed that pads of different brands but broadly similar design will be equally acceptable or effective (Grade of Recommendation B).

- **Combinations of designs:** Absorbent products vary greatly in price and performance and suitability for individual needs. Users may therefore find combinations of designs preferable and cost-effective. For example, women might use pull-ups (expensive, but discreet and good for leakage) for going out, and inserts (cheap, less good for leakage) for staying at home. Men might use disposable diapers for daytime, and washable terry-towelling products for night-time (Grade of Recommendation B).

- **Freedom from leakage:** In general, pads containing superabsorber should be selected in preference to those without (Grade of Recommendation B). Nobody wants their pad to leak but compromises have to be made: the pad needed to contain a person’s most severe accident may be substantially more bulky and expensive than is needed most of the time. Some users choose to tolerate a higher risk of pad leakage in exchange for being able to use cheaper, smaller (more discrete) pads. The balance of priorities for a given user should be investigated in making product selections (Grade of Recommendation C).

- **Comfort and skin health:** In general, pads containing superabsorber should be selected in preference to those without (Grade of Recommendation B). Shaped pads should usually be selected in preference to unshaped (Grade of Recommendation C).

- **Staying in place:** No product is effective if it slips from position. Inserts should be used with pants, preferably mesh pants (Grade of Recommendation B). Robust, stretch (e.g. cotton / lycra) pants may also help to provide a snug fit and minimise leakage. Shaped pads are preferable to rectangular (Grade of Recommendation C).

- **Ease of putting on and taking off:** The ease of putting pads on and taking them off should be considered, especially for caregivers and for incontinent users with reduced mobility or dexterity (Grade of Recommendation C).
13. RECOMMENDATIONS RELATING TO WASHABLE PADS

- **Laundry issues:** Access to good, reliable washing and drying facilities should be checked before washable products are introduced (Grade of Recommendation B). Laundry – especially of bedpads – can be heavy work, beyond the capability of frail incontinent people or their caregivers. The number of washable products needed per user depends on laundry turn-around times. Drying times for washables can be long and expensive, especially for bodyworns for heavy incontinence and for bedpads.

- **Personal preferences:** Personal preferences (of both users and caregivers) with regard to choosing between washable and disposable products should be taken into account carefully (Grade of Recommendation C). Some users prefer the chore of laundering washables to anxiety over whether their next consignment of disposables will be delivered on time. Washables generally require less storage space than disposables. Discreet disposal of disposables can be a challenge. The possibility of using a mix of disposable and washable products should be considered (Grade of Recommendation C).

- **Aesthetics and discretion:** A possible preference for small, more discrete pads (even if they are more likely to leak) should be considered, especially for those wishing to wear close fitting clothing (Grade of Recommendation C). The possibility of plastic backing materials rustling noisily should be considered (Grade of Recommendation C).

- **Independence and lifestyle:** The ability of a user to change his / her own pad should be considered (Grade of Recommendation C); those able to change their own pad can often manage with a smaller (less absorbent) one than those reliant on a caregiver. Users who travel should consider in their choice of product(s) the practicalities of carrying a supply of pads, disposing of used ones, and dealing with laundry (Grade of Recommendation C).

- **Costs:** Cost issues should be approached with caution (Grade of Recommendation C). Expensive pads do not necessarily work better than cheaper ones. Cheaper pads do not necessarily save money. If pads leak more they may have to be changed more frequently and / or lead to higher laundry costs. More pad changes will mean increased caregiver workload. However, more absorbent pads will not necessarily reduce pad consumption rates: pads are often changed according to ward or personal routine.

Some users who choose disposables when at home prefer washables when travelling because of the space that disposables occupy in luggage and the possible inconvenience of disposal. Others use washables at home and disposables when away as they see the balance of disadvantages and advantages differently.

- **Personalisation of products:** In institutions, the chore of personalizing washable products and sorting them after each laundry cycle should be considered before they are introduced (Grade of Recommendation C). Washable bodyworns are often personalised to particular users. In institutions this means marking products with users’ names and sorting them after laundry, an extra task for caregivers. Washable bedpads are not usually personalised.

- **Staining:** Washable products should not usually be used by those with faecal incontinence – beyond occasional light smearing – because of staining (Grade of Recommendation C). Skin sprays and ointments may stain washables too.

- **Costs:** Cost comparisons between washable and disposable products should be made with caution (Grade of Recommendation C). Key factors are: local arrangements (mostly laundry and transport costs); the durability of the products (which depends on how carefully they are used and the criteria for deciding when they should be replaced); the costs of ordering, transporting and disposing of disposables; and product purchase costs. Much of the cost of washables is encountered with the initial capital outlay for stock. This also represents a commitment to use the products for an extended period and so expensive mistakes can be made if it transpires that a better product was / has become available. It will usually be wise to experiment with samples of a variety of alternative products before committing to major purchases.

### VII. SHEATHS

Close-fitting penile sheaths (sometimes called condom catheters, urodomes or external catheters) are commonly used male incontinence devices and they are used in combination with a urine drainage bag. They are suitable for males who are experiencing moderate to heavy urine loss, or have limited mobility and are experiencing frequency and urgency and may even be considered in combination with intermittent catheterisation (IC) for males who are leaking urine as a consequence of bladder emptying problems. Sheaths may not be suitable for males who are experiencing confusion, considered psychologically
vulnerable or have decreased sensation through spinal cord injury [85-87]. There is strong opinion expressed in the literature that suggests assessment, selection and use of penile sheaths and the accompanying urine drainage systems needs to be undertaken with the guidance, education and monitoring of health professionals who have a knowledge of continence products. Failure to do so, according to this expert opinion [86-87], may result in serious penile trauma, impaired penile skin integrity and leakage of urine.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important in relation to sheaths include: physical, mental, cultural, gender and socio-economic factors. This incorporates assessment of the cognitive and dexterous ability of the male or carer to apply the sheath and empty the drainage bag, the integrity of the penile skin, length and circumference of the penis and whether it is retracted, or retracts on sitting or bending down, history of latex or adhesive allergy and, most importantly, recognition that the assessment from the health professional needs to be ongoing. It is also important to assess factors known to encourage or discourage sheath usage. Expert opinion [86, 89,90] suggest factors that encourage usage include: level of reimbursement, cultural expectation, resonance with masculine image, and ability to keep urine off the skin when the skin integrity is at risk because of incontinence. Factors which they suggest discourage usage include: ignorance of product efficacy by professionals and consumers and embarrassment between carer and client.

An effective sheath is one that stays securely in place for an acceptable period of time, is leak-free, comfortable to wear, easy to apply and remove, avoids skin damage and channels the urine effectively into a urine drainage bag.

1. PRODUCT CATEGORIES AND FEATURES

Sheaths come with a variety of features (Fig VII-1) of which the following are the most important to consider in making selections:

- **Material**: sheaths may be made from latex, silicone rubber or other synthetic polymers. Some men will be allergic to latex.
- **Size**: most sheaths are supplied in a range of lengths and sizes. Most companies supply them with diameters in the range of about 20 – 40 mm, in 5-10 mm increments.
- **Adhesive**: the adhesive may be integral to the sheath (one-piece systems) or come as a separate strip or spray (two-piece systems). Some men will be allergic to some adhesives.
- **Applicator**: some sheaths come with an applicator intended to help users and carers to put the sheath on.
- **Anti-kinking / twisting features**: some sheaths come with features intended to improve drainage by reducing kinking and twisting at the distal end, near the connection to the drainage bag tube.
- **Anti-blow-off features**: some sheaths come with features intended to reduce the likelihood of the sheath blowing off at high urine flow rates; for example, at the beginning of a void (eg the distal end of the sheath may be thickened and bulbous to stop the internal walls sticking to one another between voids).
- **Connection to the drainage bag**: some sheaths come with features intended to increase the ease and security of connection to the drainage tube (eg a push ring or ridge at the end of the outlet tubing)
- **Retracted penis features**: with or without specific features intended to accommodate a retracted penis (eg a shorter sheath or a wider adhesive seal).
- **Durability**: some sheaths are intended for use over a limited time period (eg 24 h) while other (generally, more robust) designs are intended for extended wear.
- **Transparency**: some sheaths are transparent allowing for observation of the condition of the skin along the shaft and glans of the penis.

2. QUALITY OF DATA

Some controlled comparative evaluations of different sheaths have been performed; one extensive market survey to identify the needs and priorities of sheath users; and one study to compare a sheath with an indwelling urethral catheter. Other studies report on the problems encountered by various groups of sheath users.

3. RESULTS

Although many men use sheaths successfully, problems have been reported in the literature. In a study on an unspecified number of spinal cord injured men, Goli [91] found that 15% experienced side effects or complications when using sheaths. These were irritative, allergic or compressive in nature. Jayachandran et al. [92] reported similar experiences with six incontinent men of widely varying aetiology and highlighted the importance of ensuring that the sheath does not become twisted near the distal end to avoid stagnation of urine and the risk of UTI. They also stressed the importance of good genital hygiene to avoid problems with infections. In a study of 94 men on medical / surgical wards, Hirsh et al. [93] found that none of the 79 who were judged as cooperative and able to manage their sheaths properly developed UTI (mean period of use, 21.2 days). By contrast, eight of 15 patients who tended to tug and kink the drainage tube attached to their sheath.
developed UTI within a mean of 9.6 days. In a retrospective study, Johnson et al. [94] compared the frequency of UTI in users (mean period of use, 35 months) and non-users of sheaths amongst 64 elderly men on an extended care unit. He found that 63% of users but only 14% of non-users developed UTI. No difference was found between men who did and did not tug and kink their tubing. Ouslander et al. [95] reported that 40% of 30 nursing home sheath users (mean period of use, 35.9 months) developed at least one UTI. The need for proper fitting of the sheath and regular monitoring of the skin integrity of the penile shaft, glans penis and prepuce of males who are regular sheath users has been highlighted in two articles that report a combined total of eight cases of fibropithelial polyps of the glans penis and prepuce of which six had a history of long term sheath use [88] [96].

A trial to compare sheaths and indwelling catheters in terms of infection, risk and patient satisfaction has been reported by Saint et al [97]. This was a prospective, randomised unblinded controlled trial which compared one type of sheath drainage with one type of indwelling urethral catheter using a small group of participants (N=75) across several locations in one hospital. There are important limitations of the study, including the low numbers drawn from a specific population, and the lack of comment on the changing / care routines associated with the sheaths and catheters. After making adjustments for age, mental score, history of UTI and history of catheterisation the conclusions of the study were that for males without dementia the use of sheaths has the potential to reduce infection compared to indwelling catheters and is more acceptable to patients in terms of comfort and pain. For males with dementia no significant difference in infection rates was found.

Nichols and Balis [98] reported the results of a survey undertaken for marketing purposes of an international cohort of 216 men who had used sheaths for at least three years, and their carers. Their responses to 19 brands of sheath were gathered using a questionnaire in the form of a Likert scale. It was found that catheter security (presumed to mean staying in place and freedom from leakage) was the most important issue for both wearers and carers, followed by comfort and ease of application and removal.

There have been a number of comparative evaluations of different sheaths. Peifer and Hanover [99] reported on an evaluation in which 20 men compared a new branded sheath system, that consists of three parts: a tubular sheath impervious to urine with a drainage tube connection at one end and a ring at the other; an undergarment with a frontal opening through which the penis is extended; and a ring-like collar which is used to keep the sheath and penis in the correct position, with the variety of external sheaths they had previously been using. The participants were a convenience sample identified through pharmacy medication files. In all 32 men were approached and

Figure VII-1: A variety of sheaths (top left and bottom right), a sheath applicator (top right) and an external fixation strip (bottom left).
20 consented, all experienced users of urinary sheaths. A questionnaire was developed to test the participants pre and post intervention. The new sheath – which was used for a week - proved more popular with the participants: it was judged to provide superior security (13/20 experienced increased dryness by day; 10/20 by night), and considered easier to apply (19/20) and remove (20/20).

In a multi-centre study involving 35 men (age range 22-87y; mean age, 54y; 34 living in their own homes), the UK Medical Devices Agency [100] compared four latex sheaths: two with integral adhesive; and two in which the adhesive was supplied as a separate strip. They found the products with integral adhesive to be more successful in both overall performance and ease of application. Fader et al. [101] conducted a multi-centre study to compare all six sheaths with integral adhesive on the UK market in 1998. Five were made from latex, one from silicone rubber. Four were supplied with an applicator, two without. Fifty-eight men (age range 26-88y; mean age 53y) were given the opportunity to try each sheath in turn for one week. The silicone rubber sheath was found to be significantly better than four of the other sheaths in overall performance (p<0.01). The ease with which a sheath could be put on was found to be the best predictor of overall performance. Surprisingly, sheaths with an applicator were found to be unacceptable to a significantly higher proportion of subjects than sheaths without an applicator (p<0.0001). Subjects found that the silicone sheath fell off / blew off significantly less frequently than two of the other products (p<0.01).

Pemberton et al [90] report a randomised prospective open crossover design trial to test user preference for an established one-piece silicone rubber self-adhesive sheath with a new one-piece silicone rubber self-adhesive sheath in a study sponsored by the distributor of both products. To be included the males had to be currently using at least one, one-piece urinary sheath, per day. Fifty three males from seven centres participated in the trial and were each given 10 sheaths of each product. Data from the 44 participants who had evaluated at least three of each product were analysed. No reason was given for why nine males did not complete the trial. The data shows that there were some problems with both products, however, it is difficult to understand why the new product was preferred, as the report does not mention any differences in the features of the two products.

Watson & Kuhn [102] describe a crossover study with six male participants that found the choice of leg bags may influence the performance of penile sheaths. Goldyn, Buck and Chenelly [103] conducted an exploratory study on 10 patients in an extended care hospital to consider the efficacy of a brand name external sheath and a hospital constructed sheath. The brand name sheath was found to be more secure and the preferred nursing choice but it was recognised that the hospital-constructed sheath was useful for patients with fragile skin and limited mobility. A study by Saint et al. [104] provided further evidence (although low level) to support the importance of security and comfort to sheath users. Using questionnaires, they interviewed a convenience sample of 104 older men (response rate = 90%) and surveyed 99 nurses (response rate = 92%) about the relative merits and problems of sheaths and indwelling catheters. The study population was drawn from a university-affiliated Veterans Affairs Medical Centre in the USA.

The patients using the sheaths were more likely to believe their product was comfortable (p = 0.04) and less likely to believe it was restrictive (p = 0.002) or painful (p = 0.008) than those using an indwelling catheter. This viewpoint was supported by the nurses surveyed, the majority of whom (no numbers given) believed that sheaths were more comfortable and less restrictive than indwelling urinary catheters for male users, but required more care time because they fell off or leaked.

4. SUMMARY

For incontinent males, sheath drainage can provide a good alternative to pads. However, the increased risk for complications such as local skin breakdown, bacteriuria and infection - especially in the frail confused elderly male – should be borne in mind (Level of Evidence 2). Also, there is the risk of urinary retention if the condom twists or the external band is too tight, leading to poor drainage to the urine bag (Level of Evidence 3). Sheaths with integral adhesive are more popular with users and easier to apply than those with separate adhesive strip (Level of Evidence 2/3). Secure fixation and the ease with which a sheath can be put on are the best indicators of its overall performance (Level of Evidence 2). Sheath applicators are often ineffective and unpopular (Level of Evidence 2). There can be considerable differences in performance between products with somewhat similar designs (Level of Evidence 2).

5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

- Prior to applying the sheath, ensure any remaining adhesive or barrier cream is removed from the penis and that it is thoroughly washed with soap and water and thoroughly dried.
- Trim long pubic hairs to prevent them being caught up in the adhesive.
- Protective skin wipes can be used to protect the skin, but make sure the skin has dried properly before applying the sheath.
- Leave a gap at the end of the sheath between the glans penis and the drainage tube to avoid trauma to the glans / prepuce. However, make sure the gap is not too large such as to cause kinking or twisting of the sheath [105].
• After the sheath has been applied, snip any reinforced ring or unrolled section of sheath sitting at the bottom of the shaft of the penis.

• Penile sheath removal should not be rushed and is made easier by gently rolling it off while bathing the penis in warm soapy water.

6. RECOMMENDATIONS

• Since there can be considerable differences in performance between products of similar design, men should be given the opportunity to experiment with different products before making a final selection (Grade of Recommendation B).

• The key performance characteristics which should be considered in selecting products are: security (ie ability to keep a leak-proof seal and channel urine to the drainage bag without leakage) and ease of putting the sheath on and taking it off (Grade of Recommendation B).

• In general, sheaths with integral adhesive (one-piece systems) should be selected rather than those in which the adhesive is supplied separately (two-piece systems) (Grade of Recommendation C).

• It should not be assumed that a sheath applicator will make sheath application easier: often it does not (Grade of Recommendation B).

• Potential sheath users should be asked if they have an allergy history and regular users should be routinely checked as their latex allergy status can change over time and with continued use. (Some health settings are moving to reduce or eliminate latex usage whenever possible and some manufacturers have moved to offer non-latex sheaths) (Grade of Recommendation C).

• Sheath users should be monitored for skin health, tissue damage and UTI (Grade of Recommendation C).

• When possible the external sheath rather than indwelling urethral catheter should be the urinary collection device of choice. (Grade of recommendation B).

7. PRIORITIES FOR RESEARCH

• Although products are continually being developed, changed, withdrawn and released, comparison studies that are controlled and use multiple sites to achieve larger numbers are recommended to further evaluate the effectiveness of the variety of sheaths available.

• Comparison studies of the risks of complications between the use of sheaths, pads and catheters are required.

• Since leg bag features may influence the performance of the sheath, further evaluation of design features claimed to reduce twisting and kinking at the drainage bag connection site and increase ease and security of connection to drainage bags is required.

• Well designed studies to generate and validate procedures to help identify the type of sheath most likely to suit an individual are needed.

VIII. URINE DRAINAGE BAGS AND ACCESSORIES

Urinary drainage bags are attached to an indwelling catheter or penile sheath to collect and store urine. Features of effective drainage bag systems include ease of operation of all components (connectors, taps, and support devices), comfort and discreetness.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding urine drainage bags are patient / carer dexterity (86;106), and eyesight. Both are necessary to manage the urinary drainage bag system, including using the outlet tap to empty the drainage bag. It is also important to assess the patient’s preferred and usual mode of dress (86;106); for example, a male whose preferred mode of dress is shorts will want a drainage system that is not visible and allows easy access for emptying.

1. PRODUCT CATEGORIES AND FEATURES

Urine drainage bags fall into two major categories: leg/ body worn bags for day-time usage; and large capacity body-free bags for night-time use (night drainage bag) which are suspended from a stand or bed hook.

Leg / body worn bags come with a variety of features of which the following are the most important to consider in making selections:

• Volume: most bags have a volume in the range of 350-750 ml, but some are bigger.

• Material: most bags are made from transparent PVC (polyvinyl chloride) but PVDF (polyvinylidene fluoride ) (less noise from rustling), polyethylene or rubber / latex may be used.

• Sterility: bags may or may not be supplied sterile.

• Wear position: bags may be designed for wearing over the knee, across or down the thigh, down the calf, or against the abdomen.

• Attachment / suspension system: most leg bags are attached to the leg with straps, which are usually made from latex or a (usually elasticated) fabric. A variety of hooks, loops, buttons / button holes and Velcro may be used to secure straps and to attach bags to straps. Some bags are designed to be
suspended around the waist. Some straps and suspension devices can be bought separately from bags, but they are generally not suitable for use with all bags (Fig VIII-1).

- Connecting tube: bags come with a variety of connecting tube lengths (eg the length required for wearing a bag on the calf will be greater than that for the thigh). With some products the tube can be cut to the preferred length.
- Drainage tap: Drainable bags come with a variety of drainage tap designs (Fig VIII-2).
- Sampling port: bags may or may not have a sampling port in the drainage tubing for taking urine specimens.
- Comfort features: some bags come with features intended to increase comfort – most commonly, a fabric backing against the skin to reduce sweating.
- Discretion features: some bags come with features intended to increase discretion – most commonly, internal welds between the front and back faces to reduce bulging and / or sounds caused by a large volume of liquid moving about as the user mobilises.
- Anti-kinking / twisting features: some bags come with features intended to improve drainage by reducing kinking and twisting in the connecting tube.
- Infection reduction features: some bags come with features intended to reduce the risk of infection for the self-carer and cross-infection between bag users by care givers. Such features may include; a non return flap valve, designed to help reduce reflux of urine up the tubing when the bag is moved by users or carers, a sampling port and / or a tap with an outlet sleeve which allows the overnight bag to be connected to the body worn bag. This linkage provides a mechanism to maintain a closed catheter drainage system designed to minimise the risk of cross-infection by reducing the handling of the catheter. Having connected the night bag to the leg bag sleeve, the leg bag tap is opened and urine flows freely from the sheath or catheter through the leg bag into the night drainage bag. Pre-sealed drainage systems to prevent breaking the closed system are also available.

Night drainage bags are usually held on a suspension system away from the body. They may be connected directly to the catheter or sheath or they may be connected to the drainage tap of the leg / body worn bag to avoid the need for repeated connections and disconnections with the catheter or sheath (Fig VIII-3). They usually have a capacity of 2000-4000 ml and come with a variety of design features many of which are similar to those for leg / body worn bags. Night drainage bags are available without a tap for single use as well as with a variety of drainage tap designs for emptying and reuse. Glass bottles are also available for high volume or overnight urine drainage.

2. QUALITY OF DATA

Several controlled comparative evaluations of urine drainage bags and suspension systems have been performed, as well as a small number of studies addressing infection and cross-infection issues. There is also one case controlled study which has investigated the purple urinary bag syndrome.

3. RESULTS

a) Evaluations of urine drainage bags

Kennedy et al. [108] tested the performance of ten different drainage bags in a simulation study involving 40 subjects (mostly health-care staff) which focused particularly on taps. Significant differences (p<0.05) were found between many pairs of bags with regard to each of the performance aspects studied: ease of tap opening and closing, ability to empty the bag without urine wetting fingers; and how easy the tap mechanism was to understand. Taps comprising caps or bungs were found to be particularly fiddly and messy to use.

In a study which focused primarily on the cross-infection risks associated with leg bags, Wilson and Coates [109] evaluated four leg bags. Each of ten long-term catheterised patients was invited to try each bag for a week in turn. The authors concluded that no one bag suited every patient; rather, each was liked by some users. The popularity (or otherwise) of many features was a matter of personal preference. Adverse comments mostly related to the tap (difficult to operate, opened accidentally, causing leakage) and the straps.

The UK Medical Devices Agency [110] evaluated all 14 sterile 500 ml leg bags on the UK market in 1995 in a multi-centre study involving 83 test subjects (58 men, 25 women). About half [44] lived in their own homes and almost all the rest in nursing / residential homes. Subjects were divided into pairs matched for each) to try for a week in turn. Preferences varied but the main concerns of users consistently focused on taps (many subjects found many taps difficult to operate), straps (discomfort was common) and the minimisation of leakage (through faults in bags and / or connectors; onto the fingers when emptying; or by the tap accidentally opening in use). The most popular bags tended to perform well in these three respects.

In a multi-centre study involving 34 men (age range 27-84y; mean age 55y; all sheath users) Fader et al. [111] evaluated all seven non-sterile 500-700 ml leg bags on the UK market in 1997. Twenty-five of the men lived in their own homes and the rest in residential/
Figure VIII-1: Body worn urine drainage bags held in place using leg straps (left) and a waist band suspension system (right).

Figure VIII-2: A variety of urine drainage bag tap designs.

Figure VIII-3: A night urine drainage bag on a stand.
nursing homes or long stay wards. Conclusions were substantially similar to those for the earlier MDA study.

Some international standards have been developed which provide general advice on bag performance and test methods [112]. These standards can be useful to laboratories asked to advise on bulk buying choices.

b) Urine drainage bag suspension systems

Little research has been undertaken on urinary drainage bag suspensions apart from a study by Thelwell et al. [113]. Thelwell et al. conducted a cross-over study using 52 subjects (20 men, 32 women). This study compared four suspension systems for fastening leg bags with the leg straps they had used prior to the study. Each subject evaluated each product for a week in turn and recorded their findings on a weekly questionnaire. Again, difficulty of application, comfort, discreetness and cost were key issues. However, there is suggestion in the literature that urinary drainage bag suspensions have an important role to play not only in the comfort and security of the wearer but in the prevention of urinary tract infection regardless of whether the drainage system is connected to a sheath or an indwelling catheter.

Munnings and Cawood [114] report the findings of a pilot study designed to evaluate the use of a belly bag of 1,000ml capacity and worn 24 hours a day, thus eliminating the need to use two separate bags and reducing the number of times the closed system is broken. Twenty-nine patients from a variety of areas from within an acute care setting who were using continuous catheter drainage systems were invited to participate, with 27 of the participants completing the study. All agreed to wear and then compare the belly bag with their previous leg and night drainage bag system. Worn around the waist, the belly bag is not positioned below the bladder: the manufacturers claim that the pressure of the bladder muscles is sufficient to ensure that urine flows through the catheter from the bladder into the bag. The residual pressure of the bladder is reported to be around 10-25cm H₂O, while the manufacturer asserts that a pressure of only 6cm H₂O is necessary to ensure the urine drains into the bag. Following education of how to use the drainage bag, users were given a questionnaire designed to facilitate comparison between the previous drainage system used and the belly bag. This was followed up with a telephone call. All agreed the belly bag was an improvement over their previous system of leg and overnight drainage bags, and found it more convenient, comfortable and less likely to cause pain with movement.

It has been suggested that current standard drainage tubing / bag designs evacuate the bladder sub-optimally, leading to retention of residual urine. Outflow obstruction can be caused by the development of airlocks in the dependent curls of tubing. A new drainage tubing design which incorporates a coiled downward spiral shaped configuration has been reported to eliminate air-lock obstruction (107) in experimental and clinical studies. However the importance of this in relation to infection requires further study.

There is opinion in the literature that positioning standard drainage bags below the bladder in a manner that averts kinking will prevent reflux of urine, and associated infection[115-117]. When doing so care must be taken not to increase traction or friction [106]. This can be achieved with the use of supports especially designed to divert accidental pulling on the catheter or sheath. When using these support systems allowance should be made for penile erection and tumescence [106].

The drainage system for indwelling catheters should be positioned off the floor to reduce the risk of cross infection[115-117]. Some sterile and unsterile leg bags come with a variety of tubing lengths or tubing that can be cut according to the needs of the individual, and leg straps that can be adjusted to allow positioning of the bag on the thigh or calf. Night bags - even if the tubing can be cut - rely on uniform stands or hangers to ensure that they are off the floor. Roe et al [118] raised the issue of poorly designed support systems for night bags. Expert opinion suggests that this still remains an issue.

c) Infection and cross-infection issues for management of urine drainage systems for indwelling catheters

Usage of urinary catheters and their drainage systems increases the risk of urinary tract infection and cross infection (See Section XII.2.h). There is evidence to suggest that catheter associated infections are reduced with the use of closed urinary drainage systems. A randomised controlled trial was reported by Platt et al [119]. This trial compared the incidence of infection (measured as 10^5 cfu/ml in catheter urine or drainage bag urine) between sealed junction catheters and unsealed junction catheters in a hospital setting with a median period of catheterisation of three days. For subjects not taking antibiotics there was no difference in infection rates between sealed junctions and unsealed junctions. The infection rate appeared to be consistently lower in the subjects taking antibiotic than the ones not taking antibiotic (p=0.01). For subjects taking antibiotics there was no difference in infection rates between sealed junctions and unsealed junctions.

There is little research to support the common practice of changing drainage bags every five to seven days (or any other particular change regime). The practice appears to be based upon expert opinion, anecdotal evidence and manufacturers’ recommendations. Of interest is the study outlined by Keerasuntongpon et al. [120] which was a randomized controlled study that compared the incidence of catheter-related urinary tract infections in a group of 79 hospitalised patients
whose catheter bag was changed every three days with that for a group of 74 patients who had their bag changed at the time of the catheter change or if the bag became faulty. A urine sample for culture was obtained for each participant every seven days, on the day the catheter was removed or on the day the participant was suspected of having an infection. The findings suggest that urinary drainage bags could be left for longer than three days but the authors were reluctant to define how long as the sample size was considered too small to rule out a false-negative result. They recommended additional study.

There is no evidence to support the practice of adding in situ antiseptic agents to drainage bags to reduce catheter-associated infection. A paper by Thompson et al. [121] which was primarily looking at the effectiveness of hydrogen peroxide instilled into closed drainage bags in reducing infection in drainage bags and in catheters also raises the question of whether catheters are infected primarily via drainage bags or vice versa. This prospective randomised study in a hospital setting involved daily sampling for bacteriuria (See Section XII.2.h for further discussion of outcome measures for catheter-associated infection) in catheters (≥10^5 cfu/ml) and drainage bags (≥10^3 cfu/ml) and identifying the infecting bacteria species.

In a sample size of 688, infection was found in 68 catheters and 78 bags. Although bag contamination was 8% in the H2O2 group and 16% in the control group (p<0.001) there was no significant difference in catheter bacteriuria (11% and 9%, respectively). One of the reasons given in the paper for questioning whether the drainage bag is the main source of catheter infection was that 77% of the bags in this study were contaminated later than the catheters.

Best practice guidelines to prevent infections associated with short term indwelling urethral catheters are available. The most recent of these, the EPIC 2 guidelines, were revised in 2005 and reported by Pratt et al. [117]. Designed to prevent short term, indwelling urethral catheter associated infection in NHS Hospitals in England, the guidelines are based upon a series of systematic reviews that include the best available evidence (experimental and non-experimental research as well as expert opinion). These guidelines recommend a closed catheter system where drainage bags are changed according to the manufacturer’s recommendations (5-7 days) or the patient’s clinical need. The guidelines also recommend that antiseptic or antimicrobial solutions are not added to urinary drainage bags.

The quandary for health professionals involved in the education and support of clients, who are self-managing and often financing their long term indwelling catheter drainage systems while living at home, is that they are aware that many of them are leaving the bags on for much longer than the manufacturers recommend and are often washing the bags out with a variety of solutions and reattaching the bags directly to the indwelling catheter. There is a paucity of studies that have explored long-term self-management of urinary catheter drainage systems in a community setting.

Madigan & Neff [122] undertook a literature review (50 studies) that explored the complications and long term management of long term indwelling catheters used for urinary retention and incontinence. Their recommendation in relation to management of drainage bags was that closed drainage systems were preferred best practice. However they also indicated that leg and bed bags may be used for up to four weeks if the system is broken daily to allow daily bag decontamination with a diluted (1:10) bleach solution. This recommendation appears to be based on the following two trials, one of which involved 54 participants sampled from an acute care rehabilitation centre and one involving 14 community dwelling participants.

Dille et al [123] report a randomised group parallel study with a pre-test and multiple post-tests utilised to determine the safety of a 4 week re-use of vinyl leg and bed bags compared to the usual practice of one week when de-contaminated daily with a procedure that utilised dilute bleach (sodium hypochlorite). Set in an acute rehabilitation unit, 54 participants (18 female and 36 males) completed the four week data collection period. Randomised by the flip of a coin, 28 participants were in the experimental group and 26 in the control group.

All participants had an indwelling catheter and were using a leg bag during the day and a bed bag at night. Both groups received identical daily bag decontamination and weekly bag and urine cultures. A standard of 0 to 100 cfu/mL was used to measure bag decontamination effectiveness and the urine cultures were processed by the Associated Regional and University Pathologists Inc. No significant differences were found between groups and the authors concluded that it is safe and cost effective to reuse vinyl bags for four weeks as opposed to the previous practice of one week, if the protocol for daily decontamination described is used. This study does not compare the practice of washing out the drainage bags with the chlorine solution either weekly or for a period of four weeks with a closed urinary catheter system to determine if that would result in fewer UTI’s.

Rooney [124] reported a study of 14 people with neurogenic bladders living at home. They changed from using daily sterile leg bags to non-sterile leg bags which were washed out after use each day with a dilute chlorine solution. Nine participants were on Foley catheter drainage and five were using sheaths. Bedside urine collection bags were used by all participants at night and there was no change made
to the standard practice of rinsing the overnight bag with water each morning and recapping the drainage tubing. The study ran for three months including a preliminary baseline phase of one month. No comment was made on whether the non sterile bags were changed. There were no symptomatic UTI infections during the study and urine samples with bacteriuria (>10^5 cfu/ml) did not increase. However the sample was very small and no statistical tests were applied to the results.

d) Urinary drainage bag features intended to reduce the risk of cross infection

The cross-infection risks of leg bags (particularly via the tap or sampling port) have been studied by Glenister [125] and by Wilson and Coates [109]. In her study Glenister [125] concluded that designs in which the tap and outlet spouts were most widely separated were most effective at preventing contamination of the hands with urine. Wilson and Coates [109] studied sampling ports and contamination of leg bag spouts. They suggested that the night connector tubing attached to the taps on the four leg bags in their study made decontamination difficult.

A small comparative study of two sets of closed system bags with a double non-return valve and two set of bags with a single non-return valve - all inoculated with Escherichia Coli and using simulated laboratory conditions in two separate microbiological laboratories blinded to each other - found that the colonisation of a simulated bladder was significantly delayed when the double non return valve was used [126].

e) Purple urine bag syndrome

There are occasional reports in the literature of purple discolouration in urine drainage bags - termed, purple urinary bag syndrome (PUBS) – and there is considerable debate and diversity of opinion over the cause and significance of the phenomenon. Mantani et al [127] conducted a case controlled study on 26 patients in three long-term wards. Fourteen (two men and 12 women) had exhibited PUBS while 12 (four men and eight women) had not. The clinical, microbiological and bacteriological backgrounds of the subjects in the two groups were compared to identify possible causes of PUBS. The findings suggest that women with urine that is alkaline and has a high bacterial yield are most likely to exhibit PUBS. There is no evidence to suggest detrimental effects on patients' health or functioning of the drainage system. However, the smell can be very distressing.

Studies which have compared leg bags and catheter valves are reviewed in Section XII.

4. SUMMARY

Taken together, published studies agree that the main factors to consider in selecting leg bags are the ease of tap operation, the comfort of suspension systems and the minimisation of leakage (Level of Evidence 2). Bags in which the tap and outlet spout are widely separated are most likely to be effective at preventing contamination of the hands with urine and cross-infection (Level of Evidence 3). There is high level evidence from studies – predominantly in acute care settings - to support the use of closed urinary drainage systems (Level of Evidence 2).

5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

Provision of clearly presented information based on the best evidence available is needed for clinicians, carers and patients as many aspects of caring for a urinary drainage bag system are supported by scant or conflicting evidence or by custom.

There is agreement that the hands must be cleansed and clean non-sterile gloves put on prior to caring for the urinary drainage bag system and that, on completion of handling the system, the gloves must be discarded and the hands cleansed again [117], [128].

There is also mention of confusion arising for clinician, patient and carer because of the many different designs of urinary drainage bag taps, and the regularity with which such features are changed [129]. Manufacturers should ensure that the instructions and accompanying literature that they develop for their urinary drainage bag systems are clearly presented and easily understood [129] in a format which is convenient to retain and refer to.

6. RECOMMENDATIONS

- In making urinary drainage bag selections particular attention should be focused on: the ability of the user to operate the tap; comfort (especially visibility beneath clothing); freedom from leakage (especially from the welds and the tap); and discretion (especially from the welds and the tap); and discretion (especially from the welds and the tap); and discretion (especially visibility beneath clothing) (Grade of Recommendation B).
- The patient’s individual needs and personal preferences should determine the use of leg / suspension / attachments and position of where the bag is worn (Grade of Recommendation C).
- Maintain closed urinary drainage system for indwelling urinary catheterisation where the system is only broken to change the sterile bag according to manufacturer’s recommendation or in a shorter period of time if clinically indicated (Grade of recommendation A).

7. PRIORITIES FOR RESEARCH

Jones, et al [128] identify many of the issues concerning the handling of urinary drainage bag...
systems that require further research, including the issue that has already been discussed above, of how long a closed urinary drainage system can be left unbroken before the urinary drainage bag is changed. Jones et al [128] also suggest research is needed into:

- How often and how drainage bags should be emptied?
- If a closed urinary drainage bag link system is used, does the night bag that is connected to the leg bag need to be sterile or can it be a reusable one?
- If a reusable night urinary drainage bag can be used, how should it be cared for when not in use?
- What is a reasonable method to dry reusable bags after they have been washed?
- To establish whether the incidence of UTI is increased in hospital, community or residential aged care settings when urinary drainage bags in closed drainage systems are changed at different intervals (eg the time of catheter change rather than weekly).
- To determine in own home settings whether a closed catheter drainage system is more effective at preventing urinary tract infections than a reusable non-sterile urinary drainage bag washed out each day with soap and water.
- To determine in own home settings whether a closed catheter drainage system is more effective at preventing urinary tract infections than a reusable non sterile urinary drainage bag washed out each day with a diluted solution of chlorine.

3. PRIORITIES FOR RESEARCH

There is a need for leak-free, comfortable and aesthetically acceptable body-worn urine collection devices for women and improved (in these respects) products for men.

IX. BODYWORN URINALS

1. FEMALE BODYWORN URINALS

Pieper [130] has reviewed the many attempts to design bodyworn urine collection devices for women. The major challenge is in achieving a comfortable and aesthetically acceptable leak-proof seal with the body. Various designs have sought to achieve this by holding a collection device over the urethral meatus with the help of suction, straps, adhesive or close-fitting underwear. While none have found widespread success and usage, they are available commercially in some countries.

2. MALE BODYWORN URINALS AND Dribble Containers

The urine collection devices most commonly used by men are sheaths (see Section VIII) but a variety of other products such as pubic pressure urinals are available. They comprise a ring-shaped opening or cone-shaped component which is worn around the penis (and held firmly against the pubis by means of a belt and straps) and channels urine to an integral collection bag (Fig IX-1). Such devices are not widely used but they can be effective for individuals whose penis is too retracted for a sheath to be suitable. There are no published evaluations of these products.

They should be fitted by a specialist: a good fit is crucial for comfort and to avoid leakage. It is also important that the wearer / carer understands how to use the device and the importance of skin care. The wearer / carer will need good manual dexterity to manage the device. Several urinals will be needed to use in rotation, allowing each to be properly washed and dried between periods of use.

Dribble pouches are also available for light incontinence (Fig IX-2) but there are no published evaluations of these products.

3. PRIORITIES FOR RESEARCH

There is a need for leak-free, comfortable and aesthetically acceptable body-worn urine collection devices for women and improved (in these respects) products for men.

X. MECHANICAL DEVICES FOR WOMEN WITH URINARY INCONTINENCE

Female mechanical devices are designed to prevent urinary leakage in different ways and fall into three main categories: those that are applied over the urethra at the external meatus; those that are placed within the urethra (intraurethral devices) and those that are inserted into the vagina (intravaginal devices). Both designs of urethral device are intended to occlude the urethra and the intravaginal devices are intended to provide some support to the bladder neck and possibly some compression to the urethra. These devices are also known as occlusive devices and are primarily used for women with stress incontinence. There has been one Cochrane review of these devices [131].

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding mechanical devices are high levels of motivation and acceptability of the concept of use, good cognition and good manual dexterity. They should probably be avoided by those with skin sensitivity or if avoidance of urinary tract infection is a priority.

1. DEVICES THAT OCCLUDE AT THE EXTERNAL MEATUS

Urethral occlusion devices have been developed to
Figure IX-1: A variety of pubic pressure bodyworn urinals for men.

Figure IX-2: A dribble pouch.
block urinary leakage at the external urethral meatus (Fig X-1). Several devices have utilized either adhesive or mild suction to achieve occlusion. In addition to the simple barrier effect, compression of the wall of the distal urethra has been hypothesized to contribute to continence.

Miniguard (Uromed Inc., but no longer available) is an angularly shaped foam device which utilizes an adhesive hydrogel to adhere to the peri-meatal area. The device is single use, removed prior to voiding, and disposable. FemAssist (Insight™ Medical Corp., but no longer available) is a hat-shaped silicone device, which adheres by applying an adhesive gel to the edge of the device, squeezing the central dome and creating a vacuum. The device is then placed over the urethral meatus and, upon release, the meatal mucosa is drawn up into the device and the urethral lumen is occluded. It may be worn for up to four hours or until voiding, after which the device is washed in hot soapy water and reapplied. The device was reusable for one week. CapSure (CR Bard Inc., no longer available) was applied and retained by suction. A petroleum based lubricant is applied prior to device use. The device is removed for voiding and re-utilized for up to two weeks.

Miniguard: Eckford et al. [132] studied the efficacy of a single application of this device during a one hour pad test and reported that 25% of patients were continent, 50% were improved, but 25% had worse incontinence. Brubaker et al. [133] enrolled 411 women to their study; 390 used the device, and 346 completed the study. Results showed significant improvement in symptoms. The incontinence impact scores significantly decreased from a mean of 41.0 (out of 300 – high scores worse) to a mean of 10.5 at 17 weeks. Twelve hour pad test showed mean urine loss decreased significantly from 15.8 to 6.9 ml and incontinence episodes from 14.2 episodes per week to 4.9 episodes at week 17. Symptoms of vulvar irritation or lower urinary tract discomfort occurred in a small percentage of subjects but it was generally transient, and only three women discontinued using the device for this reason. There were no statistically significant differences in the proportion of subjects reporting urinary tract infection during device use compared to beforehand. The authors concluded that the device was safe and effective (Level of Evidence 3).

FemAssist: Versi et al. [134] studied 155 women with stress or mixed incontinence, of whom 133 attempted to use FemAssist and 96 enrolled in a four-week study. Their mean pad test loss fell from 27 g to 9.4 g (p< 0.001) and 49% were dry. Symptomatic cure was more likely in those with mild incontinence. Of the nine women who had a positive pad test (>2 g) without the device, five were dry (<2 g) with the device (p<0.05). VAS scores showed a significant improvement for the symptom of stress incontinence (p<0.05). QoL scores improved significantly by 38% (p<0.05) for the IIQ and 29% (p<0.0 1) for UDI (Level of Evidence 3).

Moore et al. [135] reported on 57/100 recruited women who completed a one-month trial. Reduction of incontinence was statistically significant on pad testing, which revealed that 47% of the patients became continent and 33% had more than 50% benefit compared to baseline, while 9% had worse leakage. Those with severe baseline leakage were as likely to respond as those with mild or moderate pad test loss. Women with stress, urgency or mixed incontinence appeared to respond equally well. Dropouts included 13% who were unwilling to utilize the device (Level of Evidence 3).

Tincello et al. (136) in a 3-month prospective study involving 27 women with urodynamic stress incontinence found the median (range) loss with and without the device was 4.9 (0-65) ml and 21 (1-94), respectively (p< 0.01); and 20 patients were less wet when using the device. Discomfort was greater among the women with a greater loss. The acceptability correlated negatively with discomfort (r = -0.53) and negatively with embarrassment (r =-0.39); 15 patients (56%) reported that they would use the device in the long-term (Level of Evidence 3). Tincello et al.[137] later reported on 41 women recruited to use the device over a three month period, but 10 declined to participate, six withdrew before two weeks, 10 failed to attend two week follow-up and 11 did not attend three month follow-up. Only two completed the study. There was no difference in pad test or voiding diary grades. The authors concluded that the device had low acceptability and was ineffective, and could not be recommended for non-surgical management of stress incontinence (Level of Evidence 3).
**CapSure**: Bellin et al. [138] reported on 88/100 completers after 12 weeks, with 82% elimination of leakage on pad test, 91% continent on provocative stress test (single cough assessment of leakage), and 48% dry and 40% improved on urinary diaries. Pad test leakage decreased from 6.67 g (range 0.55-25.95 g) to 0.19 g (range, 0-2.5 g) by week 12. Five patients withdrew secondary to vaginal irritation and three due to poor device fit (Level of Evidence 3).

Shinopulos et al. [139] carried out a multi-centre study enrolling 100 women with stress incontinence who wore the device for 12 weeks. Eighty-four women completed the study. Mean pad weights reduced from 6.7g at baseline to 0.19 by week 12. Complications affected seven patients, including urethral / vaginal swelling and vulval abrasion, but none of the affected patients withdrew from the study. The IQOL tool showed significant mean improvement from 62.3 to 90.4.

**b) Summary**

External urethral occlusive devices were found to be of varying efficacy, with minimal morbidity. Efficacy of the combined studies reveals a continence rate of approximately 50% dry and two-thirds of patients improved, but this data is from open studies (typically pre-test / post-test with no control group) and there have been no randomised controlled trials. Devices achieve occlusion either by blocking at the meatus or compressing the distal urethral lumen and adherence to the peri-meatal area is essential to success. However, the method and degree of adherence is also the determining factor for the type and severity of local irritation.

Patient selection based on motivation, appropriate anatomy, and manual dexterity, in combination with efficacy and morbidity will determine overall satisfaction. There is no data which compares one extra-urethral device to another, or to other categories of products. Cost comparisons for disposable versus short-term reusable devices are not available. Efficacy for different grades of incontinence has not been established.

The objective degree of continence improvement in the clinical laboratory (pad and stress tests) is greater than in community use (diaries). The devices tested in these studies are no longer available and there are no external urethral devices currently on the market.

**c) Recommendations**

Although these devices have proved effective for some women (limited mainly to those with high motivation, manual dexterity and cognitive function), it appears that they have failed to find popularity with users and clinicians. They are no longer commercially available and so no recommendation on their use can be made.

**d) Priorities for research**

Further research on the development and role of devices which block urinary leakage at the external urinary meatus, with a focus on improving patient acceptability is recommended. One half of patients utilizing these devices in monitored studies were dry and two-thirds of the patients were improved with minimal morbidity. These devices may have a future role in the algorithm of conservative treatment based on patient acceptance, availability and cost, especially in those patients with mild or moderate stress incontinence, for occasional or intermittent use and/or for those who prefer to avoid pads or surgery.

### 2. INTRAURETHRAL DEVICES

Urethral inserts are silicone cylinders that are self-inserted or removed at the patient’s discretion. They are intended for daytime use, especially during vigorous physical exercise. While some women manage exercise incontinence by limiting fluid intake before or during exercise, by choosing sports that allow frequent bathroom access, or wearing absorbent pads, 20% to 40% of women cope with leakage by ceasing exercise (140). These devices have external retainers or flanges to prevent intravesical migration and proximal balloons to hold the device in place. They act by causing occlusion either in the urethra itself or at the external urethral meatus [141]. (Fig X-2)

The FemSoft (Rochester Medical Corporation) is the only urethral insert currently distributed. It has a soft, compressible, mineral oil-filled silicone layer with an insertion probe. Before insertion, the fluid distends the proximal end of the cylinder, as the user pushes the device (guided by the insertion probe) into the urethra, fluid transfers automatically to the distal end, allowing the device to pass through the urethra. Once in place, fluid flows back to the proximal end to hold

**Figure X-2: A female intraurethral occlusive device.**
the device in place. None of these devices are recommended for reuse after removal. The FemSoft Insert is currently packaged in a box of 28 inserts and each box is priced at $49.95. The Viva [142], Reliance and other intraurethral devices mentioned in this subsection, are not currently marketed.

a) Quality of data and results

The objective efficacy measurements utilized were the one-hour pad test, voiding diary and quality of life questionnaires. There have been no randomized control trials.

Nielsen et al. [142,143] and Peschers [144] studied the Viva device. Peschers et al. screened 53 patients with USI and 21 patients accepted treatment with the two sphere device. During a four month study, the investigators analyzed subjective improvement and performed pad-weight and cough tests. The authors reported that 67% of patients had improvement in symptoms. Nielsen et al. [142] studied forty women who tested two variants of the device (with one or two spheres) each for two weeks in a cross-over study. They then continued with what they judged to be the better plug in period three (two months). Only 45% (18/40) completed this period but almost all (17/18) were reported to be subjectively and objectively continent or improved. Six women developed urinary tract infections and two of these had retained a plug in the bladder.

Staskin [145] reported on a four month study of 135 of 215 patients who utilized a disposable balloon tipped urethral insert made from thermoplastic elastomer, inflated with an applicator on insertion and deflated by pulling a string at the meatal plate for removal during voiding (Reliance, Uromed Corp., but no longer available). Eighty subjects discontinued the device prematurely, mostly because of discomfort and inability or unwillingness to use the device. Miller et al [146] and Sand et al [147] then reported on 63 of the 135 patients from the above cohort who utilized the device for one year.

The Reliance device provided 72% complete dryness with 17% improvement on diary, and 80% complete dryness and 15% improvement on pad weight testing in the study by Staskin et al. [145], and 79% complete dryness and 16% significant improvement on objective pad weight studies consistent with the improvement in subjective diaries (p<.0001) for Miller et al. [146]. In the Miller study the patients reported improved comfort and ease of use over time. Sensation of device presence decreased from 35% at week one to 7% at 12 months. The volume of urine lost during exercise decreased from a median of 20g (range 4.9-80.2g) without the insert to 2.6g (1.3-6.8g) when the insert was worn (p=0.03). On a 5-point scale, in which 1 represented very comfortable and 5 very uncomfortable, subjects rated the mean comfort for the sessions performed with the insert in place as 2.1.

Boos et al. [149] reported in an abstract, a randomized prospective parallel group trial comparing the Reliance intra-urethral insert with the FemAssist external meatal occlusive device. Assessments at baseline, one month, and three months included subjective efficacy, seven day diary, and pad test (1 hour). Fifty-three females were randomized to the FemAssist and 49 to the Reliance device. There were some initial problems with sizing the Reliance. Once this was corrected, 40.8% (20) of women were subjectively dry and the remainder improved on completing the trial. Of women using the FemAssist, 28.3% (15) were dry, 60.4% (32) were improved, 9.4% (5) were no better and only one subject was made worse with device use. Problems experienced were few and minor with no serious adverse events. The conclusion was that both devices are efficacious, the FemAssist was more comfortable, but required a greater degree of user skill to achieve control of leakage (Level of Evidence 2).

Recent studies have investigated the efficacy of the FemSoft which is the only intra-urethral device which is currently available. Dunn et al. [140] measured pad weights during four standardized aerobics sessions during which six subjects were randomly assigned to exercise twice with the insert and twice without it. The medians of the averaged pad weights for the two different types of sessions were compared. Median urine loss during standardized exercise sessions decreased from 20g (range, 4.9 to 80.2g) without the device to 2.6g (range, 1.3 to 6.8g) with the device (P=0.03). Five women used the device at home during unsupervised exercise; one subject had urinary tract infection. At the end of three months, satisfaction and comfort were rated high on a 5-point scale. The conclusion was that the FemSoft urethral device is an effective, safe, and comfortable treatment for exercise incontinence in women (Level of Evidence 3).
Results from a prospective three-year study, (FDA post-approval device safety data submitted by Rochester Medical Corporation, 2002 unpublished), for evaluation of the long term effect of the device involved 41 subjects. Of the group, nine women were 65 years or older (22%, 9/41); 80% were post-menopausal with 24 women (59%) being on hormone replacement. Thirty-eight, (93%) used absorbent products to contain urine leakage prior to enrolment. A total of 66 follow-up visits took place with an average participation period of 4.2 years. Seven patients withdrew in the third year, three due to non-study related health problems and one because of dissatisfaction due to urge symptoms. Two were lost to follow up. There was a significant difference in the rates of incontinence at the three-year follow-up between users and non-users of the device: 0.83 versus 2.64 episodes per day, according to voiding diaries. The difference in urine loss during pad weighing tests was also significant. There were 24 reported adverse events in the 41 subjects enrolled. None of these events required medical intervention except for antibiotic prescription in cases of urinary tract infection. The 24 events included: bacteriuria (11); symptomatic UTI (3); urinary symptoms (3); device performance problems (2); irritation (2); and migration (1).

In 33 women a total of 38 cystoscopies were performed at three years. Only one patient was reported to have an abnormal finding, but this was due to mucosal irritation produced by an indwelling Foley catheter during one hospitalization for a problem unrelated to the device. Patient satisfaction had not changed over the follow-up time interval. The Quality of Life questionnaire (I-QoL) scores at three years were compared to those at 12 months and there was improvement from the baseline of 60.6 to 74.0. No safety concerns concerning urethral integrity were identified after the three years of continuous use. The incidence of urinary tract infections, given the high number of insertions and removals, was considered low risk (Level of Evidence 3).

b) Summary

Intraurethral devices have demonstrated high efficacy, but have been associated with urinary tract infection, hematuria and discomfort. Bacteriuria, without symptomatic infection, was similar to extraurethral device use, which approaches screening urinalysis data [133] or may be similar to the rates seen with self catheterization. Device migration into the bladder, which requires endoscopic removal is the most serious reported problem. Long-term results are limited. Patient and clinician acceptance of this form of therapy has also been limited and there is currently only one intraurethral device on the market. High cost is also a factor that probably precludes more widespread application but 'occasional' use, for example during vigorous exercise may be helpful and affordable for some patients. Good hand dexterity is necessary to use the device (Level of Evidence 3).

c) Recommendations

Intraurethral occlusive devices may be considered for women with stress incontinence but they are invasive devices with high cost and have had limited evaluation. They may be most appropriate for intermittent and occasional use (such as during vigorous exercise) (Grade of Recommendation C).

d) Priorities for research

It is important that new devices - particularly invasive ones - are evaluated by randomized trials and comparing to control approved devices. Long-term follow-up results are needed to demonstrate the effects of such devices on the urethra and / or bladder and will determine the real value and safety of devices that initially have been adopted enthusiastically.

Further development and study of the use of intraurethral devices for the treatment of urinary incontinence is recommended. In particular assessment of their cost-effectiveness and effects on quality of life, when used intermittently or for particular activities, is recommended.

3. INTRAVAGINAL DEVICES

Support of the bladder neck to correct urinary stress incontinence has been achieved, with varying success, utilizing traditional tampons, pessaries and contraceptive diaphragms, and intravaginal devices specifically designed to support the bladder neck.

a) Quality of data and results

1. TAMPONS / PESSARIES

Nygaard [150] performed a prospective, randomized, single blind, and laboratory based study testing 18 patients (age 33-73) with three 40 minute standardized aerobics sessions, utilizing a Hodge pessary, a super tampon, or no device. Urine loss was determined by a change in the weight of the pad worn while exercising. Statistical analysis of the log of urine loss revealed that women lost significantly less urine when exercising with either the pessary or the tampon than when exercising with no device. Continence rates were 6/14 cured and 2/14 improved with tampons, 4/10 improved with a diaphragm (Level of Evidence 2).

2. DIAPHRAGMS / PESSARIES

Realini et al, [151] analyzed the benefit for one week, in 10 selected patients of a coil-type diaphragm ring, which was softer than a pessary, utilizing diaries and a two hour pad test. They also gave an overall subjective evaluation of their experience. Urodynamic findings were essentially unchanged by wearing
diaphragm rings. Four of the 10 women experienced clinically significant improvement in the amount of urine lost during pad tests, number of leaks per week, and overall assessment response (Level of Evidence 3).

Suarez et al. [152] included urodynamic testing in his evaluation of a contraceptive diaphragm in 12 patients. Complete resolution of SUI was achieved in eleven of twelve patients (91%) but two of them withdrew from the study because of associated discomfort from the diaphragm, therefore, complete resolution of SUI was achieved in 9/12 patients (75%) (Level of Evidence 3).

Bhatia et al. [153] reported on the urodynamic effects of the Hodge pessary on 30 women aged 29 to 71 with a history of UI. With the pessary, 24 of the 30 patients became continent when tested in supine position with a full bladder, three of the 24 patients lost urine with coughing in the standing position and demonstrated a positive cough profile despite the presence of the vaginal pessary. Uroflowmetry data show that the vaginal pessary did not produce any obstruction to the free flow of urine and suggested this is a modality to predict the outcome for bladder neck support surgery.

3. INTRA-VAGINAL DEVICES DESIGNED SPECIFICALLY TO SUPPORT THE BLADDER NECK

Included in this category are:

1. Removable reusable intra-vaginal ring, composed of silastic, and constructed with two prongs which are placed behind the symphysis to support the bladder neck (Introl, no current distributor).

2. Single-use disposable devices: (i) A clam-type device composed of polyurethane foam, which is folded up upon its long axis and placed into the sagittal plane in the vagina, and when moistened, its dimensions expand by 30% and create a supportive cushion under the urethrovaginal junction (originally called the Conveen Continence Guard, now known as Contrelle Activgard); (ii) A version of the expanding polyurethane design, with similarities to a tampon, (Conveen Continence Tampon, Coloplast, Denmark (no longer available) (Fig X-3); (iii) An expanding polyvinyl alcohol sponge (Ladycon, Home Care Engros, Norway); (iv) a simple surgical foam cylinder with drawstring e.g. Rocket stress incontinence device (Rocket Medical PLC)

4. REUSABLE INTRA-VAGINAL RING (INTROL)

A pilot laboratory study was carried out by Biswas [154], the developer of the device, employed a straining cystogram. Eighty-six percent of the patients were continent when tested with the device in place on cystogram. Following this study, the number of device sizes was increased from eight to 25. Evaluation studies followed examining efficacy, safety and satisfaction. Davila [155] initially demonstrated that 83% of patients were dry on pad weight test. Later [156] the researchers enrolled seventy women (53 completed) aged 24-76, 29 with stress, and 24 with mixed incontinence in a one month study. A statistically significant reduction in incontinence was noted on pad testing (stress mean 46.6-16.6; mixed, mean 31.9-6.8 g) and in bladder diary (stress, mean 28.6-7.8 losses per week; mixed, mean 30.2-15 losses per week). QoL scores (I-QoL) improved in both groups. With the device in place, urodynamic testing indicated normalization of urethral function without evidence of outflow obstruction. Subjects found the device comfortable, easy to use and convenient. Side effects included five urinary tract infections and 23 cases of vaginal soreness or mild irritation (Level of Evidence 3).

Moore et al. [157] detailed problems with both sizing and efficacy. Of the 80 recruits, four could not be fitted, and 11 did not satisfy all entry criteria. Of the 65 participants, 39 (60%) withdrew; 20 for distorted vaginal anatomy which made fitting difficult, five for lack of efficacy, four for constipation, and ten for unrelated patient events. In the remaining 26 patients, pad test weights decreased from a baseline median of 19g to 2g (p<0.001), 62% were continent, and 15% were >50% improved, and wished no further therapy. Moore et al. commented that the device was difficult to fit in women who have had multiple vaginal surgeries or were oestrogen deficient. Long-term follow-up showed that 18 of 26 (from the original 65) continued to wear the device at six months (interim dropouts being due to concurrent illness in half, the remainder had declining efficacy). Of these, 78% continued to wear the device for a minimum follow-up of two years (Level of Evidence 3).

In a separate study of patients with mixed incontinence by Moore et al.[135], five of 21 recruits never wore the device home, leaving 16 participants. A further two did
not reach week four, because of poor efficacy or inability to fit the device. In the 14 who reached week four, the median number of leaks/day declined from 4.3 to 1.0 (p = 0.002). Median pad weight loss fell from 53 to 7g. (p = 0.012). Cystometry showed an increase in maximum bladder capacity (p < 0.05) and a modest reduction in severity of detrusor overactivity, with no evidence of outflow obstruction. Three women discontinued because of poor efficacy or a poorly fitting device, leaving 11 of 16 participants (69%) at week eight, when median pad weight decreased to 2ml (Level of Evidence 3).

Kondo et al. [158] found no urinary flow obstruction with the device in place. Urine loss decreased from 20.6 to 4.8 gm. per hour (p < 0.001) on the 60-minute pad weight test. Twenty-two patients (29%), reported complete continence, and 39 (51%) had decreased severity of incontinence by more than 50%. Minor adverse effects occurred in 26% of the patients. According to the global usefulness rating which was employed, 62 patients (81%) had some or maximum benefit (Level of Evidence 3).

5. DISPOSABLE INTRA-VAGINAL DEVICES

Thyssen et al. [159] tested the Continence Guard in 26 women with stress incontinence before and after one month’s use: four women discontinued the treatment because of discomfort or difficulties in using the device 9 (41%) were subjectively cured of incontinence, 10 (45%) improved while three (14%) claimed unchanged incontinence. With the device in place all had decreased leakage at the 24-hour pad weighing test and unchanged urodynamic tests. No vaginal or urinary infections were found (Level of Evidence 3).

Thyssen et al. [160] reported on 19/22 women with stress incontinence, subjectively and objectively cured or improved in a short-term study, and who then continued the treatment with the device for one year. All 19 completed the study, 13 (68%) were subjectively dry, (26%) were improved and one (5%) reported unchanged incontinence. All but one had decreased leakage at the 24h pad test, and 67% a greater than 50% decrease. Subjectively cure was 41%, and 36% were dry on 24 hour pad test. Overall reduced leakage was statistically significant (p < 0.0005) No significant changes were found in the other urodynamic measurements, specifically, urinary flow rate.

Sander et al. [161] found subjective cure in 11/55 women (20%) and improvement in 27/55 (49%) was reported. Results of the 24-hour pad test and mean leakage and episodes in the voiding diary significantly decreased. After three months, 58% of the 55 patients desired to continue device usage. There was a highly significant improvement in QoL scores using the IIQ, as well as two additional incontinence-related quality of life questionnaires. Responses to the SF-36 general health questionnaire showed no significant changes

Hahnet al. [162] reported on 121 women, in a four week study. Patients dropped out because of vaginal irritation (25%), other product-related reasons (6%), lack of time (6%), or failure to complete a user questionnaire. Of the remaining 90 (mean age 47.5), 85 performed a 24 hour pad test, which showed that baseline leakage of 42 ml/ 24h decreased to 14 ml/ 24h (p <0.001). Of these, 39 (46%) were continent. The device was considered unpleasant by 8%, and caused some local discomfort in 62% on direct questioning: 75% of those wished to continue using the device. The authors noted that older women (age 56-65) tolerated the device and appeared more motivated to continue. Coexistent atrophic vaginitis and the use of topical oestrogen was not discussed.

Thyssen et al. [163] reported on 94 women recruited in a cross-over study, which compared two versions of the same device; the Conveen Continence Guard (CCG) and the Contrelle Continence Tampon CCT. 62 women (66%) completed the study with withdrawals mainly due to discomfort or for unknown reasons. Both devices reduced leakage significantly but the CCT was significantly better than the CCG. Few side-effects were reported. Thirty-two women continued the treatment for one year or more with 63% preferring the “tampon” type design for its ease of use.

The report on the polyvinyl sponge by Glavind [164] was an acute laboratory study of only six women utilizing a pad test measurement during 30 minutes of aerobic exercise Without the vaginal sponge the patients had a mean loss of 7g (range 2-18g) during exercise. With the vaginal sponge in situ there was no leakage.

There has been a recent report of a novel disposable intravaginal device (ConTIPI ltd. Israel) which may come to market. This device has a resin core with support ‘poles’ covered with a soft nylon mesh that stretches between the arms of the poles to act as a suburethral sling. Ziv et al. [165] recruited 60 women with severe stress incontinence to test the product. A seven day ‘control’ period was followed by a 28 device usage period.

There was no control arm or comparison product. Pre-weighed pads were used during the test period and the primary end point was the percentage of women achieving at least a 70% reduction in pad weight gain from the control period to the last 14 days of usage. Ten women withdrew from the study during the test period, four for device related reasons. Using intention to treat analysis 85% of women achieved at least 70% reduction in pad weight gain. The most common adverse events reported were mild and included genital tract discomfort, pain and spotting with blood; the only report of a moderate event was of candidiasis. The authors conclude that the device is easy to use, well-tolerated and effective. Further evaluation will be needed.
b) Summary
Support of the bladder neck resulting in improved continence is possible with intravaginal devices without evidence that they cause significant lower urinary tract obstruction or morbidity, but the evidence is limited. (Level of Evidence 3).

Studies performed in the acute setting, regardless of the device type, demonstrate better performance than diary based studies performed over time. Efficacy appears to be higher in patients with minimal to moderate urinary leakage.

Relatively high drop-out rates in monitored studies, during which patient support is provided, indicates the need for proper patient selection and patient and provider education, but may also indicate limitations in product efficacy, difficulties in application or other factors such as discomfort (Level of Evidence 3).

c) Recommendations

Vaginal support devices may be considered as a treatment option when managing women with stress urinary incontinence, dependent upon the availability of product, patient ability to manage the product (particularly manual dexterity) patient acceptance, and cost (Grade of Recommendation C).

d) Priorities for research

Long-term results are not available and studies comparing these therapies to other forms of conservative therapy or surgery are needed.

4. OVERVIEW OF MECHANICAL DEVICES WOMEN

a) Overall summary

The recent Cochrane review of mechanical devices for urinary incontinence in women [131] review found only six trials that met their criteria and concluded that the role of such devices is questionable. The authors state that there are indications that using mechanical devices might be better than no treatment but that the evidence was weak and that there was insufficient evidence to recommend any specific device or to show that mechanical devices are better than other forms of treatment.

In this section we have attempted to review all available evidence including many trials that did not meet Cochrane criteria. Most trials were open pre-test post-test trials with no comparators and the strength of this evidence is relatively weak. Although most trials showed positive effects on symptoms, this was often combined with relatively high drop-out rates and unwanted effects, such as discomfort, skin irritation or urinary tract infection.

Although many products have appeared on the commercial market, few have stood the test of time and are currently marketed – there are no external urethral devices available and there is only one intra-urethral device. There are at least two intra-vaginal devices available on the market and these may have potential to be more acceptable to women because of their similarities to familiar tampons. The relative lack of market success for these products may indicate low efficacy and unwanted effects, but may also reflect their relatively high cost compared to pads which are the main alternative.

b) Overall recommendations

It is possible that some of the mechanical devices currently marketed are effective and acceptable to a minority of women and, given that they are relatively non-invasive (with the exception of intra-urethral devices), they may be suggested to patients for consideration and testing, particularly for short-term or occasional use.

c) Overall priorities for research

The substantial withdrawal rate and the frequency of unwanted events indicates that there is a need to establish efficacy of these devices (compared to no treatment) over longer time periods (more than a year), with careful identification of unwanted effects.

There is also a need to compare devices with simple, cheap devices. The Cochrane review recommends an intravaginal tampon as a suitable comparator.

There are indications that the devices may best be used occasionally or intermittently for specific activities and there is a need for this type of use to be tested, possibly compared to the most common alternative - an absorbent pad.

As these devices aim to prevent urine leakage there is also potential for testing their efficacy compared to other treatments such as pelvic-floor exercises or surgery.

XI. MECHANICAL DEVICES FOR MEN WITH URINARY INCONTINENCE

Male mechanical devices aim to prevent urine leakage by compressing the penis. A variety of designs are available but occlusion is usually achieved with either a clamp or a peri-penile strap (Fig XI-1). Such devices have the potential advantages of low cost and simplicity compared with a sheath and drainage bag. However there is potential for tissue damage and these devices should be used with caution.

Careful assessment is necessary for use of these devices because there is potential for damage to the penis from ischaemia (restriction of blood to the penis).
Such devices should be fitted by a trained health professional and subject to regular review. Use should be limited to men who are assessed as being cognitively intact, are aware of bladder filling, have normal genital sensation and intact penile skin, have sufficient manual dexterity to open and close the device (Moore 2004) and are motivated and willing to use such a device.

1. QUALITY OF DATA

The use of penile compression devices is described only rarely in the literature (166); (167) and is usually referred to as a last resort where other forms of management have failed or been judged inappropriate. There has only been one published evaluation (168).

2. RESULTS

Moore et al. [168] evaluated three different devices (Timms C3 penile compression device; Cunningham clamp; and U-Tex male adjustable tension band) in a cross-over study in which twelve men with stress urinary incontinence following radical prostatectomy tried each device in turn. Each of the devices significantly (p<0.05) reduced mean urine loss (measured using a 4h pad tests) compared with baseline measurements. There was some objective or subjective improvement in continence for each of the 12 men with at least one of the devices, although none completely eliminated urine loss when applied at a comfortable pressure.

Ten of the 12 men rated the Cunningham clamp positively; two, the C3; and none, the U-Tex. However, the C3 and U-Tex allowed good cavernosal artery blood flow while the Cunningham clamp significantly reduced it. Overall Moore et al. concluded that, used correctly, the Cunningham clamp can be an effective method of controlling urinary incontinence (although it should be noted that complete control i.e. no leakage, was not achieved) in men with stress urinary incontinence who are cognitively intact and aware of bladder filling, and have normal genital sensation, intact penile skin and sufficient manual dexterity to open and close the device.

Expert opinion and anecdote suggest that penile clamps may be more successful when used for short periods, for example when undertaking activities such as swimming or jogging. Such activities may not only exacerbate incontinence but also preclude the use of bulky and / or absorbent products.

3. SUMMARY

Male mechanical devices can partially control urinary leakage (but not eliminate it at comfortable levels of use) but are likely to lead to reduced cavernosal artery blood flow and therefore care must be taken to ensure regular removal or release (Level of Evidence 2).

4. RECOMMENDATIONS

- Male mechanical devices may be considered for selected men with stress urinary incontinence who are cognitively intact and aware of bladder filling, and have normal genital sensation, intact penile skin and sufficient manual dexterity to open and close the device (B).
- The devices should be fitted by a trained health professional and reviewed regularly (Grade of Recommendation C).
- The devices may be considered for short-term use when undertaking sport or other activities, as an adjunct to management with other products (Grade of Recommendation C).

5. PRIORITIES FOR RESEARCH

- There is a need for mechanical devices for men which are discreet, easy to use and which prevent leakage without risk of tissue damage.

XII. CATHETERS

Urinary catheters can provide an effective way of draining the bladder in either the short-term or long-term, by intermittent or indwelling catheterisation, where alternative strategies are unsuitable or unsatisfactory. However, indwelling catheters are rarely completely trouble-free and the risk of catheter-related complications is high, with substantial detrimental impact on patients, carers and healthcare services. It is generally agreed that catheter use should be avoided wherever possible and only adopted for those in whom alternative strategies are unsuitable or unsatisfactory, after careful assessment of the patient and their particular problem [169].
This section examines the characteristics of urinary catheters, and provides a critical review of existing evidence to guide decision-making on choice of catheters, equipment and management strategies to minimise associated risks. Specific issues relating to short-term catheterisation are addressed, but the main focus of the section is on long-term management of bladder dysfunction, by intermittent catheterisation (least invasive) or indwelling catheterisation (most invasive). An overview of factors influencing choices of catheterisation strategy is provided in Table XII-1. Detailed discussion of key issues is provided under the following headings: user characteristics, catheter characteristics, associated risks / problems, catheter management.

The bulk of research evidence on catheter use relates to short-term catheterisation. In particular there are numerous trials which focus on catheter-associated urinary tract infection since this is well recognised as a major source of healthcare associated infection. The quality of data is very variable and many studies are limited by being underpowered and by other design issues, including poorly defined outcome criteria and highly selected study populations. Much less research has addressed intermittent or long-term indwelling catheter-related issues and guidance to healthcare practitioners remains largely based on expert opinion. Some of the difficulties in conducting research on use of continence products are discussed in Section III. Further discussion related specifically to catheters is provided within the following sections (Table XII-1).

1. INTERMITTENT CATHETERISATION

Intermittent catheterisation (IC) is the act of passing a catheter into the bladder to drain urine via the urethra, or a catheterisable channel such as a Mitrofanoff diversion. The urine can be drained into a toilet, urinal, plastic bag, or other reservoir. The catheter is removed immediately after drainage. This technique avoids many of the problems associated with indwelling catheters. Intermittent catheterisation may be carried out using a sterile technique in some care settings, but clean intermittent catheterisation (CIC) or clean intermittent self-catheterisation CISC [170] is widely accepted as a safe technique for people who are self-caring in their own homes. Since some studies do not distinguish between CIC and CISC, the term CIC has been adopted to cover both throughout the following section. CIC provides much greater convenience than urethral catheterisation, without unacceptable increases in infection rate, and has become a method of choice for management of bladder drainage for neurogenic and non-neurogenic bladder dysfunctions where urinary retention is a significant symptom and not easily remedied by other relatively simple means, eg TURP for prostatic obstruction. CIC can be taught to people of all ages, including the very elderly and children as young as four years old, with parental supervision [171,172] CIC can also be taught to carers, where this is an acceptable procedure to both patient and carer.

a) Quality of data

The majority of research evidence on intermittent catheterisation relates to catheter-associated urinary tract infection (CAUTI) and catheter materials and coatings. The most frequent complication of CIC is urinary tract infection (UTI) but it is unclear which catheter types, techniques or strategies, affect its incidence. There is wide variation in practice and important cost implications for using different catheters, techniques or strategies. Two relevant Cochrane reviews were identified; ‘long-term bladder management by intermittent catheters in adults and children’ [173]; and ‘urinary catheter policies for long-term bladder drainage’ [174]. The objective of the first review was to examine which intermittent catheter types, techniques or strategies, affect the incidence of UTI. Fourteen trials were included but sample sizes were small and attrition of participants was problematic. Definitions of outcome variables and follow-up periods differed, making it difficult to draw clinically useful conclusions. Several of the trials were more than 10 years old and were typically less rigorous in design and analysis. The authors concluded there is insufficient evidence to state that incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy. The objectives of the second review [174] were to determine if certain catheter policies are better than others in terms of effectiveness, complications, quality of life and economics. Comparisons included type of catheterisation (intermittent, indwelling urethral and indwelling supra-pubic) and antibiotic prophylaxis. Seven trials were included but all were small and confidence intervals were wide. There was limited evidence which indicated that prophylactic antibiotic therapy was associated with reduced episodes of bacteriuria (asymptomatic and symptomatic) in subjects using intermittent catheterisation. In both reviews, the trials which met the inclusion criteria were limited by small sample sizes and methodological weaknesses. A third review on ‘catheter policies for management of long-term voiding problems in patients with neurogenic bladder’ [175], which aimed to assess the effects of different types of urinary catheter (IC): in managing the neurogenic bladder, found there were no trials that met the inclusion criteria. Other research in this area is dominated by retrospective reviews of bladder management outcomes of patient cohorts. Long-term follow-up studies are almost exclusively of patient groups with neurogenic bladder disorders. Small scale, comparative studies of new products are common and are often industry-sponsored. Quality of life issues are vitally important for continence product users but studies are often limited by outcome
### Table XII-1. Catheter choices. Catheters should only be considered where there is no satisfactory, non-invasive alternative to manage bladder drainage.

<table>
<thead>
<tr>
<th>Product category</th>
<th>User characteristics / priorities / contexts which: FAVOUR use</th>
<th>DISCOURAGE use</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Intermittent catheters (IC)       | • If more than 100ml retained in bladder (C)  
• Concept of IC acceptable to user (or carer)  
• User has sufficient dexterity and cognitive ability to manage regular drainage | • In general (as with all catheters), where alternative, non-invasive management is satisfactory  
• If user lacks motivation or unable to cope with regime | • See Section XII.1  
• Greater independence for users  
• No need for urine collection bags  
• Reduced risk of catheter-associated complications  
• Greater freedom for sexual activity. |
| Long-term indwelling catheters (LTC): general | • Only for voiding problems which cannot be managed satisfactorily by other strategies (pads, other products or IC) (A)  
• User or carer able to empty drainage bag regularly | • In general (as with all catheters), where alternative, non-invasive management is satisfactory  
• Avoidance of UTI is a priority (A)  
• Cognitive impairment (danger of interfering with catheter) (C)  
• High risk of recurrent catheter encrustation & blockage (B) | • See Section XII.2  
• May be required: (i) to drain the bladder where there is urinary retention; (ii) to improve care of for those with severe incontinence who cannot manage otherwise, are terminally ill, or need secure urine drainage to heal skin lesions / wounds affected by the presence of urine |
| LTC: urethral insertion           | • Concept is acceptable                                                                                                           | • History of urethral trauma  
• Haematuria of unknown origin  
• High risk of catheter being expelled (bladder spasm) |                                                                                                                                                        |
| LTC: supra-pubic insertion        | • Concept is acceptable                                                                                                           | • Haematuria of unknown origin,  
• Bladder tumour  
• Small, contracted and fibrotic bladder  
• User is obese |                                                                                                                                                        |
| Short-term indwelling catheter    | • Post-operative controlled drainage  
• To monitor urine output  
• To irrigate the bladder  
• To instil medication  
• To relieve retention of urine | • In general (as with all catheters), where alternative, non-invasive management is satisfactory  
• Avoidance of UTI is a priority (A) |                                                                                                                                                        |
measures predominantly based on user satisfaction, in the absence of clear criteria. Few studies have directly compared CIC with other methods of bladder drainage.

**b) User characteristics:**

CIC is a commonly recommended procedure for people with incomplete bladder emptying not satisfactorily managed by other methods. CIC can be appropriate for post-void residual urine volumes of 100ml or more in:

- Patients with neurological disorders that result in urinary retention problems, including failure to empty the bladder, incomplete emptying, detrusor sphincter dyssynergia.
- Patients with difficulty emptying the bladder after surgical procedures, if outflow obstruction occurs either in the short or long-term.
- Patients who accumulate a build up of residual urine caused by detrusor overactivity and inadequate bladder emptying.
- Acute urinary retention (most commonly in men).
- Management of urethral stricture.
- Emptying the bladder following continent urinary diversions such as a Mitrofanoff diversion.

CIC may be a practical option for patients who are:

- Sufficiently motivated to manage their bladder drainage by this technique.
- Sufficiently dexterous to perform the technique. An appropriate level of manual dexterity is essential but generally if people can write and feed themselves they have sufficient dexterity [176].
- Sufficiently cognitively aware to adhere to a regime and empty the bladder at appropriate time intervals to prevent bladder over-distension and preserve upper urinary tract function.
- Unable to perform the technique themselves but willing to accept the procedure from a carer.

Most men require some form of lubrication to aid catheterisation, which can be on the catheter surface or instilled into the urethra [177] (Level of Evidence 3). For those with preserved urethral sensation, a local anaesthetic gel may be needed. Many female patients also use a catheter lubricant / anaesthetic gel although some choose not to. In developing countries, where resources are limited (or sometimes through patient choice), patients sometimes use plain water as lubricant [178] (Level of Evidence 4).

Regular bladder drainage is important to avoid potential damage to the upper urinary tract from urine reflux and raised intravesical pressure from build up of residual urine. Patients require individualised care plans to help identify appropriate catheterisation frequency, based on discussion of voiding dysfunction and impact on quality of life, frequency-volume charts, functional bladder capacity, and ultrasound bladder scans for residual urine. Some people need to catheterise several times per day, others less frequently. Catheterising frequently enough to avoid residual urine greater than 500ml is a general rule for adults but further guidance is also provided by urodynamic findings, detrusor pressures on filling, presence of reflux, and renal function. Disabilities such as blindness, lack of perineal sensation, tremor, mental disability and paraplegia do not necessarily preclude individuals from mastering the technique if they have sufficient manual dexterity [176]. Lack of motivation is the most common reason for failure, often linked to difficulty managing the technique or adhering to the required regime.

Children at school need a multi-professional assessment which may include a continence advisor, paediatric community nurse or school nurse, the child’s consultant, the child and parents. With adequate training, suitable facilities and supportive teaching staff many children are able to carry out CIC themselves either on a toilet or from a wheelchair. CIC has been shown to be a viable therapeutic option for children with a large post-void residual urine volume in the absence of any neurological abnormality [179]. Intermittent catheterisation has also been shown to be an effective technique for elderly patients with post-void residuals more than 50% of the bladder capacity, resistant to other treatment [180]. In a group of 21 patients (mean age 76.5 years), 12 mastered the technique of CIC, with the remainder catheterised by their partners or nurses. Urinary continence was restored, urgency, frequency and nocturia decreased and UTI rate diminished, resulting in improved quality of life.

Advantages of intermittent over indwelling catheterisation include:

- Greater opportunity for individuals for self-care and independence.
- Reduced risk of common indwelling catheter-associated complications.
- Better protection of the upper urinary tract from reflux.
- Reduced need for equipment and appliances e.g. drainage bags.
- Greater freedom for expression of sexuality.
- Potential for improved continence between.

**c) Catheter characteristics**

Types and characteristics of catheters used in intermittent catheterisation vary considerably so evaluation and selection of products is complex [173].
Plain uncoated catheters (typically clear plastic PVC) are packed singly in sterile packaging. As per industry standards, all disposable catheters are intended for one-time use but PVC catheters are frequently cleaned and reused by individual users because of cost or concern about environmental issues. Some healthcare professionals make a distinction between ‘single-use’ (i.e. disposed of after insertion) and ‘single patient use’ (cleaned and re-used by the same patient for a limited period of time, such as one week). Where products are used in ways which differ from manufacturers’ guidance, both patients and healthcare professionals should recognise their personal, professional/legal responsibilities. In some countries, including the US, there are very clear governmental directives that catheters identified as single-use devices should not be re-used in any setting. US patients should be provided with an adequate number of catheters to use a sterile catheter for each catheterisation, and patients and carers must be informed that catheters are identified for single use only.

Most uncoated intermittent catheters are used with separate lubricant, although this is a matter of personal choice. Cleansing for re-use (where this occurs) varies from being washed with soap and water, boiled, soaked in disinfectants, or microwaved. Cleaned catheters are air dried and then stored in a convenient container (often plastic containers/Zip loc bags or paper bags). Metal catheters made from silver or stainless steel can be sterilized by heat or chemicals and may be used repeatedly for longer periods than other reusable materials.

Coated catheters are single use only (they are not currently suitable to be cleaned and reused) and are designed to improve catheter lubrication, ease of insertion and convenience. Coated catheters may reduce urethral trauma and CAUTI although good quality research evidence remains limited. The most common coatings are hydrophilic (which require the addition of water to the catheter to form a lubricious layer) or pre-lubricated (whereby the catheter is supplied pre-packed with a coating of water soluble gel). There are also several pre-lubricated products with an integrated collection bag (all-in-one) which gives flexibility for the user and are efficient for hospital use.

Intermittent catheters range in size from 6-20 Ch, with most common sizes being 10-12 for females and 12-16 for males (Fig XII-1). Intermittent catheters are generally around 40cm long (male length) and are more rigid than indwelling catheters to aid insertion. A variety of aids to assist catheterisation are available (Fig XII-2).

Some women find a stiffer catheter easier to handle and some designs are slightly curved and made only in female length (around 18cm) to accommodate their requirements. Some manufacturers produce conveniently packaged ‘catheter-sets’ where the catheter is already attached to a urine containment pouch inside the pack and a non-touch, clean technique is facilitated by holding the catheter inside the bag and gradually advancing it from the bag during insertion. Catheter designs may include a protective tip to help reduce the transfer of bacteria from the distal region of the urethra further into the bladder. Patients should have the opportunity to try different catheters and choose which best suits their needs and lifestyle. Different catheters/packs may be appropriate at different times e.g. when added convenience for quick and efficient use and disposal is important, such as going to work or on holiday.

An effective intermittent catheter should have the following characteristics:

- Smooth for comfort, but sufficiently firm for easy insertion and maintenance of lumen patency.
- Minimal friction on insertion or removal.
• Smooth edges to catheter eyes to avoid tissue trauma on frequent catheterisation.
• Shaped for easy passage through urethral contours.
• Easy to hold and manipulate for those with limited dexterity.
• Easy to identify correct end for insertion and for drainage, for those with visual impairment.

Although there is an increasing range of intermittent catheter types on the market - including many pre-lubricated products with integrated collection bags - the quality of evidence for clinical benefit is poor. De Ridder et al [181] conducted a prospective, randomised, parallel, comparative trial of a hydrophilic coated catheter with an uncoated PVC catheter with 123 male spinal cord injured (SCI) patients. Only 57 completed the 12 month study but fewer patients with the coated catheter experienced one or more symptomatic UTIs (p=0.02). There was no difference in haematuria, leukocyturia and bacteriuria. However a recent Cochrane Review [173], concluded that overall current research evidence is weak, most studies are underpowered and conclusions are limited by serious design issues. An earlier literature review (182) also indicated the wide variety of materials and techniques used for intermittent catheterisation. It concluded that there was no one best technique or material and that choice of both depend greatly on the patient’s individual anatomic, social and economic status.

d) Associated risks / problems

Urinary tract infection is well-recognised as the most frequent complication of intermittent catheterisation [173;182]. The accumulation of urine in the bladder provides a reservoir for infection, but it has also been proposed that the increased intravesical pressure reduces the vascular supply to the bladder tissue rendering it more susceptible to bacterial invasion [183]. A post-void residual urine volume of 150ml has been demonstrated to be an independent risk factor for the development of UTI, in stroke patients [184] (Level of Evidence 2).

In Wyndaele’s review of complications of intermittent catheterisation (82 studies), prostatitis was identified as a risk in men but epididymitis and urethritis were relatively rare [182]. Trauma from catheterisation, measured by haematuria, was noted to occur regularly but lasting effects were more limited. The prevalence of urethral strictures and false passages increased with longer use of CIC but the review concluded that the most important preventative measures are good education of all involved in CIC, good patient compliance, use of an appropriate catheter material, good catheterisation technique and the avoidance of bladder over-filling. Similar findings were reported by Campbell [185] in a follow up of children with spina bifida who had used intermittent catheterisation with uncoated PVC catheters for at least five years. The incidence of urethritis, false passage, or epididymitis was very low whilst adherence to the protocol was excellent. However, Ku et al [186] found a higher incidence of epididymitis in their cohort review of 140 male, SCI patients followed over 16 years.

1. Urinary tract infection

It is difficult to know the prevalence of UTI associated with intermittent catheterisation as reports vary widely and definitions of UTI are inconsistent, sometimes based on bacteriuria alone (asymptomatic) and sometimes on symptomatic UTI (with or without clearly defined criteria). Other variations include the evaluation methods used, catheterisation techniques, frequency of urinalysis / culture, administration or not of prophylactic antibiotics, and the patient group studied (including gender, functional ability, behavioural and personal hygiene factors). In a prospective study of 128 SCI patients, where the incidence of UTI was calculated as the number of episodes per 100 person-days, the overall incidence of UTI was 0.68. The rate for males using CIC was 0.41, compared to 2.72 for those using an indwelling catheter [187]. Biering-Sorensen et al. (188) studied 77 SCI patients on CIC after five years and found that 81% had been treated for at least one UTI, 22% had two-three UTIs/year and 12% had four or more per year. The technique of intermittent catheterisation used does not seem to be a risk factor and despite different catheterisation techniques used, the number of episodes of clinically significant nosocomial urinary infections and the mean species turnover remains similar [189] (Level of Evidence 2).

In the Cochrane review cited above [173], the primary outcome measure was catheter-associated infection (definition of infection as used in the trial reports). Fourteen trials met the inclusion criteria but too little data could be entered into a metaanalysis to produce meaningful data summaries. Based on the available data, the authors concluded that there appeared to be no clear difference between various methods of catheterisation (sterile catheterisation techniques, clean catheterisation with a single-use sterile catheter, or clean catheterisation with a clean reused catheter). Whilst the outcomes of this review raise questions over efficacy and cost-effectiveness of expensive coated catheters it is clear that further robust research is needed. All sample sizes in the trials were small and only two included statistical power calculations, although they were unable to achieve their predicted sample sizes. Most studies suffered from high attrition rates and several reports were more than 10 years old.

The challenges of obtaining sound data in this clinical area continue to hinder the accumulation of evidence to help guide healthcare practitioners. A common difficulty is in the establishment of robust outcome
measures. UTI remains the most clinically important primary outcome variable but bacteriuria/positive urine culture is not clinically relevant unless accompanied by symptoms. Symptoms themselves may present in vague and imprecise ways, especially in elderly and/or SCI patients where symptoms can be masked or unclear.

A Cochrane review on urinary catheter policies for long-term bladder drainage [174] reported limited evidence that prophylactic antibiotic therapy was associated with reduced episodes of bacteriuria (asymptomatic and symptomatic) but all trials were small and confidence intervals were wide. The authors caution that possible benefits from prophylaxis must be balanced against possible adverse effects such as the development of antibiotic resistant bacteria.

In order to improve rigorous clinical evaluation of current and innovative products for CIC, more epidemiological data on user populations and characteristics of catheter use is needed. A recent Canadian national survey of intermittent catheterisation practices following SCI [190], reported on 912 responses to a 36-item self-report postal questionnaire. Fifty five per cent of respondents used intermittent catheterisation regularly, with users forming a significantly younger group than non-users (P=0.001). The majority of users (73%) used a clean technique. The remaining 27% reported using a sterile technique. Uncoated catheters were used most commonly; 74% only used uncoated catheters; 15% used hydrophilic coated catheters; and 11% reported using both types. These notable differences may be partially related to patient education, costs to patients and health insurance funding constraints. The majority of uncoated catheter users used their catheter only once (53%) but a further 30% used their catheter more than nine times. The mean frequency of self-reported CAUTIs in the past 12 months (symptomatic but not necessarily confirmed by laboratory evidence) was 2.6, with females experiences significantly more infections than males (P=0.003). Although the use of hydrophilic coated catheters was associated with a lower rate of CAUTI (2.46 v 2.62 for those using uncoated catheters), this difference was not reported as statistically significant. However UTI rates are multifactorial and are unlikely to be fully accounted for by the variables investigated. A significant relationship between number of catheterisations per day and CAUTI rates was identified, with those who catheterised only once a day having the highest rate of infections (P=0.03). This is consistent with previous suggestions that increasing the time that colonised urine is present in the bladder is associated with increased infection rates [181]. It is interesting to note that, while extra fluid intake was positively related to reduced rate of CAUTI (P<0.001), catheter re-use, catheter disinfection and antibiotic prophylaxis were not significantly associated with CAUTI rate. Clearly there are potential limitations in this study as with any which employs self-report methodology. These include self-selection of respondents, accuracy of recall and quality of information provided, but the large number of respondents and the degree of internal consistency reported by the researchers provide credibility to these results.

Several studies have sought to determine whether the antibacterial effects of cranberry extract will reduce or eliminate bacteriuria and pyuria in patients using intermittent catheterisation, particularly in SCI populations [191,192]. In a randomised, double-blind, placebo-controlled study of 48 SCI patients living in the community and using intermittent catheterisation or external urine collection device, participants ingested 2g concentrated cranberry extract in capsule form or placebo daily for 6 months [192]. There were no differences between groups with respect to number of urine specimens with bacterial counts >10^5 cfu/ml, types and numbers of different bacterial species, numbers of urinary leukocytes, urinary pH, or episodes of symptomatic infection.

2. Tissue Trauma, strictures and other complications

Long-term follow-up studies have examined other complications associated with intermittent catheterisation and found urethral trauma to be common [193,194]. Urethral bleeding is frequent in new patients and has been noted to continue to occur in up to 30% on a long-term basis [194,195], however risks of tissue trauma may be reduced with newer catheter products which are designed to reduce friction. Consequently the outcomes of older studies need to be considered with caution. The withdrawal frictional force was compared between two hydrophilic coated catheters and one uncoated catheter in a prospective, randomised, participant-blinded, crossover trial by Stensballe et al [196]. Forty participants completed the study and it was interesting to note that while one coated catheter (SpeediCath) exerted a lower mean withdrawal force than the other catheters, the second coated catheter (LoFric) exerted a significantly higher mean friction force than both the other catheters. Both hydrophilic coated catheters were associated with less microscopic haematuria than the uncoated catheter. Similarly, there was a lower incidence of microscopic haematuria reported in two of the coated catheter groups compared to uncoated catheters in trials included in the Cochrane review [173]; 0.31v0.65 [197]; 6/14 (43%) v 11/14 (78%) [198]. Trauma of the urethra, especially in men, can cause false passages. Treatment for false passages in SCI patients by six weeks indwelling catheter use and five days antibiotics, has been reported to be effective [199] (Level of Evidence 3). The false passages had disappeared on cystoscopy and CIC could be restarted.

It has been claimed that the long term risk of urethral
stricture formation may be less when hydrophilic coated catheters are used [200]. The degree of urethral inflammation, measured by urethral cytology in two groups using CIC (one using ordinary PVC catheters with lubricant; the other using hydrophilic coated catheters), showed significantly less urethral inflammation in the hydrophilic coated catheter group. Although this data suggests some benefit in using hydrophilic coated catheters to minimise stricture formation in the long-term comparative studies are limited. One recent follow-up study of 31 females with spina bifida, using CIC for a median of 15 years, examined risk of urethral lesions. There were few problems reported (only on 20 occasions in a total of 459 patient-years), despite long-treatment periods and use of non-coated PVC catheters [201].

The relative importance and cost-effectiveness of hydrophilic catheter coatings has not been adequately addressed in large scale studies to date. Hedlund et al. [202] in their review of 28 CIC studies, called for a prospective, randomized, long-term, multi-centre study to address clinical benefit and cost effectiveness. Data on patient characteristics should include age; gender; diagnosis of bladder dysfunction; reason for CIC; physical and mental disability; manual dexterity; and previous treatments. Effect parameters should include number of catheterisations; urinary tract infection (symptomatic or asymptomatic); early and long-term urethral complications; patient satisfaction, preferences; and drop-out rates. Robust studies of this nature are still awaited.

3. OTHER COMPLICATIONS

Formation of bladder stones has been found to be associated with long-term use of CIC in a number of studies [203] (Level of Evidence 2). Barroso et al. [204] reported an increased risk of developing bladder calculi in children performing CIC based on the records of 403 children. Stones were diagnosed in 28 patients. The incidence was slightly higher in those with a Mitrofanoff conduit but was not influenced by bladder augmentation (Level of Evidence 3). A retrospective study of 140 SCI patients, followed up from 1987 to 2003, identified 27.9% of patients diagnosed with epididymo-orchiditis. This problem was more common in patients using CIC compared to indwelling catheterisation (42.2% v 8.3%, P= 0.03). Multivariate analysis showed CIC to be an independent risk factor for epididymo-orchiditis, with SCI patients in this study subject to a 7-fold higher risk (OD 6.96; 95%CI, 1.26-38.53 [186].

e) Catheter management

1. Education, support and quality of life (QoL)

Good education of all involved in CIC, good patient compliance, use of an appropriate catheter material, and good catheterisation technique have been identified as the most important measures to prevent adverse complications [182]. Factors affecting adherence to self-catheterisation procedures have been explored, addressing both initial mastery of technique and both short-term adherence and long-term adherence [205,206]. Time taken to build confidence is variable and may range from days to years [206]. General determinants of adherence related to knowledge, complexity of the procedure, misconceptions, fears, shame, motivation, quality and continuity of professional care. Integration of the CIC regime into everyday life was a recognised difficulty and for younger patients, in particular, availability of materials, physical impairments and resistance to ‘sickness role’ were factors which could also compromise adherence. Qualitative research studies using a grounded theory approach have identified similar factors influencing variations in quality of life (see also Section XII.4).

These include sex; lifestyle; frequency of duration of carrying out CIC; technical difficulties; type of catheter; co-morbidities; and individual predispositions [207]. In the large scale Canadian survey above (190) 71% reported that CAUTIs had negatively impacted on their QoL score (a 10-point scale). Severeable significant variables associated with CAUTI and QoL were determined. Interestingly, time lost from social activities was more strongly associated with compromised QoL than actual number of infections or days lost from work.

2. Catheter cleaning for re-use

Where catheters are cleaned for re-use they may continue to be used many times, up to weeks or even months. However, health professionals and users need to recognise their personal responsibilities and liabilities in supporting this approach since manufacturers’ guidance will normally relate to single use only (see also Section XII.1.3). Questions over how long the same catheter may be safely reused require further examination, and may be particularly important in developing countries, where access to new supplies may be limited [208].

Methods of cleaning or re-sterilising include soaking in a variety of antiseptic solutions or boiling water or microwave sterilisation. In a study which compared three home cleaning methods used by patients performing CIC, all of the following were found to be effective: 0.6% hydrogen peroxide; bleach in a 1:4 solution with tap water; and betadine in a 1:2 solution with tap water [209]. None of the cleaned catheters showed detectable bacterial growth for 48 hours after the cleaning procedure was performed (Level of Evidence 4). Lavallee et al. [210] also compared the effectiveness of hydrogen peroxide, vinegar, dishwashing detergent, and tap water alone to clean catheters contaminated with Pseudomonas aeruginosa and Escherichia coli. They also examined the effect of immediate rinsing and drying before cleaning.
Table XII-2. Intermittent catheterisation

Patient education & support:

• Discussion of individual bladder dysfunction and reasons for CIC.
• Personal anatomy and identification of urethral orifice.
• CIC technique — comfortable position, frequency, observation of patient’s technique.
• Hygiene.
• Discussion of any psycho-sexual anxieties (body image, sexual function etc).
• Single use versus reusable catheters (cleaning, storing, re-use, disposal). NB including awareness of personal / legal issues.
• Difficulties and what to do.
• Dietary advice and avoidance of constipation.
• Obtaining supplies.
• Follow-up visits and consultations.

Guidance for common problems:

• Catheter will not go in at first attempt – relax for a while and try again a bit later; lubricate catheter (eg dipping in water or gel); if necessary seek professional guidance.
• Catheter inserted into vagina by mistake – withdraw, wash and re-insert.
• Catheter will not come out – leave for a few minutes, relax and try to ‘let go’, cough gently and withdraw catheter.
• UTI – report changes in urine (eg blood, sediment, smell). Know how to recognise signs of symptomatic infection and seek treatment and review of CIC technique.

Results indicated that rinsing and drying immediately after use was the most effective at reducing bacteria to near zero (Level of Evidence 4). Microwave sterilization has been advocated by some, but has not been adequately evaluated. A study by Sherbondy, et al. [211] showed that even where standardized instructions (both verbal and written) were provided, microwave sterilization techniques by patients performing CIC varied considerably. Many patients surveyed did not follow the study instructions recommending sterilizing used catheters on a daily basis, cleaning with soap and water and air drying before inserting into a microwave oven on a paper towel. Microwaving on a high setting for six minutes on a rotation table was recommended together with a heat sink – a cup of water in a microwave-safe container placed in the microwave to absorb extra heat. Catheter melting was reported by 63% and was significantly associated with the absence of a rotation

If microwaving is to be accepted as an appropriate sterilization method then users must be provided with a standardised, evidence-based, protocol to follow. A recent study reported the development of titanium dioxide-coated catheters for CIC which were easily sterilized under certain light sources and were shown to be safe in experimental studies [212]. Preliminary clinical analysis with 18 volunteers was also promising.

1) Comparisons between intermittent and indwelling catheterisation

A systematic review of risk factors for UTI in adults with SCI reported evidence of fewer infections in patients using intermittent catheterisation compared to indwelling catheterisation (213). Twenty two studies met the inclusion criteria for evaluation but the authors noted that many had important methodological deficiencies. Intermittent catheterisation has also been shown to be associated with fewer UTIs compared to indwelling catheterisation in elderly patients after surgical repair of hip fractures [214] and in a comparative study of patients at a hospital department of urology [215].

Patel et al.[216] examined the outcomes of different forms of urinary drainage for men with acute urinary retention. After a short period of indwelling urinary catheterisation patients were taught to use CIC (34 men). Patients who failed this were re-catheterised and taught to manage a valve or failing this a leg bag (16 men) and then discharged home. The CIC group had a higher rate of spontaneous voiding (56% v 25%) and a lower incidence of UTI (32% v 75%). At TURP 20% in the CIC group had a UTI compared to 69% in the indwelling catheter group. Patients using CIC preferred it and had fewer complications. The authors concluded that CIC was well accepted by those patients who were able to manage the technique, resulted in fewer UTIs and should be considered in patients presenting with acute retention.

In a recent 2-week prospective study of intermittent catheterisation versus indwelling urethral catheterisation in older female patients in a rehabilitation setting, 81 females >65 years with post-voiding residual volume persistently >300 ml were randomized to one of two groups[217]. Both groups demonstrated similar success in regaining bladder function and similar rates of bacteriuria. The authors concluded that intermittent catheterisation was justified in managing this patient group, particularly since indwelling catheters were deemed to hinder rehabilitation and adversely affected quality of life.

In a prospective RCT of CIC versus supra-pubic catheterisation (SPC) for post-operative bladder care following hysterectomy in 40 women there was no significant difference in the length of bladder care between the two groups[218]. Bacteriuria was higher
in the CIC group at days 3 and 5 (p=0.05 and 0.004 respectively) although it is unclear whether there was evidence of symptomatic infection. However, there was a higher incidence of symptoms / problems arising from the SPC site, of which 23% were shown to have a positive wound swab. The authors concluded that despite a higher rate of bacteriuria, the high incidence of site problems with SPC could be avoided by CIC. The technique of CIC was seen to be more acceptable to patients (p=0.009); allowing fewer disturbances at night (p=0.006); greater freedom to lead a normal life during the day (p=0.000); and less anxiety / embarrassment (p=0.005) compared to SPC.

**g) Summary**

CIC is the optimum method of urinary drainage in patients with neurogenic bladder dysfunction and others with problems of bladder emptying. It can be taught to patients of all ages who have sufficient manual dexterity and motivation to manage the technique. Urinary tract infection is the most frequent complication and the most important preventative measures for all complications are good education of all involved in CIC management, good patient compliance and support, use of an appropriate catheter material and good catheterisation technique. Difficulties in carrying out the procedure such as physical and technical difficulties, embarrassment, time involved and lack of appropriate public facilities may deter users from adhering to the regime. Hydrophilic-coated catheters confer benefits in terms of comfort and minimised tissue trauma compared to non-coated catheters (Level of Evidence 2/3) but evidence of benefit in relation to urinary tract infection is less clear.

The available data on intermittent catheterisation does not provide convincing evidence that any specific technique (sterile or clean), catheter type (coated or uncoated); method (single use or multiple use), person (self or other), or strategy is better than any other for all clinical settings. This reflects lack of reliable evidence rather than evidence of no difference. Currently clinicians will need to base decisions about which technique and type of catheter to use on clinical judgment, in conjunction with patients. Differential costs of catheters / techniques may also inform decision making.

In particular, CIC has been shown to have benefits over indwelling catheterisation in the following ways:

- Avoidance of common problems associated with LTC use such as catheter leakage and / or practical management of drainage systems
- Avoidance of complications linked to bacterial biofilm formation, including catheter encrustation and blockage. Strong evidence for reduced risk of CAUTI is less clear.
- Maintenance of some level of bladder capacity and muscle tone by allowing the bladder to fill periodically, compared to free drainage by indwelling catheter.
- Less urethral inflammation (measured by cytology) than urethral indwelling catheterisation (Level of Evidence 2/3).
- Lower incidence of bladder calculi than indwelling catheterisation (Level of Evidence 2/3).

**2. INDWELLING CATHETERISATION**

Indwelling catheters (Fig XII-3) may be used in the short-term to manage an acute need for controlled bladder drainage or as part of a long-term management strategy (Table XII-1).

Catheters may be inserted into the bladder urethrally (UC) or suprapubically (SPC) through an incision in the abdominal wall. The continued requirement for indwelling catheterization should be reviewed at regular intervals and the catheter removed promptly if no longer necessary, since catheter use is associated with a number of risks. The major complication associated with short-term, indwelling catheters used in acute care, is nosocomial (healthcare acquired) catheter-associated urinary tract infection (CAUTI), which can lead to life-threatening bacteraemia in vulnerable groups and may also contribute to reservoirs of antibiotic resistant microorganisms [169] [117] [219]. Long-term catheters (LTC) are also associated with increased risk of CAUTI and a further range of problems including: recurrent blockage due to encrustation by mineral deposits; meatal tissue damage - often caused by excessive weight from heavy drainage bags; frequent bladder spasm with potential expulsion of the catheter; formation of bladder calculi; and potential for long-term neoplastic changes.

![Figure XII-3: A Foley catheter (left) and a suprapubic catheter with a sharp trocar for introducing the catheter (right).](image-url)
in the bladder (although further long-term studies are needed to establish this risk). Although for some patients an LTC catheter can provide satisfactory management of bladder problems and greater independence, others experience pain and discomfort with a catheter in situ and / or, are distressed by the impact of a catheter on their body image and sexuality. Intermittent catheterisation (See Section XII.1) is less invasive and is generally associated with fewer risks.

**a) Quality of Data**

Seven Cochrane reviews relating to short and long-term indwelling catheter use were identified. Reviews on short-term (<14 days or other temporary short-term use as defined by triallists) catheter issues included: types of urethral catheters for management of short-term voiding problems in hospitalised adults (220); policies for bladder management [221]; the role of prophylactic antibiotics [222]; and policies for removal of short-term indwelling catheters [223]. The objective of the first review [220] was to determine the effect of type of indwelling urethral catheter on the risk of UTI. Twenty-three trials - comparing different types of standard catheters or a standard catheter with an antiseptic catheter (silver alloy or impregnated with silver oxide), or an antibiotic impregnated catheter (either minocycline and rifampicin, or nitrofurazone) - met the criteria. The reviewers concluded that currently available evidence suggests that silver alloy catheters prevent asymptomatic bacteriuria in the short-term catheterised patient, although trials are generally of poor quality (Level of Evidence 2/3).

They also recommended that further economic evaluation is required to confirm that infection compensates for the increased cost of the silver alloy catheters. Catheters impregnated with antibiotics were also beneficial in reducing bacteriuria in hospitalised adults catheterised for less than a week but data were too few for those catheterised longer. However, it is important to note that although bacteriuria is a commonly used outcome measure in CAUTI studies there is much debate over the clinical utility of this measure. Many studies fail to distinguish between asymptomatic bacteriuria and symptomatic infection. This is discussed further in Section XII.h.2.

The second review [221] included 14 trials which reported on comparisons between SPC and UC for short term (up to 14 days). Higher relative risks scores were found for UC related to more bacteriuria (RR 2.60; 95% CI 2.12 to 3.18), more frequent re-catherization (RR 4.12; 95% CI 2.94 to 7.56) and increased discomfort (RR 2.98; 95% CI 2.31 to 3.85) (Level of Evidence 1). The third review [222] included six parallel group RCTs and reported weak evidence that antibiotic prophylaxis reduced the rate of symptomatic UTI in female surgical patients, compared to antibiotics given when clinically indicated. The review of policies for catheter removal reported suggestive, but inconclusive, evidence of benefit from midnight removal of the catheter (larger volumes at first void) and shorter hospital stay after early rather than delayed removal. There was little evidence on which to judge other aspects of management such as catheter clamping, prior to removal.

Of the three Cochrane reviews relating to long-term catheter use, a review of comparative methods of using catheters for neurogenic bladder management [175] failed to find any trial that met the inclusion criteria. A second review [224] to compare types of indwelling catheter for long-term use (defined as >30 days) found only three trials which met the inclusion criteria. One trial compared antiseptic impregnated catheters with standard catheters and two compared different types of standard catheter. The authors reported ‘an astonishing lack of evidence for this clinically highly relevant problem’.

Since the included studies were very small and showed methodological weakness, the authors concluded that the available evidence was insufficient as a reliable basis for practice and catheter choice remains largely based on clinical experience. In the third Cochrane review on ‘urinary catheter policies for long-term bladder drainage’[174], seven trials met the inclusion criteria. All were small, with wide confidence intervals. No appropriate trials addressed comparisons between: indwelling UC and SPC; UC and intermittent catheterisation; or SPC and intermittent catheterisation.

Evidence pertaining to whether antibiotic prophylaxis is better than antibiotics given when clinically indicated, was insufficient as a basis for clinical practice. A Cochrane review protocol for washout policies for the management of long-term catheters in adults has been published [225] but there is little published clinical evidence to review, to date. Overall long-term catheter care practices remain poorly supported by research evidence. This is at least partially due to difficulties in conducting trials in long-term catheterised populations for a variety of reasons, many of which have been discussed in earlier sections.

The impact of long-term catheters on users’ quality of life (QoL) is a very important issue which has not been studied adequately. No Cochrane reviews have dealt with this topic directly, although several reviews have included issues with an impact on QoL such as catheter related complications and comfort. One RCT addressed education needs of catheter users. Other studies include a small number of prospective cohort studies, with the remainder being retrospective studies and case series reports, providing evidence at Level 3. Much relevant research uses qualitative research methodologies, aimed at understanding the nature of long-term catheter-related issues and patient concerns. Measures of QoL used commonly rely on a single question of quality of life or satisfaction on a 3- or 10-point scale.
Validated QoL instruments, such as SF 36 are not only infrequently used, but are likely to lack sensitivity for the specific issues which concern catheter users. There are currently no device-specific measures as advocated by ICS (226), although work in this area is continuing.

b) Prevalence of indwelling catheters use

Short-term catheterisation is common in acute care settings, with up to 25% of patients receiving a catheter during their hospital stay [169,227]. The prevalence of LTC use in home care or community care settings varies widely and can be more difficult to determine. A large scale survey of 4010 older people (>65 years) receiving home care in 11 European countries, found a mean prevalence of LTC use of 5.4%, ranging from 0% in the Netherlands to 23% in Italy [228]. In another large study of 1004 frail older women living in the community the reported LTC prevalence rate was 38.1% [229].

There is evidence that older patients aged 65 years or more are often catheterised inappropriately [230-232]. Gokula et al. [231] surveyed a 10% random sample of patient charts from 2845 elderly patients who received an indwelling catheter during hospital admission in one year. Less than half the selected charts recorded an appropriate indication for catheterisation. An explicit reason for catheter insertion was documented in only 13% of charts and there was no written order for catheterisation in 33% of the charts. Only 18% had documented care plans for catheter removal.

Expert opinion and experience suggests that even when there is an appropriate clinical reason for initial catheterisation, patients may remain catheterised unnecessarily if medical and nursing staff fail to review ongoing need (Level of Evidence 3). Problems of inappropriate catheter use may be compounded when patients are transferred from one clinical setting to another without adequate information on why the person was catheterised [233]. Wald et al [234] reported that 32% of patients catheterised during treatment for hip fracture in their study were discharged to nursing homes with the catheter still in place.

The prevalence of catheterized patients in nursing homes is generally higher than in people living at home and has been reported to be around 9% in the UK [235], but there may be considerable variation between homes [236]. In nursing homes in the US, it has been estimated that between 7-10% of the residents have an LTC [237], although figures vary from state to state. More recent data from analysis of a US National Nursing Home Survey [238] and a point prevalence study of nursing home-associated infections in the Department of Veterans Affairs nursing home care units [239] demonstrated similar prevalence. Tsan et al. [239] reported a prevalence of 10.7% for indwelling urethral catheters and 2.46% for suprapubic catheters amongst a nursing home population of 11,475 in 133 care home units. There is some evidence of decreasing rates of urinary catheterisation in some places. A retrospective cohort study of the use of urine collection devices in skilled nursing facilities (SNFs) in five US states examined the characteristics of 57,302 patients who remained in an SNF for one year in 2003 [240]. The prevalence of indwelling catheterisation was 12.6% at admission and 4.5% at annual assessment (P<0.001). Paraplegia, quadriplegia, multiple sclerosis and comatose state were strongly associated with LTC use. Male residents were more likely to use a catheter at every assessment, as were obese patients; individuals with diabetes mellitus, renal failure, skin conditions, deep vein thrombosis, aphasia or end-stage disease; and those taking multiple medications.

Duration of catheter use in home settings varies widely, with a median of 3-4 years and some individuals using them over 20 years [241-243]. Management regimes for continence problems in older people continue to demonstrate a predominance of containment strategies, using pads and catheters [244] and consequently unwarranted use of LTCs for incontinence continues in many places despite known catheter-associated risks.

c) User characteristics

Short-term catheterisation (usually defined as up to 14 days) is most commonly used:

- During surgical procedures and post-operative care.
- For accurate monitoring of urine output in acute illness.
- Instillation of medication directly into the bladder.
- For relief of acute or chronic urinary retention.

Long-term indwelling catheters - routinely changed and replaced, often over many months or years - may be required to aid those who have difficulty emptying their bladder due to obstruction or neurological disorders, where intermittent catheterisation is not a satisfactory option. LTCs may also be used to provide supportive care for those with severe incontinence who cannot manage otherwise, are terminally ill, or need treatment to heal skin lesions or surgical wounds affected by the presence of urine.

Long-term catheterisation is most commonly used to help manage:

- Bladder outlet obstruction (BOO), where patients are unsuitable for - or waiting for - surgical relief.
- Chronic retention, often as a result of neurological injury or disease (where intermittent catheterisation is not possible).
• Debilitated, paralysed or comatose patients (in presence of skin breakdown and infected pressure ulcers).

• Intractable urinary incontinence where catheterisation enhances the patient’s quality of life (as a last resort when alternative non-invasive approaches are unsatisfactory or unsuccessful).

d) Routes of catheter insertion

For some patients the insertion of an indwelling catheter suprapubically (SPC) into the bladder, through the abdominal wall, offers advantages over the urethral route (UC). SPC may be necessary following urethral or pelvic trauma but also offers advantages in acute and long-term care. In frail elderly men, and / or those prone to infection e.g. diabetes mellitus, SPC can be preferable to a urethral insertion to avoid urethritis, orchideepidymitis and prostatitis [245]. Strategies to support the SPC may be required (e.g anchoring to the abdominal wall with a BioDerm tube holder) to prevent traction and potential displacement of the catheter or balloon [246].

Advantages of SPC compared to UC are:

• Avoidance of risk of urethra trauma to men and women during catheter insertion and withdrawal.

• Avoidance of risk of urethral destruction / necrosis from pressure caused by the weight of poorly supported catheter bags, expulsion of the catheter (particularly in neurologically impaired women), or sitting on the catheter in wheelchair bound women.

• Ease of access to entry site in patients with reduced mobility, who are wheelchair bound, have restricted hip mobility, or experience urethral pain.

• Facilitation of post-surgical trial of voiding (by temporarily clamping the drainage tubing).

• Greater freedom for expression of sexuality, although this may be counteracted by perceptions of altered body image.

• Reduced risk of contamination where faecal incontinence is a problem.

SPC insertion is generally contra-indicated in patients with haematuria of unknown origin, bladder tumour, or small contracted or fibrotic bladders which may have resulted from long-term urethral catheterisation on free drainage. In obese or immobile patients the traditional SPC stoma site may become concealed by an apron of excess anterior abdominal wall fatty tissue which can lead to sub-optimal care by both patient and carer. SPC is an effective and well-tolerated method of bladder management for many SCI patients [247-249]. In Sheriff et al’s study [247] the general level of satisfaction with SPC was very high with 70 % of patients awarding a satisfaction score of 9/10 and 95% awarding 7/10 or more. It is of interest to note that in 18% of cases, an SPC was inserted following the request of the patient, having heard about this form of bladder management from others. A review of current literature on SPC in the neuropathic bladder, by Feifer & Corcos [249] identified some notable differences between early studies and more recent reports. Problems and complications of SPC identified in earlier studies of SCI patients were less common in the more recent investigations, in which patients were managed with anti-cholinergics, frequent catheter changes and volume maintenance procedures. Recent studies demonstrated similar morbidity profiles to clean intermittent catheterisation.

Although SPC has gained wide acceptance for bladder drainage and many regard SPC insertion as a simple procedure, it is not without risks. The initial insertion of the SPC requires a minor surgical procedure which presents a potential risk of injury to adjacent structures to the bladder, especially the small and large intestines with resultant peritonitis [247] [250]. Other complications of initial SPC insertion include misplacement [251-253] and incisional hernia [254,255]. There are a number of SPC techniques for insertion described in the literature and training models have been developed to facilitate teaching [256]. Some modern catheter insertion kits employ the initial introduction of a guide wire into the bladder, to facilitate accurate positioning of the catheter introducer. However, where patients are at high risk of bowel injury (eg previous abdominal surgery or small fibrotic bladders which do not expand well at cystoscopy), some authorities recommend introduction of the SPC by percutaneous technique using intraoperative ultrasonography combined with flexible cystoscopy [257,258]. In low risk patients nurse specialists may undertake first insertion of an SPC, according to agreed policy and protocols [259]. Subsequent SPC changes can be competently managed by skilled nurses [260].

e) Catheter characteristics

An effective indwelling catheter should have the following design characteristics:

• Retained in the bladder effectively, yet easily removable without trauma to tissue.

• Soft ‘tip’ within the bladder to avoid pressure damage to the mucosa.

• Effective drainage while minimising risk of bladder mucosa being ‘sucked’ into drainage channel.

• Conforms to shape of urethra.

Despite some notable efforts to improve catheter design, the original Foley design has changed very little over the years and remains the most common. However traditional drainage systems may fail to drain the bladder to completion, due to potential outflow obstruction caused by air-locks within the curled, redundant drainage tubing segments. A novel, spiral-
shaped, drainage tubing design has recently been reported which appears to optimize flow and minimize residual urine [261]. Further evidence of efficacy is awaited.

f) Catheter materials

An ideal catheter material requires the following properties:

• Soft for comfort.
• Causing minimal tissue reaction or friction.
• Sufficiently firm for easy insertion and maintenance of lumen patency in situ.
• Elastic recoil so that an inflated balloon can deflate to almost its original size.
• Resistant to colonisation by micro-organisms and to encrustation by mineral deposits.

Catheters are made of a variety of materials including polyvinyl chloride (PVC or plastic), latex rubber with or without a coating, silicone or metal. Plastic catheters are relatively cheap to manufacture, have a thin wall and relatively large lumen, and are designed for short-term use (in situ up to 14 days). Latex catheters are restricted to short-term indwelling use (and commonly avoided where possible) because of potential discomfort due to high surface friction, vulnerability to rapid encrustation by mineral deposits from the urine and the implication of latex allergic reactions in the development of urethritis and urethral stricture [262-267] or anaphylaxis [268].

Attempts to minimise friction during catheterisation and to reduce tissue reactions have led to the coating of latex catheters with tightly bonded materials designed to provide a smoother, less irritant surface which also minimizes absorption of water by the latex (and subsequent changes in internal and external catheter diameters). Polytetrafluoroethylene (PTFE or teflon) coated latex catheters are sometimes used for medium-term use (catheter can remain in situ up to 28 days) but the materials known to cause least friction and tissue reaction are silicone elastomer and hydrophilic polymer-coated catheters, or all-silicone catheters [269] (Table XII-3). These materials are therefore recommended for long-term use (i.e. expected to remain in situ for 14 days or more, and changed regularly for a new catheter as part of a long-term strategy of care). LTC materials are also less vulnerable to rapid colonisation by bacteria and encrusting by mineral deposits than short-term catheter materials. There is evidence that silver-alloy coated catheters can help to reduce risks of CAUTI in the short-term (where bacteriuria is used as the outcome measure) (See Section XII.2.h), but no currently available material or surface coating is completely immune to microbial colonisation.

Inflation of silicone catheters with water can sometimes lead to water loss from the balloon over time, with an associated risk of the catheter falling out [270]. Consequently some manufacturers recommend filling the balloon with a 10% aqueous glycerine solution.

Most catheter materials are suitable for either UC or SPC, however not all UC catheters are also licensed for SPC. Suprapubic catheter removal is sometimes associated with trauma of tracts or stoma site where overgranulation has occurred, with bleeding and patient discomfort [260;271]. This can be a particular problem with catheter materials such as all-silicone, which are prone to hysteresis, leading to balloon cuffing on deflation. This problem may also occur with hydrophilic coated catheters but is less common [272,273]. Management of this and other catheter-related problems is considered below in Section XII.2.k

The main finding of a recent Cochrane Review of types of indwelling urinary catheters for long-term bladder drainage in adults [224] was a remarkable

<table>
<thead>
<tr>
<th>Table XII-3. Catheter materials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of catheterisation</strong></td>
</tr>
<tr>
<td>Intermittent</td>
</tr>
<tr>
<td>Indwelling, short term use</td>
</tr>
<tr>
<td>Indwelling LTC</td>
</tr>
</tbody>
</table>
lack of evidence for this clinically, highly relevant problem. Despite consideration of 11,000 abstracts and 74 full papers, only three trials met the inclusion criteria. Since these were very small and showed methodological weakness, the authors concluded that there was insufficient evidence to provide a reliable basis for clinical decision-making and catheter choice remains largely based on clinical experience.

g) Catheter size – catheter gauge, length and balloon size

Indwelling catheters are formed either by building up layers through dipping and coating on a shaped ‘former’ or by a process of extrusion of a single material. Catheter size is measured in Charriere (Ch) – also called French gauge (Fr) - which refers to the circumference of the catheter shaft in millimetres. Internal diameter varies depending on the manufacturing method, with the extrusion process resulting in a catheter with relatively thinner walls and a larger lumen for the same Charriere size. A size 12Ch catheter made by dipping and coating will have an external diameter of around 4mm and an internal diameter of around 2mm or less.

Urinary flow rate is related to the internal diameter of the catheter but 12-16 Ch catheters (usual sizes for adults) easily drain normal quantities of urine, including larger volumes produced by diuresis [274]. Although larger sizes may be needed following urological procedures where blood clots and other debris are a problem, large catheters are generally associated with increased bladder irritability and spasm [108], and with potential blockage of para-urethral glands and tissue damage, including urethral strictures. Therefore large catheter sizes should be avoided wherever possible. Small balloon sizes are recommended for all patients (10ml for adults and 2.5-5ml for children) to minimise the risk of discomfort and bladder irritation. Larger balloons tend to sit higher in the bladder with potential for increased residual urine volumes to collect below the catheter eyes. Larger balloons are also associated with increased risk of mental tissue damage caused by bladder spasm and possible expulsion of the catheter with a fully inflated balloon.

The most common sizes of SPC catheters for adults are also 12-16Ch. Some SPC kits provide a specific catheter in the kit and therefore dictate the sizes available; others allow the insertion of a range of Foley catheters. Since the catheter is inserted into the bladder via an artificial stoma it is possible that slightly larger sizes may be better tolerated than for UC although there is no research evidence to support this.

The standard male length catheter (41-45cm) is available to males and females but a shorter female length (25cm) can be more comfortable and discrete for some women. The female length catheter should not be used for males as inflation of the balloon within the urethra can result in severe trauma. Paediatric catheters are usually approximately 30cm long.

h) LTC–associated risks / problems: catheter-associated urinary tract infection (CAUTI)

The urinary tract is recognised as the commonest site for nosocomial infection in hospitals and nursing homes, accounting for between 21% and 45% of all healthcare-associated infections [239,275-278]. National nosocomial infection surveillance systems monitor CAUTIs and provide guidance for benchmarking [279]. The presence of an indwelling catheter is a key risk factor in around 80% of nosocomial UTIs. The risk of bacteriuria increases by 5-8% per day of catheterisation [280-282] and all LTC patients are likely to be bacteriuric within 4 weeks. A majority of microorganisms derive from the patient’s own colonic and perineal flora or from the hands of health-care personnel during catheter insertion or management [169].

Access is gained in two ways: (1) extraluminally during catheter insertion or via the periurethral space; (2) intraluminally following breaks in the closed system or contamination of urine in the drainage bag. The comparative importance of these routes is difficult to determine, but animal models have demonstrated rapid colonisation via the intraluminal route following a break in the closed system, compared to the extraluminal route (32-48 hours v 72-168 hours respectively) [283]. However, clinical studies have shown that colonisation will occur even when strict infection control practices are adhered to [284].

Indwelling catheters rapidly become colonised by micro-organisms which form a strongly adherent biofilm on catheter and drainage equipment surfaces. Biofilm formation begins by deposition of a conditioning layer of proteins, electrolytes and other organic molecules from the urine [285] which may then mask catheter surface properties designed to inhibit colonisation. Micro-organisms attached to catheter surfaces divide to form micro-colonies, ultimately developing a complex three-dimensional structure, including fluid filled channels through which the biofilm members receive nutrients, diffuse away wastes and send chemical signals to each other [286].

Catheter biofilms commonly comprise mixed communities of micro-organisms embedded in a matrix of host proteins and microbial exopolysaccharides [287,288] (Figs XI-4, XII-5 and XII-6). Microorganisms growing as a biofilm are less susceptible to antimicrobial therapies than free-living organisms and are a major source of resistant, nosocomial pathogens [169] [219,289]. Decreased susceptibility arises from multiple factors including; physical impairment of diffusion of antimicrobial agents, reduced bacterial growth rates; and local alterations of the micro-
Figure XII-4: Biofilm - ‘pillars, mushrooms and water channels’ (Reproduced with the permission of Montana University Centre for Biofilm Engineering).

Figure XII-5: Scanning electron micrograph of biofilm.

Figure XII-6: SEM of bacteria colonising catheter surface – Proteus mirabilis, Enterococcus faecalis, lactobacillus sp.
environment that may impair activity of the antimicrobial agent [286]. The close proximity of cells within a biofilm can facilitate plasmid exchange and the spread of antimicrobial resistance [285].

1. Prevalence of CAUTI

The majority of research on the risks of CAUTI has been conducted in acute care settings where catheters usually remain in place for less than 14 days and many patients’ health is already compromised by co-morbidities [290]. Less is known about the prevalence of CAUTI in long-term and home care settings or about the potential for reduction of CAUTI and improved cost benefits in the LTC population [282]. In the multi-national survey of 4010 older people (>65 years) receiving home care in 11 European countries, the risk of a UTI was found to be 6.5 times greater for catheterised individuals than for non-catheterised patients [228]. Prevalence of a UTI amongst 1004 frail older women living in the community was 21% in catheterized women compared to 10% in non-catheterised subjects (P>0.001) [229]. Furthermore, catheterised subjects were more likely to die within a year (RR1.44; 95% CI 1.01-2.07). Tsan et al’s point prevalence survey [239] of Nursing Home acquired infections found 13.2% of 11,475 residents had an indwelling urinary catheter. Of those, 13% of residents with a UC and 9.5% of those with a SPC had a UTI. In catheterised SCI populations the overall rate of urinary tract infection has been quoted as about 2.5 episodes per patient per year [291]. Although randomized trials are lacking there is some evidence of reduced rates of bacteriuria and CAUTI with SPC, condom catheters and intermittent catheterisation compared to UC [239;245;291].

Bacteriuria resulting from CAUTI invariably represents a serious complication which may occur in approximately 4% of catheterised patients with bacteriuria in acute care settings [290;292;293]. In their review, Saint et al. [292] statistically pooled results from several prospective studies on short-term indwelling catheterization (in which the definition of bacteriuria varied between studies, ranging from \( >=10^3 \text{ cfu/ml} \) to \( >=10^5 \text{ cfu/ml} \)) and estimated (Level of Evidence 2) that:

- 26% of patients (not receiving systemic antibiotics) with a short-term, standard non-coated indwelling catheter in situ for between two and 10 days will develop bacteriuria.
- 72% of patients developing bacteriuria will remain asymptomatic and not require treatment.
- 24% of those developing bacteriuria will develop a symptomatic UTI without bacteraemia.
- 4% with bacteriuria will develop bacteraemia.

This data is interesting since it provides supporting evidence that bacteriuria remains asymptomatic in a majority of catheterised patients. However, it can be difficult to generalize such data from acute care contexts to other practice settings. Unfortunately, few epidemiological studies or comparative catheter evaluations are conducted on long-term catheterised patients in community settings.

2. Outcome measures and criteria for CAUTI

Interpretation of the literature on CAUTI is often confused by the range of definitions and outcome measures used. In this chapter, the terms symptomatic infection and asymptomatic bacteriuria have been employed to distinguish as clearly as possible between symptomatic and asymptomatic conditions. However, many studies make little or no distinction between these states, referring to both as infection. This can be particularly confusing when attempting to interpret results in terms of the magnitude of infection-related problems, clinical importance and implications for services and individuals.

Bacteriuria is commonly used as a surrogate outcome measure for the clinically more important outcomes of symptomatic UTI. Although symptomatic infection is far less common than asymptomatic bacteriuria, the frequency of catheter use produces considerable overall morbidity for patients and high costs to healthcare services [294], often including unnecessary antibiotic drug therapy which may then become a major source of antibiotic resistant pathogens. Asymptomatic bacteriuria can lead on to symptomatic infection, but not necessarily. Questions about the significance of long-term asymptomatic bacteriuria in its own right (e.g. effects of chronic tissue inflammation) are currently unanswered.

In non-catheterised patients the criterion for ‘significant’ bacteriuria is commonly accepted to be \( >10^5 \text{ cfu/ml} \) but since growth of micro-organisms in catheterised patients is rapid, many authorities consider \( >10^2 \) or \( 10^3 \text{ cfu/ml} \) in a urine sample collected from the sampling port of the catheter, to be indicative [169]. Most definitions of symptomatic UTI (e.g. US Centres for Disease Control [295]) are based on those used for non-catheterised patients and include significant bacteriuria. For catheterised patients, these include presence of pyuria (>10,000 wbc/mm\(^3\)) plus one or more clinical signs and symptoms for which no other aetiology is apparent: fever, suprapubic or flank discomfort, bladder spasm. For SCI patients signs and symptoms may also include increasing spasticity and/or worsening autonomic dysreflexia (usually manifested by increase in blood pressure, headache, sweating above the SCI lesion, flushing below the SCI lesion) [296].

However, commonly used criteria for symptomatic urinary infection have been questioned by Tamblyah and Maki [290] in a prospective study of 1497 newly catheterised patients. No significant difference in
reported symptoms of pain, urgency, dysuria and fever was found between patients with a catheter-associated infection and those without, nor was there statistical evidence that peripheral leukocytosis was predictive of infection (p=0.14) (Level of Evidence 2). The criterion for bacteriuria (catheter-associated infection) in this study was \( \geq 10^3 \) colony forming units (cfu/ml urine). This finding raises further questions over the selection of the most appropriate outcome measures in studies of CAUTI. Indeed concerns have also been raised over current UTI criteria for non-catheterised populations, particularly for elderly groups, including nursing home residents. Consensus criteria (e.g. Loeb criteria 2001) have been found to be limited in terms of sensitivity, specificity and predictive value by Juthani-Mehta et al. [297] and these authors have called for clearer identification and evaluation of evidence-based clinical criteria associated with laboratory evidence of UTI. A further complication to difficulties in confirming ‘best criteria’ for UTI and CAUTI is the variation in the clinical and scientific definitions required for specific populations, for research purposes or to meet stipulations for reimbursement from governments and medical agencies. It is important that efforts to resolve these issues are progressed as quickly as possible to provide greater clarity in the interpretation of existing research, the design of new studies and the application of clinically important findings.

3. Reducing the Risk of CAUTI

Risk factors which are independently predictive of increased risk for CAUTI have been identified in a number of large prospective studies of short-term catheterised patients [169] (Table XII-4). There is evidence that females have a substantially higher risk than males (relative risk: RR 2.5-3.7) but the greatest risk is associated with prolonged catheterisation > six days (RR 5.1-6.8). A recent retrospective cohort study of 35,904 undergoing major surgery reported that 86% of patients had a perioperative indwelling catheter [298]. Multivariate analysis showed that postoperative catheterisation for longer than two days was associated with increased risk of UTI.

Although there is some evidence to suggest there may be a reduced risk of CAUTI when SPC is employed compared to UC, the data is limited, studies are often small and most catheterisations are for post-operative care in acute care settings. One large scale point prevalence study of nursing home acquired infections in >11,000 residents [239] reported that 9.5% of residents with a SPC had a UTI compared to 13% of those with a UC. These data just fail to demonstrate a statistically significant difference between UC and SPC (one-sided, Fisher’s exact test; \( P = 0.066 \)). A review of five published RCTs comparing SPC with urethral catheters following colorectal surgery [299] reported that sample sizes were small, catheters were used short-term and there was no apparent difference in the duration of catheterisation between the two techniques. Significant UTI was defined in different papers as bacteriuria with either \( >10^4 \) or \( 10^5 \) organisms or cfu/ml. Frequency of UTI was less in the SPC group in three of the studies, with no significant difference in the other two. The SPC groups reported less pain and discomfort than the urethral groups and SPC was preferred by those patients who experienced both. The authors concluded that the results favoured SPC over urethral catheterisation as UTIs are reduced, particularly in females, and the ability to attempt normal voiding is facilitated, particularly in males (Level of Evidence 2).

Much of the recent research on reduction of risk of CAUTI has centered on the development of catheters with antimicrobial surfaces, such as silver. Silver ions are bactericidal [300], non-toxic to humans when applied topically, and have been used successfully in other areas of infection control such as burn wounds. Silver is also purported to have broad spectrum activity against Gram-positive, Gram-negative, aerobic and anaerobic organisms. Early silver-coatings incorporated silver oxide into the external surface of the catheter material only, but efficacy against CAUTI was limited [301]. Subsequently, silver-alloy coatings were developed to provide an integral coating on both internal and external surfaces and promote a slow release of silver ions. Other developments have been directed towards impregnation of catheter materials with antibiotic or antiseptic agents such as nitro-

### Table XII-4. Risk factors for catheter-associated infection based on prospective studies and use of multivariate statistical modelling (adapted from Maki & Tambyah 2001 [399]).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged catheterisation &gt;6 days</td>
<td>5.1-6.8</td>
</tr>
<tr>
<td>Female</td>
<td>2.5-3.7</td>
</tr>
<tr>
<td>Catheter insertion outside the operating room</td>
<td>2.0-5.3</td>
</tr>
<tr>
<td>Other active sites of infection</td>
<td>2.3-2.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2-2.3</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>2.4</td>
</tr>
<tr>
<td>Ureteral stent</td>
<td>2.5</td>
</tr>
<tr>
<td>Renal insufficiency (creatinine &gt; 2.0mg/dL)</td>
<td>2.1-2.6</td>
</tr>
<tr>
<td>Using a catheter to measure urine output</td>
<td>2.0</td>
</tr>
<tr>
<td>Improper position of drainage tube (above bladder or sagging below drainage bag)</td>
<td>1.9</td>
</tr>
</tbody>
</table>
furazone [302-305]; minocycline and rifampicin [306]; chlorhexidine, silver sulfadiazine, triclosan [307] and others. Although a large number of studies (both laboratory models and clinical studies) have attempted to examine the potential benefits of antimicrobial catheters, most have used bacteriuria - rather than symptomatic UTI - as a surrogate end-point. Most reports were either prospective cross-over studies [308] or prospective surveillance of outcomes associated with introduction of new catheter types, in comparison with historical or baseline outcomes associated with previously used catheter types [309-311]. Almost all have examined short-term catheter use in acute care settings.

A recent Cochrane review [220], designed to determine the effect of type of indwelling urethral catheter on the risk of UTI, examined 23 trials, comparing different types of standard catheters or a standard catheter with an antiseptic catheter (silver alloy or impregnated with silver oxide); or an antibiotic impregnated catheter (either minocycline and rifampicin, or nitrofurazone). The reviewers commented that trials were generally of poor quality but concluded that current evidence suggests silver alloy catheters prevent asymptomatic bacteriuria in the short-term catheterised patient (Level of Evidence 1). They recommended that further economic evaluation is necessary to confirm the extent to which reduction of clinically important infection compensates for the increased cost of the silver alloy catheters. Catheters impregnated with antibiotics were also found to be beneficial in reducing bacteriuria in hospitalised adults catheterised for less than a week, but data were too few for patients catheterised longer.

An earlier systematic review of antimicrobial urinary catheters to prevent CAUTI in hospitalised patients [312] identified 12 randomised or quasi-randomised trials of silver-alloy coated (n=9) or nitrofurazone-coated catheters (n=3) compared to standard silicone or latex catheters. Pre-post study designs were excluded. No study addressed symptomatic UTI and therefore analysis was based on bacteriuria. Although all studies indicated some benefit in prevention or delay of onset of bacteriuria the effect size varied substantially between studies. Variations were related to catheter type, patient characteristics, control group bacteriuria rate and year of publication (i.e. prevailing clinical conditions at the time of the study).

Post enrolment exclusions, absence of intention to treat analysis, highly selected study samples and lack of data on clinically meaningful end-points, all limited the ability to draw definitive conclusions on efficacy. The authors concluded that, according to fair-quality evidence, antimicrobial catheters can prevent bacteriuria in hospitalized patients during short-term catheterisation (Level of Evidence 1), but trial results are highly context dependent. The relevance of results to other institutions or patient groups depends on the similarities between settings with respect to a range of variables, including: background bacteriuria rate, baseline catheter type, local catheter use and maintenance practices, patient groups and patterns of antimicrobial usage. The authors cautioned that older data may lack current relevance, particularly where background rates of bacteriuria have changed notably in the intervening period. Although there is evidence that antimicrobial-coated catheters prevent bacteriuria during short-term catheterisation, there is a lack of corresponding data to demonstrate clinical benefit [313]. Further well-designed and adequately powered randomised trials, with clinically relevant endpoints are needed to clarify comparative clinical utility and economic value.

In contrast to the majority of trials of silver-coated latex catheters Srinivasan et al [314] found no significant reduction in bacteriuria with silver-impregnated, silicone catheters despite similar performances in vitro. However, outcomes may have been affected by notable differences in the study groups in this prospective, cross-over study. The authors drew attention to the fact that not all silver products are the same and clinical trials of new products remain critically important. Any potential advantages of silver alloy catheters (or other antimicrobial catheters) for LTC patients remain uncertain, although clinical experience suggests some benefits for individuals with frequent symptomatic infections. It is not known whether argyria (deposition of silver in the skin) may be a potential problem for long-term care patients or whether silver-resistant mutants may be selected by repeated exposure [315, 316].

A common concern over the use of antimicrobial impregnated catheters is that elution of sub-inhibitory levels of the antimicrobial agent into the urine may induce resistance in resident organisms with prolonged catheter use [317]. Antiseptic agents are generally considered more likely to confer resistance to surface colonization than antibiotics and not to select for infection with antimicrobial drug resistant bacteria. Alternative approaches to inhibiting biofilm development include development of catheter surfaces which reduce protein absorption [318]; inflation of the balloon with a biocide solution, such triclosan, which then diffuses throughout the catheter material and into the surrounding area [319,320]; or efforts to disrupt matrix or glycocalyx components with agents such as heparin [321].

Relatively few studies have examined the cost benefits of different catheters. Those that have tend to rely heavily on assumptions that a certain proportion of patients with bacteriuria will develop the clinically important outcomes of symptomatic UTI or bacteraemia. The focus of economic studies generally falls on acute care settings and, as discussed earlier, it can be difficult to generalise results from one practice setting to another. Practitioners and/or institutions
who are considering introducing a new product (e.g. catheter type) for a majority of their patients on the basis of claims of improved cost-effectiveness from clinical research studies, are advised to look carefully at the similarities and differences between their own local practice (and patient groups) compared to that described in the research. Economic studies are frequently required to make assumptions about certain data (e.g. increased length of hospital stay for CAUTI) which is then applied to an economic model. (Cross ref to economics chapter). Such assumptions may or may not be applicable in local settings.

Numerous trials of oral antibiotics, antimicrobial bladder washes, drainage bag solutions and topical disinfectants all lead to the common conclusion that bacteriuria and UTI may be suppressed temporarily at best, but resistant organisms are highly likely to emerge [287]. The application of devices to secure catheters in place, to prevent a ‘to and fro’ pistoning effect that could favour invasion of catheter tracts by microorganisms, has been shown to reduce the incidence of catheter-related blood stream infection in central venous catheters. Only one prospective, randomised trial has examined a similar device for urinary catheters (StatLock) [296]. Although the study in 118 SCI patients failed to achieve statistically significant results the authors reported a clinically important reduction in the rate of symptomatic UTI of 45% and called for further larger scale trials. They also noted the polymicrobial nature of infections including the presence of a Candida species in more than 20% of infections.

4. Treating CAUTI - antibiotic use

Some studies have suggested that methenamine hippurate may have a beneficial effect in preventing bacteriuria in patients requiring short-term catheterisation during and post-surgery. However, a Cochrane review [304] designed to address this issue concluded there is not enough reliable evidence to conclusively support its use for urinary prophylaxis and identified a range of methodological limitations in existing studies. Caution is needed in translating research on reducing CAUTIs in short-term catheters to LTCs but treatment of asymptomatic bacteriuria is not recommended in either for either group. Urine cultures should be obtained before initiating treatment to permit selection of specific therapy for the infecting organism and the extensive use of broad spectrum therapy should be avoided [322].

Studies of LTC patients can be difficult given the relatively high proportion of disabled or elderly patients, many of whom are very frail. However, routine use of prophylactic antibiotics in LTC patients is not supported by research evidence and has been shown to favour the emergence of resistant organisms. In a double-blind, cross-over study of 34 elderly nursing home patients with urethral catheters [323] subjects were randomised to receive antibiotic prophylaxis (200mg/day norfloxacin) or placebo for three months, followed by cross-over. Urine cultures were obtained once monthly. Episodes of UTI, catheter-related complications (obstruction, encrustation, leakage, suprapubic pain, inflammation of meatus, haematuria and side effects of treatment were monitored weekly. Symptomatic UTI was defined as bacteriuria >=10^5 cfu/ml and (i) a temp>38.5°C for two days in the absence of other clinical sources of infection or (ii) flank pain or unexplained mental disturbance or abdominal discomfort.

Only 23 patients completed the study and although norfloxacin failed to reduce asymptomatic bacteriuria, there was a significant reduction in symptomatic UTIs (1 v 12, p<0.02) and a decrease in catheter-associated complications of obstruction and leakage (p<0.05). Of the 11 patients who did not complete the study, six died (of non-infectious causes), one died of septic shock and four were withdrawn. However, norfloxacin treatment was also strongly associated with the acquisition of gram-positive norfloxacin resistant flora (RR 4.66, 95% CI 2.47-8.80), and there was a rapid recolonisation by norfloxacin-sensitive, gram-negative bacteria on cessation of treatment. Overall the study concluded that norfloxacin failed to prevent bacteriuria in long-term catheterised patients and favoured the emergence of quinolone-resistant organisms, although there were some clinically observable benefits in some patients.

Similarly there is little strong evidence of benefit in prophylactic antibiotics prior to re-catheterisation. One RCT in which 70 residents in a long-term care home were allocated to a treatment group (1gm IV meropenem given 30 minutes before re-catheterisation) or control group (no antibiotics) showed no significant differences in urine cultures at 3, 7, 14 or 28 days [324].

When catheterised patients are prescribed a course of antibiotics for symptomatic infection a common question from healthcare practitioners is whether the catheter should be changed to a new one prior to starting antibiotics. There are concerns that this may allow time for a new biofilm to become established on the catheter within a few hours (and provide a source of re-infection) before the antibiotics have taken effect. There is little research to guide practice but in one RCT of 54 nursing home residents managed by long-term catheterisation, subjects were randomised to undergo catheter replacement, or no catheter replacement, before antibiotic intervention for clinical diagnosis of UTI [187].

Clinical outcomes (reduction in polymicrobial counts, time to achieve afebrile status and clinical status at 72 hours) were significantly better among subjects randomised to catheter change immediately before institution of antibiotics (Level of Evidence 2).
Replacement of the catheter, in patients suspected of having a UTI, prior to collecting a urine sample for culture and sensitivity testing has also been shown to reduce the number of pathogens identified, the number of antimicrobials prescribed and laboratory costs [325]. There is evidence that certain bacterial strains may be particularly difficult to eradicate. In a prospective study of infection in catheterised nursing home patients a single genotype of P. mirabilis was shown to persist in the urinary tract despite many changes of catheter, periods of non-catheterisation and antibiotic therapy [326].

Cranberry juice has long been advocated as a treatment for urinary tract infection and there is some evidence of decreased symptomatic infections in some study populations [327]. However current evidence to date is limited to non-catheterised patients and caution needs to be applied in extrapolating results to catheterised patients (see also Section XII.2.9).

i) LTC-associated risks and problems: recurrent catheter blockage

Recurrent catheter encrustation by mineral deposits, leading to catheter blockage occurs in up to 50% of LTC users, with resultant increased costs to services and patients [328-331]. Heavy encrustation on external surfaces of the catheter tip and balloon can also cause painful tissue trauma on catheter removal. The major components of encrustation are calcium phosphates and magnesium ammonium phosphate (struvite) (Figs XII-7 and XII-8) which precipitate from the urine, most commonly under alkaline conditions.

The precipitation of different ionic species (ie Ca++, Mg++, and phosphates) is influenced by their ionic concentrations in the urine. In addition, the urinary pH at which different ions precipitate from the urine varies, not only for different ions, but also between individuals and at different times[332,333]. These factors contribute, at least in part, to individual variability in terms of susceptibility to catheter encrustation and time to blockage. Catheterised patients can usually be classified into ‘blockers’ or ‘non-blockers’ [328,329] where ‘blockers’ are those individuals who experience recurrent catheter blockage within a few days to a few weeks.

Early recognition of recurrent ‘blockers’ facilitates proactive care through appropriate catheter change regimes [329]. Urine from recurrent blockers tends to have a very narrow ‘safety margin’ between ‘voided’ urinary pH and the pH at which crystallisation (or nucleation) occurs. This margin is much wider in non-blockers [334]. Precipitates occur most commonly under alkaline conditions caused by the presence of urea-splitting micro-organisms such as Proteus mirabilis, in the catheter biofilm [329,334-336].
using a model of the catheterised bladder, none resisted biofilm formation by a clinical strain of *P. mirabilis* [338,339]. Relative times to catheter blockage were: silver-coated latex 17.7h; hydrogel-coated latex 34h; silicone-coated latex 38h; all-silicone 47h. However, the authors note that the internal diameter of the coated latex catheters was much smaller than the silicone catheters (1.5mm compared to 2.5mm).

Although it is not possible to examine the effects of polymer surface properties on microbial adhesion and formation of catheter encrustation in detail here, recent studies have shown that strongly electron donating surfaces are less prone to adherence by *P. mirabilis* than more hydrophobic materials [340]. Some copolymer, polyurethane blends are associated with less microbial adhesion and improved resistance to encrustation in an artificial bladder model [341]. The effect of iontophoresis produced by passing an electric current through silver electrodes attached to catheters has also been shown to inhibit bacterial growth [342]. Another potentially promising innovation is the use of the antiseptic agent triclosan in the catheter balloon [319,320,343]. In laboratory models of the catheterised bladder infected with *P. mirabilis*, silicone and latex-based catheters, with balloons inflated with triclosan, drained freely for seven days compared to 24h for controls inflated with water.

Triclosan became impregnated throughout the silicone catheter material and strongly inhibited the formation of the crystalline biofilm. However, latex-based catheters required a higher concentration of triclosan (>1mg/ml) than silicone catheters to produce similar inhibitory effects on *P. mirabilis*. Diffusion through the latex balloon occurred but the latex-based catheter did not become impregnated with triclosan throughout. The potential benefits of triclosan in catheter balloons now needs to be tested in clinical trials but it is also important to note that not all microbial species responsible for CAUTIs are sensitive to this biocide and emergence of resistant strains is a common concern [320].

2. **Reducing Catheter Encrustation - Interventions**

A number of studies have employed *in vitro* models of the catheterised bladder to examine the influence of urinary composition on bacteria growth and encrustation, and the ability of acidic irrigations to reduce encrustation build up. There is good evidence from laboratory studies that increased fluid consumption (leading to lower concentration of encrustation components) increases the time to catheter blockage [344]. Increasing citrate concentration in fluid intake and urinary output (eg through drinking orange juice or other fruit juices such as lemon or lime) has also been shown to increase time to catheter blockage (see below). Cranberry juice has frequently been advocated to reduce UTIs, microbial adherence and biofilm development but an in vitro study by Morris and Stickler [345] drinking cranberry juice did not produce urine which was inhibitory to the development of *P. mirabilis* biofilms and catheter blockage, although increased fluid intake was beneficial. Although some studies have claimed drinking cranberry juice can decrease urinary pH in healthy volunteers [346], this is unlikely to be accomplished in catheterised patients, in the presence of continued ammonia production by the action of urease-producing micro-organisms [347].

Urease inhibitors, including acetohydroxamic acid (1.0mg/ml) and fluorofamide (1.0microg/ml), have been shown to restrict the increase in urinary pH of *P. mirabilis* infected urine from 9.1 to 7.6, in a simple physical model of the catheterised bladder [339]. Significant reductions in precipitation of calcium and magnesium salts were also noted but the impact of possible side-effects remains unclear, and therefore clinical potential is uncertain. Clinical studies on the prevention or management of catheter encrustation are extremely limited and only two relevant studies addressing the use of urease-inhibitors were identified. One early clinical study [348] examined oral administration of a urease inhibitor (acetohydroxamic acid) to five patients who required frequent catheter changes (>=1 every 2 weeks) due to encrustation and blockage. The dose was based on body weight (eg. 250mg three times daily for patients between 50-70kg). The degree of encrustation decreased significantly during therapy (p<0.05) and the authors reported minimal adverse side effects experienced by patients, but acknowledged the potential for more severe side effects to occur. A subsequent double-blind, RCT of acetohydroxamic acid in the palliative treatment of infection-induced urinary calculi, demonstrated lowered urinary pH in urine infected with *P. mirabilis* but the side effects were unacceptable to patients [349] (Level of Evidence 1).

An alternative approach to reducing catheter encrustation, aimed at increasing the ‘safety margin’ between urinary pH and the nucleation pH (pHn) (i.e. the pH at which crystals of calcium and magnesium are formed in the urine) warrants further clinical investigation. In laboratory studies using models of the catheterised bladder, the pHn of the urine was shown to increase when urine concentration was decreased and also by addition of citrate to the urine [350]. In models supplied with urine containing citrate at 1.5mg/ml or above, catheter drained freely for the 7 day experimental period. Drinking 500ml pure orange juice per day can achieve concentrations of citrate of up to 1.2mg/ml urine [333] and further clinical evaluation of the effects of increasing a patient’s fluid intake with citrate containing drinks is awaited. Viable cell counts of *P. mirabilis* in the model suggest that results were unlikely to be due to direct effects of citrate on the growth of metabolism of *P. mirabilis* in
the catheter biofilm, but rather on the process of mineral crystallization.

The reduction of encrustation and corresponding extension of ‘catheter life’ by regular instillation of an acidic catheter maintenance solution into the catheter has been advocated by some researchers, particularly where frequent catheter changes for recurrent blockage are difficult and / or unacceptable to patients. Solution G (Suby G) and Solution R (Table XII-5) have been shown to be effective in vitro models of the catheterised bladder [351-353] and in vitro models of struvite stone chemolysis [354]. In response to concerns over potential damage to the bladder mucosa from acidic catheter maintenance solutions, Getliffe et al. [352] advocate the use of small volumes of solution so that less enters the bladder. Under controlled laboratory conditions smaller volumes of acidic solutions (Suby G) (50ml), retained in the catheter for 15 minutes, were shown to be as effective as the commonly available commercial standard of 100ml. Getliffe et al. also showed that two sequential washouts with 50ml were more effective than a single washout.

There is relatively little clinical evidence to draw on in this area and outcomes remain to be tested in well-controlled clinical trials. Most clinical studies are small-scale and descriptive although both Getliffe[355] and Kunin et al. [328] compared groups of ‘blockers’ and non-blockers’ to identify characteristics of recurrent ‘blockers’. One small-scale, comparative trial of Suby G, Solution R and saline catheter ‘washouts’ in 14 older female patients [356] reported a higher incidence of red-cells in the retrieved washout fluid with Suby G compared to saline (mean incidence of 28% and 14%, respectively. However, increased shedding of uroepithelial cells was present in the retrieved washout from all three solutions suggesting this was at least partially related to the physical process of administration. This issue was previously raised by Elliot et al. [357] who also demonstrated increased uroepithelial shedding following washouts with up to 60ml saline 0.9%; chlorhexidine 0.02% or noxythiolin 2.5%.

A more recent RCT, which aimed to compare weekly catheter flushes with saline or an acidic solution, with no flushes, reported the mean time until catheter removal was very similar between groups. Importantly, there was no evidence of detrimental effects, such as increased risk of symptomatic infection, from breaking the closed system in order to apply catheter flushes. However the study was underpowered and subjects were only followed for a maximum of eight weeks. There were considerable difficulties with recruitment of patients and target numbers fell short within each group (Level of Evidence 2) [358]. Other clinical studies have focused on chemolysis of infection stones (principally composed of struvite). Stronger acidic solutions such as Solution R have been shown to dissolve fragments of struvite renal calculi following lithotripsy [359] but potential benefits may be outweighed by the greater risk of inflammatory tissue reactions when used as a catheter maintenance solution. Renacidin solution is approved for kidney stone disintegration in the US but although it may be

Table XII-5. Catheter maintenance solutions.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suby G or Solution G</td>
<td>3.23% citric acid solution, pH 4, containing magnesium oxide to minimise tissue irritation, aimed at reducing encrustation. Used where routine catheter maintenance is required to reduce build up of encrustations.</td>
</tr>
<tr>
<td>Solution R</td>
<td>6% citric acid solution, pH 2, containing magnesium carbonate, aimed at dissolving encrustations. A stronger acid than Suby G and therefore not recommended for frequent, regular use.</td>
</tr>
<tr>
<td>Renacidin</td>
<td>A citric acid solution, pH 3.5-4.2, containing glucono-delta-lactone to minimise tissue irritation and magnesium carbonate, aimed at reducing encrustation.</td>
</tr>
<tr>
<td>Mandelic acid 1%</td>
<td>An acidic solution, pH 2, aimed at inhibiting the growth of urease-producers. A stronger acid which is not commonly used to reduce catheter encrustations</td>
</tr>
<tr>
<td>Saline 0.9%</td>
<td>A neutral solution, pH 7, recommended for flushing of debris and small blood clots. Neutral pH solutions will not dissolve catheter encrustations.</td>
</tr>
<tr>
<td>Chlorhexidine 0.02%</td>
<td>An antiseptic solution aimed at preventing or reducing bacterial growth, in particular E. coli and Klebsiella species (but will not prevent biofilm formation on long-term catheters)</td>
</tr>
</tbody>
</table>

1 Available in the UK pre-packed in a sterile delivery devices designed for instillation into a urinary catheter.
2 Renacidin® is approved in the USA for kidney stone disintegration only. Although it may be effective in certain situations for persistent catheter blockers, there are no supporting studies.
3 Saline is widely available
effective for recurrent catheter blockers, there is no published research evidence of its use in this group.

Overall, methodological issues make it difficult to draw robust conclusions on the effectiveness of acidic solutions in managing catheter blockage. It is unlikely that any currently available strategies will completely prevent catheter encrustation and a more practical aim is to extend catheter life to a period which is acceptable to users and manageable by healthcare professionals. 

_j) LTC-associated risks and problems: urethral trauma, bladder calculi and bladder cancer_

1. **Urethral trauma**

Urethral trauma and discomfort can occur during catheterisation but may be minimised by using a sterile lubricant or anaesthetic gel [360] (see also Section XII.2.k), however clinical practice remains variable. More studies have considered the use of lubricants for male catheterisation but few have considered the procedure for women or for supra-pubic catheterisation [361]. A recent randomised, double-blind study with 62 alert, cooperative females requiring urethral catheterisation, demonstrated that the group receiving lignocaine gel had a significantly lower median procedural pain score compared to the group receiving a water-based lubricating gel [362]. Supra-pubic catheterisation can sometimes lead to urethral leakage which may require surgical closure of the urethra, especially in women.

2. **Bladder calculi**

Most long-term follow up studies of LTC use have addressed SCI populations. Indwelling catheters (UC and SPC) have been significantly associated with increased risk of bladder calculi formation in SCI patients, compared to intermittent catheterisation [203,363]. In a retrospective cohort study of 457 patients, controlled for variable follow up times by regression analysis, both UC and SPC were significantly associated with increased risk of bladder calculi formation compared to intermittent catheterisation IC (hazard ratio 10.5; p<0.0005 and 12.8: p<0.0005) respectively [364]. This increased risk was independent of age, sex, level and degree of injury but calculi were no more likely to form with SPC than UC (hazard ratio 1.2, p=0.6). Another case series of SPC in 118 patients with neurogenic bladders [365] found common complications were bladder calculi (25%), (particularly associated with high urinary pH) and urethral leakage (10%). Bladder calculi-free rates at five and 10 years were 77% and 64% respectively, falling to 50% at 20 years.

Where SPC has been compared to CIC the main difference appears to be in a lower incidence of bladder calculi in the CIC group. A prospective comparison of long-term outcomes between 34 quadriplegic patients managed by SPC (mean period 8.6 years) and 27 paraplegic patients managed with CIC (mean period 9.9 years) reported no significant difference between groups in respect of symptomatic UTI, renal stone, degree of bother and overall satisfaction [248] but there was a significantly increased incidence of bladder stones in the SPC group. However a recent review of current literature [249] (56 studies), concluded there were variations between older and more recent studies. More recent studies showed morbidity profiles to be similar for SPC and CIC, where patients were managed by anticholinergic medications, frequent catheter changes and volume maintenance procedures (Cross reference Neuro Chapter). A dedicated catheter clinic established to aid the management of patients having problems with LTC, reported the majority of patients were elderly with chronic disabilities. A significant proportion of those with catheter encrustation and blockage (45% of 147 patients) were shown to have formed bladder calculi [366].

3. **Bladder cancer**

A number of retrospective, cohort reports of SCI patients have linked bladder cancer with long-term indwelling catheterisation [367-369]. The reported incidence of squamous cell and transitional cell carcinoma associated with chronic indwelling catheterisation varies widely between studies but Groah et al. [369] in their follow-up of 3670 subjects, calculated that patients with SCI and an indwelling catheter were 25 times more likely to develop bladder cancer than the general population (Level of Evidence 3). For SCI patients without an indwelling catheter, the risk of bladder cancer was 15 times that of the general population. Since SCI patients are already at increased risk of developing bladder cancer compared to non-SCI groups, the influence of an indwelling catheter on bladder cancer requires further clarification, including the potential relationship between duration of catheterisation and cancer development. Bladder calculi have been identified as an independent risk factor for bladder cancer by some authors [367].

Most reports have grouped UC and SPC together as indwelling catheters but a small number of case study reports have drawn attention to long-term risks of carcinoma within the cystostomy tract with SPC, with or without further extension into the bladder [370-372]. However, in a retrospective analysis of screening biopsies for bladder malignancy in 36 patients with SPC for more than 12 years, Hamid et al.[373] found no tumours in the screened group although histological findings were frequently abnormal (Level of Evidence 2). These authors raise concerns over the interpretation of screening cystoscopy and biopsy in this population.
and note the importance of the distinguishing between histological changes and confirmed cancers when interpreting study results. Recently published guidance on management and prevention of catheter-associated urinary tract infection, based on an extensive survey of the literature, includes a recommendation that patients with urethral catheters in place for 10 years or more should be screened annually for bladder cancer [374] (Grade of Recommendation C).

k) Catheter management strategies

Although guidelines and protocols for catheter-care practices are abundant, relatively few practices are supported by research evidence and even fewer by evidence from randomized controlled trials. For example, in the ‘Guidelines for prevention of healthcare associated infections in primary and community care’ commissioned by the UK’s National Institute for Clinical Excellence [375], of 29 recommendations relating to urinary catheterisation only six were Grade A (directly based on Level 1 evidence); six with one each at Grades B and C. The remaining 21 were all grade D, being based on evidence from expert groups or clinical opinion.

1. Catheter change procedures and catheter comfort

Indwelling catheters can cause substantial patient discomfort but although anecdotal information on the discomfort experienced by many catheterised patients is readily available, there is a general lack of published evidence from research studies. Further investigation and guidance to practitioners is needed. Catheter-related pain or discomfort can occur as the catheter is passed, in situ and on removal. Local anaesthetic lubricant gels are commonly used to aid the insertion of indwelling catheters in males and protect the sensitive urothelium from trauma [376]. Similar use of anaesthetic gels is generally recommended for females although the procedure may be less consistent in some places and where only small amounts of lubricant are applied to the catheter tip this may be insufficient to coat the urethra adequately. There is little research evidence to underpin clinical practice in this area although the NICE guidelines on infection control [375] recommend: ‘an appropriate lubricant from a single-use container should be used during catheterisation to minimise trauma and infection’. The choice of lubricating gel is usually left to practitioners but not all gels containing anaesthetic agents (e.g. lidocaine) are suitable for both urethral and suprapubic use. One prospective, randomized, double-blind, controlled trial of plain lubricant versus lidocaine gel prior to female catheterisation in an accident and emergency department found no significant differences in pain ratings, based on lubricant type or catheter size amongst 100 women recruited to the trial [377]. Anaesthetic gels may be contraindicated in patients with damaged or bleeding urethral membranes and should be used with caution in those with cardiac conditions, hepatic insufficiency and epilepsy [378]. Lubricants which contain chlorhexidine have been reported to trigger anaphylaxis in a small number of patients during catheter insertion and consequently a careful history is required to screen for sensitivities [92;379].

Catheters can be painful when in situ. In one study at a US Veterans Affairs Medical Centre, 42% of catheterised patients reported it was uncomfortable, with 48% complaining it was painful, and 61% stated it restricted their activities of daily living[104]. If bladder spasm is the cause of pain when a catheter is in situ a low dose of an anticholinergic medication can help [380]. Other helpful approaches include treating constipation if present, ensuring that the catheter is the smallest size to provide adequate drainage, and ensuring that the drainage bag is well supported to prevent dragging on the catheter. Bladder discomfort related to an indwelling catheter can exacerbate postoperative pain by mimicking overactive bladder syndrome that is resistant to conventional opioid therapy. Sub-lingual oxybutinin has been shown to be an effective treatment for pain after radical retropubic prostatectomy, with significant reduction in other pain relief requirements [381]. Cuffing of the catheter material on balloon deflation (see below) and/or encrustation of the catheter by mineral deposits may cause pain during catheter removal. Encrustation is discussed further in Section XII-2.i and management of these problems is also discussed below.

Protocols on indwelling catheter change frequency vary widely from monthly to up to three months if the catheter is trouble-free. In the absence of clear supporting evidence this remains an area of controversy amongst clinicians with advocates of early change believing this to reduce the incidence of complications while others argue that frequent changes increase the risk of infection, trauma and long-term histological changes. SPC changes can be competently managed by skilled nurses [260], often in the patient’s own home, but the new catheter should be inserted as quickly as possible whilst the track is still easy to follow. A delay of only a few minutes can result in partial obliteration of the tract [382]. It is also possible to insert the new catheter too far through the bladder so it enters the urethra with resultant trauma when attempts to inflate the balloon are made. Careful observation of the length of catheter external to the abdomen and the angle of protrusion prior to catheter change can help to ensure correct positioning of the new catheter [383]. Dressings around the stoma site are not normally required unless there is excessive discharge, causing staining and/or sticking to clothing.

Urinary catheter ‘deflation cuff’ formation can be a problem in both SPC and UC, causing difficulty in removal and great discomfort to patients. Evidence suggests deflation cuff formation can be a particular
problem for all-silicone SPCs. A retrospective study of 113 patients cared for by community nurses showed that 30% of nurses had experienced problems changing catheters in the previous 12 months [384]. In vitro studies have confirmed increased retention force and resistance to withdrawal caused by cuff formation and although cuffs can form with other catheter materials (eg hydrogel coated-latex) the retention force is less than with all-silicone material [272]. It has been suggested that slow deflation may enhance the probability of the silicone balloon returning to its pre-inflation shape [273]. Alternatively, reinsertion of 0.5-1ml water is sufficient to fill the catheter inflation lumen and eliminate the balloon cuff. Subsequent use of lubrication with gentle removal of the catheter has been well-tolerated by patients and produced virtually no trauma.

2. PERSONAL HYGIENE AND INFECTION CONTROL

Meatal cleansing by simple washing with soap and water during routine bathing or showering is recommended (Level of Evidence 1) [385;386]. No consistent reduction in bacteriuria has been demonstrated by any other meatal cleansing regimes, using povidone-iodine solution or cream, chlorhexidine, polymicrobial creams, 1% silver sulfadiazine or antiseptic lubricating gels, compared to routine bathing or showering [117;245]. Effective handwashing by healthcare professionals, carers and patients, before and after handling catheters and drainage equipment is generally accepted to be the most important component of any infection control strategy. Healthcare professionals and formal carers should also wear gloves. Catheters and drainage equipment are commonly supported in position by tapes, Velcro and other securing devices (eg CathSecure, StatLock) but the importance of these in reducing risks of CAUTI and the mechanism involved are not well-established [296] (See also Section XII.2.h).

3. URINE COLLECTION – CATHETER VALVES

Urine may drain continuously from the bladder into a drainage bag attached to the catheter (See Section VIII) or intermittently via a catheter valve. The valve is a small device connected to the catheter outlet in place of a bag. Closure and opening the valve allows bladder filling and intermittent drainage rather than continuous drainage into a bag. Valves are available in a variety of designs (Fig XII-9) ranging from simple inexpensive types used for up to a week, to more expensive, complex, forms which last longer and which may permit one handed action. However, valves are not available or licensed in all countries.

Most valve designs can be attached to a drainage bag at night to allow free drainage while the patient sleeps. A valve can provide a discreet alternative to conventional urine drainage bags and may offer improved maintenance of bladder tone and capacity for appropriate patients. A spigot is not a suitable alternative to a valve since it must be removed from the catheter to allow drainage thereby breaking the ‘closed system’. Patients must be able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling, with accompanying risks of back pressure on the upper urinary tract. Valves are generally inappropriate for patients with poor manual dexterity, poor bladder capacity, detrusor overactivity, ureteric reflux, renal impairment or cognitive impairment. There is relatively little research-based literature on catheter valves with much of the evidence supporting beneficial effects derived from the level of expert opinion. Concerns over possible increased risk of infection associated with valves have not been realised although there is a paucity of research in this area. The flushing mechanism resulting from bladder filling and emptying may be expected to contribute to reduction in problems of encrustation and blockage but, again, clinical research evidence is lacking.

There is stronger evidence of benefits in terms of patient comfort and independence since this is a common finding in most studies. Five studies comparing a catheter valve with standard drainage (leg bag) were identified: three were cross-over designs, with 28, 16 and 18 subjects respectively [387-389] (Level of Evidence 3); two randomized their sample of 100 subjects to either catheter valve or standard drainage [390,391] (Level of Evidence 2). None of the studies identified any significant difference in urinary tract infection and a majority found a high level of preference or acceptability of catheter valves (>72%). There were no differences in reported incidence of bladder spasms or discomfort; however, there was a higher incidence of nocturnal frequency and episodes of bypassing with valves. It was suggested that a combination of a valve during the day and free drainage at night through an open valve connected to a drainage bag could be an appropriate management strategy.

Several studies have evaluated a single valve design [392,393] but only one has compared a broad range...
of valve designs [394]. Fader et al undertook a comparative evaluation of the seven catheter valves available on the UK market in 1996. Each valve type was tested for one week by between 19 and 36 subjects, followed by completion of a product evaluation questionnaire. Performance scores (and costs) varied widely between products but critical characteristics were: being easy to manipulate, leak-free, and inconspicuous. The authors concluded that prescribers need to be aware of the strengths and limitations of different valves for appropriate product selection (Level of Evidence 3). A more recent development concerns the design of a prototype, novel, automatic valve system for LTC patients [395] which may be helpful for patients who lack sufficient dexterity to manage a manual valve. In summary:

- Catheter valves provide a well-accepted system of bladder emptying for suitable patients who are able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling (Level of Evidence 2).
- There is no evidence of increased risk of urinary tract infection with valves compared to conventional drainage systems (Level of Evidence 2).
- Valves may promote maintenance of bladder tone and capacity (Level of Evidence 4).

4. MAINTAINING EFFECTIVE CATHETER DRAINAGE

Use of urinary catheters is rarely completely trouble-free. Catheter drainage can be compromised by a variety of factors from simple causes such as kinked tubing or the position of the drainage bag, to bladder spasm, pressure of a constipated bowel on the adjacent urethra, suction of bladder mucosa into the catheter eye, or blockage by blood clots, mucous or encrustations formed by deposits of mineral salts. The algorithms in Figs XII-10 to XII-12 combine current evidence-based knowledge and expert opinion to provide some guidance on trouble-shooting common problems.

5. RECURRENT CATHETER ENCRUSTATION AND BLOCKAGE

Factors affecting persistent catheter encrustation leading to recurrent blockage have been discussed earlier in Section XII.2.1. The day to day management of recurrent catheter encrustation and blockage is largely a nursing responsibility but there are few options available. Maintenance of dilute urine by a suitably high level of fluid intake has been shown to reduce encrustation in laboratory studies [344] and increased urinary citrate concentration produced by drinking orange juice or other fruit juices may also be beneficial [344] (see Section XII.2.1 above). However the amounts required may be relatively high and clinical studies are needed to assess benefits and possible detrimental side effects e.g on bowel behaviour. Use of a catheter valve in suitable patients may also help reduce build up of encrustation by facilitating periodic flushing but clinical evidence is currently unavailable. In a majority of patients a characteristic pattern of ‘catheter life’ can be identified with careful record-keeping of three or more catheter episodes [237; 329; 396]. This may allow pro-active strategies of care designed to change the catheter before likely blockage. However, very frequent catheter changes can be unsuccessful or unacceptable for some patients, as well as being costly in terms of health service resources [330].

An alternative strategy is the regular prophylactic instillation or irrigation of the catheter with an acidic ‘catheter maintenance’ solution to dissolve mineral deposits. In older literature the term ‘bladder washout’ appears but as the aim is to wash the catheter, rather than the bladder, ‘catheter maintenance solution’ is a more appropriate term. A range of commercially available catheter-maintenance solutions is indicated in Table XII-5, although these are not necessarily available in all countries. Support for irrigations is strongly divided between those claiming benefit for specific patients who experience very frequent blockage and those who consider any break to the closed system to increase risks of infection. Research evidence is primarily derived from laboratory models of the catheterised bladder, as considered above in Section XII.2.1. The few clinical studies which have addressed this issue have been limited by methodological deficits and small sample size.

1) Levels of evidence relating to catheter-associated risks and complications

- All currently available catheter materials are subject to bacterial biofilm formation (Level of Evidence 1).
- Silver alloy coated catheters are associated with a statistically significant reduction in incidence of asymptomatic bacteriuria in short-term catheterised, hospitalized adults (studies of varying quality included) (Level of Evidence 1). There is less robust data to show that silver-alloy catheters reduce symptomatic infection (Level of Evidence 4). Silver oxide coated catheters are not associated with a statistically significant reduction in bacteriuria (Level of Evidence 2).
- Antimicrobial catheters can prevent bacteriuria in hospitalized patients during short-term catheterization (<30days) (Level of Evidence 1). Trial results are highly context dependent and the effectiveness of specific antibiotic preparations may be limited to specific groups of microorganisms. Potential toxicity and/or antibiotic resistance is unknown (Level of Evidence 2).
- There is little evidence to guide the precise timing of catheter change when antibiotic cover is required for a particular patient. One study has shown that clinical outcomes (i.e. reduction in polymicrobial
Figure XII-10: Troubleshooting long-term catheter problems: urine does not drain (N = No; Y = Yes). (Always have a spare catheter available)
counts, time to achieve afebrile status and clinical status at 72 hours) are significantly better among subjects randomised to catheter change immediately before institution of antibiotics (Level of Evidence 2).

- A majority of health services have clear policies on the use of antibiotics, designed to limit unnecessary use. Current evidence does not support routine use of antibiotic cover during catheter changes unless the patient’s condition renders them particularly at risk (Level of evidence 4).

- Meatal cleansing by simple washing with soap and water (i.e. not with antimicrobial agents) during routine bathing or showering is recommended (Level of Evidence 1).

- Recurrent urinary catheter blockage caused by encrustation occurs in 40-50% of all long-term catheterised patients (Level of Evidence 2). In the majority a characteristic pattern of ‘catheter life’ can be identified (Level of Evidence 3).

- Evidence from in vitro models of the catheterised bladder indicates that i) dilute urine; ii) high urine citrate content (> 1.5mg/mL) reduce risk of blockage (Level of Evidence 2).

- Evidence from in vitro models of the catheterised bladder indicates that acidic ‘catheter maintenance’ solutions may have a role in dissolving encrustations in persistent blockers (Level of Evidence 2). There is insufficient evidence from RCTs to assign an in vivo level of evidence.
THE INFLATION BALLOON DOES NOT DEFLATE

PROBLEM ACTION

Blocked deflation channel?

- try to remove or dislodge debris blocking the deflation channel by gently 'milking' the catheter along its length
- try to remove or dislodge debris by inserting a few drops of sterile water into the inflation channel (no more than 1-2ml) with a sterile syringe

Faulty valve or syringe

- try a different syringe, withdraw water very slowly or leave syringe in place, the water may seep out over a period of time
- insert the needle of a sterile 10ml syringe into the balloon drainage channel just above the inflation valve. If the valve is faulty the water may be withdrawn gently via the syringe

? constipation, present - may cause pressure on the inflation channel

try to relieve constipation

consult local policy for further advice or seek medical help

**do not cut the catheter**
- it may recoil inside the urethra

**do not cut the inflation valve off**
- if the balloon does not deflate it will no longer be possible to try alternative simple methods

**do not attempt to burst the balloon by over-inflating it**
- a cystoscopy will be required to remove fragments!
- remaining fragments may result in formation of calculi

**do not cut the inflation valve off**

Record problem, actions and outcome.
Record catheter details, lot number etc and report to manufacturer

*Figure XII-12: Troubleshooting long-term catheter problems: the inflation balloon does not deflate.*
• Suprapubic catheterisation (SPC) is an appropriate alternative to urethral catheterization for many patients following appropriate risk assessment (Level of Evidence 1).

• There is some evidence for a reduction in catheter-associated infection in SPC use during short-term catheterisation (Level of Evidence 2), compared to urethral catheter insertion. However, there is no corresponding evidence for long-term catheterisation.

• Patient comfort, quality of life and satisfaction with SPC is generally good compared to urethral catheters (Level of Evidence 1).

• Catheter valves provide a well-accepted system of bladder emptying for suitable patients who are able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling (Level of Evidence 2).

• There is no evidence of increased risk of urinary tract infection with valves compared to conventional drainage systems (Level of Evidence 2).

m) Urinary catheters versus other care strategies

Very few studies have compared urinary catheterisation with other strategies to manage urinary incontinence, not least because of the difficulties in recruiting to and conducting robust trials. For male patients who do not have problems with retention of urine external urine collection systems are an option (See Sections VII, VIII and IX). One recent prospective, randomized, unblinded, controlled trial on men >40years in a US Veterans Affairs Medical Centre reported that the use of condom catheters was less likely to be associated with bacteriuria, symptomatic UTI or death than the use of indwelling catheters (97). Patients reported that condom catheters were more comfortable (P=0.02) and less painful (P=0.02) than indwelling catheters.

A small number of studies have attempted to examine preferences for different urinary incontinence treatments in long-term care. In a descriptive, comparative study of preferences for treatments for frail older adults, residents in long-term care facilities were interviewed and groups likely to serve as proxy decision makers were surveyed (family members of residents and nursing staff) [397]. Forced choice comparisons of continence treatments were measured. Although there was wide variation within and between groups, most preferred non-invasive strategies (diapers and prompted voiding) to invasive strategies including indwelling catheterisation. Older adults stated they would choose a treatment based, in part, on feeling dry, being natural, not causing embarrassment, being easy, and not resulting in dependence. Similar results, showing urinary catheterisation as the least favoured choice, were found in a study of 117 medical inpatients aged 80 years or over, their physicians, nurses and family members [398].

3. CATHETER-RELATED QUALITY OF LIFE

Use of a LTC is often a last choice for bladder management when other options such as CIC, for males a sheath (condom) catheter, or other voiding treatments like Crede procedure, are either unsatisfactory or no longer practical. Catheter users must deal with a variety of problems that disrupt their daily activities and negatively affect QoL, such as CAUTI, blockage, leakage and catheter dislodgment. In addition, the visibility of a catheter or drainage bag can contribute to shame or stigma, and urine odour can be embarrassing. A catheter can also be a reminder of vulnerability associated with illness / mortality and a symbol of a loss in control of bodily function. Yet catheter users also acknowledge catheter-associated benefits of freedom from wetness, convenience, and utility in promoting urine drainage. While this section focuses on long-term catheter use, even short-term catheters can have a detrimental impact on QoL. For instance in a study of short term catheter use prior to surgery for acute urinary retention, leaking, blocking, urgency, and pain at the penis or during erection were all reported [399].

Studies of QoL issues commonly utilise qualitative research methodologies, such as phenomenology or grounded theory approaches (see also Section XII.1.e). In-depth interviews with catheter-users and carers provide important insights into aspects of ‘living with a catheter’ and contribute research based evidence to support development of effective care strategies. Measurement of QoL and the impact of factors which may affect it is complex. Most validated QoL instruments fall into one of two groups: i) generic measures designed to encompass domains including physical, mental and social wellbeing; ii) disease specific measures designed to measure change in QoL resulting from treatment (Cross reference QoL chapter). For those people whose urinary symptoms are managed by products or devices, including catheter users, it is particularly difficult to assess the impact of the product on QoL (see earlier in this Chap). This is partially because changes are more likely to be related to improved management of ongoing symptoms rather than actual change in symptoms, and partially because QoL is also dependent on the underlying disease process.

Much of the literature on LTC use involves people with neurogenic bladder, particularly those with spinal cord injury (SCI) or multiple sclerosis (MS). Thus, QoL in catheter users must be considered from a perspective of how the disease and the device affect the individual's life. For instance, in one postal survey of 230 people with SCI, the factors which had most impact on QoL were social activities and accom-
plishments, including employment, attending school, and other activities. There was no association between QoL and different bladder drainage methods [400]. A particular problem for people with spinal cord injury or disease is autonomic dysreflexia (AD), an autonomic nervous system syndrome causing symptoms which include severe hypertension, headache and sweating. A blocked urinary catheter can be a common cause. AD can be a serious problem requiring emergency medical attention, but lack of knowledge and awareness of the risks by some health care providers can cause high levels of anxiety for SCI patients [241;401] (Level of Evidence 3).

There are currently no validated instruments measuring quality of life in people with urinary catheters, though these are being developed in the US [243] and in the UK (Level of Evidence 3).

The published literature addressing QoL in catheter-users is small, and is commonly limited to reports addressing levels of satisfaction with a device. Studies which include a broader perspective of QoL are discussed below under the following headings: changes in bladder management, embarrassment, sexuality, catheter-related pain, catheter adjustment, and self-management.

a) Changes in Bladder Management

Changes in bladder management are often made to promote QoL but there are trade-offs that require weighing up the pros and cons of various methods. People sometimes switch from CIC to an indwelling catheter - despite the inherent problems with an indwelling catheter - because quality of life might be improved. In particular, women with cervical spinal cord injury (SCI) may need an indwelling catheter because of difficulties in transferring to the toilet, limited hand dexterity, or dependence on caregivers [402]. Moreover, many people have used different bladder drainage methods over time. In one study, of 30 long-term catheter users, 80% of the sample had used another form, and 33% had used two or three different types [242]. In another small study with a sample of 11, 100% had used another method, and 27% had used two or three other types [243]. Reasons for non-compliance with CIC in relation to QoL or satisfaction have been addressed in Section XII.1.e and in some studies comparing drainage methods (Level of Evidence 3).

Two studies provided additional evidence of how changes in bladder drainage methods are made to improve their quality of life. In a retrospective study assessing compliance with bladder management, 50 new spinal cord injury (SCI) patient records were reviewed after admission, discharge, and follow up from 1994-1997 [402]. Of 38 patients on IC at hospital discharge, 20 (52%) were back to UC at follow up. Six of 10 females on IC had resumed UC. Reasons for not continuing with IC were: the need to depend on caregivers, poor hand functioning, spasticity, incontinence (despite anticholinergic drugs), and for females with cervical injury, toileting inconvenience (Level of Evidence 3). In contrast, a retrospective chart review and follow up questionnaire was used with 236 SCI injured people (at least 10 years post injury) between 1956-1990 [403]. An 85% response rate was achieved in the sample, with 82% males who had tetraplegia (47%) or paraplegia (53%). Although 46% changed their bladder management method over time and 28% considered the method a problem, in 58% of those who had tetraplegia, the use of CIC went up from 11% at discharge to 36%. Suprapubic tapping decreased from 57% to 31% and Crede increased from 5% to 19%. CIC alone, or with other methods, was the most common method (Level of Evidence 2).

b) Embarrassment

Embarrassment and a sense of lack of bladder control are two major catheter-related issues that are ongoing problems for many people. In one study at a US Veterans Affairs Medical Centre, 30% of catheterised patients surveyed found the indwelling catheter embarrassing, and 61% stated it restricted their activities of daily living [104]. The catheter is placed in a position in the body normally considered ‘private’, yet health care providers frequently need access to the site to provide care. Also, the force of urine flow is something that catheter users must deal with on a daily basis. In a qualitative phenomenological study of 14 people with long-term catheters, people told stories of how getting wet in public was embarrassing and how the force of the urine was like water that had built up pressure [404]. They used the metaphor of “flowing water” to describe the force of urine flow, the weight of the drainage bag, and the sound of urine sloshing around in the bag.

Living with the catheter was described in one qualitative study [241] as a swing back and forth between stigma, when it contributed to embarrassment or shame, and acceptance when it was working right and did not cause problems. The catheter became a source of embarrassment during catheter changes, bag emptying, and when it leaked or spilled in public. Individuals used planning and great care when going out (e.g. mapping out the toilets) to prevent urine accidents. They were bothered also by their lack of bodily control, the monotonous care, and how it was a reminder of their condition and mortality (Level of Evidence 3).

Catheter related embarrassment is a common experience stemming from exposure to the opposite sex, the visibility of the urine bag, and unpredictability of urine accidents [(405,406] [241]. Breeches in privacy were identified in two qualitative studies of the lived experience of catheter use [407] [241;408;409]. To
care providers, catheters may seem commonplace, but male / female sensitivities may occur during catheter care, particularly catheter changes, including men who are embarrassed by a female care provider [405]. Embarrassment can be minimized by providing privacy during catheter changes and same sex care providers when possible [241] [407,408]. Acknowledging the embarrassment that exists if the nurse is of the opposite sex paradoxically may diminish the vulnerability [241]. Humour is often used by care providers, catheter users, and caregivers, and a professional approach by the health care provider may help the catheter user accept the situation [241] [407,408][Level of Evidence 3].

A few studies have examined QoL issues related to practical aspects of living with the catheter, such as managing the drainage bag (See Section VIII). While most people who are self-caring cope with the management of their catheter drainage system, many find them restrictive and report a negative impact on QoL. In a small pilot study based on a postal questionnaire to LTC catheter users (n=59) [410], almost 25% of respondents stated that wearing a bag had a major negative affect on everyday living. Concealment of the bag was one of the most important concerns raised (89%). Keeping the urine drainage bag covered and its visibility minimized can help reduce embarrassment and the stigma related to using a catheter. The visibility of the bag can be considered demeaning and it exemplifies a loss of bladder control; [241,408]. Moreover, if a bag is unreliable, and springs a leak for instance, it contributes to vulnerability. Even using a catheter for a short time can be an assault to one’s dignity. In a study in post-operative short-term catheter use, people complained about feeling “on display” and objectified [407] (Level of Evidence 3).

c) Sexuality
In a study of experiences of 25 men with prostate cancer, many of whom were treated with a urinary catheter, subjects reported the catheter contributed to feelings of shame, excess hospital visits for complications, and with other treatments for cancer, an end to sexual activity [411]. Men viewed healthcare professionals as having responsibility for medical decisions and they alone felt responsible for the catheter, mictunition, and sexual life (Level of Evidence 3).

Issues related to sexuality were dominant in several other studies. Using a catheter compounded changes in sexual life caused by illness or injury [406,409]. In one study, catheter users complained that care providers did not provide enough information about sexuality and how to adapt to a catheter [409]. Despite some care provider’s reluctance to address these issues, sexual health should be a part of assessments [412], and information about sexual activity should be provided proactively, while recognizing that some catheter users will wish to engage in sexual intercourse and others will not (Level of Evidence 3-4).

The underlying disease may also impact on sexuality. For instance, a urinary catheter complicates sexual activity in people with spinal cord injury (SCI). Moreover, men may have changes in sexual performance related to ejaculation, erectile function, and arousal [413]. For females with SCI, experimenting with positions, lubrication, and preventing spasticity may be helpful in sexual activity [414] (Level of Evidence 2). For people with SCI, sex-related autonomic dysreflexia (AD) occurs most often in people who suffer from AD during bladder or bowel care (415) (Level of Evidence 2). Autonomic dysreflexia is an autonomic nervous system syndrome that occurs in people with spinal cord injury or disease. Symptoms include severe hypertension and excruciating headache as well as sweating and goosebumps. It can be a serious problem—even life-threatening—requiring emergency medical attention, yet it is sometimes ignored or disregarded by health care providers [401]. A blocked catheter is also a frequent cause of AD. In a qualitative study (409), several people complained that care providers did not know much about AD and often dismissed their anxiety and concerns (Level of Evidence 3).

d) Catheter-related Pain
Pain related to catheter use is not always recognized although anecdotal information suggests that many people find a urethral catheter uncomfortable (see also Section XII.2.k on catheter comfort and catheter change procedures). In Saint et al’s study [104] 90% of catheterised patients surveyed reported they found the indwelling catheter uncomfortable or painful. Sometimes women complained about the pain because of sitting on the catheter or sores in the vaginal area [401], however it is unclear whether sores or skin irritation are related to latex sensitivity, friction, or wetness or a combination. Bladder spasms, CAUTIs, blockage, and dislodgement can all contribute to catheter-associated pain, as well as insertion and removal procedures[401,408,418] (Level of Evidence 3). Pain arising from AD in SCI patients can result from catheter blockage and has been discussed above.

e) Adjustment to a Catheter
Adjusting to living with a catheter may take a considerable time. In Roe’s study [417] participants reported it had taken them up to a year. Similar lengths of time are commonly reported in anecdotal evidence. An educational booklet for catheter wearers has been shown to significantly improve knowledge and acceptance of the catheter [418]. Though the implications for this type of intervention are positive (Level of Evidence 1-2), the sample was small (n=45)
and the study has not been replicated. The core category identified in a study using a grounded theory approach to examine older people’s experiences of living with a LTC was ‘all about acceptance’. Two further categories defined as ‘at ease’ and ‘unease’ reflected the extremes of their experience and these were mediated by ‘interaction with others’[419]. The presence of a catheter can affect the individual’s view of their own body and such shifts in body image can cause some people to exclude themselves socially. New catheter users (both urethral and suprapubic) may resist the "intrusion of the catheter" prior to acknowledging the need for it [420]. Qualitative studies have shown that although some people felt ill prepared for a catheter, and even viewed it as distasteful, most learned to accept the device over time [408,420]. Catheter-users have described their changed perceptions of the body and of how they learned to pay attention to urine flow to prevent catheter related problems. Though most acknowledged feeling vulnerable because of disruptions caused by the catheter, they noted also that keeping urine flowing was critical to their well being [404] (Level of Evidence 3). 

Health care providers need to provide proactive support and education about the catheter and its care, particularly since some catheter users are uncomfortable in asking for help or support. Male / female sensitivities can interfere, for example, a woman might be disinclined to talk about her catheter with her son [408,420] (Level of Evidence 3).

Guiding and supporting an individual’s adjustment to living with a catheter involves promoting dignity, supporting the changed body image so that the catheter becomes a part of self (and almost not noticed), and learning self-management and self-care, and in planning for active life in the community. It is essential that catheter users know how to select suitable equipment. Simple advice such as not using a coloured catheter in the summer when white clothing would allow it to show can be very helpful. Knowing where toilets are and planning for outings (rehearsing) can prevent urine accidents [401] (Level of Evidence 3). Ambulatory females who use a belly bag need to face the toilet when emptying the bag. Since this position is associated with male toileting rather than female it can sometimes cause embarrassment. Some women may prefer to use a unisex toilet where possible.

While adjustment takes time, emotional distress with the catheter can swing back into the picture at any time if problems develop. Depending on whether the device is working well or not, people can move back and forth between acceptance and estrangement from the catheter [241] when the problem in the background emerges and brings the issue once again to the foreground [421] (Level of Evidence 3). Learning to live with a catheter involves recognizing that the benefits can outweigh the problems (409), watching for signs of problems, and adjusting to the interpersonal and sexual changes [420] (Level of Evidence 3).

f) Self-management

Self-monitoring, a component of self-management, involves awareness of what to notice and related measurements or observations [422]. Self-monitoring urine flow was found to be helpful in preventing or minimizing catheter-related problems in a pilot study with 11 community-based individuals over a six months’ time[243]. In this study, a 3-day urinary diary of intake and output was combined with an educational program, individualized to the interests of participants. Most participants said they learned to pay attention to urine flow, through observing continuous drainage into the drainage bag, increased awareness of the urine colour, position of the catheter, and by monitoring the consistency of their fluid intake [243]. Health care providers can help catheter users to learn to manage their catheter themselves, (i.e., self-care) by identifying where they are in the process of learning self-care and by working with them [420] (Level of Evidence 3).

g) Summary

Most published studies of patients with indwelling catheters have focussed on short-term catheters (< 14 days) in hospitalised patients and relatively few have compared different modes of catheterisation (urethral, suprapubic, intermittent). The main subject of research on catheter use has been the risk of catheter-associated infection and the surrogate outcome measure of bacteruria (asymptomatic) is commonly employed. However, there are important questions over the appropriateness of this as an outcome measure. Although there is clear evidence to support a small proportion of catheter care procedures (indicated below) the majority of procedures are based on clinical experience and expert opinion. Long-term studies are difficult to carry out for a variety of reasons (not least the frailty of many long-term catheterised patients) and there are relatively fewer studies based on community dwelling patients. RCTs may not be the most appropriate or pragmatic design for these groups. Although there are now a number of Cochrane reviews relating to long-term catheter use it is clear that the quality of studies available frequently precludes drawing robust conclusions.

The published literature on SPC use is still relatively small, with much of it based on single centre cohort or case studies, or on short-term post-operative care following surgical procedures (not necessarily related to lower urinary tract symptoms). The majority of reports on SPC for long-term bladder drainage focus on the management of neurogenic bladder. Robust conclusions are often difficult to reach given the relatively short follow-up time frame of many studies.
and the lack of precise definitions of key outcome measures such as measurement of infection. Overall the risks associated with short and long-term use of indwelling catheters are common to both urethral and SPC insertions, including CAUTI, tissue trauma, catheter encrustation leading to blockage, formation of bladder calculi and histological changes.

Quality of life measures, including evaluation of psychometrics, need to be developed further and tested in this population, which may have different needs than others with incontinence. Studies of incontinent people that include catheter users should present data in ways that give the reader information about this sub-population. Sensitivity and a proactive stance from care providers could prevent or minimize some of the stigmatizing effects of the catheter, including those related to privacy needs, dignity, and sexuality. Further product development may help catheter users attain a higher quality of life. Additional research on the effects of self-management/self-care may provide direction for teaching that could contribute to a higher quality of life for catheter users.

4. OVERALL RECOMMENDATIONS RELATING TO CATHETERS

a) Intermittent catheters

• Clean intermittent catheterisation (CIC) is a treatment of choice for those with ongoing bladder emptying problems and residual urine > 100ml who are able to manage the technique (Grade of Recommendation A).
• CIC technique can be taught to all ages of people with appropriate motivation and manual dexterity (or to a carer where this is acceptable to both parties). Appropriate education and ongoing support is needed (Grade of Recommendation C/D).
• Frequency of catheterisation needs to be based on individual need, to prevent over-filling of bladder (Grade of Recommendation C).
• An external lubricant or lubricant-coated catheter is recommended to minimise urethral trauma (Grade of Recommendation C).
• CIC users may benefit from access to different catheters or catheter-packs for different purposes (eg ease of use may be particular important when at work or in public) (Grade of Recommendation C).

b) Indwelling catheters

• Indwelling catheters should only be used after alternative management strategies have been considered and rejected as unsatisfactory (Grade of Recommendation A).
• Duration of catheterisation should be minimal (Grade of Recommendation A).

• A closed drainage system should be maintained to reduce risk of catheter-associated infection (Grade of Recommendation A).
• Asymptomatic bacteriuria should NOT be treated with antibiotics (unless urological instrumentation is planned) (Grade of Recommendation B).
• Routine urine culture in an asymptomatic patient is not recommended (Grade of Recommendation C).
• Silver-alloy catheters should be considered for short-term catheterised patients to reduce the risk of catheter-associated infection (Grade of Recommendation A) but further economic evaluations are required to determine cost-benefit to institutions.
• Catheter materials designed for long-term use (all-silicone, silicone or hydrogel-coating) should be used where a catheter is expected to be used long-term (i.e. >14days) (Grade of Recommendation B).
• Meatal cleansing with plain soap and water (not with antimicrobial agents) is recommended (Grade of Recommendation A).
• Addition of disinfectants to drainage bags, bladder irrigation and antibiotic prophylaxis are NOT recommended as routine infection-control measure (Grade of Recommendation A).
• If an indwelling catheter is being considered, SPC should be considered alongside UC, following appropriate risk assessment (Grade of Recommendation B).
• SPC insertion should be carried out only by appropriately trained and skilled practitioners (Grade of Recommendation C).
• UC and SPC catheters and drainage bags should be adequately supported to prevent meatal or cystostomy damage from traction (Grade of Recommendation C).
• In patients with recurrent catheter encrustation and blockage, careful monitoring should be undertaken to identify of a characteristic pattern of ‘catheter life’ and instigate pre-emptive catheter changes prior to likely blockage (Grade of Recommendation C).

c) Catheter valves

• A catheter valve can provide an effective means of catheter drainage following appropriate patient assessment (Grade of Recommendation B).
• A combination of a valve during the day and free drainage at night through an open valve connected to a drainage bag could be an appropriate management strategy (Grade of Recommendation D).
5. PRIORITIES FOR RESEARCH

a) General

- Despite much published research (primarily on short-term catheter use in acute care settings), catheter studies have been hampered by methodological weaknesses. There is a need for agreement on key criteria to permit robust comparisons between studies: (i) criteria for symptomatic UTI, (ii) significant bacteriuria in a catheterised patient and its clinical/research usefulness (iii) standardised time frames for following patients in studies of catheter-associated infection eg 48h, 5 days, 7 days, 14 days 21 days etc (iv) documentation of the use of antibiotics prior to and during a study eg preoperatively in surgery or commencement of antibiotics for other conditions during the study, (v) patient follow-up to include post catheter removal.

- A standardised definition of UTI should be adopted as the primary outcome variable. At present the most recent CDC/NHSN surveillance definition of health care-associated UTI is recommended [295]. Although criteria for both symptomatic UTI and asymptomatic bacteriuria are defined by the CDC, it should be recognised that definitions are applicable to non-catheterised populations and specific to acute care settings.

- Better adherence to CONSORT guidelines [423]eg double blind randomization with appropriate power calculations, intention to treat analysis with inclusion of study drop-outs

- Need for clinical studies which are adequately powered to detect differences in clinically and economically important endpoints in preference to (or in addition to) more easily measured surrogate endpoints such as bacteriuria.

- Comparative studies of different patient groups eg. males and females, different age groups, patients at home and those in institutional care, including patients’ comfort, satisfaction and quality of life measures.

- Further research on the development of biomaterials that resist microbial adherence and biofilm formation and/or prevent catheter-associated bacteriuria in both long-term and short-term catheter users.

- Further efforts aimed at reduction of LTC use, particularly in nursing home populations. Targeted areas to include evaluation and management of skin problems, and alternative measures for people with diabetes mellitus, obesity and communication problems.

b) Intermittent catheters

There is lack of evidence demonstrating the effectiveness of any particular catheter type, technique or strategy. Variations in clinical practice and growth in the use of single-use catheters (particularly coated catheters) with associated increased costs mean that large, well-designed, parallel group RCTs are needed. RCTs are difficult to conduct in this area and must focus on the most important pragmatic questions, for both clinical and cost-effective reasons. Key issues are identified below.

- What evidence is there that coated (single-use) catheters are superior to uncoated (multi-use) catheters and in what ways (eg infection, comfort, convenience)? Further studies are needed on the risks / benefits of single use catheterisation (new catheter used at each insertion) versus single patient use (patient cleans, stores and re-uses the same catheter for several days) for patients whose long-term bladder management is by CIC.

- To assist assessment of cost-effectiveness, it is recommended that patient acceptability / satisfaction with procedure and a measure of health state utility are measured for different situations (eg. at home and when away from home) as a secondary outcome variable.

c) Indwelling catheters

- Epidemiological studies of CAUTI in LTC use in community care settings.

- Better prospective data on long-term sequelae of indwelling catheter use, eg ongoing symptoms, strictures, calculi, bladder cancer.

- Studies comparing catheterisation techniques eg CIC, suprapubic and urethral catheters, on CAUTI and other risks or potential benefits

- Studies to determine whether the frequency of regular re-catheterisation make a difference to CAUTI and other complications

- Studies to ascertain if there are detrimental effects on bladder tissue from persistent asymptomatic bacteriuria in long-term catheterised patients.

- Clinical evaluation of strategies to reduce recurrent catheter encrustation and blockage, including maintaining a dilute urine, increased level of urinary citrate, role of acidic ‘catheter maintenance’ solutions.

- Further development of catheter materials resistant to microbial biofilm formation, new approaches to disruption of the biofilm, or alternatives to catheterisation.

d) Catheter valves

- Clinical investigation of effect of catheter valves on incidence and frequency of catheter encrustation and blockage.
• Cost-effectiveness studies of disposable versus re-useable valves.
• Studies designed to demonstrate if catheter valves promote maintenance of bladder tone and capacity.
• Further examination of combination management strategies such as valve during the day and free drainage overnight.

**e) Quality of life**

• Identification of appropriate quality of life indicators/criteria and measures for catheterised patients.
• Development of a quality of life measurement instrument including both subjective measures and objective measures, including factors such as: frequency of catheter blockage, catheter-associated infection, hospitalization, unplanned catheter changes, adequacy of equipment, knowledge about self care, interaction with caregivers in catheter management.
• Case study analyses to maximise evidence gained through clinical experience and expert opinion, particularly where opportunities for formal research are likely to be unrealistic.

### XIII. PRODUCTS FOR PREVENTING OR CONTAINING Faecal INCONTINENCE

The broader issues of conservative management of faecal incontinence are dealt with comprehensively in chapter 16 while this chapter deals with products for preventing or managing faecal incontinence. They fall into three main categories:

• Products that aim either to prevent or contain leaked stool.
• Products that seek to prevent or mask the offensive odour that occurs from leaked stool or flatus.
• Products for preventing or treating perianal skin damage associated with faecal incontinence (one of the primary complications of faecal incontinence and an important part of care).

Products dealing with skin health and odour are covered in Sections XIV and XV, respectively, while products for preventing or containing faecal incontinence are covered in this section (apart from absorbent pads, which are included in Section VI).

#### 1. PRODUCTS TO PREVENT OR CONTAIN LEAKED STOOL

Products fall into three groups:

• Plugs to prevent leakage of faeces.
• Devices to channel faeces from the rectum into a storage container.
• Absorbent pads to contain leaked faeces (see Section VI).

An anal plug (Fig XIII-1) consists of a foam, cup-shaped plug that is collapsed and held by a film for insertion; the plug opens when the film comes in contact with the moist rectal mucosa [424,425]. It is inserted like a suppository using a lubricant gel. It has a string for removal or it can be expelled by raising intra-abdominal pressure and pushing like during normal defaecation. The anal plug has been used mainly by community living people, both adults and children, who are independent in managing faecal incontinence and toileting. Another type of experimental anal plug consists of a balloon at the end of a catheter connected to a notification device. The catheter is intended to be inserted into the rectum by the user and the inflated balloon acts as the anal plug; there are also vent holes on the distal tip of the catheter (Fig XIII-2). The disposable, double lumen, balloon-cuffed rubber catheter has an infra-red photo-interrupter sensor that is connected to a pager [426]. When faeces enter the rectum, a photosensor signal is sent to the pager which then notifies the person to inflate the balloon. Before a bowel movement, the balloon is deflated and the catheter is withdrawn. To prevent ischemic bowel damage, patients are advised to deflate the balloon for 10-15 min every 3-4 hours.

By contrast, devices for channelling faeces from the rectum to a storage container are used primarily by people who are acutely ill, critically ill, confined to bed, or in long-term care institutions and receive assistance in incontinence management and toileting by caregivers [427-431]. These devices do not prevent faecal incontinence and are used primarily for preventing or treating skin damage associated with faecal incontinence. They include rectal tubes, catheters, trumpets, and pouches.

Rectal tubes and catheters are inserted into the rectum and drain faeces through openings at their proximal end into a collection bag (Fig XIII-3). Sometimes a balloon slightly distal to the proximal tip is inflated with the aim of preventing leakage of faeces around the catheter and to retard inadvertent expulsion of the tube during defaecation [428]. This arrangement works best with liquid stool which is most likely to be able to flow without blocking the drainage lumen [431,432]. Bowel management programs often include daily saline irrigations through the rectal catheter to maintain liquid consistency of stool and catheter patency. Differing amounts and frequency of irrigation have been reported (300 to 900 ml). Cutting the tip of the catheter off at an angle to facilitate drainage of stool of thicker consistency has been reported [433]. A rectal tube / catheter is contraindicated in patients who have intestinal mucosal disease, immuno-
Figure XIII-1: Anal plugs.

Figure XIII-2: Procon anal plug with infra-red photo-interrupter sensor and pager. (Reproduced with the permission of Wiley-Blackwell Publishing)

- a: infrared photo-interrupter sensor and flatus vent holes incorporated into the catheter
- b: 20 cc air cuff (similar to a regular bladder catheter)
- c: flatus venting charcoal filter
- d: cuff fill valve
- e: monitor connector
- f: monitor that resembles a “beeper” or pager

Figure XIII-3: Rectal catheters; Flexiseal Fecal Management System, Convatec (Nordic Capital Fund VII and Avista Capital Partners); Princeton, NJ (top); and Zassi Bowel Management System, Hollister, Inc. Libertyville, IL (bottom).
suppression, gastrointestinal bleeding or bleeding tendencies, recent myocardial infarction or prostate surgery [433,434]. Use of a rectal tube with or without inflating the balloon is controversial because of concerns of perforating the rectum, damaging the anal sphincter or rectal mucosa, stimulating intestinal secretion worsening diarrhoea and thus incontinence [432,433,435]. Critically ill patients, who often receive a rectal tube, may be at greater risk for intestinal ischemia and rectal damage because they experience shunting of blood from the gastrointestinal tract during shock or low perfusion states.

A rectal trumpet is a nasopharyngeal airway that is inserted into the rectum and connected to a collection bag at its distal end. The flange end of the trumpet is inserted into the rectum [436] (Fig XIII-4). A possible advantage of the rectal trumpet over a rectal tube is that it is shorter and has less contact with the rectal mucosa, so limiting the area of possible damage. Other limitations are similar to those for the rectal tube / catheter regarding risk of expulsion from forceful valsalva movements and dislodging during linen changes or from tugging on the collection bag [436]. Nasopharyngeal airways that can be used as a rectal trumpet are produced by several manufacturers.

An external anal pouch consists of a pliable wafer, which has an opening at its centre, an adhesive on the body side, and a collection bag on the other. The wafer adheres to the perianal skin (Fig XIII-5). The bag has a resealable port at its distal end through which faeces can be drained without the need to remove the wafer from the skin. The port can also be connected to a larger, gravity drainage bag. Some pouches have a small folded flap that allows flatus to escape so that it doesn’t inflate and rupture the bag. The pouch avoids the risks of rectal or sphincter damage associated with the rectal tube or trumpet. If used without the additional drainage bag, it can collect leaked stool of any consistency without clogging. A limitation of the rectal pouch is difficulty in applying it on people who have a small space or severe oedema between the anus and vagina or scrotum. Other reported disadvantages include difficulties in maintaining the seal (especially when the perianal skin is already damaged); break of the seal when repositioning the patient; and skin tears by traumatic removal of the adhesive [436,430].

An intra-anal stool bag is composed of a latex bag (20 cm non-extended, to 26 cm extended) that is inserted into the anus and an adhesive attachment (10 cm in diameter) applied perianally [437] (Fig XIII-6). There is a cut-out on the ventral urinary side of the adhesive wafer.

Aspects of patient assessment that are relevant to products to prevent or contain leaked stool include the following: a) physical characteristics (e.g., some anal plugs may be too large to fit smaller sized children),

Figure XIII-4: A rectal trumpet.

Figure XIII-5: An anal pouch.

Figure XIII-6: Interanal stool bag (left) and Outer attachment wafer of Interanal stool bag (right). (Reproduced with the permission of Wiley-Blackwell Publishing)
b) dexterity (e.g., some degree is needed to insert or remove an anal plug), c) mobility (e.g., rectal catheters are mainly used for patients who are in bed vs. ambulatory), d) nature of incontinence (e.g., bowel catheters will require irrigation when stool consistency is not loose or liquid in order to remain patent; and e) personal priority and lifestyle (e.g., some persons will wear an anal plug on certain occasions such as when swimming, despite discomfort).

2. QUALITY OF DATA

There have been eight published evaluations of anal plugs for controlling faecal incontinence and one of the anal catheter plug (Procon, AnaTech, El Paso, TX). Five reports included children of which two studied children exclusively [438,439]. The study designs were one randomized clinical trial, four repeated measures (cross-over), one pre-post design, one cross-sectional survey, one case series, and one case report. All of the studies of anal plugs except one evaluated products from the same manufacturer (Coloplast, Denmark). One study in children [438] compared the Coloplast device with one by Med.SSE-System, Germany. There has also been one published evaluation of a rectal trumpet using a case series design [436] and one each of an external anal pouch and an intra-anal stool bag in which no comparison group or pre-post measures were included.

3. RESULTS: ANAL PLUGS

Most evaluations of anal plugs have involved relatively small cohorts of ambulatory subjects. The largest sample had 48 subjects and 26 of 31 persons in the intervention group who wore the anal plug completed the study [440]. The aetiologies of faecal incontinence varied across studies and included spina bifida, imperforate anus, spinal injury, post-surgical incontinence, sphincteric injury, and obstetric trauma. Faecal incontinence was measured by self-report using a daily stool diary in six studies [424-426,439-441]. A questionnaire /survey was used in one descriptive study [442] and one repeated measures study [438]. The main reported outcome measures were: the number of episodes of faecal incontinence per number of anal plug uses overall. Faecal incontinence occurred in 10% to 12% of times one of the three anal plugs used due to self removal or need for defecation. Two of seven child respondents stopped using an anal plug because of pain [439]. Two or fewer soiling accidents occurred in 74% using the polyurethane plug, and in 65% using the polyvinyl alcohol plug [438].

A survey of adults and children showed that a higher percentage of children tolerated using an anal plug over a longer period of time [442]. Five of eight (63%) adult survey respondents who had faecal incontinence of various aetiologies stopped using an anal plug immediately while three used it periodically for 12 to 20 months. Two of seven child respondents stopped using an anal plug immediately while five (71%) used it weekly for an average of 2.5 years. The most common reported problems associated with wearing an anal plug included discomfort and failure to retain the plug. Despite efficacy, approximately two-thirds of the subjects in two studies [425,441] said they would not continue to wear the plug due to discomfort. Discomfort occurred in 10% to 12% of times one of the three anal plugs were worn in another study [424]. In more recent studies, three of 23 subjects (13%) reported discomfort [440], and 25% of 16 withdrew from another study because of pain [439]. Two of the children who
withdrew from the paediatric study had complained of discomfort [438]. There was no association between comfort of the plug and anorectal sensitivity during anal-rectal physiology tests in adults [425]. Approximately 20% of children reported that insertion of the polyvinyl alcohol plug was painful while 17% found removal of the polyurethane plug to be painful; one child experienced bleeding on removal of this second plug. Rectal bleeding also occurred in adults but infrequently [424]. Failure to retain the anal plug was reported by 13% of subjects in two studies [439,440] and was noted by one child in the paediatric study as a reason for withdrawal [438]. The size of any plug tested was too large for six children in one study [438]. Other tolerance problems were fairly uncommon. In one study, adults rated all three anal plugs that were evaluated as relatively easy to insert. Two plugs were difficult to remove in only 5% and 6% of uses, respectively, while the third was difficult to remove in 23% of uses [424]. Other reported problems were feeling a need to defecate [425], inconvenience or difficulty in managing [425,426], and local irritation [442].

4. RESULTS: RECTAL TRUMPET

One case series study evaluated the use of a rectal trumpet in 22 acutely or critically ill patients with faecal incontinence and perineal skin damage (436). For 90% of the subjects, the skin damage had been caused by wearing a rectal pouch immediately prior to the study. Subjects used the trumpet for periods varying between 36 hours and 16 days (mean 6.5 days; sd 4.4 days). The reasons for any discontinuation of use were reported. Outcome was determined using a daily questionnaire completed by patients' nurses and the health of the perianal skin was noted by subjective assessment. No standardised definitions or criteria for restoration of skin integrity or healing of skin damage were reported. Two subjects were lost to follow up. Faeces were successfully diverted to and contained by the collection bag in all patients. Recovery from skin damage was reported in 7 (39%) patients and partial healing of skin in the remaining 11 (61%). Discomfort on insertion was noted for 41% of subjects (Level of Evidence 3).

5. RESULTS: RECTAL CATHETER SYSTEMS

Closed rectal catheter and collection bag systems specifically designed for extended use and diversion of faeces are commercially available primarily for acutely-ill or bed-ridden patients (Flexi-Seal® Fecal Management System, Convatec A Bristol Myers Squibb Company; Princeton, NJ; Zassi® Bowel Management System, Hollister, Inc., Libertyville, IL). The catheters of these systems typically contain a retention cuff that collapses to assist with insertion (US FDA approved for up to 29 days) and a port for irrigation. In one system (Zassi) there is also a collapsible zone below the cuff that resides in the anus to allow normal anal sphincter function during use and a second port for sampling intestinal fluid. A third catheter has an inner balloon that can be inflated to serve as an anal plug to promote retention of an enema, for instance (Kim, US Patent 5 689 216, apparently not currently commercially available).

Six studies evaluated use of a rectal catheter system. Three studies used one type of catheter while the other three studies used three different types of systems. One study was of children [443]. The designs included a prospective single cohort in four studies [427;428;443, 444], a pre-post descriptive design [445], and a retrospective case-matched pre-post design [446]. The largest sample size was 106 in the retrospective chart review whereas sample sizes in the prospective studies were relatively small, ranging from 20 to 42 subjects. In the studies of adults, subjects were acutely or critically-ill patients in three studies [427;428;445]. In three studies, irrigation of the catheter with saline, a combination of lactulose and saline irrigation or use of an enema was used to keep the stool liquid and the rectal catheter patent [428;444;446]. In only two studies was the effectiveness of the rectal catheter system in reducing faecal incontinence reported (Level of Evidence 3). In the one paediatric study, 31 children (11 females) participated. Eight families refused to stop using the rectal catheter to complete an incontinence diary without use of a catheter. Two children had balloon extrusions and three were noncompliant resulting in their study withdrawal. The mean number of daily faecal incontinence episodes as reported on a daily diary decreased from 3 to 1.5 in males and from 1.6 to 1.1 in females (p<.05 for both) [443]. Three children experienced no improvement of faecal incontinence. In the one adult study, 39 of 42 subjects (62% female) with diarrhoea in intensive care units in seven hospitals completed the study. There was up to 29 days of follow-up. Varying degrees and types of leakage around the rectal catheter were reported in 71% of 198 assessments; 35% of these leakages extended to pads on the bed or beyond [427]. Seven (17%) of subjects had difficulty retaining the rectal catheter. Section VI.k discusses use of a small gauze dressing for absorbing small amounts of stool leakage and a moisture barrier as skin protective strategies that might also help prevent damage from stool leakage around a rectal catheter. Skin damage from the tape holding the catheter in place and rectal bleeding are other reported but uncommon complications [427;444].

The effect of a rectal catheter on various outcomes associated with stool leakage has also been studied. One study reported that the number of bed linen changes in burn patients with diarrhoea decreased eight-fold and dressing changes in hospitalized or burn patients decreased in half after a bowel system was introduced [444].
Other outcome measures of rectal catheter use included urinary tract infections, incidence of skin/soft tissue damage or infections, prevalence of pressure ulcers, and number of liner changes (Level of Evidence 3/4). In a retrospective review of medical records, approximately twice as many burn patients had skin/soft tissue or urinary tract infections before a bowel catheter system was introduced than after (p<.01) [446]. A prospective study of acutely and critically-ill patients showed that 41% who had normal skin in the perineum or buttocks at baseline maintained normal skin during use of the bowel catheter, 44% with some degree of skin damage improved, and 8% had worsened skin condition [427]. The percentage of intensive care unit patients with a stage II or greater pressure ulcer was observed to be less at nine months after use of a bowel catheter was introduced. The total number of patients observed was not reported. The length of time during which the prevalence of pressure ulcers was determined prior to catheter use was also not reported [445].

The condition of the rectal mucosa was observed endoscopically in 40 patients total across three studies; the evaluations were not blinded or independent and did not use a rating scale [427,428;444]. All endoscopic observations were reported as being normal after rectal catheter use. Few complications associated with use of the rectal catheter system were reported. Leakage around the rectal catheter seemed to be the most frequent problem. Catheter expulsion occurred in a small number of patients and skin damage from trying to secure the tube occurred only in one patient. Altered rectal sphincter function occurred using one of the catheters [428] (Level of Evidence 3).

6. RESULTS: ANAL POUCH

One case series study evaluated the use of an external anal pouch (Technoline, Concordia, Moderna, Italy) in 120 nursing home or hospitalized patients (65 men, 55 women, ages 45-96 years) [447]. The nursing home residents (n = 92) were bedridden and had faecal and urinary incontinence or were treated for constipation for rectal enemas that drained into the pouch. Ten had a pressure ulcer. They used the pouch for four weeks or more. Acute care patients (n = 28, of which 10 were in the intensive care unit) had diarrhoea and were temporarily bedridden. Forty-five patients who had surgery of the perineal area received a pouch to collect post-surgical drainage for up to three days. In the nursing home residents free of pressure ulcers, no new ulcers developed. In those with a pressure ulcer, healing occurred in five residents, ulcer diameter was reduced by 50% in three residents, and there was less than 50% reduction in two residents. Of the nursing home and acute care participants, 77% found the pouch comfortable and 75% thought it was better than a sanitary napkin. Seventy-seven percent of the nurses thought the anal pouch was easy to apply and 78% thought is easy to remove. Reported complications included moderate pain on removal in 18 (15%) patients in the nursing home or acute care (Level of Evidence 3).

An internal anal stool bag (Terumo Corp., Tokyo, Japan) was applied to five bedridden patients (3 female, 2 male) aged 68-90 years [437]. Persons were administered a bisacodyl suppository prior to insertion of the stool bag into the anus to control excretion of faeces. The bag was successful in collecting stool 50% of the time (Level of Evidence 3). The bag was removed after each stool was collected.

7. SUMMARY

- An anal plug can successfully prevent faecal incontinence but it is associated with high levels of discomfort, especially in adults (Level of Evidence 3).
- A rectal catheter system diverts faeces to a collection bag and promotes healing of damaged perineal skin but requires liquid stool consistency to remain patent. Some catheter systems enable irrigation of the rectum to maintain liquid stool consistency. Non-blinded and non-independent endoscopic observations suggest the catheter does not cause rectal mucosal damage during the recommended length of use (≤ 29 d in the US) (Level of Evidence 3).
- A rectal trumpet can successfully channel faeces to a collection bag and there is some evidence that it can thereby enable damaged perianal skin to recover but it has been associated with discomfort and its safety has not been determined (Level of Evidence 3).
- An external anal pouch and an internal anal bag can be used to collect stool (Level of Evidence 3) but the adhesive wafers used to adhere them can cause skin damage upon removal. The internal anal bag has been primarily used when a bowel movement is induced using a suppository.

8. RECOMMENDATIONS

- Anal plugs may be tried but many patients are likely to use them on a limited basis or reject them due to discomfort (Grade of Recommendation C).
- The use of a rectal trumpet (i.e. a nasopharyngeal tube inserted into the rectum) in patients with loose/liquid stool consistency offers an alternative to the rectal pouch when pouch adherence is a problem and may preserve perianal skin integrity or facilitate healing (Grade of Recommendation C). The safety of the rectal trumpet has not been determined, but it suggests a lower risk due to its shorter length than a standard, longer rectal tube (Grade of Recommendation C).
9. PRIORITIES FOR RESEARCH

- Development of an anal plug that is more comfortable and tolerable.
- More rigorous evaluation of anal plugs using larger subject cohorts and more objective outcome measures over longer periods of use.
- More rigorous evaluation of rectal tubes / catheters and trumpets using larger subject cohorts and more objective outcome measures (e.g., for assessing health of the rectal mucosa) over longer periods of use.
- Development and evaluation of an external anal pouch that is easy to apply and remove, adheres to skin better and, perhaps, even promotes healing of damaged skin to which it would be applied. Further evaluation of an internal stool bag with similar adherent properties (as recommended for the external anal pouch) is needed.

XIV. SKIN HEALTH AND CONTINENCE PRODUCTS

1. BACKGROUND

The skin of an incontinent individual will be regularly exposed to contact with urine and / or faeces and damage to the skin is the main physical health consequence of urinary and faecal incontinence. The majority of current knowledge about the effects of urine and faeces on skin has been obtained from studies with pads or pad materials on animals, healthy infants, and on body areas such as the forearm or back of adults. Where clinical trials have been conducted, they have usually been on infants and rarely on adults using pads. Skin irritation within the pad occlusion area is usually termed diaper dermatitis in infants. In adults the term perineal dermatitis (PD) has commonly been used, but more recently it has been proposed that incontinence-associated dermatitis (IAD) is a better term because affected skin areas are not confined to the perineum [448]. The more inclusive label ‘Incontinence-associated skin damage’ has also been applied [449] and may be preferable when describing skin problems on the buttocks, hips and sacrum where erythema or skin surface damage may also be caused by pressure, shear or friction.

a) The role of urine and faeces in skin irritation

Prolonged exposure to water alone has been shown to cause hydration dermatitis [450;451] and prolonged occlusion of the skin (as within a continence product) has been demonstrated to reduce skin barrier function [452] and significantly raise microbial counts and pH [453,454]. Repeated wetting and drying makes the skin more vulnerable to substances that are usually innocuous, e.g., bile salts [455;456]. A product that simply maintains wet and occluded skin (even without the additional constituents of urine and faeces) is therefore likely to cause skin irritation and increase skin permeability to other irritants.

Using a hairless mouse model Buckingham and Berg [457] examined the role of faeces in the aetiology of diaper dermatitis. They identified proteases and lipases as the major irritants and noted that these faecal enzymes not only irritated the skin directly but also increased the susceptibility of the skin to other irritants such as bile salts. The irritant effect of faeces was virtually eliminated by heating, which destroys enzymes, and was restored by the replacement of specific enzymes (e.g. lipase and protease). Skin damage appeared dependent on the concentration and length of exposure to enzymes in faeces [458].

A similar mouse model was used by the same researchers to examine the role of urine in the aetiology of diaper dermatitis [456]. They found that the irritant potential of urine by itself was minimal over short periods (48 hours) but after continuous exposure (10 days), skin damage became apparent. The researchers also measured skin permeability and found that continuous exposure to urine greatly increased skin permeability (more than 15 fold) compared to occluded skin or skin exposed only to water.

However, the combination of urine and faeces caused significantly higher levels of irritation than urine or faeces alone. The authors concluded that the presence of faecal urease results in the break down of urinary urea causing an increase in pH, which increases the activities of faecal proteases and lipases leading to skin irritation. The role of microorganisms - which comprise approximately 50% of the solid component of faeces - in skin damage is unresolved. Microorganisms on the skin of infants with and without diaper dermatitis were similar [459]. Zimmerer [460] sampled the microflora of the skin after pre-loading with pre-wetted patches containing urine and found that the microbial counts were significantly higher for wet patches relative to the dry patch controls. It was nearly
impossible to establish infection with the opportunistic organism, Candida albicans, on normal skin without complete occlusion of the site [461]. Therefore, it is thought that bacterial or fungal infection is secondary to alterations in the skin barrier that allow penetration of the microorganisms [462].

Zimmerer et al. [460] examined the role of skin wetness in the development of diaper dermatitis by using the volar forearms of adult volunteers. They aimed to determine the effects of wet and dry diaper materials on skin health with respect to friction, abrasion damage, permeability and microbial growth. Pre-wetted patches of baby diapers were placed on the volar forearms of adults for two hours and then the skin was subjected to friction and abrasion. The coefficient of friction for the 'wet' skin was significantly higher than for 'dry' skin although increased fluid loading of wet patches did not further increase skin friction. Similarly, skin hydrated with a wet patch showed a significant increase in skin abrasion damage relative to a dry patch. Again, variations in the fluid loading of the patch did not produce significant changes in abrasion damage.

Although the volar forearm is most commonly used for skin experimentation, it has not been shown to be a valid model for the skin exposed to an incontinence pad, i.e., buttocks and groins. Schnetz and colleagues [463] demonstrated that trans-epidermal water loss (TEWL) measurements (used to measure both skin barrier function and excess water in the skin) from the volar forearm did not correlate with those taken from the face, although the left and right side of the face showed good correlation. The researchers concluded that TEWL measurements for the study of facial cosmetics should be taken from the face rather than the forearm. Similarly, studies using the volar forearm may not be valid for the buttocks and groin. Skin in the perianal area was shown to be more sensitive to faecal irritation than that on the inner arm [464].

Berg [465] analysed the aetiological factors contributing to infant diaper dermatitis and developed a model (Fig XIV-1) to show its development and resolution. However, the applicability of this model to adults with incontinence has not been tested, and other factors such as low mobility and prolonged pressure - which are common in frail, older adults - are not accounted for in this model. In addition, this model assumes the presence of urinary and faecal incontinence, which is much less common in adult populations than urinary incontinence alone.

b) Prevalence of perineal dermatitis

Perineal dermatitis (PD) is an inflammation of the skin characterized by redness, tissue breakdown or denudement, vesiculation, oozing, soreness, itching, and in its more severe form, pain and fungal patches [466;467] within the pad area. In the largest study of assessment records of more than 59,000 residents in 510 nursing homes located in 31 US states, Bliss et al. [449] reported a prevalence of perineal dermatitis of nearly 6%. In studies with smaller sample sizes and other populations, perineal dermatitis (Table XIV-1) has been shown to affect about a quarter to a half of patients.

There is no widely accepted, valid or reliable tool for the assessment of PD / IAD although three instruments have been published [475-477]. One of these tools, the Perineal Assessment Tool, despite its name, appears to be an instrument primarily for assessing the risk of PD (versus assessing skin health) and it has been described and used by its developer as such [478]. Most researchers have reported ratings of colour changes (degree of erythema) based on visual inspection, which may be confounded by the

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Prevalence of dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyder et al. 1992 [716]</td>
<td>15 older people: hospital psychogeriatric wards</td>
<td>33%</td>
</tr>
<tr>
<td>Keller et al. 1990 [717]</td>
<td>95 older people: long stay</td>
<td>53%</td>
</tr>
<tr>
<td>Brown 1994 [718]</td>
<td>166 adults (acute medical wards)</td>
<td>35%</td>
</tr>
<tr>
<td>Bale et al. 2004 [719]</td>
<td>79 nursing home residents</td>
<td>25% baseline prevalence</td>
</tr>
<tr>
<td>Zehrer et al. 2005 [720]</td>
<td>398 nursing home residents on a skin damage prevention regimen</td>
<td>4% baseline prevention</td>
</tr>
<tr>
<td>Bliss, Savik et al. 2006 [721]</td>
<td>59,558 nursing home residents</td>
<td>5.7%</td>
</tr>
<tr>
<td>Bliss, Zehrer et al. 2006 [722]</td>
<td>1,918 nursing home residents on a skin damage prevention program</td>
<td>3.5% baseline prevalence</td>
</tr>
<tr>
<td>Ehman et al. 2006 [723]</td>
<td>45 adult intensive care unit patients</td>
<td>36%</td>
</tr>
<tr>
<td>Junkin et al. 2008 [724]</td>
<td>698 paediatric and adult hospitalized patients</td>
<td>20%</td>
</tr>
</tbody>
</table>
presence of reactive hyperaemia on areas subject to pressure (particularly the buttocks, hips and sacrum). In some studies (mainly those finding higher proportions of PD) trained staff or researchers have been utilised to carry out skin inspections at pre-specified times and in others (mainly those finding lower proportions of PD) the usual care staff have been asked to report skin problems or written records have been used; this may explain the wide range of prevalence reported.

Bliss et al. [479] prospectively investigated the development of PD using assessment data of 1,850 elders who were free of PD at admission to a nursing home. The preliminary report showed that at three months after admission, faecal incontinence alone and double incontinence were significant predictors of PD, but urinary incontinence alone was not a significant risk. The prevalence of PD appears to be influenced not only by the type of patient (nursing home versus hospitalized) but also by the type of incontinence and whether or not a skin damage prevention program is followed.

Few studies report the severity of PD. In a prospective surveillance study of 981 nursing home residents with incontinence of urine and/or stool over six weeks, the most common anatomical locations of PD were the buttocks (73% of those with PD) and perianal area (70%) followed by the genitalia, scrotum and groin (36%) and thighs (24%) with the smallest percentage near the sacrum (9%). Approximately one-third of residents had PD in more than one location. Mild PD was by far the most common (69% of residents); severe PD affected only 8% of residents [472].

**c) Pressure ulcers and incontinence**

The role of urinary and faecal incontinence in the development of pressure ulcers is uncertain. Studies aiming to identify risk factors for the development of pressure ulcers have generally found that the presence of both urinary and faecal incontinence was a risk [480,481-483], but some studies have only found faecal rather than urinary incontinence to be a risk factor [484,485]. Pressure ulcer risk assessment scales all have a sub-scale of incontinence or moisture-level, and the main mechanism for the development of pressure ulcers has been thought to be the increased friction and increased vulnerability to abrasion of wet skin.

Some researchers have used pressure ulcer classification systems, such as those published by the National Pressure Ulcer Advisory Panel (NPUAP) or the European Pressure Ulcer Advisory Panel (EPUAP), to measure skin health. The validity and reliability of most of these tools have not been established. Doughty et al [486] and Bethell [487] described numerous other limitations of pressure ulcer staging systems and despite recent revisions of the NPUAP and EPUAP staging systems, many of the shortcomings still apply. The reliability of the EPUAP staging score (which is a modified version of the NPUAP score) has been tested recently in three studies using photographs of pressure ulcers. These photographs included ‘moisture lesions’ (defined as lesions resulting from prolonged exposure of the skin to excessive fluid because of urinary or faecal incontinence, profuse sweating or wound exudate). A high degree of reliability for classification of moisture lesions was found amongst 44 pressure ulcer experts.

![Figure XIV-1: Berg’s model of diaper dermatitis (1987).](image-url)
2. CLINICAL STUDIES OF THE IMPACT OF pressures.

formation of pressure ulcers by raising interface pressures. It is therefore possible that pad folding and compression may contribute to pad / mattress. Peak pressures were frequently found pressures recorded between the buttocks and the and substantially (around 20%) increased the peak pressures. Using an articulated model or “phantom” as the subject and found that the presence of a pad significantly prevention relieving devices / measures. Fader et al. [491], examined the effects of absorbent continence pads on mattress interface pressures using an articulated model or “phantom” as the subject and found that the presence of a pad significantly and substantially (around 20%) increased the peak pressures recorded between the buttocks and the pad / mattress. Peak pressures were frequently found at the locations of pad creases and it was considered that pad folding and compression may contribute to raised interface pressures. It is therefore possible that continence product use contributes to the formation of pressure ulcers by raising interface pressures.

2. CLINICAL STUDIES OF THE IMPACT OF PRODUCTS AND PRODUCT MATERIALS ON SKIN HEALTH

In the 1980s, product manufacturers introduced diapers with super-absorbent polymers (SAP), which were designed to reduce skin wetness, buffer pH and reduce urine / faecal contact in order to help prevent diaper dermatitis. This led to clinical and laboratory studies to evaluate the efficacy of diapers with different materials, in particular, super-absorbent polymers (SAP) compared to those without, and compared to conventional washable diapers.

a) Quality of data

There are three types of studies testing the effects of different products or product materials on skin health: (i) clinical trials of normal infants wearing diapers; (ii) laboratory wet patch testing of adult forearms with diaper or continence pad patches; and (iii) clinical trials of adult absorbent pads containing different materials. The infant diaper studies were randomised controlled trials with large samples and blind measurement of outcomes. It should be noted that these studies were carried out by industry-employed staff. The infant and laboratory studies used a probe comprising two hygrosensors and thermistors (an evaporimeter) placed on the ‘wet’ skin to measure trans-epidermal water loss (TEWL), an indicator of skin hydration level. However, there is uncertainty about the optimum procedures for measuring TEWL, and different procedures and outcomes were used in the studies, making it difficult to compare results. Probably the most important threat to the validity of these studies is the selection of products or materials used in the study. None of the studies adequately described the products used - in particular, regarding their total absorbency. Thus it is possible that an alternative explanation for the fairly consistent findings that disposable pads with SAP perform better on skin outcome measures may be that those with SAP simply had greater absorbency than those without.

b) Results

1. CLINICAL STUDIES OF INFANT DIAPERS

Campbell and colleagues[492] conducted four clinical studies involving 1,614 infants randomly assigned to either disposable diapers with SAP, disposable diapers without SAP or washable cloth diapers. Disposable diapers with SAP were associated with significantly reduced skin wetness as measured by TEWL, lower pH and lower ratings of diaper dermatitis when compared to the two other diaper products (Level of Evidence 2).

Lane et al., [493] randomised disposable diapers without SAP and disposable diapers with SAP to 149 newborn infants and assessed their skin condition seven times over a 14 week period. Skin rash ratings were significantly lower for infants wearing diapers with SAP at only one time period (14 weeks) (Level of Evidence 2).

Davis and colleagues [494] assessed 150 infants over 15 weeks in a cross-over study involving four different disposable diaper types, two with different levels of

(Kappa =0.80) [488]. However, inter-rater reliability was found to be much worse (Kappa = 0.37) when photographs were viewed by 473 non-expert nurses (489) and subsequently in a European study of 1,452 non-expert nurses from five European countries (Kappa = 0.36). The authors concluded that better descriptors needed to be incorporated into the EPUAP system and more education was needed.

To investigate the validity of classifying moisture lesions, Houwing et al. [490] examined the histology of 14 biopsy samples of damaged patient skin. Skin damage was classified using the EPUAP system: 12 were moisture lesions, one was a grade 4 pressure ulcer (extensive tissue destruction / necrosis) and one was a combination of a moisture lesion and a grade 1 pressure lesion (non-blanchable erythema). Both pressure ulcers had a histological pattern suggesting ischemic pathology; the histology of the moisture lesions, however, was either of an ischemic or irritation pattern. Because of the overlap in histology patterns of some of the moisture lesions and the pressure ulcers, the authors concluded that there is no justification for classifying moisture lesions separately from pressure ulcer lesions. This finding requires further study as there are several limitations of their study. First, the true aetiology of the skin damage and the veracity of the EPUAP classification were not determined; some moisture lesions seem to be partially over a bony prominence so that a mix of pressure and moisture damage cannot be ruled out, which might explain the mixed histology patterns. Secondly, the moisture lesions and the pressure ulcer were both described as having blanchable erythema. Identification of moisture lesions as distinct from pressure ulcers is sought as a way to solve the tension between inadequate prevention / treatment of a pressure ulcer and inappropriate use of costly prevention relieving devices / measures.
SAP and two with different levels of fluff pulp only. Both diapers containing SAP were associated with significantly less skin wetness and significantly lower pH. Clinical skin ratings showed significantly lower ratings for the SAP-containing pads compared to the lower weight fluff pulp pad, but not compared to the higher weight fluff pad (Level of Evidence 2).

2. LABORATORY STUDIES OF DIAPER PATCHES

Wilson and Dallas [495] used the adult normal volar forearm skin model to compare patches taken from 16 different infant diapers. They found that disposable diapers containing SAP left the skin significantly drier than washable diapers and disposable without SAP (p < 0.01). Disposable diapers without SAP did not differ significantly from reusable diapers and there were no significant differences between products within any of the three groupings (Level of Evidence 2).

However, in a subsequent study involving 20 disposable and washable adult incontinence pads incorporating a similar range of materials to the baby diaper study Dallas and Wilson [496] found significant differences between products within each of the three product groupings but not between groupings (Level of Evidence 2). Grove et al. [497] used a similar approach to compare three infant diapers and found a significant difference in skin wetness between two that contained similar quantities of SAP (p < 0.001). The one in which the SAP was in a layer near the water-proof backing kept the skin dryer than that in which it was near the coverstock. The third diaper – which had a microporous (breathable) backing kept the skin significantly dryer than each of the other two (p < 0.001) (Level of Evidence 2).

3. CLINICAL STUDIES OF SKIN-CARE PRODUCTS AND NURSING PRACTICES TO MAINTAIN OR IMPROVE SKIN HEALTH

The skin of incontinent people requires frequent cleansing to remove urine and/or faeces. Soap and water is in common use [498] but it is known that repeated exposure to anionic surfactants (common in soaps) results in skin irritation [499:500]. In addition, the action of washing is also considered likely to contribute to mechanical damage of the stratum corneum.

Cleansing of skin soiled with urine and/or faeces should occur immediately if possible or promptly after episodes of incontinence [448;501-504]. In addition, an individualized schedule for cleansing the perineum according to patients' needs or preferences [505;506] or at routine intervals, such as daily or at bath time [448;501,507;508] has been recommended (Level of Evidence 3).

The practice of cleansing or wiping the perineum front to back is recommended as standard practice in the literature - particularly for women [509-513]; this recommendation is based on the physiological rationale of lowering presumed risk of contaminating the urethra with fecal bacteria and subsequent urinary tract infection [513]. One retrospective study of pregnant women found a significantly higher association of urinary tract infections in women who self-reported they wiped back to front (25.8%) than among those who wiped front to back (18.5%) [514](Level of Evidence 2).

To minimize friction damage of the skin during the perineal cleansing process, gentle cleansing and patting dry the skin [515,516] rather than rubbing or using a soft cloth is recommended by clinical experts [472,517,448,503,504;518] (Level of Evidence 4).

However there is some evidence that drying the skin
by patting may be less effective than gentle towel-drying or drying with a hair dryer [519]. Damp skin is more vulnerable to friction damage and special care may therefore be needed to ensure that the skin is dry. For already damaged skin, there are clinical anecdotes of using a small hand-held hair-dryer set on a low and cool setting rather than drying with a cloth. Further research into cleaning and drying techniques and products is encouraged.

Alternative cleansers are available which have been formulated with the intention of overcoming some of the limitations of soap and water. Although overhydration of skin is detrimental, an excessively dry stratum corneum develops cracks and fissures and can be as ineffective a barrier as an over hydrated one [520].

The use of topical products aiming to prevent or treat skin irritation is common but there is a lack of standardisation in definitions and descriptions of products, which makes comparisons difficult. Products such as ‘moisturisers’ or ‘barriers’ may be applied to the skin after cleansing, and some cleansers also incorporate moisturisers. The aim of moisturisers (also known as emollients) is to hydrate the skin by reducing trans-epidermal water loss through occlusion (e.g. petrolatum), by drawing water into the stratum corneum by the addition of a humectant (a hygroscopic substance, e.g. glycerol) or by adding water in the applied water-miscible product. These modes of action are often combined in the same product, but there are exceptions - such as petrolatum - which only work by occlusion [521]. Some products are designed specifically to prevent penetration of water into the stratum corneum (‘barrier’ products) such as liquid skin sealants containing polymers, and may allow trans-epidermal water loss whilst preventing external water penetration. Simple occlusive products such as petrolatum may also act as barrier products to water but also occlude trans-epidermal water loss.

The application of skin barriers is recommended on areas that would come in contact with leaked urine and / or faeces. In general these areas include the buttocks and perianal area, groin, and inner thighs. Community-living persons report leaking small amounts of faeces that remain between the buttocks. Clinically, nursing staff have observed seepage of faeces around a rectal catheter in hospitalized patients. In both groups, perianal skin protection is important, and skin barriers are recommended (Level of evidence 4).

Topical creams are commonly used to prevent and treat dermatitis but controlled experiments to assess efficacy on human and animal skin have produced equivocal results. Ghadially et al. [521] showed that barrier recovery (measured by TEWL) on experimentally irritated skin was accelerated by the application of petrolatum and De Paepe K et al. [522] showed similar results using a different moisturising cream. Hannuksela and Kinnunen [523] showed that treatment with moisturisers prevented the development of irritation in an experiment involving frequent skin washing with liquid detergent. However, Gabard [524] was unable to demonstrate significant acceleration of barrier recovery to chronically irritated skin following application of different moisturisers using a chronic irritation model and also found that some creams enhanced irritation.

The efficacy of barrier products in preventing water penetration of the skin has been tested in laboratory settings. Vinson and Proch [525] applied wet patches with a water-soluble marker to skin coated with three different barrier products and measured dye extracted from the skin by absorbance spectrophotometry. One multiple barrier product performed significantly better than a petrolatum-based and an allantoin-based protectant. Waring and Hoggarth [526] used a Chromameter to measure skin colour change after staining skin with a water-soluble dye, covering it with a barrier product and washing the skin. Petrolatum products were found to be more effective barriers than dimethicone-based products. In a later study, Hoggarth et al. [527] investigated the barrier function and skin hydration properties of six skin protectants when applied to the volar forearms of 18 healthy volunteers. The researchers found that each had different performance properties with the water-in-oil products containing petrolatum performing better than the oil-in-water products containing dimethicone for protection against irritation or maceration. However the dimethicone products had higher hydration properties compared to the petrolatum products. Overall the water-in-oil petrolatum-based product was the only product to be efficacious for all performance variables. A limitation of some petrolatum-based moisture barriers compared to a non-alcohol barrier film for individuals wearing absorbent pads or briefs is that the petrolatum-based products have been shown to transfer from the skin onto the absorbent product and reduce fluid update by 54% to 90%. [471]. However this has not been tested in clinical trials and the effects of different topical products on the leakage performance of absorbent pads is unknown.

Other practices that may affect skin health include frequency of pad changing. Increasing pad changing may reduce skin wetness by application of a dry pad and may therefore benefit skin health. Increased pad changing is commonly recommended to prevent or treat dermatitis particularly in infants [465] Level of Evidence 4.

a) Quality of data

Several studies of skin cleansing and / or moisturising / barrier products to prevent perineal dermatitis have been limited by being uncontrolled [528-531] and of small size and lacking adequate power calculations [532,533; 468], or not including any clinical outcome
results of barrier products use. In addition there was one randomised crossover trial of pad changing frequency.

b) Results

1. Skin cleansing / moisturising products to prevent dermatitis

Byers et al. [532] compared four different cleansing / moisturising regimes including soap and water using a multiple cross-over design. Despite having a very small sample size (n = 12 elderly women) they found statistically significant differences in TEWL, pH and erythema between some of the regimes, and soap and water was found to be the least effective product for skin health. No clinical outcomes were measured and differences in outcomes were small (Level of Evidence 2).

i) Cleansing products

Cooper and Gray [534] randomised 93 long-term elderly subjects to skin cleansing with soap and water or with a foam cleanser over a 14 day period and blindly assessed perineal skin photographs at zero, seven and 14 days. The skin of 37% of subjects using soap and water remained ‘healthy’ compared to 66% of subjects using the foam cleanser. However, statistical analysis was not carried out (Level of Evidence 3).

Lewis-Byers et al. [518] randomised 32 nursing home residents with incontinence to a soap and water or no-rinse cleanser regime over a period of three weeks. No significant differences in skin condition were found but no power calculations were included (Level of Evidence 3).

Although these studies did not demonstrate robust differences in skin outcomes when using different cleansing regimes, they do indicate other benefits - in particular, that savings in nursing time and care costs may be made [478,518,532,533] and that staff opinion was favourable towards cleansers rather than soap and water.

ii) Costs of barrier products to prevent dermatitis

Zehrer et al. [471] compared the cost and efficacy of three incontinence skin barrier products in 250 nursing home residents from four facilities. A polymer-based barrier film was used either once daily or three times weekly, and one of two petrolatum ointments was used after each episode of incontinence. Residents were monitored for skin damage for six months. There were no significant differences in effectiveness among the various barrier film and ointment protocols of care.

Time and motion measures were used to determine the costs of the products and associated nursing labour. Daily cost of barrier product ranged from $0.17 for the barrier film applied three times per week to $0.76 for a petrolatum ointment applied after each incontinent episode. When nursing staff labour to apply the barrier products was included in the cost analysis, costs increased from $0.26 per day for the less frequently applied barrier film to $1.40 per day for the more frequently applied petrolatum ointments (Level of Evidence 3).

Bliss et al. [472] randomly selected 16 nursing homes to compare the cost and effectiveness of four skin damage prevention regimens. In three of the four skin prevention regimens, a moisture barrier ointment or cream of different compositions (43% petrolatum; 98% petrolatum; and 12% zinc oxide + 1% dimethicone) was applied after each episode of incontinence, while in the fourth, a polymer-based alcohol-free barrier film was applied three times per week. All regimens used a pH-balanced, moisturizing cleanser of the same manufacturer as the barrier. Time and motion measures were documented for the amount of skin care products used, the number, type, and time of caregivers performing IAD prevention care, and the number and type of supplies used. Compared to the three regimens in which a barrier was applied after each episode of incontinence, the use of a regimen in which a barrier film was applied three times weekly had significantly lower costs for the barrier product, labour associated with barrier application, and total cost which included products, labour, and supplies. There were also savings in total product (cleaner and barrier) and total labour costs. The total cost was lowest for the regimen using the barrier film compared to the other regimens in which a barrier needed to be applied after each episode of incontinence. The total cost savings ranged from $0.40 to $0.85 per episode of incontinence (Level of Evidence 2).

Although both these studies demonstrated cost savings when using barrier-film products such savings are dependent on relatively infrequent application of the barrier-film product. This may be achieved by assigning product application to care staff on particular shifts but uncontrolled use of such products may be expensive.

2. Skin products to treat dermatitis

In a double blind controlled trial of 64 subjects, Anthony et al. [535] compared the efficacy of cream formulated to treat dermatitis (Sudocrem) with zinc cream BP. Thirty subjects showed inflammatory lesions of the buttocks and a significantly greater proportion of subjects allocated to Sudocrem showed reduction in skin redness at both seven days and 14 days. No differences were found in the prevention of inflammatory lesions between the two groups. Skin
measurements were made over the ischial tuberosities but the effect of reactive hyperaemia was not accounted for. There was no control group receiving no skin treatment and therefore it was not possible to establish the efficacy of using cream as treatment per se (Level of Evidence 2).

Baatenburg de Jong & Admiraal (536) determined the cost of treating moderate to severe IAD in 39 nursing home patients in the Netherlands randomly assigned to treatment with a non-stinging barrier film or zinc oxide oil. The barrier film was applied every 48 - 72 hours for less severe skin damage and 24 - 48 hours for more severe damage. Zinc oxide oil was applied twice per day and after each episode of incontinence. Both barriers reduced IAD but the non-stinging barrier film was significantly associated with reduced severity of skin redness and skin loss, although skin assessments were not blinded. The cost per day of the nursing staff labour in the regimen using the barrier film was €68.58 (sd = € 23.61) compared to €88.20 (sd = €22.88) in the regimen using the zinc oxide oil. The total cost (including barrier, labor and supplies) per day of the regimen using the barrier film (€76.13, sd = €25.48) was also less than for the regimen using the zinc oxide oil (€102.96, sd = €23.25) (Level of Evidence 2).

3. Pad changing frequency

Fader et al. [491] investigated the effect of different frequency of night-time pad changing on 81 incontinent nursing / residential home subjects from 20 homes. Following a two week baseline period, subjects were randomised by home to pad changing at 22.00 and 06.00 for four weeks followed by 22.00, 02.00 and 06.00 for four weeks, or vice versa. Blinded skin measurements of instrumental erythema (using an erythema meter), visual rating, trans-epidermal water loss and pH were made at baseline and during the last two weeks of each regime with instrumental erythema measurements used as the primary outcome variable. Trans-epidermal water loss measurements were significantly higher when pads were changed less frequently (22.00 and 06.00) indicating that skin was wetter.

No other significant differences were found. However, five subjects developed stage II pressure ulcers in the less frequent pad changing regime compared to none in the frequent pad changing regime. Although more frequent pad changing did not demonstrate less dermatitis / erythema, the pressure ulcer findings - though non-significant - make it unwise to conclude that less frequent pad changing does not damage skin health (Level of Evidence 2).

4. SUMMARY

- Perineal dermatitis is a common problem amongst absorbent product users (Level of Evidence 2).
- Skin wetness overhydrates skin and potentiates the effects of other irritants (Level of Evidence 2).
- Faecal incontinence is more irritating than urinary incontinence, but the combined effects of urine and faeces are particularly damaging to skin (Level of Evidence 2).
- Absorbent pads containing super absorbent polymers are associated with reduced skin wetness (Level of Evidence 3).
- Wet skin is more vulnerable to friction and abrasion injury (Level of Evidence 2).
- Pressure ulcers are associated with urinary and faecal incontinence (Level of Evidence 2).
- Bodyworn absorbent products may raise interface pressures measured under the buttocks (Level of Evidence 3).
- There are indications that skin cleansers may be more cost-effective than soap and water (Level of Evidence 3) and may be better for skin health (Level of Evidence 2).
- Barrier skin products may prevent water penetration into the stratum corneum (Level of Evidence 3).
- A regular and structured skin care regimen using topical preparations such as moisturisers or barrier creams is associated with a low incidence of perineal dermatitis (Level of Evidence 4).
- More frequent pad changing has not been shown to prevent dermatitis, but less frequent pad changes may be associated with pressure ulcers (Level of Evidence 3).
5. RECOMMENDATIONS

- Absorbent pads with SAP should be selected in preference to those without (Grade of Recommendation B).
- Absorbent pads should be changed regularly to minimise skin wetness (Grade of Recommendation C).
- Patients with faecal or double incontinence should be changed as soon as possible after incontinence has occurred to prevent the development of dermatitis from protease and lipase activity (Grade of Recommendation B).
- Patients should be washed gently at times of pad change with either soap and water or cleansers. Cleanser may be less time-consuming than soap and water (Grade of Recommendation C).
- Skin barrier products should be applied to areas that potentially come in contact with leaked urine and/or faeces (Grade of Recommendation D).
- Barrier products may be applied to skin within the pad area to reduce water penetration of the skin (Grade of Recommendation C).
- Buttock and sacral areas should be protected using topical skin barrier products, containment products or diversion devices in patients vulnerable to perineal dermatitis or pressure ulcers (Grade of Recommendation C).
- Cost effective approaches such as those that save nursing time and labour costs are recommended (Grade of Recommendation B).

6. PRIORITIES FOR RESEARCH

Controlled randomized trials that investigate the effectiveness of skin care products to prevent or treat perineal skin damage due to urinary and faecal incontinence are recommended. The studies should determine appropriate sample sizes using power analyses. Analyses need to be powered to distinguish effects on participants with faecal or double incontinence. Objective measures from instruments, standardized clinical assessments, and patient symptom ratings can be included. Comparisons among products of various compositions are encouraged.

XV. ODOUR CONTROL PRODUCTS

Fear of smelling is a major concern that preoccupies many people suffering from incontinence and it is an issue that has been raised in several qualitative studies that have explored the subjective opinion of the patient (eg [537, 538]) (5). Accordingly, there is a demand for products which will mask odour or, preferably, prevent it.

1. PRODUCTS FOR URINARY INCONTINENCE

Fresh, infection-free urine smells only slightly but bacterial action on urea over time yields pungent smelling ammonia.

A variety of anti-microbial solutions are available for washing such products as hand-held urinals or for treating urine spillage onto soft furnishings such as carpets. They aim to prevent smell by destroying the bacteria responsible for break down of urea. There are no robust published studies that have sought to evaluate such products. Another approach is to mask the smell of stale urine using a strong but (hopefully) pleasant smelling liquid. There are no robust published studies on such products either but anecdotal evidence suggests that, in time, the masking smell comes to be associated with the incontinence that it is intended to disguise. Several companies supply products (washable bedpads, carpets, chairs, clothing and bed linen) made with fabrics that have been treated with anti-microbial agents intended to reduce the smell of any urine on or in them. However, again, there have been no robust published studies to investigate efficacy.

One of the 12 disposable bodyworn pads for lightly incontinent women evaluated by Clarke-O’Neill et al. (19) was treated with a lavender scent but it was not found to perform significantly better than the other products in terms of preventing smell. However, the scent was appreciated by 18% of the 50 test subjects, who commented favourably on it.

2. PRODUCTS FOR FAECAL INCONTINENCE

Odour associated with faecal incontinence may occur from involuntarily leaked stool or flatus. In a study with subjects eating a self selected diet, Moore et al. [539] identified the volatile chemicals primarily responsible for faecal odours as the methyl sulphides: methanethiol, dimethyl disulphide, and dimethyl trisulphide. Hydrogen sulphide was thought to make a smaller contribution. In a subsequent study with persons consuming a bolus of pinto beans and lactulose (a non-absorbable carbohydrate) Suarez et al. [540] attributed the odour of flatus to the sulphur compounds, hydrogen sulphide, methanethiol, and dimethyl sulphide. The intensity of the odour in flatus was related to the concentration of the sulphur-containing compounds: the ability of the human nose to recognise malodorous odour appears to be related to the amount of gas expelled [540]. Different states of health and gastrointestinal function, diet composition, relative concentrations of sulphide gases and, possibly, short chain fatty acids or ammonia are expected to contribute to the odour of faeces and flatus [539] and [540].
There are several commercially available devices that are designed to absorb the odour of flatus. One such product originally called the “Toot Trapper” and renamed the “Flatulence Filter” (UltraTech products, Inc., Houston, TX, USA) is a cushion or pad (which can be placed directly against the anus) that is lined with activated charcoal. Both the cushion and pad are encased in either a washable or a disposable cover. There are similar products by other manufacturers (e.g., Flat-D by Flat-D Innovations, Inc., Iowa, USA and GasMedic and GasBGon by Dairiair and manufactured by ECVC, Greenville, NC, USA). Pads comprising fabric covered activated charcoal that can be worn next to the anus or attached to a brief (GasMedic underair pad by Dairiair and Flat-D, Flat-D Innovations, Inc., Cedar Rapids, IA). There is also underwear (briefs) entirely made of covered activated carbon cloth (Underease protective underwear (UltraTech Products, Inc., Houston, TX). Ohge at el. [541] compared the effectiveness of 11 devices containing activated carbon in six normal adults (50% female) under controlled conditions in absorbing odoriferous rectal gases. Five types of seat cushions, four types of pads, and two types of briefs (one that held a pad next to the anus and one made of activated carbon fiber fabric) were tested. A mixture gas comprising 100 ml of nitrogen with traces of hydrogen sulphide (40 ppm), methylmercaptan (40 ppm) and hydrogen (5,000 ppm) was instilled into the rectum of the subjects via a rectal tube. Since hydrogen does not react with charcoal, the amount of unabsorbed sulphide was determined from the ratio of sulphide to hydrogen collected from the pantaloons relative to the ratio in the instilled gas. The subjects wore mylar pantaloons that were sealed at the thighs and waist with elastic bandages to reduce convection to the air. The subjects’ clothing, apart from any device, absorbed approximately 22% of sulphide gas. The cushions absorbed an amount comparable to usual clothing, 20%. The various pads and the brief with an attached pad held near the anus absorbed 55-77% of the rectal gas. The underwear made of charcoal fabric was the most effective and removed nearly all (95-99%) of the sulphide gas. The charcoal fabric briefs are reusable and the charcoal is allegedly regenerable with heat. There are no reports of any odour absorbing devices being evaluated in persons with faecal incontinence. In vitro studies showed that each device had the capability of absorbing the rectal gases and that their performance efficiency depended on contact between the charcoal element and gas. Briefs entirely made of activated charcoal fabric appear to provide the greatest surface area for contact with malodorous rectal gas. The absorption of odorous gas by clothing suggests that washing outer clothing as well as underwear is important to reduce odour.

Some products aim to reduce the amount of malodorous flatus that is produced. Administration of the probiotic, Lactobacillus plantarum, (5 x 10^7 cfu/ml) in a randomized trial of 60 patients with IBS significantly reduced flatulence (by half in 44% of patients). Only 18% of the placebo group reported reductions of flatulence [542]. Although administration of charcoal, yucca and zinc acetate reduced the percentage of episodes of malodorous gas [543], there are inconsistent findings about reductions in flatulence from ingesting activated charcoal in humans [544,545]. Two clinical trials involving small sample sizes (19 and eight persons, respectively ) showed that the over-the-counter product, Beano, which contains α-galactosidase, reduced flatus frequency in normal persons following the ingestion of beans (546;547). A significant reduction in cumulative breath hydrogen excretion over an 8-hour period after α-galactosidase vs. placebo suggests α-galactosidase reduces flatus production [547]. Although Ganiatas et al., 1994 reported a significant decrease in flatus using 240 galactosidic units (GalU), Di Stefano reported that effects of 1200 GalU but not 300 GalU were significantly different from placebo. One GalU is the amount of galactosidase that releases 1 µmol of galactose from its substrate in one minute [547]. Differences in the test diet or lack of adequate statistical power may explain these differences since neither study reported a power analysis. Although a reduction in the amount of intestinal gas produced may decrease the volume of odour, it may not decrease its potency or perceived odour.

A few products are available that aim to prevent, absorb, or control odour associated with involuntarily leaked stool or flatus associated with faecal incontinence. These include cushions and pads that absorb odour as well as probiotics and enzymes, which aim to reduce production of malodorous gas.
3. RECOMMENDATIONS

- Briefs made of activated charcoal fabric are recommended over pads or cushions containing activated charcoal for absorbing odoriferous rectal gas (Grade of Recommendation C).
- Since some pads absorb up to 75% of gas, there may be value in offering patients who have smaller amounts of gas the opportunity to compare pads and briefs for themselves. (Grade of Recommendation D).
- For those persons experiencing stool leakage due to flatus, over-the-counter -galactosidase containing products, which reduce flatus frequency, can be tried in an attempt to reduce FI frequency (Grade of Recommendation B).
- Washing of outer as well as under clothing after flatus is recommended to reduce odour due to absorption of gas by clothing (Grade of recommendation of C).

4. PRIORITIES FOR RESEARCH

- Investigation of whether probiotics or changes in dietary intake can modulate or reduce the odour of flatulence or leaked faeces.
- Development of an absorbent product that can reduce the odour of leaked faeces while protecting the skin.
- Investigation of the efficacy of anti-microbial agents in textile products (soft furnishings and bedding) for reducing odour associated with urinary and faecal incontinence.

REFERENCES

29. Macaulay M, van den HE, Jowitt F, Clarke-O’Neill S, Kardas...


72. Cottenden AM, Rothwell JG, Leander H, Grau C, Brooks


299. Brosnaham J, Jull A, Tracy C. Types of urethral catheters for management of short-term voiding problems in


Committee 21

Continence Promotion, Education & Primary Prevention

Chair
D. K. Newman (USA)

Members
C. H. Ee (Singapore),
D. Gordon (Australia),
V. S. Sriní (India),
K. Williams (U.K)

Consultants
B. Cahill (Australia)
Continence Foundation of Australia

B. Gordon (USA),
Interstitial Cystitis Association, USA

T. Griebling (USA),
K. Nishimura (Japan),
Japan Continence Society, Japan

N. Norton (USA)
International Foundation for Functional Gastrointestinal Disorders, USA
## CONTENTS

### I. INTRODUCTION

### II. CONTINENCE AWARENESS

1. BACKGROUND
2. CONTINENCE PROMOTION PROGRAMS
3. CONTINENCE ADVOCACY

### III. PROFESSIONAL EDUCATION

1. BACKGROUND
2. PHYSICIANS (FAMILY PHYSICIANS/GENERAL PRACTITIONERS/PRIMARY CARE PHYSICIANS)
3. NURSING PROFESSIONALS
4. PHYSIOTHERAPY AND OTHER ALLIED HEALTH PROFESSIONALS
5. IMPACT OF UI GUIDELINES
6. RECOMMENDATIONS FOR PROFESSIONAL EDUCATION

### IV. PRIMARY PREVENTION

1. BACKGROUND
2. POPULATION-BASED PREVENTION
3. RISK FACTORS
4. PREVENTION OF CHILDBIRTH-RELATED INCONTINENCE
5. PREVENTION OF PROSTATECTOMY-RELATED URINARY INCONTINENCE
6. PREVENTION OF URINARY INCONTINENCE IN OLDER ADULTS
7. PREVENTION OF PELVIC ORGAN PROLAPSE
8. PREVENTION OF FAECAL INCONTINENCE
9. RECOMMENDATIONS FOR PRIMARY PREVENTION

## REFERENCES

APPENDIX 1 – DIRECTORY OF CONTINENCE ORGANIZATIONS
I. INTRODUCTION

Continence promotion, education and primary prevention involves informing and educating the public and health care professionals that urinary incontinence and faecal incontinence are not inevitable, but are treatable or at least manageable. In addition, other bladder disorders such as bladder pain syndrome/painful bladder syndrome/interstitial cystitis and pelvic organ prolapse can be treated successfully. Taboos on mentioning disorders of the bladder and bowel are gradually lifting in most cultures. Two decades ago it was almost impossible to have urinary incontinence discussed in the media. Today, in most countries, consensus panels, government funding of continence initiatives and practice guidelines have been developed in the area of urinary and faecal incontinence, and many are referenced in this chapter. Around the world, expert panels have suggested that urinary and faecal incontinence be combined through a multidisciplinary approach to further research priorities.

Thus, there have been advances in promoting awareness of both urinary and faecal incontinence. Popular magazines, local and national papers, radio, and television, regularly cover topics on urinary incontinence in most developed countries. Many countries have run national or local public awareness campaigns, usually spearheaded by a national continence organisation. Many also have confidential help lines, which can be accessed anonymously. The World Wide Web provides a convenient source of health information for a growing number of consumers. Some experts believe that persons with incontinence might get valuable advice and comfort by using interactive services such as the chat rooms on the internet. However, in developing countries, public information and campaigns through these mediums is limited or non-existent.

This chapter updates previous International Consultation on Incontinence (ICI) chapters on three areas: continence promotion, education and primary prevention.

The majority of information available in these areas is on urinary and faecal incontinence which are the primary focus of this chapter. The first section reviews continence awareness by discussing health promotion and care-seeking behaviours for these conditions. It is evident that progress has been made in the promotion of continence on a worldwide basis but not much has changed in help-seeking behaviour for these disorders.

There is a lack of evidence on translating awareness into behavioural change and on what triggers help-seeking behaviour. Information is provided on continence promotion programs and advocacy through service delivery, models of care and worldwide organizations. Although there is a great deal of published information on building public and health care professional awareness of incontinence, there is minimal information on the effectiveness of changing public and professional attitudes and knowledge about it. Documentation of the success of campaigns is lacking and should be measured by behavioural changes and ultimately by improved patient outcomes.

A second topic reviewed in this chapter is the education of professionals in the areas of urinary incontinence, faecal incontinence, pelvic organ prolapse and bladder pain syndrome. The use of medical guidelines and care pathways will be discussed. Finally, as these conditions are prevalent but often ignored by sufferers and professional, the third topic addressed is primary prevention with identification of modifiable risk factors. There is a need for further research to substantiate the benefits of primary preventative strategies, including long term follow-up.
II. CONTINENCE AWARENESS

LITERATURE SEARCH

The online databases Medline, Embase, Biosis, Cinahl, Psychinfo, ERIC and Cochrane were searched, with focus on literatures published in and after 2003. The following search terms were used: awareness, consumer, education, urinary incontinence (UI), faecal incontinence (FI), incontinence, continence, continence awareness, continence promotion, health education, public education, public awareness, pelvic organ prolapse (POP), interstitial cystitis (IC), bladder pain syndrome (BPS), painful bladder syndrome (PBS) and outcome measures. Non-English language papers were noted but excluded from the review unless they contained English-language abstract providing sufficient information.

1. BACKGROUND

For a health-related issue like incontinence, the altruistic reason to educate consumers – referring mainly those with incontinence and their family members or informal caregivers, as well as individuals at risk – must be to increase awareness of incontinence and the benefits of prevention and management, with the noble goals of eliminating stigma, promoting disclosure and care-seeking, and reducing suffering [1]. Much of the health promotion efforts related to continence issues are undertaken by the many non-governmental continence organisations, professional and advocacy groups listed in Appendix I. Although in some countries, there is also strong governmental support, including a national advocacy on achieving an effective health literacy system. Components of such a system involving many levels of educational, health-care, and community service providers have been identified and include: (a) an information dissemination system providing materials that are readable, comprehensible, trustworthy, and culturally sensitive; (b) a coordinated health literacy learning system; (c) a measurement and assessment system; (d) a formal and informal health advice system, including a hotline, handbook, and online support; and (e) a health care professional educational system [2].

Consumer education in terms of having access to information about incontinence in this age of digital technology is a non-issue, especially for those internet users who tend to have a higher literacy level [2]. In light of the reluctance of those affected by stigmatized illnesses such as incontinence to seek treatment or to ask health care professionals for information, the internet may prove to be a useful tool for patient education and public health outreach. [3, 4].

The internet is widely accessible and frequently searched for health information. Recent estimates indicate that around 20% of U.S.A. adults use the internet for health information [5]. Among those who do not use the internet, 60% are aware of publicly available internet access points within their community [6]. Also, the internet can be searched anonymously and informally. People with low levels of education and low socioeconomic status are less likely to use the internet [7]. Health care professionals can assist consumers to find reliable information sources by providing details of reputable web sites [8].

In a national survey of internet users in the U.S.A., [9] Berger 2005, found a trend among people with a stigmatized illness such as UI to more likely report that using the internet increased their health care utilization and communication with a health care provider.

A Google search for “urinary incontinence (UI)” and “faecal incontinence (FI)” yielded about 1.7 million and 62,800 websites respectively; “interstitial cystitis (IC)” - 828,000 sites, “painful bladder syndrome (PBS)” - 38,000 sites and “pelvic organ prolapse (POP)” – 120,000 sites. Many were repetitions. For “continence promotion”, the yield was about 6,450 sites, and for “continence awareness (CA)”, it was about 2,840. There was reference to 114 sites for “continence awareness” and “UI” or “FI”; 35 sites for “continence awareness” and “IC”, and 40 sites for “continence awareness” and “POP”. Many of the sites were related to non-governmental organisations such as the International Continence Society (ICS), the National Association for Continence (NAFC) and the Interstitial Cystitis Association (ICA), and the International Foundation for Functional Gastro-intestinal Disorders (IFFGD).

a) Health promotion

Efforts to promote continence may be enhanced by adopting evidence based theories and methods from the field of health promotion. Health promotion was defined by the Ottawa Charter for Health Promotion in 1986 as “the process of enabling people to increase control over and to improve their health” [10]. Hence, health promotion is an important factor in primary, secondary and tertiary prevention efforts directed at individuals, communities and populations with or at risk of developing incontinence.

Health promotion frameworks can be used to plan and evaluate the effectiveness of strategies and programs used to promote continence. When planning health promotion interventions consideration needs to be given to the demographic features of target groups including age, gender, culture, language and socioeconomic background. Health promotion strategies need to address issues such as accessibility, availability of transport and the cost of health promotion programs [11]. Other considerations include communication strategies. As noted above, there is an increasing trend for consumers to search and obtain information from the internet.
Palmer and Newman [12] reported on a U.S.A. health promotion project conducted in 2000 to determine the needs of senior citizens concerning bladder control issues. Focus groups of older adults attending health seminars in urban, community and church settings were conducted. The primary objective of the project was to determine the understanding of older adults in the areas of general health and their beliefs surrounding the problem of UI. The 82 participants were predominantly African-American women representing all socio-economic levels. Seniors expressed confusion when asked if “overactive bladder, bladder control issues and urinary incontinence” were the same condition. Most seniors said they felt comfortable about discussing bladder control issues, but most admitted that their physician had never asked them, nor had they raised the issue. However, they did discuss UI with family members and friends and they were aware that many persons with whom they socialize might have a problem with UI. The majority of seniors answered “no cure” when asked if treatments were successful.

b) Care-seeking (help-seeking) behaviour

Despite the considerable impact of incontinence on quality of life (QoL), many people never seek help for their incontinence and are thus uncounted [13]. Current research in the area of care-seeking (also referred to as “help-seeking” or health-seeking) behaviour (seeking help from a health care provider or professional) in women with UI has determined that fewer than 38% sought help for their condition, and they waited more than a year to do so [14]. A European survey reported that patients wait from 2 to 11 or more years before seeking treatment [15]. Huang et. al. [16] reported that fewer than 50% of women in the U.S.A. with clinically significant UI reported seeking treatment. This was despite the fact that all women in this study had heath insurance that would pay for services and had continuous access to a primary care provider. Women with stress UI are more likely to seek help when there is severe leakage that is having a significant impact on their QoL [17]. Shaw and colleagues [18] surveyed adult women attending primary care practices in UK and of those who noted UI symptoms (n=3273), only a total of 15.8% of women with stress UI, 32.3% of those with urge UI and 33.7% with mixed UI had sought help for urinary symptoms during the preceding 12 months. This study also found that when women sought help for UI, only one-third will receive appropriate treatment [17].

Men tend to be less proactive in health seeking behaviour. Gender specific strategies to address this should be considered [19]. Men with lower urinary tract symptoms (LUTS) have been found to seek help less frequently than women [20]. Conversely, a study into the prevalence of UI in men in the U.S.A. found that whilst only 50% of men with continence issues sought help, these men consulted their doctor within 12 months of the onset of symptoms [21]. This time period is much shorter than the length of time taken by women to seek help [21]. Men are more likely to seek help for LUTS if they have had advice from others or received information in the media, than seeking help as a result of their symptoms [22].

In a population-based study in Sweden (a supplement to a comprehensive survey of public health and general living conditions), a postal questionnaire comprising 12 questions on UI received a response rate of 64.5% from 15,360 randomly selected residents (aged 18–79 years) [23]. The prevalence of UI was 19% (when defined as “any leakage”) and most considered their problems to be minor. Only 18% of those with UI desired treatment. Of the 17% who had reported severe problems that interfered with daily life, 42% did not want treatment. The authors suspect that lack of knowledge, worries about different procedures and negative expectations may be important factors. They concluded that UI may not be an unrecognised major problem except for a limited group, and suggested that healthcare resources should be optimized to identify and meet the needs of those who are most afflicted.

Muller [24] reported on several epidemiologic surveys conducted over a 5 year period by the U.S.A. continence advocacy group, the NAFC. These surveys indicated that UI and overactive bladder (OAB) are prevalent problems and that most people do not understand these conditions. In one survey, conducted in 2000, only 26% of respondents (18% of men and 33% of women) reporting bladder control symptoms had discussed them with a doctor. This survey attempted to examine bathroom-related attitudes and behaviours and found that most feel the bathroom is a “haven” for refuge while others feel it represents a symbol of incarceration because of the preoccupation with the need to be near one frequently.

Bathroom privacy, cleanliness and ease of accessibility were voiced as concerns with only 20% of respondents noting that they are comfortable using a bathroom outside their home. A second survey by this group was conducted online (over the internet) and includes 1,025 interviews of U.S.A. adults (ages 30 to 70). This survey showed that women wait longer (average 6.5 years) than men (4.2 years) to seek out a diagnosis for their symptoms.

Barriers to seeking help for continence issues have been frequently identified in the literature and include embarrassment, social stigma and the mistaken belief that incontinence is either inevitable, untreatable and a normal part of aging [25]. Women with POP have also reported that fear and embarrassment are barriers to seeking help. Other barriers include the perception that incontinence and LUTS are not serious [26]. However symptoms such as nocturia have been linked with serious consequences such as falls and associated morbidity in older adults.
Bladder and bowel continence is an adjustment to the social norm, especially in Western cultures, which have developed acceptable rules and behaviour for bladder and bowel emptying. [27, 28] If incontinence occurs in adulthood, persons revive those childhood beliefs and begin to internalize their condition causing a decrease in self-esteem and feelings of not being “normal” [29]. These barriers are shared by the public as well as by many health care providers [30]. Unfortunately, factors that promote health seeking behaviour for continence issues remain less well researched and the triggers for help-seeking behaviour are complex and multifactorial. With chronic problems like UI, FI, POP and BPS/IC/PBS, it is important to understand what triggers the patient to consult a health care provider [28]. Older people may be keen to seek help if they are concerned that a health issue such as incontinence impacts on their ability to remain independent and living in the community [31].

In certain parts of the world, the gender of the person with UI may be a factor in help-seeking behaviour and the gender of the health care provider may be a barrier. Doshani and colleagues [32] explored views and experiences of South Asian Indian women with UI and found that feelings of embarrassment were present, especially with male health care providers.

Rizk [33] identified reasons why women in the United Arab Emirates (UAE) were not seeking medical help for UI. Data from questionnaires was collected on 400 women (mean age 54.2) out of 448 enrolled subjects and noted that, 81 (20.3%) admitted UI and only 25 of these (30.9%) had sought medical advice. The reasons were embarrassment (38.2%), choice of self-treatment because of low expectations from medical care (38.2%), preferring to discuss the matter with friends, and assuming that UI is normal (23.3%). Women with UI were troubled by their inability to pray (90%) and to have sexual intercourse (33.3%). Saleh [34] found similar results when surveying women in Qatar who reported that UI interfered with their ability to pray (64%) because of lack of cleanliness and need to void and 47% reported that UI interfered with marital relationships.

Rizk and colleagues [35] also investigated the prevalence and help-seeking behaviour of women (n = 400, mean age 37.9) with FI using the same method. Fifty-one participants (11.3%) admitted FI; 26 (5.8%) were incontinent to liquid stool and 25 (5.5%) to solid stool. Thirty-eight patients (8.4%) had double (urinary and fecal) incontinence. Sixty-five patients (14.4%) were incontinent to flatus only but not to stools. Only 21 (4.2%) admitted FI; 26 (5.8%) were incontinent to liquid stool and 25 (5.5%) to solid stool. Thirty-eight patients (8.4%) had double (urinary and fecal) incontinence. Sixty-five patients (14.4%) were incontinent to flatus only but not to stools. Only 21 (4.1%) had sought medical advice. Women did not seek medical advice because they were embarrassed to consult their physician (64.7%), they preferred to discuss the difficulty with friends, assuming that FI would resolve spontaneously (47.1%) or was normal (31.3%), and they chose self-treatment as a result of low expectations for medical care (23.5%). Women with FI were bothered by the inability to pray (92.2%) and to have sexual intercourse (43.1%). These studies note that both UI and FI are common yet underreported by UAE women because of cultural attitudes and inadequate public knowledge. These authors felt that male provider gender may also be a barrier to seeking health care in Middle Eastern women with UI. They were also surprised to find that women perceive their problem to be a neurological or “senile” disorder rather than related to childbirth or menopause.

There are several strategies that can be used to promote help-seeking behaviours and they need to include those that are culturally appropriate [36, 37]. Minority and disadvantaged groups have lower rates of health seeking behaviour for UI that may relate to a number of factors such as access to care and socioeconomic factors [38]. Understanding the reasons why people do or do not seek treatment for incontinence is hampered by the ethnic homogeneity of the existing data as most is derived primarily from white Caucasian populations and there is a lack of comparisons with ethnic minority populations.

Factors that enhance or enable people to change health behaviours include advice given by physicians [39]. Opportunities to promote continence can present themselves during other health screening activities such as cervical cancer screening [40]. Whilst health care professionals may enable people to seek help, those who have a lack of interest in incontinence can negatively affect health seeking behaviour in consumers [41, 12]. Other initiatives to promote health seeking behavior can include providing written information [42]. Continence health promotion information provided in a brochure [43] and in a computer based program [44] were found to improve health seeking behaviour.

Language, level of education and cultural factors may also be barriers to seeking help [45]. Consideration should be given to health literacy in target populations. Health literacy affects the ability to read and understand health information in written formats. Poor health literacy results in lower rates of health seeking behavior [46].

One of the most supportive government sponsored initiatives is from Australia. The National Continence Management Strategy (NCMS) was established in 1998 by the Australian Government Department of Health and Ageing. Funding of over $33 million AUD has been allocated for the period from 1998 – 2010. More than 120 projects have received funding for research, public awareness activities, continence education, resource development and continence service development. The Strategy is now in its third phase of activity. A final evaluation report on Phase 1 and 2 of the NCMS was released in September 2006 [47, 48]. In the area of continence awareness,
the report noted that recognition of the barriers to help-seeking behaviour and identification of the most appropriate terminology and key messages would strengthen awareness raising strategies. The provision of an incontinence specific helpline (the National Continence Helpline) has been an important awareness raising initiative. Table 1 reviews the specific programs developed and implemented by the NCMS.

2. CONTINENCE PROMOTION PROGRAMS

Continence promotion programs vary across countries and cultures, but the singular aim of creating awareness is similar. There is no standard model, nor is there a standard outcome measure to determine the effectiveness of the program. While the current level of evidence for effectiveness of continence promotion program in raising awareness generally is level 4, there is a need for research to provide a higher level of evidence to affirm its effectiveness to generate higher interest and support.

Efforts to raise awareness of continence issues need to consider the following:

- **Target population** - Continence promotion programs need to consider age, gender and culture of target populations. It is necessary to consult with target groups when planning programs in order to meet the needs of these groups and to enhance help-seeking behaviour [49].

- **Target issues** - A continence promotion program needs to address risk factors and management options in different target groups.

- **Promotional material** – Newman [50] reported on a mail survey of 1,500 women, noting that most of the 422 respondents wanted more information regarding UI, and while they may not be equipped to fully understand the problem, they expect doctors, nurses, medical professionals, retail outlets, medical supply companies, and mail order houses to provide the information, including information through consumer advertising.

- **Channels of communication** – Health care professionals may launch campaigns or seminars to increase practice revenues. Commercial companies often fund public campaigns in order to sell their products. Continence organizations may be driven by missionary zeal or organizational growth. Regardless of motivation, care should be taken to avoid raising public expectations beyond what the services or products can deliver. Individualised “coaching” of the affected is one key channel that continence nurses use in the promotion of continence [51].

  a) **Creating public awareness**

In the area of UI, building awareness among the general public is usually attempted via the media.

<table>
<thead>
<tr>
<th>Table 1. NCMS Continence Awareness Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Program</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Bladder and Bowel Health website</td>
</tr>
<tr>
<td>Continence Outcomes Measures (COMS) Dissemination Project</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>National Men's Continence Awareness Project</td>
</tr>
<tr>
<td>Pharmacy Continence Care Project</td>
</tr>
<tr>
<td>Daily Living Self Management Resources</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Using the media to disseminate information in the form of Public Service Announcements (called PSAs) has been practised extensively in the U.S.A. to promote AIDS awareness and as anti-smoking campaigns. The U.S.A. National Institutes of Health, in partnership with the American Uro-Gynecologic Association, American Urological Association, American Foundation for Urologic Disease, National Association For Continence, Society of Urologic Nurses and Associates and the Simon Foundation for Continence, launched a national awareness campaign in 1997. The Let’s Talk About Bladder Control for Women awareness campaign (http://kidney.niddk.nih.gov/ kudiseases/ pubs/bcw_ez/index.htm) offers easy-to-read booklets explaining the symptoms, types and causes of poor bladder control, as well as treatment options. The materials are designed to encourage and enhance communication between and among women and their health care providers. Free consumer and health care provider kits are available through a toll-free phone number. In 2001, the NAFC in the U.S.A. produced and disseminated continence awareness PSAs to 380 television media markets, including Hispanic outlets.

In many cultures, one of the best vehicles to reaching the public is through an informed journalist. Journalists often use a “media hook,” an interesting story that will take priority over other news on the television, radio or newspaper. Having a spokesperson with the problem or finding a celebrity who is willing to speak for the cause can help [27]. These individuals can act as “influence leaders.”

The Japan Continence Action Society held a “Toll Free Telephone Clinic” and callers were asked how they heard about the line. The responses in 2006 were: 30% from television, 16% from the web, 11% from a newspaper, 9% from a book, 6% from a friend, 5% from a brochure, 3% from a magazine and 20% others and/or unknown. In a UK campaign, Norton [52] found that newspapers were by far the most common source of information, followed by radio.

A media campaign should use multiple channels to ensure the broadest coverage [53]. An initial channel should include print media, television and radio. The Internet, phones, and other mobile devices are also effective outreach channels [54]. A second channel could be specialised age and health publications. A third channel could be the use of posters and brochures placed in medical offices, hospitals, senior’s centre, pharmacies and churches. A final channel could be direct presentations to the public, such as at senior’s centres [55].

Roe [56] suggested that local initiatives on the availability of services and how to access them, as well as health education information on UI, may be more effective in raising public awareness and should supplement national campaigns. Awareness raising materials include pamphlets, self-care instructions, visual aids, pictographs, posters, banners, decals and advertisements in newspapers, magazines, newsletters, CD and films. Muller [57] believed that the change related to increased public awareness and help-seeking behaviour for continence care is likely to fuel the demand for innovation in technology and products. The Simon Foundation for Continence developed an innovative community education initiative The Bladder Health Mobil. This initiative provides education, increase public awareness, and promote early diagnosis and proper treatment of UI and other bladder control problems. It also facilitates dialogue between consumers and their health care professionals [58].

Terminology used when discussing urinary and bowel incontinence is important. The words “continence” or “incontinence”, “interstitial cystitis” or “painful bladder syndrome” and “pelvic organ prolapse” are poorly understood and simpler terms may achieve greater public recognition in many languages and cultures. The use of “overactive bladder” in advertising has increased reporting of the condition to primary care professionals in the U.S.A. In the area of bowel disorders such as FI, it is felt that people find it difficult to find the right words to discuss their symptoms [27]. The International Foundation for Functional Gastrointestinal Disorder (IFFGD) in the U.S.A. has found that people will often report having diarrhea to their physician. If the physician or nurse does not question the patient any further regarding the ability to control gas, liquid or solid stool, the incontinence may not be discovered.

**b) Program evaluation**

Evaluation methods need to be established prior to developing the continence promotion program. Evaluation should include quantitative measurements and qualitative measures. Open-ended questions may be more sensitive than “direct satisfaction” questions [59, 60].

Health promotion evaluation methods include process evaluation, impact evaluation and outcome evaluation. Evaluation measures can include the number of media responses to a media release, or numbers of people who sought help.

In the evaluation report of the Australian NCMS, a total of 16 projects were undertaken for raising continence awareness, with focus on the development and distribution of information resources for use by the general community and specific target groups [47, 48, 61]. As of June 2006, a market survey found that 9 of the completed projects with measurable outcomes had generally shown favorable outcome.

Evaluation of the effectiveness of leaflets or brochures is gathering better evidence. An Australian study found that provision of a continence education package, which included a Continence Educational Brochure...
helped to improve the health-seeking behaviours of participants who were bothered by UI symptoms [62]. Within 3 months following the education, of the 111 participants who were bothered by UI symptoms, 49 participants (44.1%) indicated that they had discussed the issue of bladder or bowel problems with someone directly because of the study or the information contained in the brochure. More than 94% of participants who remembered the brochure indicated that they believed it would be helpful if given to other people. In a study of 1175 participants, Wagg et al [63] reported that a self-help standard treatment leaflet is as effective as structured help from a continence nurse in reducing bothersome urinary symptoms in women. Similarly, a Swedish population-based study found that the distribution of a brochure on UI to the general public was well received and can be an efficient method to spread knowledge and encourage self-management [64].

The interventions that are most effective in reaching the public and triggering the desired behaviour seem to vary between countries and cultures. Television and newspapers work best in Singapore, with a “cured” patient bearing testimony to former suffering and its alleviation having the most impact. In the U.S.A., television advertising targeting OAB, funded primarily by pharmaceutical companies, has yielded a significant response. Nationwide television reaches more people than the circulation of any single newspaper or the distribution of a booklet through physician offices. In March 2008, Japanese National Television broadcast a program about UI during “golden time” (2000 to 2045 hours). The audience rating was 15.6%, the highest in a year (usual rating 12%), and more than 500 calls were received in one night, requesting repeat broadcast and more details about treatment. There are also cultural differences in the online health information is used, as well as the types of sites users prefer to surf [54].

In France, the effect of health education was evaluated in a randomized study in sheltered accommodations for the elderly [65]. Twenty centers were randomized to either a single one-hour health information meeting or control group. During a 30-minute talk, a nurse encouraged people to visit a physician if they had urinary problems. A questionnaire three months later found that the experimental group was much more likely to have had treatment if they were incontinent (41% vs. 13% controls) and 82% said that they had received some information about UI in the previous 3 months (compared to 22% controls).

A health promotion project called ‘Dry Expectations’ was developed and implemented in six ethnically diverse, predominantly minority, and inner city senior centres in the U.S.A. in 1996 [55]. The program was designed to address an older population. The project consisted of three phases: orientation and training of key staff members/peer educators at the centres (train-the-trainer model); educating seniors through four one-hour weekly sessions involving visual aids and completion of bladder records and quizzes; and follow up sessions with senior staff/peer educators to reinforce the previous training. The program was very well received by the participants, and approximately 80% felt they had more control over their bladder by the end of the last session.

The impact and success of any continence promotion program must surely be its sustained effectiveness many years down the road, be it for primary prevention or treatment. A randomized controlled study of 359 community-dwelling older women showed that group instruction supplemented with brief individual instruction as needed is an effective teaching method for the acquisition of knowledge and motor skill in bladder training (BT) and pelvic floor muscle training (PFMT). The 1 year adherence following a behavioural modification program ranged from 63 to 82% for PFMT and 58 to 67% for BT [66]. Adherence is reduced over time and the marked benefit of intensive PFMT seen short-term may not be maintained and the long-term adherence to training can be low [67].

c) Recommendations for Continence Awareness and Promotion

Based on the literature reviewed in this section, the following recommendations can be made:

- Continence awareness should be included in any national advocacy program that is working towards an effective health literacy system, as it is consistent with and requires the involvement of many levels of educational, health-care, and community service providers, namely a(n):
  - Information dissemination system providing materials that are readable, comprehensible, trustworthy, and culturally sensitive;
  - Coordinated health literacy learning system;
  - Measurement and assessment system; and
  - Professional health care provider learning system. (Grade D)

- Continence awareness should be part of the main stream and on-going health education and advocacy programs with emphasis on eliminating stigma, promoting disclosure and help-seeking behaviour and improving quality of life. (Grade D)

- There is a need for research to provide higher level of evidence on the effectiveness of continence promotion programs to increase awareness, be it for primary prevention, treatment or management. (Grade D)
There is a need for research on the most effective means to educate the public and professional groups on continence issues. Specifically, there is need for research on:
- Identification and understanding of barriers to health-seeking behaviours
- Translation of research into improved clinical practice and identification of methods by which this happens.
- Effectiveness and impact of consumer education initiatives.

(Grade D)

3. CONTINENCE ADVOCACY

Advocacy is defined as act or process of defending or maintaining a cause or proposal. Advocacy, as it pertains to incontinence, involves assisting individuals in finding necessary health care and treatment. Organisations consisting of professional and public members promote continence advocacy as a core mission.

a) Service delivery

The provision of continence care and services in each country will depend on the organisation and infrastructure of its health services. It is difficult to make recommendations that will apply in such a variety of contexts. In addition, UI is so widespread and affects so many different types of people that they can present for help to literally any health care professional. This means that there will seldom be one portal of entry to a continence service.

When new services are created, there is a temptation to focus on the high technology investigation and medical treatment elements without considering the infrastructure needed to support that service [68]. However, there has never been a comprehensive examination of an optimal service. It is not known whether academic, specialist-led centres will achieve better and more cost-effective results than primary care clinics, domiciliary services or any other model. However, most experts believe that female UI is initially most effectively diagnosed and managed by primary care providers compared to specialist services.

In 2000, the UK’s Department of Health issued guidance on continence services that outlined a good practice model to achieve more responsive, equitable, effective continence services [69]. In the U.S.A., the primary sources of care for the majority of Medicare patients (primarily an elderly population) are family physicians and primary care physicians [70]. Less than 1 person in 1000 is admitted to an academic, medical centre hospital [71]. Thus, in the U.S.A., elderly persons with UI and FI will probably be seen by primary care physicians for initial assessment. This is unlikely to address the needs of developing countries (such as the Asia Pacific area or in Africa) where dissemination of expertise to rural communities and isolated community health care workers is more logical. They are being implemented in several countries using shared teaching and educational resources through co-operative arrangements of the respective Continence Foundations. Thus, the general practitioner or family physician plays an important role in the first line treatment of UI that may be treated successfully with conservative treatments in the majority of patients [72, 73].

In some health systems, both UI and FI have traditionally been seen solely as a nursing problem, with little interest or input from other members of a multidisciplinary medical team. Except for a few isolated areas, the main intervention has been trying to help the individual and caregivers cope with symptoms rather than attempting to treat the underlying cause of the UI. For example, in the UK, it is common for an elderly person presenting with UI to be referred directly to the district nurse “for assessment for pads and pants,” with no physical examination or further investigation considered.

In fact, UI is often a complex and multi-faceted problem, particularly in frail or dependent individuals, and it may require input from a wide variety of disciplines to tackle it effectively. Symptoms typically associated with incontinence may also be indicative of other conditions as evidenced by the urgency and frequency symptoms of BPS, also referred to as IC and PBS, a chronic inflammatory condition of the bladder [74, 75]. The ICI Committee 19, addresses bladder pain syndrome. While it may not be practical for all specialties to work in close proximity, there is a need to consider carefully who does what, with protocols to guide appropriate referral and ensure good liaison. It is important that there are neither gaps, nor overlaps, in the service.

In countries such as Australia, New Zealand and the UK, where there is a national network of Continence Nurse Advisors (CNAs) or Continence Nurses. These nurses liaise, integrate services, and guide individuals through the referral route most appropriate to their individual needs.

The efficacy of Continence Nurse Practitioners (CNPs) in the UK was reported by Matharu and associates [76] who studied four hundred and fifty (450) women over 40 years of age who underwent urodynamic studies in the UK after seeing a trained CNP. In patients diagnosed with detrusor overactivity, the CNP had prescribed 79% to have drug therapy and 64.8% to have PFMT. In those with urodynamic stress UI, 88% had appropriately been assigned to have PFMT. Nursing assessment has the potential to assign patients to the correct conservative treatment thereby shortening waiting times for urodynamics and specialist assessment.
Shaw, Williams, and Assassa [77] conducted a postal survey of people in the UK receiving services for UI by CNPs. Participants expressed satisfaction with nurse-led services because of the interpersonal skills, technical skills, and communication and information-giving abilities of the nurses. There is more evidence that treatment of incontinent community-dwelling individuals by a “continence nurse” is beneficial in terms of clinical outcomes [78]. Although some might see multidisciplinary working as the ideal, the reality is not always smooth. In some situations, rivalries and competition between disciplines and medical specialities is evident. This may be because of competition for patients and revenue, or because of disputes over the demarcation of the scope of different disciplines (such as the boundary between urology and gynaecology, or between nursing and physiotherapy).

There are no studies directly comparing the effectiveness of specific delivery systems for continence care. In certain cases, enthusiasts have conducted research and results may not generalize to the wider setting. Others have combined the expertise of multidisciplinary teams to maximize service delivery. The level of evidence on service delivery models is 4.

i) The need for service

As discussed at the beginning of this chapter, the majority of people (60-70%) who admit to UI in prevalence surveys do not seek professional help [13, 71, 79]. Not all incontinent people want or need help, and this may vary considerably between different cultures. For example, a postal questionnaire asking about urinary symptoms found that nocturnal problems caused the most bother (69% were bothered by nocturnal enuresis, 63% by nocturia). Only 50% found stress UI a bother and only 56% were bothered by urge UI [80]. A community based study found that only 15% of severely incontinent women (daily incontinence requiring protective pads most of the time) were worried about it, 15% felt that their activities were restricted and the majority seemed able to cope [81]. Overall, 78% were not worried by their incontinence and the authors suggested that services should be targeted towards the minority who do find it a problem. In Japan, it has been found that 55% of elderly incontinent people do not consider incontinence a bother, but 15% did not leave home, 10% found it difficult to leave home, and 10% felt that they caused bother to family and neighbours [82]. However it is pertinent to note that, there is significant underreporting by patients of UI and the severity of symptoms [83]. It is also evident from this data that the burden of incontinence, is responsible for 20% of healthy life lost for 75 year olds and older [84] and has the third highest impact on QoL of major chronic conditions [85].

A Japanese survey of over 1,000 caregivers of elderly incontinent people in the community found that more than 80% of caregivers are female and over half were more than 60 years old [82]. The caregivers felt that incontinence caused problems with the home getting dirty (10%), extra laundry (9%), need to wake at night (7%), and not being able to go out because of incontinence (9%). When asked what kind of government service they wanted, caregivers replied “health training” (10%), “knowledge about incontinence” (10%), and “supply of a portable toilet” (3%). Only 6% wanted the government to send them professional caregivers and only 4% desired referral to a specialist physician.

Incontinence is responsible for up to 30 - 50% of admissions into nursing homes, often precipitated by the burden of care on caregivers who spend half of their care-giving time providing personal care such as toileting assistance [86]. Some people seem to cope better than others with symptoms, and some had coping strategies, which were easily undermined by any suggestion that professional help was required [87]. Few people seem prepared to take action to prevent UI.

This can create a dilemma and raises many questions. Should health care professionals attempt to persuade or educate people who do not see UI as a problem that it is an abnormal condition? Should a patient who is “not bothered” by symptoms be treated because the partner or caregiver requests the physician’s assistance? This may be of concern, as Rodriguez, et al. [88] found that physicians underestimated the degree to which patients were bothered by their symptoms 25% to 37% of the time. Is lack of bother genuine or simply a defense against having to tackle an unpleasant problem? Does early intervention prevent later deterioration in symptoms? Does delay in treatment mean that success rates are lowered? There is scant evidence on any of these issues, or on the most acceptable way of providing help.

It is the impression of all members of this committee that, specifically for the field of UI, due to the high percentage of people not seeking help (for all the above mentioned reasons), that health care professionals must develop a concept of a “reaching-out” service and to actively provide service for incontinence care, meaning promoting awareness, openly discussing and actively detecting UI and providing simple and efficient therapy.

b) Models of continence care

Continence care was defined by the Canadian Continence Foundation as “all measures directed toward the prevention, improvement and or management of urinary incontinence” [89]. In this chapter, anal and faecal incontinence will be included within the concept of continence care.
As noted above, continence care is well suited to management in the primary care setting. A range of models are described below.

1. **Single Specialist Model** - This is a service led by a consultant or specialist physician (urologist, gynaecologist or urogynaecologist), often focused around an “urodynamic unit” providing medical or surgical treatment. This is the most common model in developed countries; the best of them have a nurse continence advisor or continence nurse specialist as an integrated part of the service.

   In some countries, physiotherapists (PTs) have also developed a specialized practice with incontinent patients. In France, all women, after childbirth, are entitled to a maximum of 10 sessions of pelvic floor muscle physiotherapy, paid for by the government. In Australia, Scandinavia and the UK, research on PFMT has been led by PTs. However, there is a lack of consensus as to best practices for UI. In a postal survey of British PTs, many were providing specialized service. Gynaecologists were the most common source of referral. The majority said physiotherapy was the first line of treatment. Pelvic floor muscle exercises and electrical stimulation were the most used modalities. However, there was little consensus about optimum treatment regimes amidst a wide variety in the details of therapies used [90].

2. **Nurse Continence Advisor Model** - The nurse continence advisor (NCA) may be independent but is usually associated with community/area health centres, where they may have variable professional support from general practitioners (GP) and family physicians. Continence nurses often work in both hospital and community, and the service is focused on primary care, particularly district nurses. Key roles include patient assessment and implementation of conservative management strategies where appropriate and facilitating patient access to incontinence product subsidies or schemes.

   The Department of Health in the UK has commissioned an evaluation of different models of nursing services, with and without specialist NCAs. It was found that where there is a continence nurse, incontinent people are more likely to receive targeted referral to specialists such as an urologist, and are more likely to have had investigations such as urodynamic testing and to receive more appropriate treatment and care for their UI. These patients were also more likely to report satisfaction with the service. In contrast there is still concerns that general nurses continue to “contain the problem” instead of promoting continence despite acknowledging its importance [91].

   In a series of studies performed in Leicestershire UK, the short and long-term outcomes of a new CNP-led service for urinary symptoms (3 and 6 months after implementing the program) were examined and evaluated [87, 92, 93]. Williams, et al. [93] reported on a randomized, controlled study of 3,746 community-dwelling individuals greater than 40 years of age (61% women) who had incontinence, frequency, urgency, and nocturia all impacting QoL. The experimental group was comprised of 2,958 patients. The standard care was the control group (n=788) who accessed GP services and existing continence services in the area. The experimental group received an 8-week primary intervention package by the CNP (21 generalist nurses who trained as CNPs), delivered evidence-based behavioural interventions using predetermined care pathways in four visits over an 8-week period. Interventions included advice on diet, fluids, BT, pelvic floor muscle awareness and healthy eating. Individuals whose symptoms persisted after primary intervention were offered urodynamic testing. The CNP led service had a 10% higher cure rate than standard care with statistically and clinically significant reductions in urgency, frequency, nocturia and UI. In addition, QoL improvements were greater in users of the CNP led service and higher levels of patient satisfaction were achieved. This is the first study to show the effectiveness of nursing services on urinary storage symptoms (rather than simply incontinence) and associated QoL. The authors noted that the public health value of a 10% reduction in symptoms is substantial when applied to such a common problem.

   A similar RCT in Australia compared outcomes in 145 women presenting with stress UI, with or without urge UI, randomly allocated to a standardised regimen with the NCA or treatment by an urogynaecologist [94]. After 12 weeks, 110 women were evaluated. Sixty-four percent (n=58) of the NCA group and 52% (n=52) of the urogynaecologist group were asymptomatic with a dry pad test. There were no significant differences between the groups for incontinence scores, pad test changes, voids/day or scores on Urogenital Distress Inventory or Incontinence Impact Questionnaire. The treatment by the NCA took a median of 160 minutes, but cost AUD59.20 compared with 90 minutes of gynaecologist time at a cost of AUD189.70. At 2.5 years, 29% of the NCA group and 41% of the other group were dry. The authors concluded that similar results were achieved at lower cost using the NCA.

   An additional number of studies support the efficacy of specialist NCA in the delivery of community continence care [72, 95, 96]. In the U.S.A., urology nurses have been trained as “teachers” to successfully implement behavior modification program to groups [97].

   In the U.S.A., there has also been an increase in nurses who specialize in dealing with patients with pelvic floor disorders including UI, FI, POP, and BPS/IC/PBS, although there are no academic or clinical proficiency requirements in order to be considered a CNP or “continence nurse specialist.” Those nurses who do specialize in continence care have obtained their knowledge and skills through self-
motivated activities [98]. Masters prepared or educated “advanced practice nurses” (APNs) have become increasingly interested in and knowledgeable about the assessment, diagnosis, and treatment of people suffering with UI. These nurses are developing a nursing subspecialty in the care of individuals with UI and related pelvic floor dysfunction and provide comprehensive assessment and treatment (drug and conservative therapy) and act as educators and researchers [25].

A 2000 study in the U.S.A. demonstrated significantly improved outcomes for three clinical problems: UI, depression, and pressure ulcers when advanced practice gerontological nurses (APNs) worked with nursing home (NH) staff to implement scientifically based protocols [99]. In addition to working with NHs to provide resident evaluation as physician extenders, this research indicates that this service model using an APN can be an effective link between current research based knowledge about clinical problems and NH staff. This study also showed that consistent educational efforts with staff and NH residents demonstrated that interventions could improve or stabilize the level of UI in these individuals.

In some countries the NCA is attached to a district nursing service providing expert advice and support for non-specialist nurses with patients who have continence problems.

3. MULTIDISCIPLINARY RESOURCE AND REFERRAL CENTRE MODEL - Multidisciplinary clinics, as service models, have been shown to provide comprehensive continence care. In multidisciplinary clinics, such as a “Pelvic Floor Clinic”, gynaecologist, urologist, colorectal surgeon, and continence nurse work together [100]. Some pelvic floor clinic staffing models also include physical therapists and registered dieticians.

An Australian study took all community referrals of those who had been incontinent for at least two months and had at least one episode in the preceding 2 weeks to a continence clinic. [101]. Patients were randomised to conservative treatment or control, with a crossover design. Patients were asked subjective questions about embarrassment, odour, depression, family relationships, isolation and laundry on a 4-point scale ranging from no effect to major effect upon life. The questionnaire was completed at the start, and at 2, 4, 8, and 12 months. Seventy-eight patients entered the study: 87% improved with treatment (vs. 41% controls). Fifty-two percent were moderately or severely embarrassed at the start of the study period, but at 4 months, only 17% were. Depression decreased from 49% to 22% and isolation from 28% to 12%. Odour and the use of extra laundry also decreased. All benefits were maintained at 12 months. Controls did not improve on these items until crossed over to active treatment, despite feeling better. The authors conclude that conservative treatment in a multidisciplinary community clinic improves continence and well being.

The Continence Foundation of Australia is funded by the Australian Government to employ continence nurse advisors in the National Continence Helpline to provide advice to consumers and health professionals, including referral advice. Evaluation of the helpline by Deakin University showed the majority of callers took action to improve the incontinence issues they enquired about and, the most common course of action following the phone call was to change how they dealt with incontinence [48].

An expansion of this service provision is exemplified by the National Centre for Continence in Israel, which aimed to provide an integrated service [102]. The Center’s professional team not only treats incontinent patients but also educates GPs and nurses who come from pre-selected peripheral/outlying clinics, and provides ongoing support and advice as well as a pathway for tertiary referral. A local team (GP and nurse) are also selected to be in charge of promotion, detection and treatment of incontinence at the clinic. They later become “in charge” of incontinence in their region. This model allows national distribution of continence services with support from the resource centre and provides interdisciplinary exchange, as well as, maximum co-operation between Medical Centres and community health services. The national centre is funded by government and industry to provide a “Hotline” for the public, to promote education programmes in nursing and medical schools, hospitals and nursing homes, and to develop guidelines for diagnosis and management of incontinence by primary healthcare staff.

A report on continence care services worldwide noted that services were scattered, inconsistent and considerable discrepancies exist in their funding. It was concluded that there is a need for accessible (and affordable) continence care and multidisciplinary teamwork [103].

4. PRIMARY CARE MODEL - There are many factors that can persuade health care planners about the importance of adequate investment in community continence services: the prevalence and the number of incontinent people is likely to increase with an aging and increasingly dependent population and many frail, disabled or elderly people are incontinent for reasons extraneous to the urinary system (such as poor mobility, an inappropriate physical environment or lack of an individualised care regime). It is often best to provide an initial assessment for such individuals in their usual surroundings and to reserve hospital or clinic (specialist or academic) referral for those who do not respond to simple measures such as treatment of constipation, modifying a diuretic medication, or provision of accessible toilet facilities. A number of guidelines have suggested an algorithmic, step-wise
approach to assessment and treatment of urinary incontinent patients and many conservative treatments have a good success rate in primary care [104, 105, 106, 107, 108].

A New Zealand study of 600 family physicians found that most respondents provided continence care and 2.6% offered special clinics for continence promotion [109]. Fewer than half felt confident to diagnose the causes of incontinence. Confidence in managing incontinence in children was consistently lower than for other childhood problems. There was no difference by sex in confidence, although female respondents were more likely to consider management of continence care as part of a practice nurse’s role and to routinely ask women about UI during a ‘well’ visit. Most respondents (71.9%) could not remember having had any formal training in the management of incontinence either at the undergraduate or postgraduate level. Recall of postgraduate education was associated with greater levels of confidence in management of incontinence problems.

Family physicians have been shown to be successful in treating UI. A UK study examined assessment and treatment of 65 women, who were treated according to their type of UI [110]. Those with stress UI were treated by PFMT, those with urge UI by BT and medication, and those with mixed UI by both. Patients with stress UI or urge UI, but not mixed, improved compared to controls at 12 weeks. A Dutch study of 110 women reporting UI to a family physician was randomly assigned to the treatment or control group. Treatment was PFMT for stress UI and bladder training for urge UI [81]. Patients were interviewed at 3 and 12 months, with crossover at 3 months for controls. At 3 months, 60% were dry or only slightly continent. Mean wet episodes were down from 27 to 5 per week. Seventy-four percent felt improved or cured and there was further slight improvement at 1 year.

A study in a community clinic in Israel showed that after training, family physicians detected 98 patients with UI during a period of 19 months [111]. Mean age of the 94 females and 4 males was 71 years (range 56-89). Most patients (53) were detected by the physicians on direct questioning, some by nurses (29) and only 18 by self-referral. After a mean follow up of 10 months, 35 were dry and 32 significantly improved. Cure or improvement was achieved at the clinic with no discharge destination was altered by the presence or absence of UI – 57% vs. 82% being discharged home, respectively, and 29% vs. 12% being discharged to a nursing home or other health care venue. In addition, the time in rehabilitation was 185.6 days with UI compared with 156.8 days without UI, and geriatric costs in evaluation and management were higher in the UI group. The level of functional independence and motor function also impacted outcome.

Elder services (e.g long term care or nursing homes) There is growth worldwide in the use of APN “continence” specialists practicing in home care and LTC settings, providing expert consultation in UI and related disorders [25, 98]. Many have developed innovative approaches to management of UI in nursing homes. Bucci [114] developed the CHAMMP (Continence, History, Assessment, Medications, Mobility, Plan) tool to educate nursing home staff in the U.S.A. on a comprehensive continence assessment and to assist in implementation of individualized plans of care. The CHAMMP program improved one facility’s Quality Measure Indicator Report. ICI Committee 11 discusses services for frail elders.

Services in developing nations - The potential demand for UI services in developing nations far outstrips the resources that are available. The provision of services will depend on dedicated healthcare professionals with support by government or industry and by a local continence organisation to educate a new generation of service providers who will carry the services to remote communities. In some instances, consideration will have to be given to cultural, social mores and taboos.

For example Ethiopia’s Health Minister has stressed the need to develop rural health services to reduce the incidence of fistula and to have first time mothers examined by Traditional Birth Attendants (TBAs). The ICI Committee 18, Vesico vaginal fistula in the developing world addresses service for this specific condition. It is planned that TBAs will be trained to identify high-risk women, and thereby divert expenditure from high cost physicians and urban health services to training community health workers and health education. Attitudes on female circumcision, contraception and women’s health, which are often decided by their husbands, obviously have much wider implications than just continence care.

Continence services are a relative luxury, to which countries with a low per capita income are unlikely to devote scarce resources whilst other population health issues have precedence. For example, in Brazil, priorities for their health budget are childhood immunizations, AIDS/STDs, basic sanitation, healthy environment and literacy to help with the problem of street children.
c) Worldwide organisations

The stigma associated with incontinence is similar to other conditions and is associated with public ignorance and lack of awareness [114]. Despite all this, it is important to understand how attitudes and stigma have changed for these conditions. An important component is breaking the cycle of public and personal ignorance through education and public awareness programs. Patient advocacy organisations for UI have been formed worldwide to promote awareness. But for any advocacy group to be successful, there needs to be a partnership between health care professionals, governments, and industry groups with a vested interest to work together to break the cycle of ignorance and negative attitude.

Professionals (e.g. urologists, urogynaecologists, gynaecologists, primary care practitioners, physiotherapists, nurses) and professional organizations have been instrumental in promoting awareness of incontinence in all care settings. The International Continence Society (ICS) established the Continence Promotion Committee (CPC) to promote education, services and public awareness about incontinence throughout the world, and to facilitate communication, exchange of information and partnerships between continence organizations, health care professionals, governments, and industry. The CPC’s multinational and multidisciplinary representation aims to identify broad issues through an international forum that can facilitate translation at the local and national level. Each year at the ICS’s annual meeting, the CPC has held workshops around various themes that have a broad national focus such as prevention; general practitioner education; and promotional strategies. Its relevance, as is the case with each of the national organizations, is to recognize the interface between continence management and continence awareness and promotion. The CPC is increasing continence awareness through the hosting of Public Forums in conjunction with the ICS annual meeting. In 2009, it will sponsor World Continence Week.

Although it may not be practical to develop global and uniform strategies for continence promotion and public awareness, much can be learned from the positive and negative experiences of other organisations in other countries.

Continence promotion is a most challenging endeavour. Although the ratio between affected patient populations and continence organisations funding has not been formally studied, anecdotal information suggests that fund-raising for continence programmes is among the most difficult of medical problems for which to obtain funding. In view of all these challenges, the proliferation of new continence organisations, especially in the Far East and in South America, is a validation of both the need for continence promotion and the dedication of those who have recognized and are addressing this need.

1. **Continenice organisations** In the past fifteen years, several national organizations have been formed under various auspices to tackle issues to do with incontinence awareness, education and promotion. Organizations which promote continence are as diverse as the cultures they serve. They represent a wide diversity of models, including consumer-led, company sponsored, patient-only, professionals only, and organizations which have deliberately set about trying to bring together all relevant stakeholders in a relatively democratic model. In every part of the world, these organizations play a dynamic role in building both public and professional awareness of this underserved and underreported condition.

Most continence organizations are poorly capitalized, being either under- or unfunded (i.e. run by volunteers) and are held together initially by either a dedicated patient advocate or an energized healthcare professional. In most cases, this professional is an urologist or nurse whose patient population includes persons with UI.

As of 2008, there are 47 Continence Organisations in 34 countries world wide with an additional 2 international patient-based organisations. Appendix 1 is a directory and provides the contact details of various national continence organisations. Most of them function as multi-disciplinary bodies. The previous ICI chapter published results of a survey conducted on these organizations [117] Findings include:

- More than 50% of these organizations have been in existence for more than 10 years and that membership includes both professionals and the public.
- Organizations have oversight from advisory boards consisting of consumers (lay public) and health care professional members.
- Most have developed medical guidelines for continence care which represent solo efforts by the organization or in collaboration with the medical community and the government.
- Funding is an ongoing challenge for most of these organizations. Very few receive government funds, and most rely on support from industry or manufacturers of drugs and products for specific projects.
- Continence awareness is being provided generally to a public that has ‘very little’ to ‘no understanding’ of incontinence.
- There is now an increase in media interest in continence.

Education about incontinence has been identified as the most important method to decrease the perceived stigma associated with the disease. A successful method to educate has been through public awareness campaigns, health promotion projects, or health fairs.
Information is provided on the internet through websites developed by each continence organization. These websites provide useful information on incontinence, what it is, and how it can be managed, treated, and cured. They provide frequently asked questions (FAQs) as well as useful links to other continence related websites.

A needed service identified by several organizations concerns the management or containment of urine leakage through the use of products and devices. A guide to continence products has been developed by many organizations and is available to the members as well as health care professionals. This is aimed at providing useful information about the range of different products available.

Most have developed a directory of health care professionals who have expertise in the area of incontinence and its management. Certain organizations have this directory available through their website.

Organisations that primarily target the general public typically do not participate in educating professionals. Those countries where a consumer-based organisation does not exist do engage in educating professionals as well as raising the awareness of incontinence to the population in general. In those countries that have consumer-based continence organisations, there are national public awareness campaigns (e.g. the U.S.A. has a designated Bladder Health Week every fall and November is Bladder Health Awareness Month). It is generally felt that media coverage is inadequate. However, in a recent article, the NAFC (U.S.A.) strongly advocates enlisting the help of the media as one of the 3 main strategies that will help to improve the quality of life for many incontinence sufferers in future [57].

There is a paucity of published work on the formation of national organisations that target consumers or the general public. The level of evidence on the impact of national organisations increasing continence awareness is Level 3.

2. Networking of Continence Organisations

While there is little data on the outcomes of the use of organisations to change consumers’ views and awareness of incontinence, sharing of experience and collaboration amongst countries could lead to more efficient use of resources. For instance, in 1998, the Asia Pacific Continence Advisory Board (APCAB) was established with a mission to develop Continence Promotion programmes that work together with health care professionals and the general public to develop strategies to increase awareness and reduce the social burden of UI in the Asia Pacific Rim.

The APCAB member countries are Thailand, Korea, China, Hong Kong, Taiwan, Malaysia, Indonesia, India, Philippines, Singapore and Pakistan.

d) Recommendations for Continence Advocacy

Based on the literature reviewed in this section, the following recommendations can be made:

- Government support and co-operation are needed to develop services, and responsibility for this should be identified at a high level in each Health Ministry. Incontinence should be identified as a separate issue on the health care agenda. There is a need for funding as a discrete item and for funding, not to be linked to any one patient group (e.g. elderly or disabled), and should be mandatory. (Grade D)

- No single model for Continence services can be recommended. In all health care systems, much will depend on the local health care structure. Because of the magnitude of UI, prevalence, detection and basic assessment will need to be performed by primary care providers. Specialist consultation should generally be reserved for those patients where appropriate conservative treatments have failed, or for specified indications. (Grade D)

- There is a need for research on outcomes, not just the process of service delivery. This research should have patient-focused outcomes, evaluate the outcomes for all sufferers who present for care, use validated audit tools/outcome measures and longitudinal studies of the outcomes of services provided. (Grade D)

- There is a need for cost-effectiveness studies of services currently being provided. (Grade D)

III. PROFESSIONAL EDUCATION

LITERATURE SEARCH

The online databases Medline, Embase, Biosis, Science Citation index, Web of science and Cinahl were used to obtain the literature, additional databases of ERIC (an education database) and psycheit were also searched. The focuses of the searches were between 2004-2008, although literature from the preceding 10 years was also scanned to ensure thorough coverage. The objective was to obtain relevant literature relating to incontinence education. The following search terms were used: incontinence, overactive bladder, health education, education, allied health care professionals, doctors, nurses, consumer, and public education. There was significant overlap between the searches made on different databases as would be expected. The search largely identified the literature already used for the chapter in 2002/2004. Additional references from the preceding 4 years were included and references found which had not been previously identified were also incorporated.
1. BACKGROUND

With the continued advances in health care, increasing public pressure to provide high quality evidence-based care, limited time for health professionals to update their knowledge and the recognised ineffectiveness of passive ‘lecture style’ education provision, the need for new models to change health care providers’ behaviour is essential. Nowhere is this more relevant than in the provision of care for those with UI and FI where traditionally educational provision has been inconsistent at best.

Professional education is a key component in the provision and care of individuals with UI and FI. In their state-of-the-science statement on the prevention of faecal and urinary incontinence, Landfeld et al [1] identified that education of health care providers alone is insufficient to improve detection and treatment of UI and FI. However they recognise that in order to appropriately detect and evaluate incontinence, professional education is required along with outreach and practice-based resources. To date, the education and training of those involved in the provision of continence care has been poor.

It is well recognised internationally, that continence care provision in the area of UI has developed at different rates within differing care models, resulting in scattered and inconsistent services [103]. There are wide variations in health care professional input and a lack of continuity of care between primary and secondary care providers [117]. Central to the provision of high quality continence care is the education of the individuals providing care, including physicians, nurses, and allied health care professionals. There is limited literature on the educational preparation and ongoing training of those health care professionals engaged in continence promotion, care, and referral and even less on the evaluation of education programmes in terms of educational or practice outcomes. It has long been recognised that professional education with reference to UI and FI remains only a small part of the basic training of physicians, nurses, or allied health professionals and on-going training is largely ‘ad-hoc’ with huge variations in the types, content and quality of such training. An early survey in the UK found minimal attention given to incontinence in both medical and nurse training, and a key recommendation for improving continence care was an increase in quality and quantity of professional education [117]. This has clearly not occurred. While educational initiatives have been undertaken, they remain fragmented and inconsistent internationally. Most notable is the absence of evidence demonstrating an impact of professional or public education on the burden of suffering posed by OAB and UI. The ICS has established an Education Committee to promote, organise and co-ordinate all educational advances undertaken under the auspices of the ICS. This promises to be a step forward in defining core competencies and educational goals and objectives for trainers and trainee alike. Subcommittees in medical student and resident education, nurse education, physiotherapy education have been established. Though to date, educational initiatives are broadly medical. Details are available on the ICS website (www.icsoffice.org).

There is a paucity of published work on professional education on UI or FI. Similarly, there are few studies addressing the effectiveness of education in improving the knowledge of learners, or on whether improved knowledge impacts on patient outcomes. Since the publication of the ICI chapter in 2005 [116], the evidence has been building but the level of evidence on the effectiveness of professional education remains poor.

This section will examine the available evidence on the effectiveness of professional education on incontinence for different groups of health care professionals.

2. PHYSICIANS (FAMILY PHYSICIANS/GENE-RAL PRACTITIONERS/PRIMARY CARE PHYSICIANS)

Physicians (general, primary care, and family physicians) often have a gate-keeping role in continence provision as they are often the most likely first point of contact when patients seek formal help for their incontinence [118]. They may refer their patients to other health care professionals in primary care, such as a continence advisor (nurse or other allied health care provider), or, to a specialist in secondary care. Physicians provide this service without having undergone essential training in the management of patients with urinary symptoms, as this is largely unavailable.

a) Medical education

Most physicians have received little education about incontinence, fail to screen for it, and view the likelihood of successful treatment as low [119]. At the same time, there are no data confirming the benefits of screening as a method to reduce the burden of suffering from UI. A postal survey noted that only 18% of respondents said providers asked them to complete a questionnaire about bladder control during routine office visits and a majority (69%) felt it would be very helpful in prompting discussion if their physician or health care professional provided a form for them to check off symptoms of incontinence [50].

Traditionally, UI and FI have formed only a very small part of the undergraduate medical curriculum. Education on UI has usually been fragmented across different organ systems, with training scattered between gynaecology, urology, and geriatric medicine. Bladder and pelvic floor anatomy is poorly covered in preclinical training and relevant physiology is rarely
mentioned. A survey of urology residency directors, medical student educators in urology, and urology applicants identified UI as one of the 8 most commonly cited topics to be included in a core urology curriculum [120]. Co-ordination between the disciplines is rare, although there are some international examples of joint seminars/modules on urinary and faecal incontinence (University of New South Wales) and inter-disciplinary input into curriculum (University of Newcastle). Minimal training is provided on paediatric continence issues.

There is a clear history of inadequacies in continence care which have been acknowledged for some time. In 1983, the Incontinence Action Group published a report [121] which identified 'the huge gap which exists between available knowledge of the causes and methods of management and that which is actually known to practising nurse and doctors.' In their review of the evaluation and treatment of women with UI in the primary care setting, Walters and Realini [122] found that UI can be diagnosed accurately by family physicians using basic tests.

A later study found that outpatient geriatric assessment units were better than physicians in community based practices at identifying patients with both mild and severe incontinence [123]. There is clear evidence that there is a need for further education of health care professionals. Brocklehurst [118] found that less than 25% of patients with UI were given a full examination by their GPs. Deficits in the knowledge of GPs about UI were found by Jolley and Wilson [124] in a survey of 1284 GPs. They also found that GPs lacked confidence in their abilities to diagnose and manage UI, although this lack of confidence was not related to length of practice as a GP. In an analysis of incontinence in the community, the action taken by many GPs was found to be suboptimal, with considerable geographical variation [125]. Fewer than 5% of those who consulted a doctor in this survey were referred to a nurse or incontinence clinic. It also suggested that medication was often prescribed without clinical examination and probably without a diagnosis being made. In a study by Briggs and Williams [126], 42 of 101 general practitioners surveyed never used the service of a continence advisor for older patients although the service was available to them.

There have been efforts to educate family physicians in Australia; in 1989, the New South Wales state government gave AUD 25000 to the Continence Foundation of Australia to develop an educational package (15000 copies) on incontinence to be distributed to all family physicians in the country [127]. An evaluation of the package was undertaken to determine whether the package significantly improved knowledge of incontinence. There was no difference in initial knowledge between the intervention and control groups, but there was a significant difference in post-pack scores between the groups with no difference in scores on questions not in the pack. Sixty-three percent continued to use components of the package later in clinical practice. However, response rate from the 510 family physicians contacted was only 16%.

Two studies have reported that family physicians can be effective in treating UI by using conservative treatments when educated and motivated [95,128] with cure or improvement rates reported at 60 - 70%. Education can also increase referral rates to specialist practitioners [129]. However, the best format for education initiatives to all professionals needs further delineation. The use of road shows (e.g. continuing medical education [CME] seminars), teleconferences, guidelines, booklets and face-to-face teaching are commonly used but rarely evaluated.

There is very little available literature on knowledge amongst family doctors on faecal incontinence. A study has recently been undertaken to explore GPs awareness of surgical treatment options for FI. [130]. A postal questionnaire was mailed to 1,100 GP's in Yorkshire region in the UK, a response rate of 48.5% was achieved. The questionnaire assessed basic knowledge of FI and treatment options. Overall knowledge was poor, with the majority unaware of available investigations, treatments and specialist centres. The authors recommend better communication between specialist centres and GPs, as well as CME programme implementation.

There is growing evidence to suggest that traditional ‘lecture style’ medical education is ineffective in changing physician behaviour and ultimately patient outcomes [131]. More innovative teaching methods are clearly required. Levine and colleagues [132] used a train-the –trainer model to evaluate the management of a number of common geriatric conditions including incontinence. This model involved training, by an expert faculty, a team of non-expert peer educators. These peer educators used a toolkit, to conduct small group learning sessions.

These sessions were evaluated immediately after and 6 months after the education sessions. The model used principles of knowledge translation and active teaching using tool kits based on guidelines to train geriatricians. Results showed statistically significant improvements in self reported knowledge, attitudes and office based practices. The study concluded that modest changes in practice in relation to geriatric conditions were achieved using this peer led approach. Whilst such evaluations are promising, such models are difficult to sustain and costly. Perhaps most importantly they point to the need to use innovative teaching methods to ensure that educational efforts actually make a difference.
b) Medical specialists

There is little new published evidence on medical specialist training in the form of effective training interventions. Specialist training in incontinence is not always adequate. A survey of urological trainees between 1988 and 1994 in Australia showed many felt their training in the management of incontinence had not been adequate [133]. The Colleges of Obstetrics and Gynaecology in the United Kingdom and Australia and the American Board of Obstetrics and Gynaecology have developed courses and credentialing of specially trained urogynaecologists with separate examinations. Similarly, both the American Urologic Association and the European Board of Urology conduct courses, CME programmes and set standards in UI management. However, both UI and FI still may be perceived as exclusive to “super-specialists,” potentially alienating colleagues.

A survey of 163 urodynamic services in the UK found that half the respondents felt their training in urodynamics was inadequate [134]. This led Ellis-Jones and colleagues [135] to explore whether a recognised education and training programme for urodynamics led to changes in urodynamic practice. They asked programme delegates to complete a questionnaire (n=84) pre and post education programme and found that 79% reported a change in practice following completion of the course. This type of evaluation of an education programme is essential to determine the value of such courses, however the evaluation of programmes are often undertaken by those delivering the programme and the need for independent evaluation should not be underestimated.

Committee 7, Dynamic Testing, of the ICI recommends that invasive urodynamic studies should be performed in accredited urodynamic laboratories, by trained and certified staff, with formal control of the quality of the results. This committee highly recommends the establishment of national accreditation, training, certification and quality-control programmes.

3. NURSING PROFESSIONALS

Nurses have a significant role to play in the area of incontinence as they are the largest single group of health care professionals around the world and are often the first to become aware that the patient is experiencing incontinence. Cheater and colleagues [136] found that in the UK, an average community nurse case load will comprise approximately one-third of patients with UI. There have been a number of recent studies which explore the use of new innovative methods of education provision for nurses. Rogalski [137] reports persistence in the lack of educational emphasis on common symptoms like UI and recommends a curriculum model based on existing guidelines and the best available evidence which could address this shortfall and would increase the quality of continence service provision.

A common theme that runs through the international nursing literature over the past two decades is that nursing staff recognise a lack of knowledge of UI and indicate that they would like further training [138, 139, 140]. There are significant gaps in knowledge and clinical practice adoption related to both UI and FI although nurses worldwide have played a major role in developing new information and testing interventions [141]. Although nurses can provide effective interventions in the area of UI, there is limited research on effective interventions for FI.

Innovative methods of improving knowledge amongst nurses have undergone recent evaluation. An important study undertaken by Cheater and colleagues [142] adds to the debate by examining the value of audit and feedback and educational outreach which in the past has often focused on doctors’ behaviours rather than nurses. In this study, the researchers undertook a cluster randomised trial to evaluate 194 nurses in 157 family practices with 1078 patients with a diagnosis of UI. They found that when compared to educational materials alone, there were no improvements in care for either educational outreach or audit and feedback (all groups did improve but differences between groups were not significant). McConnell et al [41] describes how advanced practice nurses learned evidence based approaches to managing complex cases including incontinence in nursing home residents. Advanced practice skills included assessment and diagnosis appraisal of evidence for management. The authors suggest that such practices can enhance both student and facility outcomes, although no systematic evaluation was undertaken.

Ostaszkiewski [143] describes a nursing leadership model to enhance continence care in older adults. Evaluation of the programme suggests improved management and assessment of incontinence for individuals sustained after a two year period. Leadership programmes have proved effective in a number of areas in nursing provision.

Within these more recent studies, the use of innovative methods of knowledge transfer and education are beginning to be adopted, such methods, used in other areas of professional education may be well suited to UI and FI.

Some self-study materials have been developed which link issues on continence care with other regulatory and policy content such as recognition and reporting of elder abuse and neglect [144].

a) Specialist nurses

Educational courses on incontinence are available for nurses in the UK, U.S.A., Europe and Australia and are beginning to appear in Asia, notably Hong Kong and Singapore. These courses vary from 2 to 4 weeks of face to face didactic courses to distance learning.
courses lasting 4 to 6 months that lead to a post-basic nursing certificate.

In the UK, education programmes are documented at the Association for Continence advice website (http://www.aca.uk.com/education_modules.php) and comprise information on 1 day courses as well as diploma courses, degree modules and masters level study. Such databases of courses offer an excellent overview for students and providers.

Williams et al [145] conducted a small study in the UK that showed improvements in both knowledge and attitudes of nurses who undertook a specially designed full time, 3 month programme that included a continence module.

Internationally, there is inconsistency in the provision of specialist education to prepare nurses to practice as experts in the field of incontinence. Programmes of study are developed, but rarely fully evaluated. The need for innovative web-based learning programmes incorporating modern information and communication technology (e-learning) may offer one way of providing standardised programmes of study to practitioners.

Beitz and Snarponis [146] describe their innovative online learning programme which includes continence nursing. They feel that such teaching strategies are acceptable to nurses.

As with physicians, it is unlikely that improving nursing knowledge alone will translate into improved clinical practice, or into the ultimate goal of improved patient outcomes. A review of hospital policies and community nursing practice in an area with a well-established continence service and education program demonstrated very little evidence that improved education had a tangible effect on practice [147]. The authors concluded that nurse specialists are most usefully employed providing a clinical service to individual patients rather than spending their time educating other nurses.

There is a lack of consensus on what should be taught to different nursing groups at each educational level. It is not clear how educational needs can be met or who will pay for the time and expertise required to provide educational initiatives. Governments, as primary payer of nursing home care, have a vested interest in promoting continence in order to minimise costs. It is likely that the continence nursing home resident requires less nursing time than an incontinent resident. It therefore falls to the payer to underwrite the education that is needed to promote continence.

In the U.S.A., the Centers for Medicare and Medicaid Services has developed a “guidance” for UI care in nursing homes and provided web-based education to staff. (www.cms.internetstreaming.com)

More emphasis on incontinence care and the nurses’ role in continence promotion should be encompassed in basic nurse training courses. Specialist continence nurse practitioners and nurse continence advisors are likely to be the best instructors to provide this education.

Standard Setting, care pathways and level of continence knowledge - Standard setting has been one method by which general nurses can acquire skills to meet set standards of practice. But a more effective method may be care pathways which map out a timed process of patient-focused care which specifies key events, tests and assessments to produce the best-prescribed outcomes, within the limits of the resources available, for an appropriate episode of care [148].

The use of Continence Care Pathways has been evaluated amongst generalist nurses. It was found that the use of such pathways has aided in the identification of reversible causes of incontinence (e.g., UTI, medication, fluid intake, constipation, dexterity and mobility issues), and addressed poor quality of life and bothersomeness issues [149]. In a recent audit of 144 continence care providers in the UK, this group found that nearly half of them were using the guidelines and found them to be effective in helping with assessment and management of patients [150]. By using care pathways, patients could be referred to specialist nursing care more appropriately for specific treatment beyond the scope of the generalist nurse, or when they failed to respond to first line therapy. The care pathway identified the needs of the patient, directed simple investigation and primary therapy, but also identified the resources needed by the nurses (e.g., urine testing dipsticks, lists of drugs, frequency/volume charts). The pathway could be modified according to the equipment and expertise locally available. Educating large numbers of general nurses to follow a simple pathway with basic continence-care competencies [151] may allow better use of specialist nursing time and specialized skills [152].

Jha, Moran, Blackwell, and Greenham [153] conducted a small study of women attending gynaecology outpatient departments with incontinence problems. Thirty-five percent (7/20) patients did not need to see a doctor as they were symptom free following treatment recommendations by continence nurses using an integrated care pathway. The authors felt this process facilitated earlier diagnosis, improved access to specialist services and discharge from secondary care.

The level of knowledge about UI within the general nursing community appears to be less than ideal in both the U.S.A. [151, 154] and Sweden [139]. Many non-specialist nurses (referred to as general nurses) desire, and have a need for, more education about what they can do to better manage incontinent patients. Moreover, the quality of life of the incontinent nursing home resident is often more dependent upon the skill,
education, and attitudes of the nursing aide than of the qualified nursing staff.

In an older UK study of learner and qualified nurses’ knowledge, only 12% of qualified nurses had received any education on incontinence in the previous 12 months, and for those who had, most was on products [155]. Forty-four percent of charge nurses and 81% of staff nurses had received no additional training on incontinence since qualifying. Further work on attitudes via a questionnaire to qualified nurses on hospital wards found predominantly therapeutic, rehabilitative attitudes, but also a number of misconceptions. Twenty one percent thought their primary role with incontinent patients should be supplying products and 11% saw incontinence as an inevitable part of aging. Sixteen percent agreed that incontinence was often due to laziness and 28% thought that incontinence was more distressing for a younger than for an older adult [156]. In a further survey of trained nurses, the author found that nurses still focus primarily on palliative rather than therapeutic care and lacked knowledge on which to base care [157]. However, nurses with a post-basic qualification or in-service education were more likely to have positive attitudes, although it was not clear whether this was as a result of the education, or whether these nurses already had a positive attitude and had therefore self-selected to receive further education.

More recently, Rigby [158] explored whether increased continence knowledge amongst general nurses resulted in changes in clinical practice using an opportunistic sample of 130 general nurses achieving a 54% response rate to all stages of the study. The results demonstrated a significant change in knowledge score for nurses following a continence study day, but showed that application in clinical practice of this knowledge posed significant problems. This study had a number of limitations using a small opportunistic sample with poor response, however the real challenge remains of not simply increasing knowledge, but translating that knowledge into improvements in clinical practice.

In the U.S.A., although there are a growing number of nurses who are developing expertise caring for incontinent patients, there are no academic or clinical proficiency requirements to be considered a “continence nurse practitioner or specialist.” In 1993, the Wound, Ostomy, and Continence Nurses Society developed the first certification program for continence care nurses in the U.S.A. The Society of Urologic Nurses and Associates certifies different levels of nurses in the area of urology and in urodynamic testing. The norm is that most “continence” nurses in the U.S.A. obtain their knowledge and skill through self-motivated activities. A survey of nurses attending a national nursing conference on UI asked about educational preparation related to this condition [159].

Respondents reported that less than half (40%) received academic education including course work in accredited post-baccalaureate or graduate programmes related to UI. However, most nurses (76%) obtained instruction at professional conferences, continence clinics supervised by nurse practitioners or physicians, “on-the-job” training, self-study, or in-service programmes.

In another UK study of general nurses’ knowledge of UI, a clinical handbook was evaluated using a pre- and post-test design with an experimental and control group [112]. This study showed that the use of the handbook, which consisted of a decanted, user-friendly, research-based resource on continence care, improved nurses’ knowledge of incontinence. A significant improvement in reported clinical practice was found for 86% of variables in the experimental group compared to a 59% improvement in controls. However, only 54% of those approached agreed to enter the study, suggesting a general lack of interest and motivation.

4. PHYSIOTHERAPY AND OTHER ALLIED HEALTH PROFESSIONALS

Physiotherapists or physical therapists (PT) have long played a part in continence care and the management of UI. In some countries, patient self-referral to specializing physiotherapists has become commonplace. Physiotherapists’ involvement in UI appears to be either on the basis of individual interest or through association with women’s hospitals or obstetric departments, rather than as part of a general physiotherapy practice [160]. As such, they tend to be highly motivated and enthusiastic.

Pharmacists have a variety of roles to play in continence care. In Australia, they have been avid consumers of continence education programmes. In 2004, the Pharmacy Guild launched an educational and promotional program for their members with appropriate outcome evaluation measures. The public sees pharmacists as important and approachable sources of health information, especially information on medicines that may cause or exacerbate UI and FI. Many retail pharmacies display health promotion literature on a range of subjects including UI. Pharmacists may also advise the consumer on appropriate continence products. Educational seminars for pharmacists are generally well received. There are a growing number of CME programmes for pharmacists on the Internet either through new products or through sites such as www.worldwidelearn.com which aims for on-line CME for pharmacists and technicians.

There is also a need to address the training needs of nursing assistants and aides, particularly in the nursing home setting. In the U.S.A. and many other countries, one concern is the high turnover rate among first-line
caregivers in institutional and home care settings, making it difficult to maintain desired training levels. Nursing assistants are often the people providing ‘hands-on’ incontinence care and yet, often with the least training. Certainly, in terms of published evidence there are few reports of efforts to train nursing assistants.

Regulatory issues are often linked not only to quality of care, but also to reimbursement for clinical care and services. Reimbursement policies for services often determine which professionals are able to provide continence care. In the Netherlands, for example, the government pays for up to 14 visits to a physiotherapist for incontinence therapy. In the U.S.A., patient’s visits to a physiotherapist are restricted.

5. IMPACT OF UI GUIDELINES

The development of guidelines, primarily on UI and more recently FI, has increased significantly in recent years throughout the world [104,161,162,163,164,165,166,167,168]. In 1992 and 1996 (revised), the U.S.A. Agency for Healthcare Research and Quality (AHRQ) (formerly known as the Agency for Health Care Policy Research (AHCPR)), sponsored the development of clinical practice guidelines that were produced to help standardize the assessment and management of urinary incontinence in adults [104, 161]. Aimed at health care professionals, the guidelines are widely quoted, but they have failed to impact the practice of physicians or trainees [169]. A more recent study in North Carolina, U.S.A. used a multifaceted educational intervention based on the 1996 AHCPR guideline in 20 of 41 primary care practices and failed to show an effect in increasing screening or management of UI by PCPs [170]. They concluded the guidelines may not be the best approach to treating UI in this setting. Similar disappointing results have been reported in Europe [107]. However, nurses have used the AHCPR recommendations more effectively than physicians, incorporating them into curricula, evidence-based clinical practice, and care pathways [171, 172, 173].

More recently, Penning-van Beest et al [174] report on the impact of the Dutch College of General Practitioners, treatment guidelines for incontinence. They identified a cohort of women with newly identified incontinence (n=1663), they found that the majority of women did not receive active treatment within 1 year of identification, many received no active treatment and use of pads was high. They recommend that this lack of active treatment could be addressed through better physician education.

Many of the published guidelines focus on younger, healthy, community dwelling adults. Guidelines for evaluation and treatment of UI and FI in children and the elderly population or those with significant comorbidity need to be developed. These will need to take into account issues such as cognitive impairment which can influence continence status in older adults [175].

Fung [176], in a small study in a large academic Veterans Affairs medical centre in the U.S.A., used guidelines to develop condition-specific computerized templates to serve as guides for clinicians to ask questions and perform elements of a physical examination for two specific medical conditions UI and falls. This study demonstrated that a set of templates can be developed within an existing electronic health record system and can be used to prompt a clinician to obtain elements of a history and to perform physical exam elements in relation to falls and UI.

Changing the current patterns of medical care with respect to detection and management of incontinence through education is a difficult task [177]. Guidelines for medical practice can contribute to improved care only if they succeed in moving practice closer to the guideline recommendations [178]. Unless there are other incentives or the removal of disincentives, guidelines are unlikely to effect rapid changes in actual practice. It is recognized that other tools or strategies are needed to augment and build on educational endeavours [179]. Strategies that aid in implementation of a guideline include reminder systems to remember when to implement guidelines, tracking systems to identify patients who need follow-up and continuous quality improvement monitoring and regulations. Educational programmes alone may change knowledge and attitude, but rarely change behaviours. Guidelines combined with continuing medical education programmes may be more successful [105].

Even evidence-derived guidelines may not always result in better practice or outcomes. The implementation and evaluation of such a guideline in one primary care practice in the UK from which 1503 patients were randomly selected has been reported [171]. Thirty-five percent of women and 9.9% of men suffered from incontinence in the previous two months, but 61% had never sought help. Of those who did, 63% were referred to specialists, 53% had a urine test, 1 in 4 women had a vaginal examination, and 4 of 206 persons with UI were asked to complete a frequency/volume chart. After implementing the guideline, two abdominal examinations and one new rectal examination were performed, but no new vaginal examinations were performed. Frequency/volume charts were given to three people. Two patients used fewer drugs. The severity of incontinence was unchanged following the intervention. Family physicians did not effectively implement the guideline. It remains to be tested whether, properly used, guidelines can improve incontinence in practice.

In 2006, a national UK guideline was produced on UI in women [165]. Within the document the area of
surgeons competence is discussed however there is no mention of other care providers education and training (including GPs, nurses, physiotherapists etc). In order for services to be delivered effectively, primacy needs to be given to practitioners education and training in such documents.

In a 1999 repeat of a 1996 survey, among 6481 patients older than 50 years, it was found that after numerous UI awareness and education campaigns, German physicians were even less likely to address incontinence than 3 years earlier [180]. The “don’t ask, don’t tell” attitude between physicians and patients, has significant fiscal implications for health care. The consequence of not treating the condition may increase the annual cost of care by an estimated USD 3941 per individual [181]. Funding for conservative management of UI, or better-informed public demand, may stimulate more interest and improved performance among this important group. It remains critically important that PCPs have an understanding of how to manage UI effectively [182].


They used a questionnaire in a convenience sample of 558 staff attending workshops. The authors report striking deficiencies in knowledge amongst staff, and identified managerial structures as barriers to guideline implementation. They suggest such barriers need to be overcome in order to improve the quality of care.

A number of CME programmes for PCPs on UI are now available through Internet sites. One by the American Geriatrics Society covers screening for UI, history taking, ruling out other factors, urinalysis, behavioural therapy and challenges in impaired people. Pharmacy Times site offers a free Temple University program with 2 CME credits on medical management of UI.

It covers differentiation between transient and established incontinence, identification of medications which can contribute to UI and agents which can be used to manage the various types of UI, how to assess, choose appropriate pharmacotherapy and identifying which agents should not be used.

In 1998 the Japan Continence Action Society compiled a Continence Educational set (CE-set) for professionals to use in the community. The CE-set comprised text books, lantern slides, and a CD-ROM based on current evidence. Fifty five CE-sets were distributed to Health Education centres in each prefecture. In 2008, only 11 of the CE-sets had been used, whilst 44(80%) remained unused. The single factor that encouraged use was whether a continence course had been provided in the region or not.

Realistically the likelihood of obtaining adequate independent funding for effective professional education on UI and FI is unlikely in the current economic climate.

6. RECOMMENDATIONS FOR PROFESSIONAL EDUCATION

Based on the literature reviewed in this section, the following recommendations can be made:

- There remains a need for rigorously evaluated continence education programmes which adhere to defined minimum standards for continence specialists and, generalists, utilizing web-based and distance learning techniques alongside audit and feedback, train-the trainer models and leadership models as well as traditional methods. The following should be considered:
  - Compulsory inclusion of a specified number of hours of incontinence education in the basic curriculum (physicians, nurses, physiotherapists and other allied health professionals). Ideally incontinence should be identified, planned and taught as a separate topic.
  - Specific education programmes adhering to approved standards should be reported to a recognized central body linked to appropriate evidence and guidance.
  - Where possible, education programmes should be independently evaluated using appropriate research methods. (Grade D)

- There is a need for research on the most effective means to educate professional groups on continence issues. Specifically, there is need for research on:
  - The effectiveness of innovative teaching methods in improving knowledge and practice
  - Translation of research into improved clinical practice and identification of methods by which this happens.
  - Mechanisms for increasing professional motivation to acquire education and improve performance. (Grade D)
IV. PRIMARY PREVENTION

LITERATURE SEARCH


1. BACKGROUND

Urinary incontinence is a highly prevalent and chronic condition that can be prevented by addressing modifiable risk factors through primary prevention. Although the evidence base for FI and POP is more limited than that for UI, the conditions share many similarities with respect to risk and treatment, suggesting that similar benefits may derive from population-based strategies [116]. These strategies may also be relevant to people with bladder pain syndrome (also referred to as interstitial cystitis, painful bladder syndrome and urologic chronic pelvic pain), although there is no research on primary prevention for this condition.

In the past few years, substantive work has examined the evidence base for preventative strategies for incontinence. This work included a Cochrane Review of conservative management for post prostatectomy urinary incontinence [184], an extensive Evidence Report conducted for the U.S.A. AHRQ on prevention of urinary and fecal incontinence in adults, [167], and a state of the science conference also on the prevention of urinary and fecal incontinence in adults, sponsored by the National Institutes of Health in the U.S.A. [166].

Primary prevention refers to efforts directed at a community or population level to promote protective health behaviors [185] in order to reduce the incidence of UI, FI and POP. Other preventative measures include secondary prevention (where screening of asymptomatic people occurs in order to detect symptoms early and provide treatment) and tertiary prevention (where efforts are directed at curing, rehabilitating, restoring function and preventing future relapse of symptoms) [186]. This section will focus on primary prevention of UI and POP. Additional and more in-depth information is presented by the ICI Committee 4, Pathophysiology of Urinary Incontinence, Fecal Incontinence and Pelvic Organ Prolapse; Committee 12, Conservative management of urinary incontinence (men and women), and pelvic organ prolapse. Primary prevention of FI is addressed by Committee 16, Conservative and Pharmacological Management of Faecal Incontinence in Adults. There is no evidence concerning addressing secondary and tertiary prevention of bladder pain syndrome.

2. POPULATION-BASED PREVENTION

Prevention should include education about behavioural changes that increase the probability of incontinence, the normal functioning of the urogenital and gastrointestinal tracts, expected age related and developmental changes, and how to find the appropriate treatment providers. Raising awareness of health problems and providing information on terms used to describe symptoms assists in promoting help-seeking behaviour [187].

The 3rd ICI stressed the importance of all healthcare professionals promoting primary prevention of incontinence [116]. It was acknowledged that this would require raising the level of community awareness, providing public education as well as addressing healthcare professionals' education. Whilst some advances have been made, these strategies remain a priority. The challenges of dealing with an ageing population are likely to result in urological symptoms including incontinence being as prevalent as cardiovascular disease in the U.S.A. by 2025 [188, 189] and is likely to result in an increased demand for hospital and long term care [190]. As noted above, incontinence is responsible for up to 30 - 50% of admissions into nursing homes, often precipitated by the burden of care on care givers who spend half of
their care-giving time providing personal care such as toileting assistance [84]. Caregivers of people with dementia living in the community have been shown to benefit from learning strategies to assist in preventing and managing FI [191]. This study highlights the need to include carers in primary and secondary prevention strategies.

Programs developed to raise awareness of continence issues should consider targeting a range of groups including people of different ages and genders [47]. Consideration should be given to the setting in which the health promotion program is to be delivered such as schools, work places, community groups and health care institutions [192]. It is acknowledged that whilst some nations are successfully implementing primary prevention strategies, others are yet to effectively implement secondary prevention measures such as assessment and management of continence conditions [193]. In Australia, the UK and the U.S.A, continence organizations have received additional support from national governmental departments and agencies resulting in greater resources being applied to preventative and continence promotion programs.

The evidence for population-based prevention strategies remains at Level 4, Grade C.

3. RISK FACTORS

There is an increasing body of evidence linking incontinence with other conditions. These links provide opportunities to benefit from cooperative efforts with other health promotion initiatives. Identification of individuals who have the potential for becoming incontinent is an important primary prevention activity.

Level 3 Grade B evidence exists for general risk factors of age, pregnancy, parity, [194, 195, 196]. Earlier studies reported Level 3 evidence regarding the risk of overweight and obesity in women [92, 197]. More recently a systematic review has found Level 2 and Level 3 evidence that establishes overweight and obesity as independent risk factors for the development of UI in women [198]. Women with obesity and diabetes have a greater risk of developing pelvic floor disorders, including UI, FI and pelvic organ prolapse [199]. There is a 91% prevalence of these pelvic floor disorders in morbidly obese women [200].

Higher body mass index (BMI) and greater weight are independent risk factors for stress and mixed UI in middle-aged and menopausal women [198, 201]. There is Level 3 evidence to recommend that women with a BMI over 30 should be advised to lose weight to reduce their UI [165]. Randomised control trials have found that women who are overweight or obese can reduce the frequency of urine loss by losing between 3 - 5% of body weight [202] and 7% of body weight [203]. Bariatric surgery for morbidly obese women has resulted in “significant improvement” of UI and has reduced the prevalence of FI from 19% to 9% [204]. A weight reduction program focusing on avoiding weight gain and maintaining a waist circumference within a normal range may lower the risk of UI in women [205].

Diabetes - Lower urinary tract symptoms and changes in bladder function occur in over 50% of men and women with diabetes [206; 207]. In middle-aged women, diabetes is the strongest risk associated with the development of UI [197] and the increase in severity of UI [208, 209]. The risk of pathological bladder changes and incontinence may be reversed if diabetes can be prevented by lifestyle interventions including weight loss [206; 209] and physical activity [206]. Providing this information to patients may be a strategy to motivate people to take positive action to improve their health.

Fluid intake - Urinary symptoms may be adversely affected by extremes of fluid intake. Amending high or low fluid intake improves UI and OAB [165]. Patients who decrease an excessive fluid intake experience decreased urinary frequency and urgency to statistically significant levels [165; 210]

Diet - The effect of diet on urinary function is not well studied, however it has been reported that eating a diet containing vitamin D, potassium, chicken, vegetables, bread and protein may lead to a reduction in the risk of stress UI and OAB [165]. Diets containing carbonated drinks, high fat levels, cholesterol, vitamin B12, zinc [166] and spicy foods and artificial sweeteners were associated with an increased risk of UI or an increase in the severity of OAB. There are mixed results on the effects of caffeine upon nocturia and OAB, with one study of normal volunteers reporting no change in nocturia [211] and others that showed an association with caffeine ingestion and nocturia but not urinary urgency [212, 213]. A recent study with normal volunteers found that artificial sweeteners had a significant effect upon increasing urinary frequency and urgency [212].

Diet is also implicated in the exacerbation of urinary symptoms in BPS/IC/PBS. The types of food and drink reported to aggravate these symptoms include chocolate, citrus fruits, and tomatoes, carbonated drinks, [214], alcohol, coffee, and tea, [214, 215, 216].

Physical activity - Low impact physical activity in younger women appears to assist in promoting continence [217]. Conversely high impact, strenuous physical activity can aggravate symptoms of PBS [218]. Older women who engage in regular physical activity such as walking have significantly lower levels of UI [219] and are less likely to have urgency if they exercise at least weekly. It is not clear if commencing exercise could reduce urgency [165]. Severity of UI in women is related to the perception of UI being a barrier to exercise, and women with severe UI are less likely to achieve recommended amounts of
physical activity required for good health. Women with less severe incontinence are more likely to wear a pad or restrict their fluid intake in an attempt to minimize UI when exercising [220].

**Depression and mental health** - Incontinence has been linked with mental health issues, including depression and self-harm. This may be due to a common underlying causality rather than incontinence causing depression or risk of self-harm [218]. Severity of incontinence is strongly associated with major depression in women [222] and screening for depression should be considered when a women presents with severe UI. The World Health Organization (WHO) predicts that by 2020 depression will be the second highest cause of disability for all ages and genders [223]. It is likely that the prevalence of incontinence will rise as a consequence of this. IC is also associated with a higher risk of depression [218, 224]. Symptoms are exacerbated by psychological stress [215]. This syndrome is frequently associated with fibromyalgia and irritable bowel syndrome [215, 224]. A recent study however has found that women with fibromyalgia have a pattern of urinary symptoms that are distinct from those experienced by women with PBS/IC [225].

**Cigarette smoking** Whilst cigarette smoking has previously been shown to exacerbate OAB and has been linked with UI and FI [167], research has not yet demonstrated that smoking cessation results in changes to UI or FI [164, 165].

**Occupational risk factors** Increasing voiding intervals have been reported in workers who have limited access to toilet facilities (such as teachers, nurses and production workers). This is thought to result in reducing bladder sensation and lead to UI [167]. An earlier study found that women in the military and the occupations described above deliberately restricted their fluid intake in order to control their UI [226]. A recent study however has found that women with fibromyalgia have a pattern of urinary symptoms that are distinct from those experienced by women with PBS/IC [225].

Management of the second stage of labour may also affect continence. Pelvic floor muscle trauma may be reduced by allowing the woman to bear down when she has an urge to push and avoiding instrumental delivery when possible [235].

When clinical guidelines have provided an indication for the use of an episiotomy, debate has ensued as to whether a midline or mediolateral episiotomy will provide the best protection to the perineum. A case-control study found that a mediolateral incision reduced the risk of third degree tearing of the perineum. The angle of the episiotomy resulted in a 50% relative reduction of sustaining a third degree perineal tear for each 6° away from the midline [43].

Previously Level 2 and Level 3 evidence suggested that elective caesarean delivery could be considered as a UI prevention strategy. Women who had a caesarean section have less UI at three months post partum [233], however the risk of UI is not completely eliminated as 14% of women still report UI [236]. More research is required into UI occurring before and during pregnancy due to the strong link to UI occurring postpartum [237]. In addition, antenatal UI has been found to be an independent risk for postpartum FI [167; 229].

Despite a significant body of evidence that advocates PFMT before, during and after pregnancy to prevent and treat UI during pregnancy and in the postnatal period, [204]; [167], the actual number of women performing regular PFMT during pregnancy varies from 17% in Norway, 69 % in the UK and 54.5 % in Australia [238]. Poor adherence to PFMT is also an issue [239]. The effectiveness of PFMT in preventing
childbirth related UI, in conjunction with the non-invasive nature of this self-care strategy, makes it a logical focus for UI prevention efforts among women during the period of childbearing. [240]. Due to the lack of research, there is only Level 4 evidence to support the use of PFMT to prevent incontinence during pregnancy and in the post natal period.

5. PREVENTION OF PROSTATECTOMY-RELATED URINARY INCONTINENCE

Prostatectomy remains an established risk factor for UI in men [241], resulting in postoperative pad use [242] and decreased quality of life [243]. Despite advances in surgical techniques that have reduced the risk of UI, it remains a distressing post-operative complication for many men [244]. It is of concern that over 40% of men in one study claimed not to have received preoperative information that they may develop UI following prostate surgery [245].

Pre-operative UI is a significant risk for UI following a radical prostatectomy [246].

A Cochrane Review published in 2008 found few studies on the effect of PFMT undertaken prior to radical prostatectomy on the development of UI post-operatively [247].

One RCT compared subjects given biofeedback and daily home exercise to controls given usual post-operative instruction to cut off the flow of urine when urinating [285]. The intervention group achieved continence faster and suffered less severe UI than controls.

Secondary prevention of UI with men undergoing PFMT following radical prostatectomy also shows conflicting results, with some showing no change on UI [249] and others showing improvement in men who underwent PFMT compared to men who did not [250]. The Cochrane Review concluded that the evidence was inconclusive and that there was a paucity of quality research in this area, [247].

Whilst there is a focus on UI and erectile dysfunction after radical prostatectomy, a number of men experience fecal urgency and FI post-operatively, with a small percentage of men developing FI two years post-operatively. It is suggested that there may be a higher number of men with FI post-operatively than currently reported [245].

Researchers are urged to investigate preventative strategies for FI and faecal urgency following radical prostatectomy [166] as currently there appears to be no research into this area.

In regards to prostatectomy, there remains mixed Level 2 evidence to support the use of PFMT pre and post-operatively for UI. There is no evidence to either support or refute the use of PFMT pre and post-operatively to prevent FI.

6. PREVENTION OF URINARY INCONTINENCE IN OLDER ADULTS

It is predicted that the number of people aged over 60 will increase from 650 million in 2005 to over 2 billion in 2050 [223]. Whilst ageing does not cause incontinence it is acknowledged that the risk of incontinence increases with advancing age and is associated with a concomitant increase in a range of co-morbid conditions.

Older adults are a heterogeneous group, and therefore preventative strategies for older adults need to take into consideration the well aged as well as the frail aged. It is important to involve older people and upcoming generations in health promotion research and health promotion intervention programs targeted at older people [251].

Due to the association of diabetes and UI, gerontologists have an important role to play in screening older women with diabetes for UI so that they can receive treatment [206].

Well older adults - There is Level 2 evidence to support the use of preventative strategies in well older adults. These strategies include promoting self-efficacy such that the individual has a belief that they have the capacity and skills to improve their own health. In addition, self-efficacy improves the ability to cope better with symptoms and is linked to motivation, knowledge of the benefits of making changes, and adherence to behavior change [252; 253]. Self-efficacy over UI may be enhanced if women are taught self monitoring techniques such as adjusting fluid and caffeine intake, resolving constipation, pelvic floor muscle training in “Quick Kegel” contractions and monitoring voiding intervals [254]. These self-monitoring techniques resulted in decreased volumes of urine loss and improved quality of life [254]. Promoting self-efficacy results in good adherence to PFMT in older, well educated women [255]. Self-efficacy measures such as the Geriatric Self-Efficacy Index for Urinary Incontinence can be used to determine adherence to behavioural programs developed for the prevention and management of UI [253].

A behavioural modification program delivered to women aged over 55 years reported the preventative effects of increasing pelvic floor muscle strength and increasing time between voids upon continence status, suggesting that preventative strategies are effective in older women [66, 256; ]. A recent systematic review concluded that there was “moderate evidence” to support the use of PFMT and bladder training in resolving UI in women [257]. An older study reported that these interventions were “very successful” in treating UI in elderly community dwelling people [258].

Frail older people Correlations have been found between poor general health and severe urinary and/or
fetal incontinence in frail older people [259]. Incontinence is the second main reason for frail aged people to seek admission into nursing homes in the UK and the U.S.A., and is the third main reason in Australia [88]. Incontinence in nursing home residents has negative effects upon the morale of residents, families and staff. Conversely the time and effort spent in promoting continence through toileting programs and other strategies is labour intensive and also places strain upon staff [129].

A recent study has found that there is a greater risk of functional disabilities in men and women who are obese, specifically those with higher waist circumference measurements [260]. These disabilities are associated with a range of chronic health conditions, including incontinence. Prevention of obesity may prevent the development of functional disabilities, chronic health problems and incontinence in the frail aged [260].

Treatment of poor mobility and communication difficulties [259], UTI, environmental barriers and removing physical restraints [261], could reverse or ameliorate urinary and/or fecal incontinence. Despite this, a UK survey of continence practices in care homes there were few mobility programs in place to promote continence [88].

Falls have been associated with a range of factors, including UI and taking medicines such as diuretics [262, 263]. Falls have also been associated with OAB, urge UI and nocturia [264]. Opportunities exist to link with other health promotion programs targeted at older adults such as falls prevention programs [262]. However opportunities to promote continence are not currently being adopted in these programs, despite incontinence being a known risk for falls [264]. A number of factors have been identified linking the risk of incontinence to chronic health conditions in the frail aged. Screening is recommended to identify risk factors for incontinence in the early stages when it may be easier to adopt preventative strategies [167].

Whilst strategies to address these factors have been recommended there is a lack of studies to show the efficacy of these interventions. Due to the paucity of research in this area there is Level 4 evidence to recommend the use of preventative strategies described above to prevent incontinence and promote continence in frail aged adults.

7. PREVENTION OF PELVIC ORGAN PROLAPSE

Some degree of POP is reported in 51% of women aged over 50 years who have had children [265]. Whilst clinical assessment of POP has revealed higher prevalence, mild degrees of prolapse may be asymptomatic. There is mixed evidence related to risk factors associated with developing POP. Smoking, increased waist circumference and higher BMI were not associated with POP in one study [266]. Another study reported that grand multiparity (defined as five or more vaginal deliveries) and raised BMI are risk factors for POP [267]. It was also found that in older women that POP worsened and resolved over time [267]. Irritable bowel syndrome was found to be associated with POP [268].

A systematic review of POP conducted in 2007 concluded that whilst there is currently no research to demonstrate effective prevention, conservative strategies such as weight loss, avoiding heavy lifting, resolving constipation, pelvic floor physiotherapy and addressing obstetric risk factors should be considered [269]. One report presents Level II-3 evidence that symptoms of POP are relieved by the use of a vaginal pessary. This is of relevance to women who choose or are not able to have surgery and those who are awaiting surgery [265].

Pelvic organ prolapse in women may be decreased following the long term use of a vaginal pessary [265]. The use of a pessary may also assist in improving bladder, bowel and sexual functioning but there is mixed evidence for improvement of stress urinary incontinence and urge urinary incontinence [265].

A Cochrane Review of pessary use in 2004 was unable to find any randomised control trials assessing the efficacy of pessary use [269]. These authors also note that despite this lack of evidence, pessaries have been used for centuries and are currently used in clinical practice by the vast majority of gynaecologists, urogynaecologists and nurse specialists.

8. PREVENTION OF FAECAL INCONTINENCE

Whilst it appears that people are seeking help more readily for UI, the problem of FI remains under-reported [130] especially in older people [270] and few physicians ask patients about it [271]. Analysis of studies on FI is hampered by a lack of standardised terminology with regards to stool consistency, gas leakage and frequency of incontinent episodes [166, 272, 273]. Whilst acknowledging that prevention of FI is important, it is recognized that more research is needed to determine the risk factors and interventions to prevent FI [274]. An extensive systematic review of risk factors associated with FI is reported by Committee 4, Pathophysiology of Urinary Incontinence, Fecal Incontinence and Pelvic Organ Prolapse and hence only a brief summary is provided below. Risk factors for developing FI include diarrhoea [274], irritable bowel syndrome (IBS), UI [271], [272], and obesity, particularly for people with a BMI more than 40 [272, 274]. Morbidly obese women may have rates of FI as high as 63% [271]. Chronic obstructive pulmonary disease, diabetes, colectomy and cholecystectomy are also associated with an increased risk of FI [275]. An association with FI has been found in postmenopausal women [275]. Conversely it was also found that the use of hormone replacement therapy in women increased the risk of FI [275].
9. RECOMMENDATIONS FOR PRIMARY PREVENTION

Health promotion strategies aimed at individual, interpersonal, community and population levels are needed in order to promote urinary and fecal continence [192]. Educating people about continence issues and ways in which they can improve their bladder and bowel health will also assist in removing some of the stigma that surrounds continence issues [167]. Conversely, care needs to be taken to ensure that incontinence is not “normalised” as this can have the unintended consequence of people not seeking help for a condition deemed to be “normal” [276]. For moderately overweight women, the Third International Consultation on Incontinence recommended programs such as Weight Watchers® to encourage moderate weight loss as first line therapy in overweight women. There is little evidence at this stage to demonstrate that these recommendations have been followed. The acceptance of public health programs to reduce obesity, increase physical activity and promote eating fruits and vegetables can be built upon to improve their bladder and bowel health will also assist in removing some of the stigma that surrounds continence issues [167].

Based on the literature reviewed in this section, the following recommendations can be made:

- Primary prevention studies should not be limited to individual interventions, but also test the impact of population-based public health strategies (Grade C).
- PFMT should be a standard component of prenatal and postpartum care. Due to the number of women who experience incontinence prior to pregnancy, measures need to be taken to instruct women in PFMT prior to pregnancy (Grade C).
- Randomised controlled trials (RCTs) should be conducted to test the preventative effect of PFMT for men post-prostatectomy surgery (Grade B).
- Further investigation is warranted to assess the efficacy of PFMT and BT for primary prevention of UI in well older adults (Grade B).

Primary prevention efforts should be aimed at interventions to promote a healthy body weight to assist in the prevention of incontinence (Grade A).

REFERENCES


92. Townsend M.K, Danforth, K.N., Rosner, B., Curhan, G.C.,...


154. NIH State-of-the-Science Conference on Prevention of Fecal...
181. Cochran, A. Don't ask, don't tell: the incontinence conspiracy.
182. Holroyd-Leduc, J.M and Strauss, S.E.:  Management of
1676


APPENDIX 1 –
DIRECTORY OF CONTINENCE ORGANIZATIONS

AUSTRALIA
*Continence Foundation of Australia Ltd
AMA House, 293 Royal Parade
Parkville, Victoria 3052
Tel: 03 9347 2522
Fax: 03 9347 2533
website: www.continence.org.au
Email: info@continence.org.au

AUSTRIA
*Medizinische Gesellschaft fur Inkontinenzheile Osterreich
Speckbacherstrasse 1 A-6020, Innsbruck
Tel: (43) 512 58 38 03
Fax: (43) 512 58 94 86
Website: www.inkontinenz.at
Email: kontinenz@telering.at

BELGIUM
*U-Control vzw, (Belgian Association for Incontinence)
Leopoldstraat 24
B-30000 Leuven
Tel: 32 816 16 027/32 382 14 475
Fax: 32 816 16 027/32 382 14 475
Email: jean-jaques.wyndaele@uza.be

BRAZIL
*Urobel Belgian association for urological nurses and associates
De Pintelaan 185, BE-9000, Gent
Tel.: 09/240.27.65
Fax: 09/240.38.89
Website: www.urobel.be

*Brazilian Foundation for Continence Promotion
Email: seabrarios@uol.com.br

CANADA
*The Canadian Continence Foundation
PO Box 417, Peterborough, Ontario, K9J6Z3
Tel: (1) 705-750-4600
Fax: (1) 705-750-1770
Website: www.canadiancontinence.ca

CZECH REPUBLIC
*Inco Forum
Tel: (420) 02-61-082135
Fax: (420) 02-61-082135
Website: www.incoforum.cz/

DENMARK
*Kontinensoreningen-
Danish Continence Association
(The Danish Association of Incontinent People)
Vesterbrogade 64, 1620 Copenhagen V
Website: www.kontinens.dk/

FRANCE
*Feemes pour Toujours
Nicole Kremer, President
17 rue des Nanettes, Paris 75011
Tel: 33 (0) 147000002
Fax: 33 (0) 826623195
Website: www.femsante.com

GERMANY
*Deutsche Kontinenz Gesellschaft e.V.
Friedrich-Ebert-Strasse 124
34119 Kassel
Tel: (49) 561 78 06 04
Fax: (49) 561 77 67 70
Website: www.gih.de

HONG KONG
*Hong Kong Continence Society
c/o Dept of Medicine and Geriatrics
United Christian Hospital
130 Hip Wo Street, Kwan Tong,
Kowloon, Hong Kong
Tel: 852 237 94822 Fax: 852 234 72325
Email: emfleung@ha.org.hk

HUNGARY
*Inko Forum
Levelezeski cim
Budapest, Pf 701/153, 1399
Phone: 06 80 730 007 Website: www.inkoforum.hu

INDIA
*Indian Continence Foundation
273/1005 1st Block, 19th C Main,
Rajajinagar, Bangalore 560 010 India
Tel: 91 80 3131833 / 3424728
Fax: 91 80 3131833/ 3325824
Website: www.indiancontinencefoundation.org

INDONESIA
*Indonesian Continence Society
Sub Dept of Urogynecology, Dept of OBGYN Medical
Faculty of University
Dr. Cipto Margunkusuma Hospital Indonesia
Tel: 62 21 392874/392/3632
Fax: 62 21 392874/3145592
Email: urogyn@centrin.net.id

1680
ISRAEL
*National Center for Continence
Rambam Medical Centre, POB-9602
Haifa 31096
Tel: 972-485 43197
Fax: 972-4854 2098
Email: ig054@hotmail.com

KOREA
*Korea Continence Foundation
388-1 Dep of Urology Asan Center,
Ulsan University College of Medicine
(138-736) Pungnap-2dong, Songpa-gu,
Seoul 138-736, Korea
Tel: 82 2 3010-3735
Fax: 82 2 477-8928
Website: www.kocon.or.kr

ITALY
*Fondazione Italiana Continenza
(The Italian Continence Foundation)
Via dei Contarini, 7
201 33 Milano
Website: www.continenza-italia.org
Email: info@continenza-italia.org

*Associazione Italiana Donne Medico (AIDM)
Tel: 39 335 282045/39 065 811390
Website: www.donnedecho.org

*The Federazione Italiana INCONtinenti (FINCO)
Segreteria/Presidenza
V.le O Flacco, 24-70124 Bari
Tel: 080-5093389
Fax: 0805619181
Website: www.finco.org

JAPAN
*Japan Continence Action Society
103 Juri Heim, 1-4-2 Zenpukuji
Suginami-Ku, Tokyo, Japan 1670041
Tel: 81 3 3301 3860
Fax: 81 3 3301 3587
Website: www.jcas.or.jp

MALAYSIA
*Continence Foundation (Malaysia)
c/o University Hospital, Lembah Pantai, Kuala Lumpur 59100
Tel: 603 7956 4422
Fax: 603 758 6063
Email: lohcs@medicine.med.um.edu.my

MEXICO
*Asociacion de Enfermedades Uroginecologicas
ACI Mexucu AC
Tel: 53-74-36-91
Website: www.asenug.org

NETHERLANDS
*Pelvic Floor Netherlands
PO Box 23594, 1100EB
Amsterdam
Tel: 31 20 69 70 304
Fax: 31 20 69 71 191

*Society for Continence (Singapore)
Gleneagles Medical Center
6 Napier Road #06-02
Singapore 258499
Tel: (65) 6787 0337 Fax: (65) 6588 1723
Website: www.sfcs.org.sg

NEW ZEALAND
*New Zealand Continence Assn Inc
PO Box 270
Drury, Auckland 1730
Tel: 64 9 2947738 Fax: 64 9 2947116
Website: www.continence.org.nz
*Simon Foundation for Continence  
P O Box 815, Wilmette Illinois 60091  
Tel: (1) 847 864 3913  
Fax: (1) 847 864 9758  
Website: www.simonfoundation.org

*Society of Urologic Nurses & Associates (SUNA)  
East Holly Avenue, Box 56, Pitman, NJ 08071-0056  
Tel: 888-827-7862  
Website: www.suna.org  
Email: suna@ajj.com

OTHER ADVOCACY ORGANIZATIONS  
*International Painful Bladder Foundation (IPBF)  
Email: info@painful-bladder.org  
Website: www.painful-bladder.org

*World Federation of Incontinent Patients (WPIF)  
Email: presidency@wfip.org  
Website: www.wfip.org
Committee 22

Economics of Urinary & Faecal Incontinence, and Prolapse

Chairman
K. Moore (Australia)

Members
T. Wei Hu (USA),
L. Subak (USA),
T. Wagner (USA),
M. Deutekom (The Netherlands)
I. INTRODUCTION

II. BACKGROUND
1. PLACING ECONOMIC ANALYSIS OF CONTINENCE CONDITIONS INTO PERSPECTIVE
2. COUNTRY SPECIFIC ECONOMIC ISSUES
3. OTHER “FRAMEWORK” ISSUES

III. TYPES OF ECONOMIC ANALYSIS
1. OVERVIEW
2. DETAILS OF DECISION ANALYSIS
3. STATISTICAL ANALYSIS
4. BUDGET IMPACT ANALYSIS (BIA)

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD
1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES
2. “DO IT YOURSELF” - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE’S RECOMMENDATIONS

V. SUMMARY OF RECENT ECONOMIC ANALYSES
1. SURGICAL TREATMENT COST EFFECTIVENESS STUDIES
2. OUTPATIENT CONSERVATIVE THERAPIES
3. PHARMACOTHERAPY OF OVERACTIVE BLADDER
4. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING
5. LONGITUDINAL BURDEN OF DISEASE STUDIES
6. PROLAPSE TREATMENTS, COST IMPLICATIONS
7. ECONOMIC CONSEQUENCES OF FECAL INCONTINENCE

VI. SUMMARY AND FUTURE RESEARCH PRIORITIES

VII. APPENDIX – SEARCH STRATEGIES

ABBREVIATIONS

ADLs: Activities of Daily Living
AF: Attributable Fraction
BIA: Budget Impact Analysis
CCA: Cost Consequence Analysis
CBA: Cost Benefit Analysis
CEA: Cost-effectiveness Analysis
CI: Confidence Interval
COI: Cost of Illness
CMA: Cost Minimisation Analysis
CUA: Cost-utility Analysis
DRG: Diagnostic Related Group
EQ5D: EuroQol 5 Dimension Health Status Measure
FI: Faecal Incontinence
GDP: Gross Domestic Product
HRG: Health Care Resource Group
HRQOL: Health Related Quality of Life
HUI: Health Utilities Index
ICER: Incremental Cost-Effectiveness Ratio
ICI: International Consensus on Incontinence
IQR: Interquartile Range (25% - 75%)
MAU: Multi – Attribute Utility
MRC: Medical Research Council (of UK)

NCA: Nurse Continence Advisor
NIH: National Institutes of Health (USA)
NICE: National Institute for Health and Clinical Excellence (UK)
OR: Odds Ratio
PFMT: Pelvic Floor Muscle Training
QALY: Quality Adjusted Life Year
QOL: Quality of Life
QWB: Quality of Well-Being Index
RCT: Randomised Controlled Trial
SD: Standard Deviation
SF-36: Short Form – 36 Quality of Life Test
SUI: Stress Urinary Incontinence
TTO: Time Tradeoff
TVT: Tension Free Vaginal Tape
WTP: Willingness to pay

UI: Urinary Incontinence
UK: United Kingdom
USA: United States of America
UTIN: Urologic Treatment of Incontinence Network
VAS: Visual Analog Scale
Since the first publication of the ICI, which included a basic review of the economics of urinary incontinence, our knowledge about this subject has increased substantially. Initially, many publications in this field comprised simple Cost of Illness (COI) studies, in which the cost of managing incontinence conditions were tabulated, without measurement of the benefit of treatment outcomes. Since that time, continence clinicians have become increasingly aware that we need to balance the cost of the illness against the cost of a range of treatments, to yield the net benefit for the money spent. Also economic analysis should not just consider the objective reduction in leakage severity, but also consider the improvement in overall quality of life.

In the last decade, we have become increasingly aware that economic analysis of incontinence is somewhat dependent upon the condition to be studied. For example, stress incontinence can be readily cured by a range of surgical options, but the benefit may decay over time. Stress incontinence can also be cured by more time-consuming physical therapies but these depend upon patient compliance with treatment over time.

On the other hand, pharmaceutical companies have provided an increasing array of anticholinergic treatments for the overactive bladder, but these may require prolonged administration with longstanding drug costs. Such pharmacotherapy needs to be accompanied by bladder training, which also requires patient compliance to achieve success. The benefit of surgery for Botox injections is well known to decline with time. Because of these individual characteristics of the subtype of incontinence, the blanket term of “the economics of incontinence” is less applicable, one should drill down into the relevant treatments of these aetiological subgroups. The present chapter takes account of these considerations, and is arranged according to incontinence subtype.

More recently, clinicians have become aware that uterovaginal prolapse treatments require economic analysis, which have received little attention to date. As the population becomes increasingly elderly, prolapse will become more common. Resources allocated to this condition need to be spent prudently. Finally, the last taboo of faecal incontinence has come into the spotlight. As a wider range of conservative, surgical and neurostimulation treatments become available for this condition, our scientific community has realised that economic analysis of these treatments is becoming feasible and increasingly important. Thus for the first time a part of this chapter is dedicated to the economics of faecal incontinence.

In the first three monographs produced by the ICI, the broad context and some of the statistical methods of economic analyses were included. However, the range of mathematical treatments of these conditions has expanded so that a brief summary of newer methods is now included.

II. BACKGROUND

1. PLACING ECONOMIC ANALYSIS OF CONTINENCE CONDITIONS INTO PERSPECTIVE

When a patient with urinary or faecal incontinence (and to some extent prolapse) walks into a doctor’s office in any country, they will have already incurred some personal costs in managing the condition at home, such as pads or laundry expenses. He or she will then have a basic consultation, tests will probably be ordered, a range of outpatient conservative (including pharmacological) treatments may be prescribed, or a surgical procedure that may involve day-only stay or an inpatient stay may be recommended. At some stage, particularly in the elderly, the patient may suffer a urinary infection which may be associated with the incontinence/cystocele, or may slip in their urine on the way to the toilet and have a fall. These are known as the direct personal and treatment costs of the condition, which are included in Cost of Illness (COI) studies.
The patient may have lost time off work, stopped heavy lifting, or had to retire early because of the condition. These are known as Indirect Costs, which are often included in COI studies. Finally, the patient is likely to have undergone pain (from urine excoriation on the perineum) or suffering (e.g. inability to go out of the house due to constant leakage and foul smell rendering them socially unacceptable) which are known as the Intangible Costs. These are seldom included in simple COI studies, but are considered if Quality of Life tests are included in the study.

The way in which these various costs can be measured varies a great deal from country to country. Although all countries regulate health care to some degree, they do so in very different ways (e.g., the regulatory environment within which health care is provided, insurance, limitations on the building of hospitals, and control over health care costs such as drug prices [1]. Health care systems, as a nation, province, or health plan, can limit the treatments for which they will pay or set limits on the prices. This has implications for estimating costs, and places an even greater burden on researchers to describe explicitly where, when and how the costs were calculated.

Patients often observe very different "costs" for health care goods and services. Cost is the amount to produce the good, whereas a charge represents the amount on a bill, which often includes profit for the manufacturer. Therefore, different accounting systems can yield very different cost estimates.

Most of the hospital accounting systems in the U.S. focus on billing and payments. The charges listed on the bill usually overstate costs and are rarely paid in full by the payer. For example, in a recent study of the costs of surgery for female fecal incontinence (FI) in the US [2], hospital “charges” were defined as the amount that the hospital actually billed to the payer for the surgery etc, but the hospital “costs” were defined as the amount that the hospital actually received in payment! Only after understanding this definition can one make sense of the fact that hospital “charges” for FI surgery rose from $48 million to $57 million over 3 years, but the hospital “costs” increased only slightly from $23 to $24.5 million over the same 3 years (Figure 1).

In the U.S., researchers have developed imperfect methods for adjusting the charges with a hospital-specific ratio of costs to charges to better estimate costs [3]. Charges, however, are not always available. Integrated health care systems, including Canada and the U.K, do not routinely generate bills. For these systems, researchers have developed methods for generating pseudo-bills and cost estimates [4-6].

Many cost determination methods are used. Most analyses include a combination of “gross costing” and “micro costing” [7]. These terms are similar to the phrases “top-down” and “bottom-up”. Accounting and billing systems use micro-costing methods, whereby detailed estimates of time and products (inputs) are combined with unit costs to estimate total costs. Micro-costing (or “bottom-up”) is challenging to perform because a single inpatient stay or outpatient procedure might have hundreds or thousands of inputs. Even when there is just a single input, such as a tablet, the cost can vary by location or the time of purchase if prices fluctuate. At the other end of the spectrum, gross cost methods (“top-down”) identify a limited number of important characteristics such as the Health Care Resource Group (HRGs) in the U.K., Diagnosis Related Groups (DRGs) in the U.S or Australia, and length of stay. These characteristics can then be combined using different techniques to estimate total costs.

Accounting systems are limited in that they always report the health care payer’s costs or charges. Since societal costs are of most interest [7, 8], one must distinguish between and include both provider-incurred costs and patient-incurred costs. This distinction is important for urinary incontinence, since most providers do not pay for routine care (e.g., pads and protection). These costs are usually incurred by individuals, and in 1995 the routine care costs in the U.S. represented at least 50% of the total cost of urinary incontinence [9, 10].

Thus the conclusion drawn by a researcher may be heavily dependent upon the completeness of their methodology. For example, a recent study from the USA [11] analysed Medicare claims for the treatment of urinary incontinence among women aged 65 or older for 3 years (1992, 1995, 1998) including outpatient, inpatient and emergency department visits.
Such Medicare claims nearly doubled over the time frame, from $128 million to $234 million, largely due to increased numbers of women treated by office visits and ambulatory (day only) surgery for items such as collagen injections. When the per capita changes were analysed, and inflation was considered, costs had actually declined by 15%. However, the editorial comment following this article points out that Medicare claims do not quantify pad usage, and cannot record pharmacotherapy for urge incontinence. Since we know that overactive bladder is more common as age increases, such pharmacotherapy is likely to be increasingly important in the over 65 age group, so that the conclusion of a 15% drop in per capita Medicare expenditure are not likely to be valid in general. The editors pointed out that the article was mainly representative of patients with stress incontinence as a result. Such methodology issues are important.

In the example described above, the “perspective” that the researchers used was that of Medicare claims. In other words, Medicare was the “payer”, not the patient. This highlights the fact that costs can be evaluated from several different perspectives. The four most commonly used perspectives are (1) overall society costs, that include all aspects of care and treatment, (2) the payer, such as Medicare, (3) the provider, such as a hospital or managed care plan and (4) the patient.

In general, health economists prefer that a societal perspective (include all costs) is used [7,8]. This facilitates comparison of the cost of illness across different countries. The problem is that different countries use different frameworks for reimbursing some or all of the costs of various conditions, so that international comparison remains controversial.

2. COUNTRY SPECIFIC ECONOMIC ISSUES

From the perspective of a patient, large costs are often incurred when paying for routine care products, treatments, lost wages, and long-term care. These patient costs vary by country. For example, in Sweden and Spain, the government (tax based) health insurance does cover routine care products. In the UK, age-dependant patient subsidies are available for pads. In Germany and Spain, pad costs are reimbursed if prescribed by a doctor [12]. In Australia, low-income patients can apply for a subsidy to reimburse most of their routine care products, but more wealthy patients must pay all costs. In the USA, such products are not covered at all and can be very expensive.

From the patient’s perspective, out of pocket expenses for outpatient physiotherapy (pelvic floor muscle training) also varies considerably between countries. For example, a set number of physiotherapy visits (4-6) are free of charge in the UK and Spain, but patients in other European countries must give a co-payment that represents about one third to one tenth of the real cost (Table 1 below).

The degree of government subsidy to the patient varies greatly by country. In the UK, most patients use the National Health Service (NHS) so that all office visits, tests, outpatient visits and surgical treatments are free to the patient. Pharmacotherapy does attract a small out of pocket payment for each drug. In Italy and Sweden pads are reimbursed, but not in Germany. Pads are not routinely subsidized, only at the discretion of the local Care Trust. In Australia, about 70% of patients only have government insurance, similar to the UK NHS, but 30% of patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Total costs</th>
<th>Description of program</th>
<th>Costs incurred by Health Care System</th>
<th>Out-of-pocket payment patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>£ 94</td>
<td>One visit to urologist/gynaecologist/general practitioner for prescription and 10 visits to physiotherapist for training</td>
<td>£ 58</td>
<td>£ 36 unless additional complementary private health insurance</td>
</tr>
<tr>
<td>Germany</td>
<td>£ 99</td>
<td>One visit to gynaecologist for prescription and six visits to physiotherapist for training</td>
<td>£ 81</td>
<td>£ 8 co-payment on physiotherapist, plus £ 10 prescription charge None</td>
</tr>
<tr>
<td>Spain</td>
<td>£ 240</td>
<td>One visit to gynaecologist for prescription and six visits to physiotherapist for training</td>
<td>£ 210</td>
<td>£ 67 fees None</td>
</tr>
<tr>
<td>Sweden</td>
<td>£ 467</td>
<td>One visit to gynaecologist and three visits to urotherapist</td>
<td>£ 400</td>
<td>None</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>£ 64</td>
<td>Four visits to continence nurse/physiotherapist in primary care</td>
<td>£ 64</td>
<td>None</td>
</tr>
</tbody>
</table>

* Costs from Hospital Clinic, Universidad de Barcelona, Barcelona, Spain.
* Costs from PSSRU, 2003 [30].
also have private insurance so that inpatient treatments attract a rebate from their health fund. In the USA, adults over age 65 and those with a disability are covered by the Medicare program. This provides coverage for inpatient, outpatient and pharmacotherapy, although patients are generally responsible for sizable co-payments and nursing home care is capped. Those not covered by Medicare often have private insurance or Medicaid (a program for people with low incomes); nonetheless about 48 million Americans lack any insurance.

In the Netherlands, all legal residents are obliged to purchase a basic health policy (the purchase of a complementary policy covering extra health services remains voluntary). The choice of health insurer and type of health plan is free. The government establishes what is in the basic package and under what conditions people are entitled to care.

As regards long term care benefits for those in residential care, considerable variation occurs. In the USA, Medicare and Medicaid benefits are time limited for re-imbursements to nursing homes and other assisted living facilities. Usually after several months benefits stop and payment must come from private insurance or the patient’s pocket. In Australia, low income patients who have no private superannuation (pension fund) can receive the “old age pension” which covers fully funded long term care, albeit in lower-calibre facilities than would be chosen by those who could afford better (similar to the Netherlands system). In Japan, generous long term benefits are provided to long term institutional residents, so that out of pocket payments are reduced.

3. OTHER “FRAMEWORK” ISSUES

Another methodological issue that must be incorporated into any study is the context of time framework. As mentioned in the Introduction, many continence treatments are time dependant, ie their effect extinguishes over time. However, from an economic view, a standard methodology exists. First the author of any study must identify the year for which the costs were calculated. Some economic studies collect costs over many years and also make projections about the future. In this case, the costs should be adjusted so that they reflect a single year. Future costs should be discounted to represent the present value. Controversy exists about the appropriate discount rate [13-15] but most international studies use a discount rate of 3% per annum. See Adang et al. [16] for example.

Second, costs borne in past years should be expressed in the current year’s dollars. In many countries, past and future costs can be adjusted by the Consumer Price Index or other appropriate indices for all urban consumers (e.g., www.stats.bls.gov). In the UK, the Health Service Cost Index or the Retail Price Index, published by the NHS Executive, Leeds, UK, can be used to adjust the costs of health care services; other indices would be used to adjust other items, such as wages (www.statistics.uk.gov). Most countries track inflation using relatively standardized methods, thereby providing a method for inflating past costs.

Caution is needed because general inflation relates to the cost of a consistent set of goods over time, eg the goods must be of the same quality over time, and thus the costs observed five years ago can be observed today. If so, then the inflation index is informative. However, medical goods change rapidly. For example re-usable laparoscopic equipment has been replaced by disposable equipment which is usually more expensive, and the newer drugs for OAB are generally more expensive. This makes it difficult to determine whether any changes in price is due to inflation or due to improved quality. Thus, just inflating costs from many years ago can be misleading.

In summary, defining and measuring costs in health care can be difficult. Often there is large variability in costs. Given this uncertainty, researchers should use sensitivity analysis to investigate how different cost estimates can influence the results. By this we mean re-running the analysis with different input parameters. As we describe in the next section, explicitly describing these contextual issues is crucial for interpreting results.

III. TYPES OF ECONOMIC ANALYSIS

1. OVERVIEW

A typology of economic analysis for health and medicine has emerged over the past few decades. This section reviews these studies.

a) Cost of illness (COI)

As already described, COI studies summate the costs related to a condition for a given population. The costs are annualized for a given year (ie 2008). A COI is a descriptive analysis and is only as good as its assumptions and only as complete as current knowledge allows. However, COI studies provide little information to decision makers about how to allocate scarce resources for treating conditions, because there is no attempt to measure the “value” of the relevant treatments or health interventions.

b) Cost minimization analysis (CMA)

CMA compares the costs of alternative health care strategies, assuming that the benefits of the alternatives are equivalent. When the two treatments are truly equivalent in their risks, outcome, and an individual’s preference for them, then a cost minimization analysis is sufficient; the cheapest intervention is to be preferred.
c) Cost consequence analysis (CCA)

CCA is a variation on cost-minimization analysis, which involves assessing whether a new treatment results in a greater decrease in health care utilization than another treatment. Thus costs of the intervention are compared to health care utilization, such as the cost per hospitalization averted. There is a naturally appealing rationale for conducting this analysis. Unfortunately, when examined in detail, this rationale boils down to an analysis of whether the new treatment saves money in comparison to the alternative treatment. Accordingly, a cost-utility or cost-benefit analysis provides many advantages over a cost consequence analysis.

d) Cost-effectiveness analysis (CEA)

CEA refers to the broad class of calculations where the effectiveness measure is a general health outcome. CEAs with narrowly focused health outcomes (e.g., incontinence episodes) have well-accepted limitations. Most notably, the use of narrowly focused health outcomes will miss other important effects. For this reason, there has been widespread agreement on the use of quality adjusted life years (QALYs) as the preferred health outcome in cost-effectiveness analysis.

e) Cost-utility analysis (CUA)

CUA refers to a CEA when QALYs are used as the outcome measure. Gold et al [7] and Drummond et al. [8] have published texts that discuss standard techniques for conducting a CUA. In health and medicine, the CUA is considered to be the gold standard. Utilities capture all potential benefits of an intervention and allow comparisons with other health conditions, making cost-utility analysis a powerful research tool.

Compared to other medical fields, we have minimal data on utilities in incontinence or on the effect of treatment or change in incontinence severity upon preferences, to date.

Data in a CEA and CUA are represented by an incremental cost-effectiveness ratio (ICER). The ICER represents the average cost of the intervention group minus the average cost of the control group. This amount is then divided by the average utility of the intervention group minus the average utility of the control group (see Section IV.2).

f) Cost benefit analysis (CBA)

Involves measuring the benefits in dollars. When everything is measured in dollars, optimal choice can be easily found by addition and subtraction. However, it is difficult to measure benefits in dollars, and many researchers, policymakers and clinicians are averse to placing a dollar value on life. CBA is rarely used in health.

g) Summary

COI and cost-minimization analyses are simple, yet limited economic tools. Most new treatments offer additional benefits at an additional cost. The CBA, CUA and CEA were designed to determine how much money it costs to obtain another unit of effectiveness. Although the CUA is the preferred method, there are many challenges with calculating a QALY. We will discuss these issues in more depth because different methods for calculating QALYs can have a very profound effect on the interpretation of the CEA.

2. DETAILS OF DECISION ANALYSIS

Decision analysis is a tool that can be used to summarize effectiveness data, costs data, or combine both cost and effectiveness data in a CUA. The value of decision analysis is highlighted by a recent multi-site clinical trial by Albo and colleagues [17] that compared Burch colposuspension to fascial sling for stress incontinence. They concluded that the fascial sling yielded a higher rate of successful treatment, measured as a composite outcome, but also resulted in greater morbidity. Even in well-designed multi-site clinical trials, the results may be ambiguous. Decision analysis may be used to overcome this ambiguity. Decision analysis is a quantitative probabilistic tool for resolving problems when there is uncertainty with regards to treatment options.

There are two primary decision analytic methods (see below); each has its strengths and weaknesses. The starting point with any decision analysis is the delineation of a clinical question, such as how to treat women with stress urinary incontinence. The question should fully and fairly address the clinical question or questions. One might develop add on questions, such as how to treat women who had surgical failure, but it is often best to address these more specific questions as part of the broader decision analysis.

A benefit of decision analysis is that researchers can combine data from multiple clinical trials and marry that data to observational information (e.g., long-term follow-up data). Decision analytic tools are flexible and can be used to identify the treatment that maximizes quality of life. One can also use the same model to address issues of cost-effectiveness. Hence, one of the first tasks in the decision analysis is to identify the primary outcome. Outcomes such as quality adjusted life years (QALYs), that can reflect treatment and disease, are recommended. By using QALYs, one can overcome conflicting data—for example, the finding that vaginal slings have higher success rates but also greater morbidity. As is discussed elsewhere in this chapter, QALYs value all aspects of quality of life and combine that information with mortality. Next, the researcher must determine whether the model will include cost information or not. Some decision analytical models focus only on
outcomes, while others add cost data to address resource allocation questions.

By combining data from multiple sources, decision analysis can be used to model lifetime costs and benefits. Researchers are often tasked with identifying the treatment(s) that maximizes lifetime benefits or lifetime cost-effectiveness. Randomized trials, while the gold standard for assessing causation, are time limited, often following participants for less than five years. Decision analysis can extend such data to consider future events, such as surgical failure rates, nursing home admission or life expectancy. Decision analysis can also be used to understand if the analysis differs by perspective. Payers, providers and patients all have different perspectives, and decision analysis makes it relatively easy to consider each of these perspectives and whether they differ from a society perspective. Frequently it is helpful to understand where the perspectives diverge as this can highlight conflicting incentives. Aligning incentives, when possible, is often seen as socially optimal for governmental regulations and programs.

a) Steps in a decision analysis

Decision analysis can be boiled down into five steps. The first step involves identifying the structure of the problem and this requires the listing of all decision alternatives, all clinical outcomes, and a sequence of events. Once step one is complete, then step two involves assigning probabilities to all chance events (e.g., death). Step three involves assigning outcome (e.g., QALYs) to all outcomes. The fourth step involves the mathematical calculation of expected utility for each strategy. Step four will often identify the preferred strategy. The final step involves identifying the robustness of the model and this is achieved by conducting sensitivity analysis.

Every decision model involves some assumptions. Frequently assumptions are needed to incorporate clinical trial data in the model. For example, a common assumption is that the effect shown in a clinical trial is generalizable to the broader population—treating women with Burch colposuspension will result in effects like those seen in Albo and colleague’s [17] paper. Some assumptions may seem trivial, but it is best to delineate each assumption along the way. Published decision analysis should include a table of assumptions along with other data inputs; frequently this is the first table in the decision analysis.

The clinical question and the structure of the problem (step 1) should provide guidance on the decision model. Frequently decision trees are used because they address the question at hand. Decision trees are so named because they look like a tree with a trunk, branches and leaves.

While decision trees are easy to describe and conduct, it is hard to include time in the analysis. Diseases often change over time and people may transition into and out of different health states. A strength of Markov models is their ability to include these time-related transitions. We will discuss decision trees first and then Markov models in more detail afterwards.

b) Decision Tree

In the decision tree, there is a distinction between a decision node and a chance node. A decision node is a point where a choice is made by the decision maker (typically a physician or patient). For example, for a woman with stress incontinence, the choice to operate (yes or no) would be represented with a decision node. A choice must have at least two options and more than two choices are permitted. However, each choice must be mutually exclusive. A patient cannot choose both operation and no operation. A chance node is a point where chance determines fate. For example, the decision maker chooses to operate or not operate, and hopefully the treatment is successful, but treatment success or failure is a chance node. Not only must chance nodes be mutually exclusive, but they must also be collectively exhaustive (one of the changes must happen and the sum of probabilities for all of the chances must add to 100%).

In addition to chance and decision nodes, there are terminal nodes. These nodes are the final outcome for the pathway taken. Sometimes understanding the nodes makes more sense when looking at the pictorial representation. Figure 2 shows a hypothetical decision tree for treating a patient with stress incontinence. In this hypothetical situation, we structure the model to have two options: surgery or drugs. It is overly simplistic in that we do not differentiate between drugs. Also, the model is completely hypothetical in that a surgical death rate of 10% and a 10% cure rate are not realistic.

The main choice is surgery versus medical management. Surgery carries some risks—a small probability of operative death. The decision nodes are represented by squares while chance nodes are represented by circles. The terminal nodes are cure, no cure, operative death or non-adherence, which is the same as no cure. This is a hypothetical decision model, and most decision models are much more complex. Clearly this model could be expanded to include behavioral treatment and each decision node could be expanded to consider all relevant alternatives (sling, Burch colposuspension, tension-free vaginal tape) (Figure 2).

For the next step in the decision model, one must include probabilities at each chance node. We must identify the probability the disease is cured after operation. Researchers should review the published literature to find this probability and ideally some information about the distribution around this probability (e.g., probability= 58% with a 95% CI 51-68%).

After including probabilities, one must place values next
to the terminal nodes. These values must be a single outcome and QALYS are preferred, although life years are used for some diseases. With outcome and probabilities, one can then “run” the decision tree. Because there is one decision node with two options, we will be computing expected values for the two options. Running the model involves starting at each endnode and working left or backwards. The expected value for the surgical survival node is 3.8 QALYS (Figure 3).

The expected value for the surgical operative death node is 0. When we combined a 10% chance of operative death (0 QALYS) and a 90% chance of survival (3.8 QALYS), we find the expected value of surgery is 3.42 (Figure 4). If we do the math for the lower branch, we get the expected value for drug therapy is 3.76 QALYS. Because 3.76 >3.42, we would recommend surgery over drugs if the sensitivity analysis shows this result to be robust. The decision tree in the example focuses on QALYS for UI treatment and it ignores and cost differences, but it could be easily modified to include cost information.

c) Markov Model

The decision tree, as shown above, assumes the chance of events is stable over time. Our knowledge about urinary incontinence suggests otherwise. A person, for example, could get surgery for stress incontinence, but over time we need to include the potential for surgical failure. Markov models are good for incorporating changes in health states over time. At their core, Markov models are mathematical techniques, derived from matrix algebra, that describe the transitions a cohort of patients make among a number of mutually exclusive health states over time. The model works by cycling to make new calculations for each period of time.

The pictorial depiction of a Markov model is typically shown as a decision state. Figure 5 shows a very basic three-state Markov model. At each period in time, a person has to be in one and only one of the states. But with each change in time (cycle), the person can move to another state, shown with arrows, depending on the possible states and a probability. If the person dies, they are shown to enter the death state. The person cannot leave this state.

Some aspects of the Markov model construction are similar to a decision tree and some are different. Setting up the model is quite similar. One must identify the health states and the transition probabilities. What is quite different is that one must determine the cycle length—the rate at which you allow people to change states. The cycle length should be a clinically meaningful period of time and this choice is also frequently affected by the availability of data. There may be publications showing annual failure rates for surgery and so one could choose an annual cycle or choose a monthly cycle, making a correction to the probabilities so that the sum of twelve months is equivalent to the annual data.

For a Markov model, one needs to know the value for each state. Again, QALYS is the preferred metric. When the model runs, the program keeps track of the amount of time each person spends in each state.
Transitions to other states are handled by transition probabilities, and decisions, such as the decision to get treatment, can affect transition probability. Models can use cohort simulations where a large hypothetical cohort of patients is run through the model. This does not provide information on the distribution of expected values. Monte Carlo simulations run each patient through the model a large number of times (e.g., $10^4$). In doing so, this provides a distribution and variance information on patients.

With Markov models, sensitivity analyses remain a crucial step to test the robustness of the model. Recent advances in sensitivity analyses and in the graphical presentation of data general require the use of specific software. Although some people program Markov models into a spreadsheet, such as Excel, both Tree Age and Decision Maker software are well known for their ability to streamline decision analysis and provide many advanced features that would be very difficult in Excel.

### 3. STATISTICAL ANALYSIS

One of the tasks of data analysis is to provide answers to the research questions being studied. When a study examines the relationship or association between two variables, such as the frequency of incontinence and the cost of incontinence care, then a bivariate correlation is useful. The **correlation coefficient** measures a linear relationship between these two variables to show the degree of association ranging from 0 (no relationship) to 1.0 (a perfect positive relationship) or -1.0 (a perfect negative relationship). When there is more than one factor that can explain the variation of the cost of treating incontinence, such as the age of the patient, other illness conditions, and employment status, a **multivariate regression** analysis is required. For instance, in a study by Birnbaum and others [18] to examine the costs of stress urinary incontinence, their **log-linear regression** model indicated that patients with surgery would cost more than those without surgery, and patients with other co-morbidities would cost more than those without. To test the statistical significance of these covariates, a **standard error of the coefficient** of these variables is needed, for which a t-test can be used. The predicted log-linear dependent variable can be transformed into a nominal value.

Another useful application of multivariate regression model using a **dummy variable** may occur when a cost-effectiveness analysis of a particular intervention (clinical trial), is desired. For instance, in a randomized clinical trial of a behavioral therapy to reduce urinary incontinence in nursing homes Hu et al. [19] used a Dummy Variable (a value of 1 for treatment group and zero for the control group) that the treatment group’s wet episodes have been reduced by 26% over the baseline while the control group remained the same after the 22-week follow-up period. When comparing cost differences between two conditions or two programs, (e.g. [18]), the study used the dummy variable (stress incontinence equals 1 and non-stress incontinence is ‘0’) in the regression model to show that the added cost (incremental cost) for stress incontinence patients was 30% higher than non-stress incontinence costs, after controlling for other covariates.

When incontinence episodes have a **discrete probability distribution**, the probability of either having an incontinent episode or not having one episode is random, these events can be analyzed by a negative binomial distribution. Under this distribution, a mean of a given time period (such as the weekly number of episodes of urinary incontinence), and variance of the incontinence can be estimated. For example Hughes and Dubois [20] used such a **negative binomial distribution** to compare the cost-effectiveness of extended-release formulations of oxybutynin and Tolterodine for treatment of OAB.

With discrete value and skewed distribution, negative binomial distributions can also be used for the regression model, instead of using a linear regression model. In the statistical literature, the **Poisson distribution** is a special case of binomial distribution. In this case, the variable takes a value of 0, 1, 2, 3,..., $n$. Poisson regression is an extension of the negative binomial regression.

### 4. BUDGET IMPACT ANALYSIS (BIA)

Providers and payers often have priorities that are not directly addressed by a cost-effectiveness analysis from a societal perspective. The budget impact analysis (BIA) was developed to inform a decision maker on how alternative technology will affect their budget. A BIA will often focus on the decision maker’s costs and over a short time frame (e.g., 1-3 years). Other parameters in the model, such as patient characteristics or input costs, can also be tailored specifically for the decision maker. Making decision based solely on a BIA can lead to suboptimal social
results. Hence, scientists advocate that a BIA be done in conjunction with a CEA so that decision makers are informed about the broader social implications of their decision. The International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org) has created guidelines for conducting a BIA and these can be found on their website.

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD

1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES

There are a number of health outcomes that are used in economic evaluations of incontinence. These include disease-specific outcomes, health status and health value (e.g., QALY). Each is discussed in turn.

a) Incontinence specific outcomes

Cost-Effectiveness in Health and Medicine [7] recommends using QALYs as the effectiveness measure in the CEA. However, the panel also notes that analysts can use a clinical outcome measure. For incontinence, clinical outcome measures include 24-hour pad test, a voiding diary, or urodynamics. These outcomes are attractive for clinicians because they often use these measures in clinical practice.

Clinical outcomes can be very valuable in identifying when a treatment is efficacious. However, using clinical outcomes in a CEA yields results that are limited in scope. A treatment might have improved a person’s quality of life, but had little effect on the clinical outcome measure. In this case, the results would be biased. In addition, a CEA with a clinical outcome measure might not be comparable to another CEA with a different clinical outcome measure. A clear advantage of cost utility analysis is that QALYs can be generalized beyond incontinence. For this reason, QALYs and CUAs are the gold standard.

b) Health Status and Quality of Life Measures

There are a number of frequently used and highly regarded general health status measures, such as the SF-36, the Sickness Impact Profile and the Nottingham Health Profile, which describe a person’s current health state. Instruments that assess how a person perceives or feels about their health state are called quality of life (QOL) measures.

Chapter 5 in this book reviews generic and disease – specific quality of life measures, which are useful for understanding the effects of a treatment. However, because they cannot be used to create QALYs they are of limited value in economic analysis. The exception is the SF-36 for which Brazier et al. [21] have created a rudimentary utility scoring system.

c) Health value

Although there are several ways of measuring the value of a health state, the most common are willingness to pay (WTP, [22]) and the quality-adjusted life year (QALY). We focus on QALYs as they represent the current standard for measuring health value.

QALYs denote the relationship between the value of a given health state and the length of time a person lives in that health state. The value of a given health state is measured in ‘utilities’, where ‘utilities’ represent preferences for a given health state.

To understand utilities, consider the following. Most people would prefer to be healthy over a given time rather than suffer constant urinary or fecal incontinence. Utility measurement refers to valuing these preferences on a life-death scale with endpoints of 1.00 and 0.00, where 1.00 is perfect quality of life (best imaginable) and 0.00 is death equivalent quality of life. For example, the measured utility for urinary incontinence may be 0.60. If treatment improves this to 0.70, then the value of the treatment is 0.70 – 0.60 = 0.10. If this utility gain is maintained over time, say for 10 years, then the gain is 0.10 x 10 = 1.00 QALY. Because utilities fall on the life-death scale, they are (in theory) common across all health states and therefore can be used to compare the effect of interventions in different health fields, or different interventions within the same field. For example, the QALYs gained from treatment for incontinence could be compared with those gained from treatment for depression. Where treatment costs (including costs to the patient) are known, the treatment providing the lowest cost-per-QALY gained is preferred as this ensures society gains the greatest benefit from the health care dollar.

Direct and indirect methods have been used to elicit utilities [23]. The most common direct elicitation methods for valuation include time trade off (TTO), standard gamble (SG), and the visual analog scale (VAS). For description of these methods, see our previous chapter in this ICI Monograph series [24].

1. INSTRUMENTS MEASURING UTILITIES SUITABLE FOR QALY CALCULATION

Multi-attribute utility (MAU) instruments can be used instead of the direct elicitation methods. Simply, a MAU-instrument decomposes HRQoL into health domains (e.g., mobility and emotions). Respondents provide estimates for each of the parts, which are then ‘valued’ and recomposed back into a utility. The three most commonly used MAU instruments are QWB, HUI and EQ5D (as reviewed by Hawthorne & Richardson [25]).

2. QUALITY OF WELL-BEING INDEX (QWB)

The QWB has three dimensions (Mobility, Physical Activity, and Social Activity), with 3–5 levels each,
and 27 illness symptoms. [26]. The QWB requires trained interview administration (15–35 minutes), although a shorter version is available; a self-report version is under development. The upper boundary is 1.00, lower boundary is 0.00

3. Health Utilities Index (HUI)

The HUI uses 12 items that measure 8 domains (Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain). The upper boundary is 1.00, lower boundary is –0.36.

4. EQ5D

The EQ5D was developed by the Euroqol team from 7 European countries [27, 28]. It has 5 items measuring Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression. The upper boundary is 1.00, lower boundary is –0.59.

5. SF6D

Although two different algorithms have been published for deriving preference-based values from the SF-36, only the second is described here [21]. Whenever SF-36 raw scores are available, SF6D utilities can be computed. The SF6D measures physical functioning, bodily pain, mental health, physical role, emotional role, social functioning, and vitality. The endpoints for the SF6D are 1.00, and 0.30 for the worst possible health.

6. Other MAU instruments

The Assessment of Quality of Life (AQoL) includes five dimensions: Illness (not used in utility computation), Independent Living, Social Relationships, Physical Senses and Psychological Well-being [29]. The upper boundary is 1.00, lower boundary is –0.04. The Rosser Index has two dimensions measuring disability and distress, and measured 29 health states. Values (magnitude estimation) were from a convenience sample of 70 respondents [30]. A revised version in the early 1990s included discomfort as an additional dimension [30]. Administration requires a trained interviewer. The upper boundary is 1.00, and the lower boundary –1.49, which means that health states worse than death are permitted. The 15D was created in Finland. It has 15 items, measuring Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Elimination, Usual Activities, Mental Function, Discomfort & Symptoms, Depression, Distress, Vitality and Sexual Function [27]. The upper boundary is 1.00, lower boundary is +0.11.

For a full review of cost utility analysis up to 2004, see our previous chapter [24]. For subsequent studies, see Section V of this chapter.

One final note about collecting utilities is warranted. Many people with incontinence are not cognitively able to complete a MAU or go through a standard utility elicitation process. Some of the MAUs, such as the HUI 3, have been validated for use with proxies. Although not always possible, if proxies are expected then proxies should be gathered for all cases, even those patients who complete the utility measure themselves, so that the method is applied in a standard fashion.

2. “DO IT YOURSELF” - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE’S RECOMMENDATIONS

The cost utility analysis (CUA) now represents the gold standard for medical decision making. Therefore, the remainder of this section highlights ten key issues that must be addressed in a CUA. These ten principles, summarized below, comprise an appropriate minimum standard for performing and reporting cost utility analyses. The principles were identified from guidelines established by the Panel on Cost-Effectiveness in Health and Medicine convened by the United States Public Health Service [7] Each principle should be explicitly addressed in every study.

1. The Research Question must be clearly stated. All CUAs must compare at least two different treatments or interventions. One of these should include the current standard practices. For example when comparing surgeries for stress incontinence, one of the comparators should be a longstanding method; avoid comparing two new methods side by side.

2. The Time Frame over which costs and benefits are measured should be long enough to capture the economic impact of an intervention and future health outcomes. Pharmacology studies of 12 weeks duration give very little real economic information, and surgical complications/ failures seldom emerge in less than 1-2 years.

3. Perspective: The choice of perspective should be clear. Total society perspective (all payers) is the gold standard. Other perspectives, such as the payer or patient perspective, may be useful but must be stated clearly.

4. Probabilities are needed for each “chance” event, such as chance of cure or chance of an adverse event. The best sources of probabilities come from meta-analyses of randomized clinical trials, or if not available use data from individual clinical trials.

5. Costs: Units of expense and unit costs should be described in detail. Information on the source (e.g., charges, payments) and year of the cost data should be presented. If the costs were inflated and/or converted from another currency, then this must be described.

6. Outcome Measure: Measures of effectiveness depend on the type and objectives of analysis. Quality adjusted life years are the gold standard, as described previously in this chapter.

7. Analytic Model: Each intervention being assessed
must be described and possible courses of events identified, including the expected course of disease, treatments, complications, and outcomes. This may be performed using a spreadsheet/clinical trial path, or Decision Tree, or Markov Model.

8. **Discounting:** Since the value of both costs and benefits may decrease over time, discounting is used to calculate the present value of money and health states that will occur in the future. Future costs and utilities should be discounted to present value; 3 % per year is a recommended starting point.

9. **Incremental Analysis:** The purpose of a CUA is to describe the relative value of one health care strategy compared to another. An incremental cost-effectiveness ratio (ICER) is the incremental cost divided by the incremental effectiveness of intervention a compared to intervention b, and is calculated as follows.

\[
\text{ICER} = \frac{\text{Average Cost}}{\text{Average Utility}}_{\text{intervention A}} - \frac{\text{Average Cost}}{\text{Average Utility}}_{\text{intervention B}}
\]

Averages should be used rather than other measures of central tendency, such as medians, because it is important to include the effect of outliers. The leverage of the outliers should be tested in a sensitivity analysis.

10. **Sensitivity Analysis:** A sensitivity analysis should allow the reader to understand whether the conclusion of the analysis would hold true if either the Costs or the Probabilities (of cure or complications) were to vary substantially. For example if one treatment costs 5,000 Euro and has a cure rate of 90%, and the second treatment costs 2,000 Euro with a cure rate of 80%, then the ICER will assess whether the resultant benefit in QALY/Quality of Life makes the first treatment worthwhile.

Having reached this conclusion, the researcher should then vary the costs and the cure rates in the model, to see how much variation in real life would be allowed yet still maintain a valid conclusion.

Documenting these boundaries helps define the conditions under which a treatment is preferred. Researchers are developing innovative methods for conducting sensitivity analyses.

Probabilistic models that use simulations are becoming more common, although they can be computationally complex.

---

**V. SUMMARY OF RECENT ECONOMIC ANALYSES**

*Note:* the Committee strongly recommends that all studies of economic analyses should publish the timeframe in which the study was actually performed (because the date of publication is often months to years later), and that the currency employed be stated for that year/timeframe. This is essential for accurate discounting of costs over time, and for comparing economic analyses of treatments performed in different years.

1. **SURGICAL TREATMENT COST EFFECTIVENESS STUDIES**

   **a) Is treating incontinence cost-effective?**

Since the last ICI meeting in 2004, several cost-effectiveness analyses of surgical interventions for stress incontinence have been published. These analyses systematically compare costs and outcomes of surgical treatments for stress urinary incontinence. The largest number of cost-effectiveness analyses were done comparing less to more invasive procedures – tension-free vaginal tape (TVT) vs. alternative surgeries for stress incontinence and laparoscopic vs. open procedures. These are inherently appropriate for CEA since the less invasive approach is more likely to be less costly (both direct costs of surgery, hospitalization and indirect costs of shorter recovery time) yet may be less effective, be associated with more adverse events and/or result in lower health-related quality of life.

   **b) TVT vs. Other procedures**

Several studies compared the cost and cost-effectiveness of incontinence surgeries, supporting the finding that tension free vaginal tape (TVT) is more likely to be cost-effective compared with the other surgical procedures. However, there is a need for longer-term follow-up data from methodologically rigorous randomized trials to provide a better data to estimate the relative benefits and cost implications.

Cody and colleagues [31] evaluated the effectiveness and cost-effectiveness of tension-free vaginal tape (TVT) compared to standard surgical interventions for stress incontinence [31, 32]. Effectiveness and cost (2001 pounds Sterling £) estimates came from a systematic review of studies published from 1966 to 2002 that compared TVT with any alternative surgical or injectable agent therapy and utilities were estimated using the EQ5D in a surgical trial [33]. A Markov model was developed to estimate costs and quality-adjusted life-years for up to 10 years following surgery. They found that open colposuspension, laparoscopic colposuspension and traditional slings have similar cure rates to TVT, whereas injectable...
agents have lower cure rates. In economic modeling, TVT dominated open colposuspension (lower cost and same QALYs) within 5 years after surgery. The range of outcome measures used to define ‘cure’ were not described, which may affect the accuracy of these conclusions.

However, there were no randomized controlled trial (RCT) data beyond 2 years post-surgery, and long-term effects could not be ascertained. TVT was more likely to be cost-effective compared with the other surgical procedures. Increasing the absolute probability of cure following TVT increased the likelihood that TVT would be considered cost-effective. The likelihood of TVT being cost-effective was 86% if decision-makers are willing to pay up to £30,000 per additional QALYs. In sensitivity analyses, TVT’s dominance depended on the assumption that retreatment open colposuspension has lower cure rates than a first colposuspension and the rate of retreatment. In the short- to medium-term the effectiveness of the TVT is similar to alternative procedures and TVT is less costly. Yet, they concluded that the long-term performance of TVT for effectiveness and adverse effects is unknown.

Wu and colleagues [34] performed a methodologically excellent cost-effectiveness analysis of Burch colposuspension compared with TVT for stress incontinence. They developed a Markov decision model to compare costs ($2005 US dollars) and QALY’s (on Health Utilities Index) over 10 years from a health care system perspective. Probabilities, costs and utilities were estimated by literature review and used generalizable measures. After surgery, outcomes included cure, persistent stress incontinence followed by second surgery, and persistent stress incontinence and mesh erosion after tension-free vaginal tape. In their base-case, the Burch strategy cost more than TVT ($9320 vs $8081) but was slightly more effective (7.260 vs 7.248 QALY’s), with an incremental cost-effectiveness ratio of $98,755 per QALY. The model was most sensitive to cost difference between the strategies, utility, probability of mesh erosion and the relative risk of a cure. The incremental cost-effectiveness ratio was less than $50,000 per QALY when the relative risk of cure after Burch vs. TVT was greater than 1.09. In this well done study using state-of-the-art methods, Burch colposuspension was not cost-effective compared with TVT. However, if the tension-free vaginal tape failure rate was to increase over time, Burch may become cost-effective, reinforcing the need for long-term follow-up in surgical trials and cohorts.

Manca et al. [33] assessed the cost-effectiveness at 6 months of TVT compared with open Burch colposuspension as a primary treatment for urodynamic stress incontinence in 344 women in a multicentre RCT at 14 centres in the UK and Ireland. Resource use included length of hospital stay, time in theatre and management of complications and was based on UK unit costs at 1999-2000 prices. They collected primary data on QALYs with the EQ-5D health questionnaire. At 6 months TVT dominated colposuspension: TVT had lower mean costs and higher mean QALY’s. TVT resulted in a mean cost saving of £243 (95% CI £341, £201) compared with colposuspension and differential mean QALYs per patient (TVT - colposuspension) of 0.01 (95% CI -0.01 to 0.03). In sensitivity analyses, the probability of tension-free vaginal tape being, on average, less costly than colposuspension, was 100%, and the probability of tension-free vaginal tape being more cost-effective was 95% if the decision-maker was willing to pay £30,000 per additional QALY. Over six months, TVT was a cost effective alternative to colposuspension. The study was limited, however, by short follow-up.

Moreno et al. [35] performed a cost-minimization analysis of ambulatory surgery compared with inpatient surgery for TVT in a public hospital in Spain. They used activity-based (micro) costing of surgery, emergency service and admissions to hospital immediately following surgery. They observed that the mean cost for patients in the ambulatory group was 42% lower than that for the hospitalized patients and that ambulatory surgery had equal efficacy to the surgical intervention.

c) Open vs. laparoscopic colposuspension

A methodologically excellent study by Dumville et al. [36] compared the cost-utility of laparoscopic versus open colposuspension to treat female urinary stress incontinence at 6 months. Cost utility analysis was performed alongside a RCT at 6 centres within the UK. Data on costs (£) and generic health-related quality of life (EQ-5D) were collected and patient-specific quality-adjusted life years (QALYs) calculated. Healthcare costs over 6-month follow up were higher for the laparoscopic arm than for the open arm (£1805 vs. £1433; differential mean cost £372; 95% CI 274, 471) due to increased theater costs. QALYs were slightly higher in the laparoscopic arm relative to the open arm (0.005; 95% CI -0.012, 0.023).

The ICER was £74,400 at 6 months. At 24 months, higher mean QALY’s persisted in the laparoscopic arm and modeling showed the ICER was reduced to £9300 (see Figure 6 below). Limitations include few longer-term data on efficacy of the laparoscopic approach. While laparoscopic colposuspension was not cost effective compared with open colposuspension during the first 6 months following surgery, it may be cost effective over 24 months.

d) Injectable agent therapy

A cost- effectiveness and cost-consequence analysis found that urethral injection therapy is likely cost-effective compared to surgery to treat recurrent stress
urinary incontinence. However, the study was limited by lack of long-term data and choice of outcome measures. Oremus et al. [37] performed a cost-effectiveness analysis to compare each of three surgeries (retropubic suspension, transvaginal suspension, sling procedures) with collagen injection therapy to treat female stress urinary incontinence after the failure of initial surgical treatment. The analysis used decision-modeling from the Canadian health care system perspectives using probabilities from a literature review and generalizable Canadian cost data. While the treatment with the lowest average cost was collagen (2718 Canadian dollars), the surgeries had higher probabilities of success (defined as ‘cure’). The ICERs for all treatment comparisons indicated that the cost to cure an additional patient with surgery could range from 1824 - 6814 Canadian dollars in Ontario and 1388 - 3008 Canadian dollars in Quebec. These ratios were sensitive to changes in the mean number of injections for collagen patients and to a reduction in the length of hospital stay for surgery to 1 day. Each of the surgeries has a relatively small additional cost per cure for stress incontinence compared to collagen injections. Collagen injection may be cost-effective as a follow-up treatment to initial surgical failure when the number of injections is kept to a minimum and hospital stays after surgery are relatively lengthy.

Tierney et al. [38] performed a “bottom up” study of the costs of performing TVT, open colposuspension and collagen injections in Scotland but only short term hospital costs were considered.

Kobelt and Fianu-Jonasson [39] performed a cost-consequence analysis including resource utilization and utility of a urethral injection therapy (the Zuidex system of prefilled syringes of non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) gel) compared to TVT for stress incontinence. Utility was measured using the EQ-5D in 82 patients undergoing injections, and cost data were collected prospectively in a 12-month efficacy study of injections and retrospectively for TVT (n = 77). Injection therapy provided utility benefits that were similar to those previously reported for TVT(0.05 at 3 months and 0.01 at 12 months) and was associated with similar or lower overall costs in the short-term (€ 2200 at 3 months and € 3100 at 12 months for injection vis. € 4200 at 6 months for TVT). From an economic perspective, NASHA/Dx gel could be considered at least as favourable as TVT, pending the availability of long-term effectiveness data.

Kalsi et al. [40] performed a cost-consequence analysis of resource utilization and health benefits of intradetrusor injections of botulinum neurotoxin-A at 16 weeks in 101 patients with intractable overactive bladder (OAB) enrolled in a research protocol in the UK. The cost of therapy was quantified based on NHS resources used from the perspective of the UK NHS. After 16 weeks, 65% of patients showed > 25% improvement and 53% at least a 50% improvement in > two out of five OAB parameters (Figure 7). Therapy cost pounds 826 per patient, with a cost-effectiveness ratio of £ 617 per patient-year with > 25% clinical improvement. The investigators concluded that there is a role for botulinum toxin injection. However, the study was severely limited by using an outcome measure that is not generalizable and has minimal value (>25% clinical improvement), by short term follow-up and by having no comparison with a standard alternative therapy.

e) Conclusions

Current data on the cost-effectiveness of surgical treatment for stress incontinence show minimally invasive surgery (TVT, injectable therapy) vs. more invasive surgeries like the Burch colposuspension are likely cost-effective. However, the studies are limited by poor longer-term data on the effectiveness of less invasive procedures. In addition, these cost-effectiveness and cost-utility analyses are limited by lack of primary and/or generalizable data on costs,

Figure 6 : Changes in the ICER from 6 months to 24 months when comparing laparoscopic versus open colposuspension (reproduced with permission from BJOG).
clinical outcomes and utilities and not using a accepted and generalizable outcome (cost per QALY or cost per “cure”). Further, few have primary data to perform analyses over a longer timeframe. Further research suggestions include unbiased assessments of longer term performance from follow-up of controlled trials or population-based registries, more data from methodologically sound RCTs using standard outcome measures, use of accepted standards for selecting outcome measures and for decision modeling, and a surveillance system to detect longer term complications.

2. OUTPATIENT CONSERVATIVE THERAPIES

a) Prospective studies of conservative therapy costs

Neuman et al. [41] calculated the physiotherapy treatment costs for 274 women with stress incontinence in Australia. A median of 5 (IQR 4-6) treatments were given, for a median cost of 250$ (IQR 206-295). When cost of a GP visit was added, with MSU total cost of 302 AuD (in 2000). In the 208 women who completed therapy, weekly leakage episodes declined from 5 (IQR 3 -11) to 0 (IQR 0-2 leaks). Using intention to treat analysis, 64% of patients were dry on a stress test (or 84% of those who actually completed therapy). Improvement was observed using the Kings Health Questionnaire, but utilities were collected. This appears to be the first prospective study of physiotherapy costs for stress incontinence.

Williams et al. [42] of the Leicestershire UK MRC Incontinence Study Team undertook a large RCT of conservative therapy. Personal and treatment costs were measured (year 2001). Of the 29,039 men and women who leaked several times per month and had frequency, urgency and nocturia, 6,207 agreed to participate in a home interview, of whom 3,746 were randomised. They were allocated in a 4:1 ratio to either treatment by a specialist nurse continence advisor (who provided conservative treatments and urodynamic testing) or access to routine continence care by their GP and local continence nurse. Cure at 6 months occurred in 28% versus 19% [95%CI5-13, p < 0.001].

The intervention costs at 6 months (252 £, IQR 234-268) were greater than the routine costs (73 £, IQR 53-93). Cost effectiveness was calculated by dividing the between-group differences in the costs by the mean difference in outcome i.e. number of symptoms resolved. The incremental cost per additional symptom alleviated was 488 £ at 6 months: although of interest this is not a standard calculation in economic analyses.

Female participants in this study then were offered a more detailed treatment program [43]. A RCT of the effectiveness of three treatments for women age >40 with urodynamic stress or mixed incontinence was undertaken. Of the 238 women randomised between 1998 and 2001, 79 were allocated to control therapy (a brochure about pelvic floor muscle training (PFMT) followed by fortnightly visits to a continence nurse for 3 months), 79 were randomised to detailed personal PFMT by a continence nurse for 3 months, and 80 were randomised to vaginal cone weight therapy for three months.

The costs of the intervention were gathered by an interviewer-administered questionnaire (no further details), and from local and national cost data [44]. These comprised 287 £ for controls, 338 £ for PFMT, and 305 £ for vaginal cone weight therapy. There were no statistically significant differences between intervention groups (6%, 4% and 85% were cured, with 34%, 30% and 30% satisfied).

Subak et al. [45] prospectively ascertained the personal “routine care” costs of incontinence in 293 women age over 40 who had stress or urge leak more than 3 times per week, wanted help, but had not been treated in the previous 3 months. A self-report questionnaire asked about pad and laundry usage was given, quality of life was tested by Health Utilities Index Mark 3 and Willingness to Pay for incontinence was determined.

The mean annual cost (in 2005 dollars) of routine care was 492 US$ (SD 898), which increased with the severity of incontinence. The costs for those with urge leak and mixed leak were greater than those with stress leak. For the first time, it was found that the costs were 2.4 fold higher for African Americans than for white women. There was no association between household income and incontinence costs. The quality of life (on HUI) was poorer as the frequency of incontinence increased, but not as the severity increased. Women were willing to pay $70 per month for 100% reduction in the frequency of incontinence. Willingness to pay increased 2.3 fold in the highest income bracket compared to the lowest. Because
willingness to pay for improvement exceeded the routine care costs by 3-7 fold, effective continence treatment is likely to be economically feasible.

Ho et al. [46] performed a “bottom up” study of the short and long-term direct costs of conservative and surgical management of childbirth-related stress and mixed urinary incontinence (UI). A cohort of 150 women, who presented with post-childbirth incontinence during an eight-year period (1992-1999) were evaluated. Costs for treatment episodes during conservative and surgical management were calculated and related to cure. At 6-13 years follow up, personal and treatment expenditure was measured using a postal questionnaire.

During active treatment in the Unit, patients with stress UI treated conservatively incurred a median cost of AU$658 per capita (IQR 476 – 1191 AU$) compared to a median cost of $6,870 per capita for surgical treatment (IQR 6,320 – 7508 AU$). Similar cost difference was seen for the two treatment options in patients with mixed incontinence. Of regular clinic attendees, 39% of conservatively treated and 78% of surgically treated patients were cured.

At 6-13 years follow up, there were 82 women with a known address, of these, 43 (52%) responded to the survey, of whom 46% remained cured. The median treatment cost for the total group of postnatal incontinence (irrespective of continence status) was 885.80 per capita per annum (IQR 338- 2,589).

Foote and Moore [47] studied an RCT of Nurse Continence Advisor (NCA) therapy (N = 73) versus Urogynaecologist therapy (N = 72.) Both had significant improvements in leaks per week and incontinence score. QOL improvement was also similar (1.5% vs 1.2%). The economic data found a similar improvement in pad usage costs ($A2.90 vs $A3.52). The clinician costs were significantly lower for the NCA group ($A60.00 vs $A105.00, P < 0.0001). The cost per QALY was significantly lower for the NCA group ($A28,009 vs $A35,312, P = 0.03). Both groups had significant improvements in pad testing and leaks per week. The cure/improvement rates were also similar at three months (100% vs 89%).]

b) Retrospective studies of conservative and surgical therapy costs

Kinchen et al. [48] from Eli Lilly Research Laboratories (USA) undertook a retrospective analysis of private insurance and Medicare claims for stress incontinence in 8,126 women who had at least 12 months of claims data. Patients who were in “capacitated insurance cover” (i.e. managed care) were excluded because charges for their services were often “negotiated down”. Of the remaining 6,672 women, a mean of 0.4 inpatient care days and 1.6 incontinence related outpatient service days occurred, and 3.5 incontinence-related prescriptions were given. The mean (SD) annual incontinence related expenditures per person, including inpatient and outpatient services (with pharmaceutical costs) was a total of 1,382 US$. Patients who had surgery had a mean total expenditure of $3620 (SD 3958) which was about ten fold greater than those who had non-surgical services ($350, SD 724). Only 10% of patients in the study group were age over 65, so the sample was not representative of the total population but only of those with private insurance.

A more detailed study of 3 different costing methodologies, also using health care claims data, was performed by Birnbaum et al. [49], also from the Eli Lilly Company (see also Statistical Analysis section). They used individual claims data from over 100,000 women aged 18- 64 who were in a managed health care plan. A sample of 1006 women with stress urinary incontinence (SUI) were compared to 6475 continent women. The three economic analyses were as follows:

1. Costs of Treatment of stress incontinence
were summated from the all claims data for this condition. Of the continent women, 14% had surgery, 23% had medical claims, the average costs was 606$ per patient per annum (in 1998 dollars).

2. The Incremental Cost of an SUI patient was calculated by summating the total costs of patients with SUI versus the total costs of patients without SUI. The average direct medical costs of SUI was 134% greater than that for a non-SUI patient. The indirect costs were 163% higher.

3. The Incremental Cost of SUI Illness were calculated by measuring the costs of SUI and the costs of treating conditions that may be causally related to SUI, such as obesity, chronic cough, diabetes and menopause. The average direct medical cost of SUI was $5,642 per person per annum. The indirect workplace cost of SUI was calculated to be $4,208 (but little methodology was provided). For patients who underwent surgery, the average direct medical costs were $9,985 versus $5,024 for those treated without surgery.

Kinchen et al. [49] also from Eli Lilly published an analysis of the direct costs of SUI among women enrolled in Medicaid. The authors pointed out that because of the “predominantly female population served by Medicaid”, it was important to undertake this particular analysis. Claims were recorded from Jan 1999 to Dec 2002, converted to 2002 dollars, in 4 states of the USA. The use of services one year before and after diagnosis of SUI or mixed incontinence was compared. Surgical procedures and a large list of surgical complications were examined. Co-existent prolapse, and prescriptions for anticholinergic drugs, were also tabulated. Comorbidities such as hyper-


tension, irritable bowel syndrome, cancer, diabetes and depression were noted. In the 4 year period, there were 48,160 Medicaid claims for urinary incontinence in general, of whom 28% had a SUI diagnosis, 5% were mixed incontinence, 6% were urge incontinence and 61% were unspecified incontinence (suggesting general practitioner claims without a precise diagnosis). Of those with SUI diagnosis, 36% were also Medicare eligible.

About half of the claimants in all the states were aged less than 40 years. In the SUI group, about 30% received anticholinergic drugs. Surgery was performed in 13%, of these about 8% had prolapse surgery as well. Looking at the pre-diagnosis 12 months versus the post SUI diagnosis year, in those who underwent surgery the total health care costs increased by 53% (from $8,400 to $12,900). In those who did not have surgery, the total costs increased by 3% (from $11,100 to $11,600). After analysing incontinence specific costs, the surgical expenditure ($3,200) was almost tenfold greater than the nonsurgical expenses ($420). For the 4 states included in the analysis, approximately 1% of females had a diagnosis of SUI during 2002. Average total spending accounted for by incontinence related care for the SUI patients was less than 0.1% of total Medicaid spending.

More recently, Turner and colleagues [50] estimated the cost of clinically significant stress and urge incontinence for the UK to be £536 million for the NHS and a further £207 million paid for by individuals incontinence for the UK to be £536 million for the NHS and a further £207 million paid for by individuals. In the UK, however, the National Institute for Health and Clinical Excellence (NICE) requires economic review. They have denied approvals for new drugs that have an incremental cost effectiveness ratio greater than 30,000 pounds per QALY.

In response to the regulatory requirements, drug developers routinely conduct economic evaluations. In the UK, such efforts are done as part of the NICE review. In the US, developers present economic data to purchasers for post approval marketing. Many purchasers have formularies, or lists of medications that they are willing to pay for, and the economic evaluation is frequently part of the request to place the new drug on the formulary.

In the next sections, we review the existing literature on the economics of drugs for incontinence and overactive bladder. We then outline drugs that are under development, and suggest methods to enhance their economic evaluations.

1. APPROVED MEDICAL TREATMENTS

There are five commonly used medical treatments for incontinence and overactive bladder: tolterodine (Detrol), darifenacin (Enablex), trospium (Sanctura), solifenacin (Vesicare), and oxybutynin (Ditropan). These drugs are predominantly used for urge incontinence or overactive bladder and work as antimuscarinic targeting M2 and M3 receptors. There are currently no commonly used medications for fecal incontinence, although there are some medications to treat its side effects. Surgical and behavioral treatments are common for stress incontinence, although there is some recent research on duloxetine, (widely used as an antidepressant), for stress incontinence.

Many economic evaluations are funded by drug developers and compare the investigational drug to placebo or to an older compound that has known problems with side effects (e.g., immediate release oxybutynin). With independent funding, Ko et al. [51] conducted an economic evaluation of five antimuscarinic drugs in eight treatment formats for the treatment of overactive bladder. They compared immediate-release oxybutynin, extended-release oxybutynin, transdermal oxybutynin, immediate-release tolterodine, extended-release tolterodine, trospium, solifenacin, and darifenacin. Their analysis concluded that solifenacin had the lowest costs and highest effectiveness in the treatment of OAB. However, their analysis faced many limitations. It did not meet common standards set forth for cost-effectiveness analysis [7, 8]. It focused on the payer’s perspective (rather than a societal perspective), had a very limited time frame of 3 months (rather than lifetime costs and benefits), and used complete continence as the main effectiveness measure (rather than QALYs). Given these limitations, these results must be interpreted cautiously. We believe that additional studies using standard methods would be beneficial.

Most of the economic work in this area compares oxybutynin to tolterodine. Guest et al. [52] compared the cost-effectiveness of oxybutynin immediate release, oxybutynin extended release and tolterodine. They created a 6-month decision model from the payer’s perspective and used short-term clinical endpoints (daily incontinence episodes and daily micturations). They concluded that extended release oxybutynin appears to be the most cost-effective of the three treatments. Getsios and colleagues [53, 54]
conducted two economic evaluations comparing oxybutynin extended release to tolterodine, and found that evidence suggesting that oxybutynin extended release may be cost-effective to tolterodine. Hughes and Dubois [55] created a CEA model but were very cautious in their interpretation, given the data limitations.

O’Brien and colleagues [56] conducted a cost effectiveness analysis using a 1 year Markov model. They attempted to determine the cost-effectiveness of tolterodine for patients who discontinued oxybutynin, using the payer perspective. They concluded that, “The incremental cost per QALY was Can $9,982 [year of costs not stated] and appeared to be robust to alternative model parameter assumptions.”

In 2005, Getsios and colleagues [57] published a review of the economic studies for overactive bladder, highlighting many of the limitations including a lack of comparisons of drugs to behavioral training. The UTIN group, which published a paper describing its trial design [58], is currently conducting a clinical trial comparing behavioral treatments to medications for urge incontinence. This high-quality study will measure costs and utilities, and through a NIH-funded substudy, separate researchers will conduct the economic evaluation of this trial.

There have been a handful of studies involving secondary data. Nitz et al. [59] analyzed secondary data from a large US health plan to assess the association between types of OAB treatment and health care costs in 2001 and 2002. They found that differences in health care costs were associated with type of treatment. Their analysis, while interesting, had a number of limitations including relatively old data (old in terms of OAB) and use of data from a single health plan. They also do not control for some economic issues and it is unclear how they handle people who change their medications. A cleaner analysis would have been to identify new claims for OAB treatment and then followed these patients, using an intent-to-treat analysis plan.

Darkow et al. [60] conducted a statistical analysis of secondary data to assess the additional cost of having OAB. They found that people with OAB had higher medical care costs, controlling for age and many comorbid medical conditions. Their results may be confounded by a number of issues because people with OAB are different from people without OAB in many ways that are not observable to researchers. Grocela and colleagues [61], reviewed the literature to determine how the introduction of pharmacy benefits for Medicare beneficiaries would affect the OAB market.

1. **Darifenacin Hydrobromide (Enablex)**

Darifenacin was approved by the FDA in 2004, based on Phase II and III controlled clinical trials with over 8,800 patients. Short term efficacy (12 week) as well as longer term effects (24 and 52 week) were evaluated [62]. Few patients discontinued taking the drug in either the darifenacin arm (3.3%) or the placebo arm (2.6%). Patients assigned to darifenacin experienced decreased incontinence and voids/day, increased bladder capacity, and decreased urgency. Results were evident at 2 weeks and were sustained through the year endpoints.

Abrams and colleagues [63] found that darifenacin was associated with significant improvements in quality of life as measured by the King’s Health Questionnaire at 12 weeks relative to placebo. Chancellor et al. [62] found that darifenacin and darifenacin combined with a behavioral modification plan both resulted in improvements in symptoms and quality of life, as measured by the Overactive Bladder Questionnaire (OAB-q), but there were no differences between the two groups. Unfortunately, neither the Abrams nor the Chancellor study measured utilities, so it is hard to gauge the magnitude of these quality of life effects. Besides the Ko [51] article discussed above, there is little data on the cost-effectiveness of darifenacin.

2. **Trospium Chloride (Sanctura)**

Approval was based on two Phase III double-blind, placebo-controlled trials comparing the reduction in the frequency of urination and the reduction in urge urinary incontinence episodes at 12 weeks with over 600 patients. The trials selectively identify high risk patients (e.g., those who had 10 or more toilet voids per day) to increase the power of detecting a significant result. This, however, makes it hard to generalize the findings to other patients. Patients treated with trospium chloride experienced significant improvement in number of voids per day and number of incontinent events at the end of the 12-week trial, compared to patients on placebo. Besides the Ko [51] article discussed above, there is little published data on the cost-effectiveness of trospium chloride.

3. **Solifenacin Succinate (Vesicare)**

Solifenacin succinate was evaluated in 12-week, randomized, placebo-controlled phase III clinical trials with more than 3000 OAB patients. US and European studies found solifenacin succinate was statistically superior to placebo in terms of micturition frequency, nocturia, volume voided, pad use, urgency episodes and incontinence episodes. Long term data suggest that the effects are maintained at 1 year. Besides the Ko [51] article discussed above, there is little published data on the cost-effectiveness of solifenacin succinate.

4. **Tolterodine (Detrol)**

Tolterodine has been extensively tested in controlled clinical studies against placebo. Newer clinical trials have combined tolterodine with tamsulosin (Flomax) and found that the combination of drugs providers
greater benefits than tolterodine alone in terms of lower urinary tract symptoms [64]. Tolterodine has also been tested against oxybutynin, with results favoring tolterodine in terms of tolerability (e.g., dry mouth, constipation). A number of studies have assessed the cost-effectiveness of tolterodine and in comparison to oxybutynin and we reviewed these results above.

5. EXTENDED RELEASE OXYBUTYNIN:

Patients treated with extended release oxybutynin showed significant improvements with total continence and improvements in OAB symptoms. Extended release oxybutynin was well tolerated by most patients, with more than 90 percent of patients reporting satisfaction with therapy, yet moderate-to-severe dry mouth was reported by a quarter of the patients.

6. OTHER MEDICATIONS

Brunenberg [65] conducted a Markov model to assess the cost-effectiveness of duloxetine, a serotonin and norepinephrine reuptake inhibitor, for stress incontinence. The model was designed to compare two strategies: duloxetine alone and duloxetine after inadequate response to pelvic floor muscle training [PFMT] compared with PFMT or no treatment for women 50 years of age or older.

The results showed the incremental cost per incontinence episode, but a major challenge with interpreting this paper is that it is narrowly focused on a pharmacotherapy +/- PFMT and does not include other treatments for stress incontinence (e.g., surgery).

Das Gupta and colleagues [66] developed a cost effectiveness model to assess the cost-effectiveness of duloxetine for moderate to severe SUI. Their model, however, was limited in that they assumed that drug treatment was fully effective. Even so, their results were highly sensitive to the time frame of the analysis.

7. THE RESEARCH AND DEVELOPMENT PIPELINE

Although governments vary in their desire to see economic analyses with an investigational new drug application, we believe that gathering evidence in clinical trials is the best way to conduct high a high quality economic evaluation. Therefore, we searched the World Health Organization and the National Institute of Health’s clinical trial registry (www.clinicaltrials.gov) to learn about completed and ongoing studies for urinary incontinence and overactive bladder (search date 1/30/2008).

We found 64 drug trials and Table 2 summarizes the results. Each trial is listed once and there were four trials in which one drug was compared to another. In these cases, we listed the trial under the first drug listed in the registry. The greatest number of trials was on tolterodine (22 of 64)[51]. The drug with the most active number of trials was solifenacin, with 10 ongoing trials or trials that are about to start recruiting.

Of all the trials, 89% were industry funded with others being funded by US, UK and Israeli governments. The clinical trial registry includes information on the phase of the trial and the primary and secondary outcomes. Outcomes are “text fields” and there was considerable variability in how people entered data for the trials. Some trials provided the specific outcome measures, while other trials just mentioned urinary incontinence frequency and urgency. Quality of life was mentioned 18 times (28%); discussion of utilities or quality adjusted life years (QALYs) or economic outcomes (e.g., lost productivity or costs) was extremely rare (Table 2).

In 2007, the Cochrane Collaboration reviewed anticholinergics for the treatment of overactive bladder and urge incontinence [67]. The Cochrane authors reviewed twelve clinical trials and found “inadequate evidence to assess whether or not available alternative drugs are better or worse than anticholinergics in the management of people with symptoms of overactive bladder syndrome.” In their recommendation section, they conclude that “larger randomised controlled trials versus anticholinergics and conducted in clinical settings are required to further establish the role of these other medications in the management of overactive bladder.”

We agree with this statement and believe that better economic evaluations start with collecting the right information in high-quality clinical trials. We applaud the use of disease specific quality of life measures in clinical trials, but would also like to see the addition of utility measures, such as the Health Utilities Index that is being used in the UTIN network BE-DRI trial [68].

In addition, we believe that clinical trials need to include resource use questions to identify medical care use as well as routine care at home (e.g., use of pads or additional laundry). Dowell et al. [69] and Subak [45] created questionnaires for such data collection. Finally, we believe that it is easy to bias a cost-effectiveness analysis by focusing on a few treatment options, on a specific perspective, or with a limited time horizon. Therefore, while the clinical trials are the building blocks for the economic analysis, the economic analysis needs to embrace the societal perspective and lifetime costs and benefits.

4. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING

Two key aspects of cost of care for nursing homes are (1) cost of nursing home admissions attributable to urinary incontinence, and (2) the direct treatment cost of urinary incontinence.

Additional nursing home admissions cost is often a major component in the total cost of urinary incon-
In a 2001 study [70] the cost estimate was $2.4 billion in 1995 dollars. In a 2004 study [71], the cost estimate was $4.0 billion in 2000 dollars. In a recent update by Morrison and Levy [72], the attributable fraction (AF) statistics from published data was shown to be $6.0 billion in 2004 dollars. The Attributable Fraction (AF) statistics are obtained by using incontinence prevalence rates for those admitted to nursing homes, as compared to those who were not admitted to nursing homes. It shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes. The AF method has been used in the economic cost of mental illness, smoking, and cancer diseases. The new estimated magnitude shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes.

Holroyd-Leduc, et al. [73] used a population-based prospective cohort study from 1993-1995 to determine whether UI is an independent prediction of death, nursing home admission, and decline in activities of daily living (ADLs). Over 6,500 elderly (>age70) were included in the study. It was found that after adjusting for confounders, UI was not an independent predictor for death, nursing home admission, or functional decline.

Within nursing homes, labor costs are a major component of caring for incontinent patients. These costs are studied via time/motion observation, correlated with severity and type of incontinence. In 49 long-term care facilities in North Carolina, USA, it was found that the incremental labor costs (per shift) were $3.31 for patients with occasional UI and $5.61 for patients with frequent UI [74].

Bliss et al. [75] addressed the cost/effectiveness of incontinence-related treatment of skin condition in 16 US nursing homes. Care of perineal skin is crucial to incontinent persons in nursing homes. Four regiments of different moisture barriers were applied. Time and motion measurements included skin products and time spent. It was found that using acrylic barrier film spray achieved cost savings of between $854 to $1,862 per resident, with better skin protection than the use of an ointment or cream.

Bates-Jensen et al. [76] examined the effect of an exercise and incontinence intervention upon skin health outcomes in nursing home residents. However, no cost data was actually provided. A review [77] on perineal skin care protocols and skin barrier product use has been reported, but no cost data was mentioned.

In contrast to the nursing home/long care facility, Morris, et al. [78] undertook a "bottom-up" costing of both urinary (UI) and faecal incontinence (FI) in the Sub-Acute Care setting, which provides short term rehabilitation of acute physiological insults in the elderly. They costing 3,621 occasions of care in 29 incontinent patients for up to 3 weeks. Pure UI occurred in 97%, with pure FI in 62%. The median per capita incremental cost of these conditions was 49 AUD (IQR 36-59) per 24 hours (in 2003). On average, 2 hours per 24 hours were dedicated to

| Table 2. Registered Clinical Trials for Urinary Incontinence and Overactive Bladder |
|---------------------------------|------------|---------|---------|---------|---------|------|
|                                | tolterodine | darifenacin | trospium | solifenacine | oxybutinin | Total |
| Number of trials               | 22         | 10       | 2       | 16       | 14       | 64   |
| Completed                      | 12         | 8        | 0       | 6        | 10       | 36   |
| Recruiting                     | 8          | 2        | 2       | 7        | 3        | 22   |
| terminated                     | 1          | 0        | 0       | 0        | 0        | 1    |
| Not yet recruiting             | 1          | 0        | 0       | 3        | 1        | 5    |
| Industry funded                | 19         | 10       | 2       | 14       | 12       | 57   |
|                                | 86%        | 100%     | 100%    | 88%      | 86%      | 89%  |
| Phase                          |            |          |         |          |          |      |
| Phase IV                       | 12         | 6        | 2       | 8        | 6        | 34   |
| Phase III                      | 5          | 2        | 0       | 5        | 6        | 18   |
| Phase II                       | 4          | 1        | 0       | 3        | 1        | 9    |
| Phase I                        | 1          | 1        | 0       | 0        | 1        | 3    |
| QOL Outcome                    | 9          | 4        | 0       | 2        | 3        | 18   |
| QALY Outcome                   | 0          | 0        | 0       | 0        | 1        | 1    |
| economic outcome               | 0          | 0        | 0       | 0        | 1        | 1    |

(86% 100% 100% 88% 86% 89%)
continence management. The incontinence costs on the "night shift" were almost as great as those for the day shift. Hence because of reduced night staffing, continence management comprised a heavy load at night.

5. LONGITUDINAL BURDEN OF DISEASE STUDIES

For the first time in this ICI report, we find a number of studies that attempt to measure the cost of incontinence over the long-term time frame. As pointed out by Birnbaum et al. [79] the study of "the lifetime cost of illness" is a rather recent area of research. These authors combined case-control methods (to calculate annual medical costs of stress incontinence, cardiac disease and diabetes) with knowledge of the incidence of the conditions, assuming "steady state conditions" of the costs, to project the lifetime costs of each disorder. Using a dataset of medical claims covering 1996-1998 for 931 women with stress incontinence who were under 65 at that time, they extrapolated the lifetime costs base on "published government statistics". The prevalence rate for women >65 was assumed to be the same for women < age 65, which is probably an incorrect assumption. The authors calculated an annual treatment cost for stress incontinence of 15,000$USD per woman, and gave a lifetime cost of 58,000$. Treatment methods and lifetime expectancies were not given, so that the study was largely a hypothetical model with insufficient characterization of the model parameters. Nevertheless such attempts at modeling the lifetime costs do need to be performed in greater detail in the future.

As regard the Overactive Bladder (OAB) a study that reported "longitudinal" costs of medication actually reported data of 275 patients in North Carolina age >65 years receiving antimuscarinic drugs for 1-3 years [80]. The study calculated that a 10% increase in adherence to the prescribed OAB medication was associated with a decline in overall health costs of 5.6%.

As regard the impact of incontinence upon employed women, Fultz et al. [81] sent a postal questionnaire to 5130 American households, yielding 3364 female replies (age 18-60). Of the 2326 employed women, 37% had leaked urine in the past month, severity was judged by Sandvik index. Severity was slight 52%, moderate 40%, severe 8%. The impact of incontinence upon ability to concentrate, performance of physical activities, self confidence, and ability to complete tasks without interruption increased with the severity of the leak and affected nearly 75% of all those with severe leak status.

Similarly, Wu et al. [82] focused upon the work loss burden of women with OAB. The number of days absent was 15% higher among 3077 OAB employees compared to 6154 controls. Multivariate analysis showed that OAB subjects had 4.4 more days off work than non-OAB subjects, yielding an annual excess cost of $1220 per OAB employee.

Finally, Reeves et al. [83] employed a theoretical model based upon a large prevalence study of OAB [84] to derive the future cost burden for OAB in five European countries (Figure 8). They calculated an annual per capita expense of Euro 269-706 per annum.

A more detailed analysis of OAB costs in Germany [85] that included psychiatric costs of OAB-related depression, and nursing care, indicated an annual per capita expense of €609-1170 per annum.

6. PROLAPSE TREATMENTS, COST IMPLICATIONS

Despite the high prevalence of pelvic organ prolapse and frequency of surgery for prolapse, there are minimal data on costs or cost-effectiveness of medical care for this condition. One COI study estimated the annual direct cost of surgery for pelvic organ prolapse in the U.S. using national data. [86]. Direct costs of
pelvic organ prolapse surgery were US$1,012 million (1997 dollars; 95% CI US$775, US$1,251 million), including US$499 million (49%) for vaginal hysterectomy, US$279 million (28%) cystocele and rectocele repair, and US$135 million (13%) abdominal hysterectomy. Hospitalization accounted for a majority of the total cost (71%) with the remainder being physician services (29%). Twenty-one percent of pelvic organ prolapse operations included urinary incontinence procedures (US$218 million). The annual direct costs of operations for pelvic organ prolapse are substantial and similar to other surgical interventions for women (breast cancer, gynecologic cancer, urinary incontinence).

A recent Cochrane review of surgeries for the management of pelvic organ prolapse (Maher et al) emphasized the importance of CEA and CUA [87]. They observed that abdominal sacrocolpopexy is associated with a lower rate of recurrent vault prolapse and dyspareunia than the vaginal sacrospinous colpopexy yet these benefits must be balanced against a longer operating time, longer time to return to activities of daily living and increased cost of the abdominal approach. Similarly, the use of mesh or graft inlays at the time of prolapse repair may reduce the risk of recurrence and the addition of a continence procedure to a prolapse repair operation may reduce the incidence of postoperative urinary incontinence. Yet, these benefits need to be balanced against possible differences in costs and adverse effects, which have not been assessed and, like surgical treatment for stress incontinence, are inherently appropriate for CEA since there may be differences between procedures in costs, clinical outcome and health-related quality of life.

Maher et al performed a randomized trial of abdominal sacral colpopexy vs. vaginal sacrospinous colpopexy to treat vaginal vault prolapse among 95 women [88]. Secondary outcomes included the impact on cost (measured as Australian bed and operating theater costs) and general- and incontinence-specific quality of life. Two years after the operation, the subjective and objective success rates were similar between groups. The abdominal approach was associated with a longer operating time, a slower return to activities of daily living, and a greater cost than the sacrospinous colpopexy (P<.01). Both surgeries significantly improved the patient’s quality of life (P<.05). These data suggest that formal cost-utility analysis would be beneficial if further compare these two common procedures for pelvic organ prolapse. Additional data with generalizable costs and utility measures and long-term efficacy outcomes are needed.

Weber and Walters [89] compared the cost-effectiveness of preoperative urodynamic testing vs. basic office evaluation in women with prolapse and stress incontinence, using a theoretical decision-analytical model. Costs were obtained from US government data and effectiveness of urinary incontinence surgery was based on published literature (in 2000). The strategies of basic office evaluation and urodynamic testing had the same cure rate of urinary incontinence (96%) after initial and secondary treatment. The incremental cost-effectiveness of urodynamic testing was $328,601 for single extra cure of urinary incontinence. In sensitivity analyses, basic office evaluation was more cost-effective than urodynamic testing when the prevalence of pure detrusor instability was <8% or when the cost of urodynamic testing was >$103. Urodynamic testing was not cost-effective before surgery for prolapse and stress urinary incontinence symptoms. However, the current routine use of sling procedures for stress incontinence limit the broad applicability of the study.

Segal et al. [90] compared the feasibility and cost of local anesthesia with IV sedation versus general anesthesia for vaginal correction of pelvic organ prolapse (N=40). “Costs” were recorded as hospital charges. Mean operating room, anesthesia, and surgical time, use of postoperative medication, postoperative verbal numerical pain scores and length of hospital stay were similar between the two groups. However, mean recovery room and total hospital charges were significantly lower in the local anesthetic group. These data suggest that local anesthesia with IV may be less costly for vaginal surgery to correct pelvic organ prolapse. Data on effectiveness are needed.

7. ECONOMIC CONSEQUENCES OF FECAL INCONTINENCE

a) Cost of illness

A prevalence study [91] in a long-term care hospital (457 patients) showed a prevalence of fecal incontinence of 46% (defined as at least one incontinent episode per week). The prevalence rate of urinary incontinence was 62% and combined incontinence 44%. The total annual cost of incontinence (urine plus fecal) per patient was $9771. Of the total costs, 83% was associated with nursing time, and 13% with laundry.

A study in the Netherlands published in 2005 calculated the costs of fecal incontinence in outpatients [92]. Total costs were estimated to be €2169 per fecal incontinent patient per year. Production losses in paid and unpaid work accounted for more than half of the total costs and costs of health-care visits accounted for almost a fifth of total costs. Costs associated with protective material (partially reimbursable and not reimbursable) formed only one-tenth of total costs, while incontinence medication was responsible for only 5% of total costs.

b) Prevention

To date it is not completely clear what the causes are
of fecal incontinence, therefore primary prevention is difficult. Pelvic floor exercises before and after vaginal delivery could help to prevent incontinence. One study investigated in a decision analysis the effect of elective cesarean section for macrosomic infants to prevent maternal fecal incontinence [93]. It appeared that for every 100,000 deliveries, the policy of elective C-section resulted in 185.7 fewer cases of fecal incontinence, and cost savings of $3,211,000. According to the authors, this policy would prevent one case of fecal incontinence for every 539 elective C-sections performed.

c) Hospital costs

Treatment and follow-up costs for fecal incontinence are identifiable. However, economic assessment is difficult because of the lack of uniform study populations, variation in techniques, reimbursements systems and regional costs. There is a limited number of studies that systematically compare costs and outcomes of fecal incontinence treatments.

Mellgren et al followed up 63 patients with FI and estimated that the average lifetime cost associated with treatment and follow-up was $17,166 per patient in 1996, with average facility charges associated with sphincteroplasty to be $8555 per procedure [94]. Sung et al. [2] showed that in the US total charges associated with surgical treatment for fecal incontinence increased from $34 million in 1998 to $57.5 million in 2003, translating to a total cost of $24.5 million in 2003. Variables associated with increased costs included number of procedures per admission, length of stay, patient age, and race.

Different surgical options are available. In a study by Adang and colleagues performed in 1998, the costs of dynamic graciloplasty were compared with costs of colostomy and conservative treatment [16]. The costs of all activities were calculated, inside and outside the hospital, for all three alternatives. Costs were based on real prices, not on charges. A distinction was made between direct and indirect costs. For conventional therapy, direct costs outside the hospital were counted, such as diapers, enemas, tissues, and diets [16]. Hetzer et al. [95] compared the costs of Sacral Nerve Stimulation (SNS) and sphincter repair. The SNS cost analysis was performed on an intention-to treat basis. The analysis was performed from a hospital perspective; therefore only direct medical costs were assessed. These authors also transformed the results of the Adang study to 2005 Euro’s to be able to compare both studies. In figure 9 the estimated long-term costs per patient for each treatment are shown.

In a Markov model, Tan et al. [96] compared the cost-effectiveness of artificial bowel sphincter (ABS), dynamic graciloplasty (DG) and permanent end stoma (ES) for the treatment of fecal incontinence. It appeared that over the 5-year time horizon, ES gave a QALY gain of 3.45 for 16,280 £, giving an ICER of 4719 £/QALY. The ABS produced a gain of 4.38 QALYs for 23,569 £, giving an ICER of 5387 £/QALY. The DG produced a gain of 4.00 QALYs for 25,035 £, giving an ICER of 6257 £/QALY. The authors concluded that all three procedures were cost-effective. The ES was most cost-effective over 5 years, while the ABS was most cost-effective in excess of 10 years.

Finally, the direct and indirect costs of transanal irrigation for neurogenic faecal incontinence +/- obstructed defecation were compared with routine conservative management. Using micro costing over a very short time frame, transanal irrigation was more efficacious and slightly less expensive, but no QALYs were employed [97].

d) Consequences of Incontinence

The most frequently cited and most costly consequences of incontinence include admission to a nursing home or long-term care facility, and dermatitis. No study was found focusing solely on the effects of fecal incontinence, but many on the costs for urine incontinence and/or fecal incontinence. These results are described earlier.

VI. SUMMARY AND FUTURE RESEARCH PRIORITIES

In the four years since the last ICI consensus conference, several high quality economic analyses of stress incontinence treatments have been published. The Committee notes that evidence regarding cost

![Figure 9](image-url)
utility of outpatient therapies for stress incontinence remains very limited. However the economic analysis of therapy for overactive bladder syndrome requires greater effort, to encompass longer time frames and wider use of QALYs that can yield cost utility analysis (CUA). The Committee was disappointed to find that only 2 of the 64 currently registered clinical trials for OAB drug therapy included QALYs as an outcome measure.

In our previous Committee report, we provided a table giving international comparisons of the per annum expenditure from European countries, the USA and Australia, so as to provide a “global summary” of the costs of urinary incontinence. Similar data are here provided for OAB in our Table 8b [83], ranging from 200 – 1400 Billion Euros per annum. The data from Birnbaum et al [79] allow estimates to be made for per annum stress incontinence costs in the USA. However, no recent comparative studies have been published to allow us to give a global summary of all urinary incontinence costs at the present time. Indeed, with our increasing awareness of the human suffering costs arising from urinary fistulae in the developing nations, the Committee felt that it would be inappropriate to construct such a table that would include only patchy data from developed countries.

In the field of prolapse, it is not yet known whether any currently available QALYs are sensitive to treatment benefit, so that CUA may still not be feasible in this area. As regards faecal incontinence, research into Cost of Illness remains rather preliminary, so that broader more long term studies are needed. More data about Cost Utility in Faecal Incontinence is urgently needed.

The Committee commends the recent emergence of studies into the Burden of Disease for all continence conditions. The impact of both faecal and urinary incontinence upon costs in the nursing home or subacute care are becoming more fully understood but still require greater study.

As regards methodology, researchers need to consider carefully how they construct the model parameters for Decision Tree Analysis and Markov Models, so that “real life” assumptions are made. The gold standard remains Cost Utility Analysis in parallel with Randomized Controlled Trials, and we urge all clinicians to consider costs as an important outcome measure.

VII. APPENDIX – SEARCH STRATEGIES

We performed a comprehensive computerized medical literature search (PubMed) for the years 1966 through 2008 to identify all economic, health-related quality of life and cost-effectiveness analyses published on urinary incontinence, fecal incontinence or pelvic organ prolapse.

Our initial search strategy was very broad and meant to be very sensitive but not specific. We performed a search for the following Medical Subject Headings (MeSH) and keywords: cost-effectiveness analysis, health care costs, quality-adjusted life years, costs and cost analysis, sickness impact profile, or utilities and urinary incontinence, overactive bladder, fecal incontinence, anal incontinence, uterine prolapse or pelvic and prolapse. The initial searches were reviewed to identify articles appropriate for more detailed evaluation.

The literature was reviewed for studies describing costs associated with fecal incontinence. The costs for FI can be differentiated to costs for the disease of FI itself and for costs associated with the treatment of FI. Systematic searches of electronic databases were conducted, including National Library of Medicine (Medline), Cochrane economic evaluation database, Embase. The years included in the searches were 1970 – April 2008.

We combined the search terms (incontinen* AND (fecal or faec* or anus* or anal*)) or fecal incontinence [MeSH] with cost-effectiveness OR Health Care Costs [MeSH] OR “Costs and Cost Analysis [MeSH].

Inclusion criteria were: fecal incontinence as primary disease, data on costs available. Studies were excluded when they were a review, case-report or focused solely on urinary incontinence. 159 manuscripts were retrieved (Medline: n=70; Cochrane economic evaluation: n=82; Embase: n=7), of which 19 were duplicates.

The remaining 140 manuscripts were assessed for eligibility by reading title and abstract. This resulted in 24 potentially eligible citations. When full citations were obtained 19 studies could not be included. Two cost of illness studies, null on prevention studies, three on hospital cost studies and null on the consequences of incontinence
REFERENCES


37. Oremus M, Collet JP, Shapiro SH, Penrod J, Corcos J.


82. Milsom I, Abrams P, Cardozo L, Roberts RG, Theuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001; 87: 760.


Committee 23

Research

Chairman

C. Payne (USA)

Members

J. Brown (USA),
D. Castro (Spain),
F. Daneshgari (USA),
F. Haab (France),
Y. Igawa (Japan),
J. Kusek (USA),
G. Rortveit (Norway),
M-A Stothers (Canada),
P. Van Kerreboreck (The Netherlands),
P. Zimmerm (USA)
The International Consultation process focuses on exploring the current knowledge base in order to guide the clinical care of patients by using the highest possible degree of evidence. The assignment for this committee is slightly different. The charge is to define research methodology that will guide today's investigators in producing exceptional work—the kind of data that provides the convincing evidence needed to direct clinical practice, stimulates other investigators and generates new research ideas, and leads to a better understanding of physiology and pathophysiology of the disease(s) studied.

Urinary incontinence and lower urinary tract dysfunction comprise a group of common diseases, and far more knowledge of their origin, diagnosis, treatment and prevention is needed. Clinical research is a pre-condition for any progress in these areas. In this chapter the committee provides general recommendations for good research practice, including principles of clinical trial design and statistical methodology. In addition, specific recommendations applicable to types of treatments and studies of different groups of patients are presented. Other ICI committees report on the etiology, epidemiology, pathophysiology, prevention, and economic impact of lower urinary tract dysfunction. This chapter covers these areas only when appropriate and in minimal depth.

The Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (http://www.cebm.net/levels_of_evidence.asp) are difficult to apply to this section. This work differs from the clinical committees in that the findings are not based on clinical trials but rather on the statistical and mathematical science as well as expert opinion. In many cases the quality of the “evidence” is very high, even when based on expert opinion. Therefore, in order to comply with the spirit of the Consultation the recommendations in this report are graded as follows:

- **High**: Supported by strong evidence (multiple strong publications)
- **Medium**: Supported by moderate evidence (limited/moderate level publications)
- **Low**: Expert/Panel opinion

The report endorses published guidelines produced by the International Continence Society (ICS) [1-14, 193] and Society for Female Urology and Urodynamics (SUFU) [15-17]. Consistent use of the methodology and approved terminology endorsed by these groups will not only facilitate incontinence research by producing high quality studies but also facilitate communication about research.

The aim of clinical research is to evaluate potentially effective treatments that will significantly reduce symptoms of lower urinary tract dysfunction, and/or prevent them from occurring. The need for high quality research is similarly evident. The prevalence and impact of genitourinary disease coupled with an aging population observed in many countries will result in an increased demand for effective incontinence therapies.

At the same time, evidence about the etiology and risk factors for developing incontinence, the optimal treatment strategies, and effective prevention is deficient. The quality of research is of the utmost importance. While there is ample evidence that urinary incontinence is a troublesome disease resulting in reduced quality of life, investigators must compete for research funding against projects studying with heart disease, cancer, and many other life-threatening diseases. Only the highest quality work will be successful in today's competitive environment.

There are many goals of research—foremost to improve care of patients, but also to promote understanding of the disease process. We need a broad spectrum of information if we are to not only understand which treatments work but also why they work (or don't). The ultimate goal is to produce credible research. When research is inherently credible due to strong study design the impact is maximized. The clinical application of the research will be hastened and other investigators will be energized to use the information in their own quest for knowledge.
II. GENERAL RECOMMENDATIONS

1. THE PLANNING PHASE OF A CLINICAL STUDY ON INCONTINENCE

The planning stage of both prospective and retrospective studies requires the same deliberate approach. Having formulated a general research question, the investigator reviews previous and, if possible, ongoing work in the field to determine how the research question fits within the current body of knowledge in that area. A thorough knowledge of related clinical research is the cornerstone of protocol development. Care should be taken to identify studies that are well designed and clinically relevant. The research reviews provided by the Cochrane Incontinence Group (http://healthsci.otago.ac.nz/dsm/wch/obstetrics/cure) provide an excellent starting point for most major incontinence topics. This collection of carefully scrutinized data allows researchers to focus their research on key questions. Following the recommendations made by the Cochrane Group will help to ensure that future studies will be interpretable in the context of past work.

Based on a thorough literature review, the investigator clearly describes the primary research question(s), summarizes the background information, and formulates the rationale, objectives and hypotheses for the study.

A rule of thumb for all research is that one should ascertain the simplest study design which will provide the greatest likelihood of answering a given hypothesis or question. The study must attempt to provide a convincing answer to the question in a cost and time-efficient manner. In addition, it is ideal that clinical research be performed in concert with more basic investigations with the aim of discovering how a treatment works, not just whether it works. In terms of designing the study, this may be thought of a balance between breadth and depth [18]. Although the number of questions in a single study should be limited, it is still relevant to record as many as observations as is possible without jeopardizing recruitment or retention with onerous demands.

Once the concept of the study has been clearly defined, the search for an appropriate funding agency commences. The chance of a successful application increases when the investigator ensures that the application meets the mandate of the funding agency.

2. STUDY DESIGN

The type of study and other aspects of study design are the framework within which the study objectives are met. An initial decision must be made as to whether the study will be observational or experimental. Experimental studies are where the investigators control the process by which it is decided which treatment a participant should receive, while in observational studies the treatment decisions are not in any way influenced by the investigators and the research study. The strength of the scientific evidence arising from various experimental study designs are ranked as follows:

Strength of study design (ranked in descending order of strength)

a) Randomized controlled clinical trial(s)

1. DOUBLE-BLINDED: Neither the participants nor the investigators (in particular, those responsible for outcome assessment) know which subjects are receiving the active treatment while the study is in progress.

The randomized controlled trial (RCT) is the gold standard study design. The participants are assigned to a particular treatment group by a mechanism designed by the investigators and based on a chance allocation to the various treatments. Provided that adequate concealment is maintained, neither the patient nor the investigator can influence which group any particular participant will be assigned. This provides protection from allocation bias by the investigator and/or subjects. RCTs are expensive to conduct and can occasionally be ethically problematic. However, the central importance of the RCT in terms of influencing decisions about patient care should and will continue.

b) Non-randomized controlled clinical trial(s)

This category includes trials in which the basis for treatment allocation is known to the investigator prior to obtaining informed consent (for example, day of clinic appointment). A major shortcoming of this study design is that baseline characteristics of the treatment groups may be significantly different.

c) Case series

Case series are studies that describe the outcome when all subjects receive the treatment being investigated. This is the weakest study design, but researchers may have to resort to using this approach because it is the only practical approach, e.g., when they study rare diseases or when therapy becomes so established in the medical community that conducting a randomized clinical trial is not feasible. Because of an absence of an internal comparison or control group, a group external to the study must be used for comparison, raising questions about patient selection and comparability with other populations.

Properly planned and executed, the RCT is the optimal approach to limiting allocation bias [19]. RCTs compare outcomes in groups of subjects for whom treatment was allocated by chance. Using this approach,
treatment groups should not vary at time of randomization in any meaningful way thus minimizing potential bias in the characteristics of the treatment groups [20]. Subject assignment must be concealed during enrollment (for example, by separating allocation from the process of recruiting subjects, and by using remote randomization such as by telephone or web-based procedures), and wherever possible treatment allocation must be concealed during the trial (for example, using blinding with or without placebo). In some studies, blinding of subjects and health care providers may not be possible, for example in trials of some surgical procedures or health care delivery methods. In almost all cases, however, the personnel collecting outcome data should be blinded to the subjects' treatment allocation.

Observational studies include a variety of designs, from cross-sectional descriptive studies in which the primary purpose is estimation of the prevalence of incontinence in a defined population, to case-control studies and long-term prospective or retrospective cohort studies useful in studying rare diseases and identifying risk factors. Observational studies may be purely descriptive (case series), or they may be analytic when designed with a control or comparison group. Observational studies can contribute useful information on many aspects of health care [21], and may be necessary precursors to a randomized trial. Also, they may be the only source of information about the effect of natural events such as lifestyle changes in whole populations (for example the obesity epidemic). However, all comparisons based on observational data have a common limitation – the inability to ensure that one is comparing like with like. In particular, it is not possible, even with advanced statistical methods, to eliminate the bias resulting from the effects of the selection process, whether induced by the patient or clinician. Normally, RCTs are not subject to bias when comparing groups. However, external validity may be threatened through selection of participants for RCTs.

Although the classical RCT involves the study of parallel groups, other options are possible and may overcome some of the limitations of the classical approach [22]:

d) Parallel Trials

These designs offer one group of subjects the treatment under study, and a parallel group assigned to a placebo or some alternative treatment. In clinical trials of drug treatment the dose of the drug may be either held constant or varied to maximize clinical benefit and/or minimize side-effects. More complex study designs can in some circum-stances be worth considering – for example, factorial trials where two or more interventions can be investigated simultaneously [23, 24], and cluster randomized trials whereby groups of participants rather than individuals are randomly allocated to the trial arms [25]. This strategy might be employed when studying an intervention requiring policy changes in an institution, with a hospital, clinic, or health care system being the unit of randomization.

e) Crossover Trials

Subjects receive both the treatment being studied and the placebo/alternative treatment, with the order in which the treatments are received being randomly assigned. The benefit of crossover studies is that they eliminate the effect of variation between groups of participants seen in parallel trials, that is each subject serves as his/her own control. Crossover studies are particularly well suited for small studies, where the course of the disease under study is believed to be stable, and where the primary objective is to measure a short-term change in symptoms in response to treatment. The duration of treatment effect is critical in determining whether the crossover study design is appropriate – too long an effect, and the disease state may become unstable before the patient has completed all arms of the study; too short, and it may not be possible to detect the effect during the period of data collection. Carryover effects may occur, in which the results of the first treatment are prolonged and affect the results of the second treatment. To avoid this, a washout period should be planned, in which participants receive either placebo or no treatment. A run-in period in which signs and symptoms are monitored may be necessary before treatment commences to ensure that only those whose disease state is stable are included. Given these features and limitations, this design is unlikely to be widely applicable in studies of interventions for incontinence.

f) Equivalence/non-inferiority trials

The primary objective of an equivalence trial is to demonstrate that two treatments are similar in outcome or that there is no difference between treatment and controls. This design may be appropriate when one treatment is considerably more cost-effective, offers a better quality of life, or is less toxic or time consuming for the patient while producing a similar clinical outcome. The observed difference in outcome between two treatments should be clinically unimportant and be accompanied by a narrow confidence interval in order to state that two treatments actually are equivalent. For example, if separate studies indicated similar effects of pelvic floor exercises and a new drug in the treatment of stress incontinence, one might set up a study to demonstrate that no important difference in clinical effect was present between the two treatments by direct comparison. The study must have the statistical power to convince readers that there is no risk of type II error (which means that a study erroneously concludes that there is no difference between two groups). Such power depends heavily on the number of subjects in a study and must be calculated in the designing process, preferably by
help of statisticians. Clinically unimportant differences may be quite small, necessitating large sample sizes [26, 27]. The number needed in a particular study will depend on the outcome measure. An equivalence trial can be a powerful design when appropriately employed, and is not the same as failing to find a difference between two groups. Particular caution is required in applying these trials in the context of (especially pragmatic) trials where non-trivial proportions of participants switch from one intervention to another.

g) Drug trials are categorized according to the following definitions [26] [28].

- **Phase I studies**: The first studies of a drug in humans, often open label and uncontrolled, concentrating on safety and frequently but not exclusively carried out in healthy volunteers. Pharmacokinetic and tolerance information is obtained from Phase I trials.

- **Phase II studies**: The first attempts to investigate treatment efficacy, often the first use of the drug in subjects and focusing on short-term outcomes. A common objective of Phase II studies is dose finding in terms of efficacy. Two sub-types may usefully be distinguished: Phase IIA studies where single treatments are considered in relation to a minimum response prior to further investigation; Phase IIB where direct comparisons are made between interventions, albeit on a small scale and not necessarily involving randomization [29].

- **Phase III studies**: Large-scale, authoritative randomized studies performed once the most likely effective and tolerated treatment regimens have been established. The objective is often to establish that the intervention is suitable for registration/approval with the appropriate regulatory authority. Trials are conducted after submission of a new drug application (NDA), but before the product’s approval for market launch. Phase IIIB trials (between submission for approval and receipt of marketing authorization) may supplement or complete earlier trials, or seek different kinds of information (for example, quality of life or marketing). Phase III trials are also used to investigate the effectiveness and cost-effectiveness of various interventions – that is, non-drug including organizational issues – and not necessarily with reference to regulatory authorities. All Phase III trials should be subject to a formal sample size calculation – for instance to obtain sufficiently precise estimates of the comparisons between treatments or to have a reasonable chance (power) of detecting a difference if one exists (see section II C 7 below).

- **Phase IV studies**: These investigations are usually carried out after registration/approval, to investigate the drug’s safety and efficacy in different populations. Such post-marketing surveillance studies are typically larger and simpler than regulatory studies; they may lack a control group and are often conducted using surveys.

Precisely which study design to choose to answer a given primary research question depends on a number of factors, including the ability to recruit sufficient participants for a particular design (see Statistical Considerations, below), the natural history of the disease, the treatment itself, and patient outcomes. Patient-related outcomes may be short-term, such as changes in signs or symptoms, or longer-term, such as survival.

Once the sample size required to answer the primary research question has been calculated, it is usually obvious whether the study can be performed at a single institution, or whether a multicenter study will be required. Single institution studies have the benefit of being less complicated from a logistical perspective.

While multicenter trials are more complex to manage and are usually more expensive, they provide larger numbers of participants in a shorter period of time, and increase the generalizability of research findings.

Common mistakes that can occur during the planning and conduct of a study are described in Table 1.

3. STUDY CONDUCT AND STATISTICAL CONSIDERATIONS

The planning for a research study must begin early. All issues should be addressed at the start of the planning process, and many will need to be revisited at suitable times throughout the project. Many of these issues are statistical; indeed, the major statistical input to a study should be at the design stage, including planning the data analysis in advance to follow the design of the study.

The issues covered here relate to: study design; sampling strategies; randomization and stratification; primary and secondary outcomes; inclusion and exclusion criteria; blinding and effects on validity; control of bias; sample size considerations; pragmatic and explanatory trials; data analysis; and reporting of randomized controlled trials (RCTs). Only the principal features of study design and analysis will be covered here; extensive coverage is available elsewhere [27, 28, 29, 30, 31].

Regarding presentation, as part of the "Enhancing the QUALity and Transparency Of health Research" (EQUATOR) Network project a website was developed at www.equator-network.org. On the website, the Consolidated Standards of Reporting Trials (CONSORT) statement provides guidelines for reporting the design, detailed methods, and results of RCTs. Many of the points discussed here relate to those guidelines, which should be closely followed throughout the design, conduct, analysis and presentation of RCTs as is required by most leading medical journals [34]. Of note, prior to participant enrollment, the International Committee of Medical
**Table 1. Common pitfalls in preparing and writing protocols (from Spilker 1984)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Pitfalls</th>
</tr>
</thead>
</table>
| **A. Study objectives**            | 1. Expressed too generally to allow a specific study design to be constituted  
2. Ambiguous or vague  
3. Not achievable with the current study design. The study may be too complex or there may be inadequate resources to conduct the study |
| **B. Study design**                | 1. Insufficient statistical planning—the design will not adequately address study objectives  
2. The design chosen is beyond current state of the art  
3. Inadequate validation of outcome measures  
4. Inadequate statistical power. The chosen sample size is too small to detect clinically meaningful differences  
5. Inappropriate use of active or inactive controls  
6. Lack of placebo or double blind when one or both should be incorporated  
7. Dose regimen too restrictive (e.g., range of allowed doses, alterations of dosing for adverse reactions)  
8. Failure to consult with statistician regarding randomization process |
| **C. Inclusion/exclusion criteria**| 1. Too stringent to allow adequate numbers of subjects to be enrolled. Overly stringent criteria also reduce the generalizability and thus the impact of research  
2. Too broad to create homogenous groups. |
| **D. Screen/baseline/treatment**   | 1. Time periods for data collection are either too long or too short for optimal conduct of the study  
2. Too few or too many measurements are requested  
3. Subjects may be inappropriately entered into the study before complete screening  
4. Excessive blood volume removed for testing or an excessive period of fasting is required. This is especially common in pharmacokinetic studies |
| **E. Drug packaging/dispensing**   | 1. Drug packaging that does not permit all options allowed by protocol to be followed |
| **F. Study blind**                 | 1. Study blind easily broken because of "obvious" characteristics (e.g., adverse reactions, changes in laboratory parameters, drug odor) that are difficult or impossible to adequately mask  
2. Study blind easily broken by observation of drug interactions or other situations by the investigator (e.g., marked improvement in study group or changes in blood levels of concomitant drugs)  
3. Study blind inappropriate |
| **G. Data collection and analysis**| 1. Poorly designed data collection forms  
2. Incorrect statistical methods used to analyze data, including baseline comparisons  
3. Failure to make the primary research question the main focus of the analysis  
4. Reliance on within group rather than between group comparisons in parallel group trials  
5. Overreliance on p-values without presenting confidence intervals |
| **H. Overall**                     | 1. Ambiguous language that allows different interpretations  
2. Too many comparisons requested. Five of every 100 independent comparisons will be statistically significant by chance alone, when alpha is 5% and there are no true differences between the comparison groups.  
3. Lack of internal consistency in the protocol  
4. Discretionary judgments allowed by the investigator. This may seriously affect the quality and quantity of data obtained  
5. Presentation/reporting fails to accord with CONSORT guidelines |
Journal Editors (ICMJE) recommends information about trial design be placed into an accepted clinical trials registry [35]. For studies of diagnostic tests the Standards for Reporting of Diagnostic Accuracy (STARD) [36] statement fills the same role and information is also included on the EQUATOR website. Guidelines for reporting meta-analyses are described by the Quality of Reporting of Meta-analyses (QUORUM-37) and Epidemiologic research reporting guidelines are contained in STROBE, Strengthen the Reporting of Observational Studies in Epidemiology (38). There is little doubt that the quality of all medical literature, including incontinence research, would be markedly improved if authors simply follow the recommendations of these texts.

**a) Sampling strategies**

Whether a study is analytic or descriptive (that is, whether or not a comparison is involved), the first practical issue to resolve is the selection of participants. A study may require a sample that is representative of the community overall or one representative of patient groups suffering the condition/disease. In principle, this is achieved by taking a simple random sample from a known population. In practice, a list of all eligible individuals is obtained and then a sample is drawn by a method in which each member of the population has an equal probability of selection (‘epsem’). Even in ideal circumstances, however, some sophistication on this basic method is usually desirable or necessary. For example, in stratified sampling, subjects are arranged into subgroups and the sampling is performed within each subgroup separately. This ensures that the sample is representative of the population in terms of these subgroup characteristics. In multi-stage random sampling, the population is first divided into ‘primary sampling units’ (such as hospital, health center, or surgeon), and a sample of primary units is selected. The ‘secondary sampling units’ (usually individual subjects) are then selected just within the primary sampling units that have been selected. A special case of multi-stage random sampling is cluster sampling where all individuals within each primary unit are included. Standard procedures for sampling should be followed [25,39].

It is important to note that, while the technicalities of random selection of subjects for a study are closely related to the random allocation of subjects in an RCT (and indeed there are similar issues in trials relating to stratification and clustering) [25], there is an important distinction in the objectives of the two procedures. First, the (ideally random) selection from the population of eligible subjects concerns the external validity or generalizability of the study findings (RCT or otherwise). Independent of this, the random allocation of subjects in an RCT is concerned with the internal validity or comparability of the trial groups.

In principle, sampling should involve random selection. In practice, however, this ideal is rarely met outside of large-scale epidemiological studies. Rather, RCTs are drawn from a subset of the population, often limited to those with access to academic medical centers plus the willingness and ability to participate. Where this is the case, it is crucial to provide descriptive information about the study sample, so that its representativeness can be judged. Guidelines for reporting of RCTs include requirements to state the study population, give details of inclusion and exclusion criteria, and present clearly the numbers of eligible subjects who were not randomized and the reasons [33, 34, 40]. Nevertheless, “the basic logic of clinical trials is comparative and not representative” [26]. In other words, the principal benefit of conducting a randomized trial is to provide groups that allow valid comparisons of the effect of the interventions.

**b) Randomization and stratification**

Randomization is the process of allocating subjects to groups by chance [19, 20]. Neither the subject nor the clinical staff responsible for recruitment to the trial should be able to predict to which group the subject will be assigned. Randomization removes treatment selection from the hands of the clinician thereby minimizing bias.

In order to minimize bias, the randomization process must be concealed from those recruiting subjects to the trial [33, 40]. This can be achieved most effectively by the use of central telephone randomization. In drug studies, a pharmacy can maintain identical treatment and placebo already randomly allocated into individual subject portions. These are distributed consecutively as subjects are enrolled in the study.

- **Simple randomization** can use computer-generated random numbers, either prepared specifically for the trial or using existing tables of random numbers where the digits of 0-9 appear with equal likelihood in each entry. Treatments are assigned to odd or even numbers. As the total number of subjects in the trial increases, the balance of numbers and characteristics of subjects between the groups improves. In small trials, however, balance is not assured by simple randomization. Appreciable imbalances in subjects per group may be particularly important in a multicenter study where imbalances in assignment can occur within individual institutions.

- **Block randomization** is one method used to prevent imbalances in subject numbers assigned to each group, particularly when the number of subjects in the trial is small. With block randomization, the total sample size is divided into blocks of a given size. Within each block, the group is assigned so that there are equal numbers allocated to each group. To prevent investigators from learning the block size and being able to guess order of assignment, the block size can be varied, usually at random from a small number of
alternatives. In any case, blocking prevents serious imbalances in characteristics across groups when used in conjunction with stratification as described below.

Most disease states have factors known to influence the outcome of treatment, for example, pre-and post-menopausal or male and female. A form of randomization that accounts for such factors is called *stratified randomization* [19, 20]. Stratified randomization ensures equal distribution of subjects with a particular characteristic in each group when blocking is employed within strata. Stratification is usually restricted to a small number of factors, in particular those most likely to influence outcome. Despite its complexity, stratified randomization is usually helpful in a multicenter trial, so that both the numbers of subjects in each group and the important factors influencing the outcome can be balanced within each site. An alternative method exists to cater for more factors at once, known as *minimization*, where the characteristics of individuals already randomized alter in a systematic manner the chances of a given subject being allocated to the different trial groups, so as to maximize the resulting balance of these factors [19, 20, 39].

c) Primary and secondary outcomes

Specific discussions of the most appropriate outcome measures for particular studies of incontinence will be dealt with elsewhere in this book; the purpose here is to define the general concepts of primary and secondary outcomes in the context of RCTs, which are relevant to both sample size determination and data analysis. The distinction between these two sets of outcomes depends on the context of the trial, and should be decided at the planning stage of the study. Primary and secondary outcomes should not be confused with the distinction between primary and secondary analyses of trial data, which will be discussed later. Primary outcomes are those viewed by the researchers to be of central interest. Trial results that lead to major changes in patient care will be based on primary outcomes.

The number of primary outcomes in a particular trial will depend on the nature of the interventions and the number of independent domains. The number of primary outcomes is usually limited to three, and rarely will there be reasonable justification for more than six. Sample size calculation is based on the primary outcomes and is unlikely to be based on more than two outcome measures. The number and nature of outcome domains in a particular study will vary depending on the study’s perspective (e.g., those of participants, clinicians, regulatory bodies, and health care purchasers). In almost all situations, the outcome set should include both a dimension representing the viewpoint of the patient (including symptom frequency, severity, and quality of life) as well as an appropriate objective clinical outcome measure. Secondary outcomes are the remaining outcome measures and could be relatively large in number. They are not the focus of the main study objectives and are rarely used directly in sample size estimation. Secondary outcomes are often subject to the dangers of multiple hypothesis testing, for which suitable statistical corrections should be considered as described below. Analyses of secondary outcomes are best viewed as exploratory, i.e., as hypothesis-generating exercises for which independent confirmation is essential. The ideal outcome for incontinence research has yet to be determined and is beyond the scope of this committee. However, there is a growing recognition that combined or composite outcomes may be the optimal. An early example of such an outcome is the SEAPI scale [40] which includes subjective and objective assessments of Stress leakage, Emptying ability, Anatomic support, use of Protection for incontinence, and Inhibition (problems with urge). Each item is scored 0-3 (none, mild, moderate, or severe). The recent SISTEr trial from the Urinary Incontinence Treatment Network [41] used a five item global outcome measure (no self-reported symptoms of urinary incontinence, <15gm urine loss on 24 hour home pad test, no reported incontinence episodes on a 3 day diary, a negative stress test at a standardized volume of 300cc, and no retreatment for urinary incontinence). The group also reported a stress-specific outcome using three items that only measure stress incontinence (no self-reported symptoms of stress urinary incontinence, a negative stress test at a standardized volume of 300cc, and no retreatment for stress urinary incontinence). Such composite outcomes naturally produce much lower “cure” rates but may provide much greater understanding of what the patient actually experiences.

d) Inclusion and exclusion criteria

Inclusion and exclusion criteria should provide a relevant population to address the study question, and together define the heterogeneity or homogeneity of the study population. The most important inclusion criterion is how the disease in question is defined. Eligibility criteria are critical to both the interpretation of the study and its reproducibility. If possible, established international criteria for the presence and severity of disease should be used. Broadening the inclusion criteria can make a study more generalizable and facilitate recruitment. Making the entry criteria too broad, however, may dilute the effect being sought in the most suitable subjects. If the study population is defined too narrowly with many exclusion criteria, applicability of the results may be limited and subject recruitment may be difficult.

Inclusion criteria govern what patient characteristics are required for eligibility to enter the study. Some exclusion criteria such as age, weight and gender are determined implicitly by corresponding inclusion parameters. Issues of patient safety determine other
exclusion criteria (e.g., avoiding nephrotoxic drugs in subjects with renal insufficiency). All criteria should be defined precisely enough to allow the study to be reproduced by other groups of researchers.

e) Informed consent

Peer review of protocols by a multidisciplinary team may include members of the scientific community, clinicians, pharmacists, the public/patient groups, the legal profession and individuals who can provide an ethical perspective. Each member of this team reviews the protocol from their particular type of expertise and in doing so aids in safeguarding patient health and well-being.

Informed patient consent is required for participation. The length and depth of detail in consent forms vary widely between institutions. In the extreme, they involve exhaustive pages of information, which explain every alternative treatment with its pros and cons in detail. A general list of requirements for a consent form includes: name of the investigators and contact numbers, a detailed description of the new treatment and its known side effects, rationale for why the new therapy may be preferred to standard therapy. A summary table of the results of previous studies using the drug can be helpful when available. A statement that the patient may decline to be in the study with no subsequent consequence to their ongoing medical care is generally provided and whether or not remuneration is expected. Additionally, there should be a statement about payment for medical care required during the course of the study if there is an adverse event associated with the intervention. An understanding that the patient will be randomly assigned to treatment should be included, written using terms that are meaningful to potential participants. [42, 43].

f) Data Safety Monitoring Board (DSMB)

An independent (of the study sponsor) review or oversight committee, typically called a Data and Safety Monitoring Board, should be established prior to initiation of the trial. In addition to reviewing results of the study for safety monitoring they may evaluate interim analyses to ensure that a treatment is not producing unacceptable levels of side effects and/or efficacy [43; 44]. Guidelines for stopping the study should be agreed upon, prior to the start of the trial. It is important to note that interim analyses (in particular those based on efficacy) will have implications for the study power – specifically, a larger sample size will be required eventually to achieve the same power/precision compared with if such analyses are not conducted (see section II 3h below). Specialist statistical advice and support will be essential to address these issues [46-48]. It might be argued that subject safety may not be properly ensured unless the monitoring committee knows which arm of the study is the treatment and which is the control (placebo). For the same reasons, clinical staff may not feel comfortable participating in such a study, and so an important role for the DMSC is to provide implicit reassurance on this point. Investigators should not be aware of the results of interim analyses, however, since this may cause bias by influencing how vigorously any given patient is recruited into or followed up in the study. Nevertheless, emergency procedures for unblinding a patient’s allocation are required in case of a severe side effect or concomitant serious illness where knowledge of treatment assignment is essential for patient management and safety.

g) Bias, blinding and effects on validity

Bias can be introduced at many stages of an RCT including patient selection, randomization, assessment of outcomes, and statistical analysis and interpretation. Bias occurs because of previously conceived ideas held by those involved, which consciously or unconsciously affect their actions and observations. In addition to observer bias, an amount of observer error is inherent in outcome measures that require clinical interpretation. To avoid or limit bias, blinding should be employed whenever possible, with concealment of allocation and blinding of outcome assessors being the most important. Blinding is the process by which key elements of knowledge are withheld that can otherwise lead to bias. Blinding should not be confused with concealment of allocation, referring to withholding knowledge of assignment in advance, which is a prerequisite for the validity of any trial [33, 49]. While blinding is important its effect is lower than that of concealment of allocation [50].

Unblinded trials are conducted in an open manner where both subjects and study investigators are aware of which treatment has been assigned. While certain types of therapy may require investigation in this manner (e.g., some surgical trials), there remains considerable opportunity for bias. Both subjects and investigators may have preconceived ideas regarding the benefits of a particular treatment that can influence the reporting of symptoms and/or their outcome.

In a single blind trial, the subject is blinded to treatment assignment. It may be advantageous for the clinical staff to be aware of the assignment to allow them to monitor the health and safety of individuals, since the potential effects of the treatment (side effects) will often be known in advance. Single blinding ameliorates biased reporting of symptoms and/or side effects by subjects. However, clinical staff can influence data collection and change other aspects of subjects’ care when they know which study treatment subjects are receiving.

In double blind trials, both parties who could influence outcome are unaware of group assignment. Often this is just the subjects and the clinical team
responsible for their care. More generally, the term double blind relates to the participants and the research personnel responsible for the measurement and assessment of outcome [20, 33]. While this reduces potential sources of bias considerably compared with unblinded or single blind trials, it does introduce other levels of complexity. For example, safety monitoring must be performed by a third party.

**Triple blind trials** include blinding of subjects, outcome assessors, and those involved in the final data analysis. This may be justifiable for the primary analysis of trial data, but at some point in the proceedings there is often a strong case for unblinding the data analyst. For example, another opportunity for bias occurs if an appreciable number of subjects drop out or withdraw from a study. Such attrition can be particularly problematic if it is related to group assignment and if it unequally affects one arm of a parallel group design. In this scenario, both the monitoring team and the trial data analyst must carefully consider the reasons for subject withdrawals, which may well necessitate unblinding in the final analysis.

In summary, research design should strive for the highest practical level of blinding. In most drug studies placebo pills are easily manufactured and complete blinding of all relevant participants is practical. In contrast, it is rarely possible to blind the clinician in surgical, device and physiotherapy/behavioral therapy trials. Here the effort should be focused on blinding the participant to the greatest degree feasible and to complete blinding of the evaluator.

**h) Sample size considerations**

Sample size should be calculated in the planning stage of all studies. There are many formal equations to assist in this process, details of which will not be given here [29, 51-53]. Rather, the emphasis for this discussion is on the concepts involved and the information required for the calculations to proceed. Determination of sample size is not an exact science. Many decisions about design and analysis are interrelated with specifications for sample size, and there is no single solution.

There are three fundamental approaches to sample size calculation. One is based on the required precision of an estimate. The second requires that the study have adequate probability (power) of detecting a given (target) magnitude of effect. The third aims to demonstrate non-inferiority between treatment groups.

The first of these approaches is relevant to both descriptive and analytical investigations. The basic issue is one of precision (measured by the standard error, SE) or margin of error (which depends on the SE but is more specifically defined as half the width of the 95% confidence interval [CI] around the estimate). The higher the level of precision specified in advance (i.e., the smaller the SE and the narrower the CI), the larger the sample size will need to be. However, the margin of error depends on the nature of the primary outcome variable, i.e., whether it is a continuous variable (such as maximum urinary flow rate) or a binary variable (such as the presence or absence of self-reported urgency incontinence). For a continuous variable, the variability (standard deviation) of the measure must be estimated for relevant subjects; this may be derived from some combination of clinical experience, the literature, or a pilot study. The larger the variability, the larger the sample size required. For a binary variable, its prevalence must be estimated in the population to be studied, since the SE for such variables depends on their prevalence.

The second approach, based on power, is the most commonly used. It requires similar prior information, including estimates of the variability for continuous measures and the magnitude of proportions for binary variables. In addition, it requires specification of three other quantities: the **significance level**, the **power**, and the **target difference**. Significance is a statistical term that tells how certain one can be that a difference or relationship exists. It does not necessarily imply that the result is clinically relevant, just that the result is likely to be accurate. The significance level, termed alpha, is conventionally, though not necessarily, set at 5%. Power is defined as the probability that the study will detect (as statistically significant at the alpha level specified) a given target difference between the groups, if such a difference exists. Power is commonly specified in the range of 80% to 90%, which implies a risk of not detecting the target difference of between 20% and 10%, respectively. For a trial involving anything other than minor risks and expenditure, a power closer to 90% than 80% would seem preferable [27], which leads to a larger sample size (as does a stricter alpha level of, say, 1%). This is most pertinent when a lack of statistical significance is obtained in a small trial, particularly when the sample size was not planned using a power calculation [20]. This is the basis for the adage that “the absence of evidence is not evidence of absence” [26]. A planned unequal allocation to the trial groups also requires an inflation of the sample size [20], as does interim analyses. By multiplying the number of significance tests performed, studies with interim analyses generally require stricter significance levels at each analytical point [26, 54].

The **target difference** is the last, and arguably the most important, quantity that must be specified for the power-based approach to sample size calculation. The target difference is defined as the minimum difference between treatment groups considered to be clinically significant. Clinical significance is an entirely different concept from statistical significance. Investigators must estimate the clinical significance as the magnitude of difference (in means or pro-
portions) that would lead to a change in clinical management for the target group of patients. For example, a study might propose that a 20% difference in incontinence episode frequency is a clinically meaningful response. Ideally, such an assumption would be based on surveys of patient behavior but in practice, the decision is often based on clinical judgement. In any case, the smaller the clinically significant target difference, the larger the required sample size. Statistical significance means that the observed difference, whatever its magnitude, cannot reasonably be considered as being due to chance. Statistical significance (denoted by the p-value) represents the strength of evidence against the null hypothesis [55]. The degree of clinical significance can be inferred only with the additional information of a confidence interval for the comparison between groups. A very large trial may achieve a high level of statistical significance with a very small effect size and therefore be of little clinical significance. A trial designed in such a way is ethically challenged; many extra subjects are exposed to risk without meaningful benefit.

The third general approach aims to demonstrate non-inferiority between the treatment under evaluation compared to another treatment or standard therapy. [56; 57]. The same specifications are made as in the power-based approach, except that instead of specifying a particular target difference to be detected, the calculation is centered on the magnitude of difference beyond which the researchers would no longer accept that the treatments are ‘equivalent’. The study is designed to have adequate power to produce a confidence interval for the difference between the groups that does not include values greater than this limit.

There is no single answer for sample size determination; often the calculation proceeds around a ‘circle of specifications’ (involving, say, power, target difference and sample size) many times, starting and stopping at different points. For instance, it is not uncommon to commence with the ‘textbook’ approach of specifying power and target difference (along with alpha and the standard deviation) and calculating the sample size, then to reverse the argument by starting with how many subjects could be recruited and determining what differences could be detected with various probabilities! Furthermore, the ideal of the target being the minimum for clinical significance cannot always be met; rather, the aim in practice is to produce a convincing argument (among the researchers themselves, and also to funding bodies and regulatory agencies) that the sample size has an adequate chance of detecting differences that are (a) feasible, and (b) worthwhile detecting in clinical terms. A common failing is selecting a target difference that is too large, often derived from differences that have been observed or published previously rather than based on considered clinical judgment. Preliminary investigations (often termed ‘elicitation exercises’) into the levels of treatment effects that patients themselves consider worthwhile should be carried out much more commonly than is the case at present.

In all cases, appropriate adjustment for attrition (loss to follow-up) should be performed. This is commonly achieved by simply increasing the planned sample size in proportion to the anticipated attrition (i.e. to predict the reduced effective sample size that will be available for the analysis).

1) Pragmatic and explanatory trials

There is an important distinction between pragmatic and explanatory trials [58, 59], and correspondingly, between intention-to-treat and per-protocol approaches to data analysis [26, 52]. This distinction has a number of facets. For example, data from pragmatic trials are analyzed by intention-to-treat, according to the group to which subjects were randomized, regardless of the extent of compliance with the intended treatment. In explanatory trials, data are analyzed accounting for compliance. This per-protocol approach may exclude serious non-compliers, analyze data according to treatment actually received, or allow for degree of compliance in a statistical model. At first sight, the explanatory approach appears more attractive. However, there are considerable limitations to the explanatory approach, particularly when the intention is to draw inferences from the trial to wider clinical practice (generalizability).

The purpose of randomization is to produce groups that are, on average, comparable. A per-protocol analysis retains this property only in the unlikely situation when non-compliance is unrelated both to the patient’s underlying state of health and the treatment received [26]. The intention-to-treat approach in pragmatic trials retains the full benefits of randomization and has the advantage that the comparison will more closely reflect the relative effectiveness of the treatments when applied in real clinical practice, where non-compliance is a common occurrence [60].

As regards other aspects of the distinction, in pragmatic trials the interventions are designed to be as close as possible to treatment options in clinical practice (including multiple patient management choices) and entry criteria are usually relatively liberal in comparison with explanatory trials. In addition, pragmatic trials may involve a wide variety of outcome domains, including patient-completed questionnaires, and an economic evaluation of outcomes. As a result of intention-to-treat data analysis, pragmatic trials will tend to yield lower estimates of treatment differences than explanatory trials. It may be of interest to gauge the effect of treatment given full compliance; therefore, full data analysis ideally incorporates both intention-to-treat and per-protocol approaches [26]. The primary
analysis, though, should follow the intention-to-treat principle.

The follow-up time for a trial should be at a fixed time (for logistical reasons, this is in practice often a short time window) relative to randomization rather than when treatment was actually received, since again this is the only way of ensuring a valid comparison. The planned timing of follow-up at a fixed time relative to randomization should, however, allow for any likely delays in receiving treatment, e.g., due to surgical waiting lists.

In summary, it is established practice that unless there are strong reasons to the contrary the primary analyses (for both primary and secondary outcomes) of an RCT should be on an intention-to-treat basis [33, 49]. Secondary analyses incorporating non-compliance and/or which treatment was actually received may be justified in addition to the primary analyses. Appreciable loss to follow-up in a trial (which is not the same as non-compliance with intended treatment, lack of efficacy, or the observation of adverse events) may present serious problems both in terms of generalizability of the findings to the wider population and, in the case of differential loss to follow-up across treatment groups, to the validity of the comparisons. Indeed, strictly speaking any missing outcome data means that not all of those allocated to the various randomization groups can be included in the analysis [61], and this might lead to the conclusion that the term ‘intention-to-treat’ should only be used if follow-up is complete. In practice complete follow-up occurs only rarely. Under current guidelines, intention-to-treat relates more to the broad strategy adopted by the researchers for data analysis [46; 62]. Results should always be accompanied by a full and clear statement of how deviations from intended treatment and missing outcome measures have been handled in the analysis. The discussion should include how missing outcome data may have affected the conclusions [61]. Sensitivity analyses can be used to test the exclusion of, or assumptions about, missing values; practical examples of such analyses are becoming more common [63]. Another design strategy, modified intent to treat (MITT), is common in drug trials. It requires the participant to take at least a single dose of the study medication in order to be included in the analysis.

**j) Data analysis**

This section will not contain any technical details of statistical methods, which are available in standard texts [20, 64, 65], but rather will summarize concepts of data analysis. The emphasis here will be on RCTs, although many of the complex methods mentioned (e.g., multiple logistic regression analysis) are used in similar ways to analyze observational data. Appropriate techniques of data analysis will depend on the nature of the outcome variable. In practically all situations, hypothesis tests should be two-sided (i.e., allowing for the possibility that the difference could have been in either direction, that is benefit or harm), rather than one-sided. One-sided tests are only appropriate if a difference in one direction is not just unlikely, but would not be of interest.

Regardless of the type and complexity of statistical techniques used in analysis, the general underlying principles behind hypothesis testing and estimation apply. In particular, the statistical significance of a hypothesis test should be interpreted critically. The actual p-value should be considered, rather than just whether or not it is below an arbitrary threshold such as 5% [33]; indeed, the p-value is better considered a measure of the strength of evidence against the null hypothesis, on a continuum or ‘shades-of-grey’ [65, 66]. The direction and magnitude of the trial comparison should be presented with an appropriate confidence interval to indicate the possible clinical significance and precision of the comparison [67, 33].

Data analysis for numerical outcome variables may use parametric or non-parametric methods. Simple parametric methods require that the data follow a normal or Gaussian distribution, while non-parametric methods do not have this requirement. Strictly speaking, the distributional assumption relates not to the raw data but to what are termed ‘residuals’—that is, the outcome variable after the effects of, for example, the treatment effects and baseline variation have been accounted for. For example, consider a comparison of mean urinary flow rates between two groups of men reporting that they either have or have not experienced a urinary symptom such as incomplete emptying of the bladder. If this comparison involved an unpaired t-test then the assumption of a normal distribution relates not to the urinary flow rates amongst all men, but to the distributions within each symptom group separately. As noted above, to cover simple and more complex analyses, in general this concept relates to the statistical residuals from the relevant regression model. In addition, parametric methods are extremely robust (dependent on the assumption of a normal distribution) since they relate to the mean value rather than individual values.

Parametric methods of testing mean values include t-tests, confidence intervals for differences between group means, and analysis of variance. Regression techniques address more advanced issues such as stratification in randomization and allowance for baseline measures. Non-parametric methods include the Mann-Whitney test to compare two independent samples as in a parallel groups trial and the Wilcoxon matched-pairs signed-ranks test for paired data such as from a crossover trial [22]. Binary outcome variables can be analyzed using chi-square tests and confidence intervals for comparing proportions, and multiple logistic regression [68]. For time-to-event data (such as survival data), methods of data analysis include:
life tables, Kaplan-Meier survival curves, log rank tests, and Cox’s proportional hazards regression [69]. How, then, should the analysis of data from an RCT proceed? An outline of the various stages of data analysis can be gleaned from the CONSORT statement [33, 49], and it is now considered good practice for the trial team to draw up a detailed analysis plan in advance for approval by the Trial Steering Committee, which includes independent members one of whom is a statistician/trials methodologist. The following discussion will concentrate on the underlying concepts of data analysis at a particular follow-up time relative to randomization, and considers initially the simplest case of just two trial groups. Multiple treatment groups will be covered briefly, but repeated measurements of outcomes and interim analyses involve considerably more complex methods of planning and analysis, for which expert help is essential [29, 70].

The first stage of data analysis is to address the representativeness of randomized subjects compared to the target population of eligible patients. The number of eligible patients who were and were not randomized should be provided, along with reasons for the latter. In order to reflect representativeness accurately, this should include all eligible patients: in practice there is a tendency for researchers to avoid approaching certain potentially eligible patients, for any of a wide variety of reasons, and this induces a subtle investigator bias. The presentation of this information is facilitated by use of the CONSORT flow diagram [33, 49] (Figure 1)—indeed, its use is associated with improved quality of reporting of trials generally [34]. Descriptive statistics should also be given of important characteristics of health care professionals approached for involvement in recruiting subjects to the trial, both for those taking part and those declining.

The second stage of data analysis is to compare the two groups at randomization (baseline) including demographic, prognostic, and outcome variables. A common error at this point is to rely on statistical testing for these comparisons [20, 26, 52]. If the randomization procedure has been performed correctly, then any statistically significant differences in baseline characteristics must be due to chance. Statistical testing of this kind is not a test of the comparability of trial groups; rather, it is a test of the allocation procedure [20, 26, 52]. It may be seriously misleading, particularly if lack of a statistically significant difference for a given characteristic is taken to imply comparability. Trials are not designed to detect potentially important differences in baseline characteristics that might be large enough to influence the comparison of the outcomes between the trial groups. The magnitude of this potentially influential difference for a baseline measure depends on the strength of its relationship with the outcome, and not on a p-value at randomization. Therefore, baseline comparability is best assessed by simply obtaining descriptive statistics for the groups and making a judgment as to whether any observed differences are likely to be influential or not. If differences are likely to be influential, they should be considered in the analyses. Notable exceptions to this are baseline measures of the outcome variables, which should be considered in the analysis regardless of the situation at baseline, since removing variance in the outcome measure that is purely attributable to differences between individuals at baseline has potentially marked benefits in terms of precision and power [26]. Investigators should consider stratifying the randomization on any strongly prognostic variable (for
reasons of efficiency rather than bias). Since there are practical limitations as to how many variables a trial can stratify for, as indicated above in section C.2, a technique known as minimization may also be considered [39, 19, 26]. Any variables stratified or minimized at randomization should be allowed for in the analysis [26]. In incontinence research, variables such as prior failure of therapy in drug and surgical studies or the degree of anatomic support in surgical or injectable trials might be considered important enough to stratify, or to include in the analysis if unequally distributed.

The next stage of data analysis is to perform the primary (comparative) analyses for the outcome variables. First, though, it is essential to derive and report actual numeric data – even if simply in the form of descriptive statistics – rather than just reporting for instance a percentage change, even if the latter are relevant and provided as well. Graphs can be misleading, especially when sub-sections of the scales are magnified, and should be used to supplement or clarify the numerical data, not to replace it. Primary outcomes should initially be analyzed by intention-to-treat comparisons of the groups as randomized, both using hypothesis tests for statistical significance and CIs for comparisons between the groups to assess clinical and statistical significance, usually adjusting for baseline measurements of the outcome variable. With a small number of primary outcomes, multiple testing is not a concern. However, when a large number of statistical tests are performed for secondary outcomes, corrections to the observed p-values should at least be considered.

The most commonly used procedure for multiple testing of many outcomes is the Bonferroni correction [20, 26, 64]. The Bonferroni correction is fairly conservative in reducing the risk of a statistically significant effect occurring purely by chance, at the cost of reduced power for individual outcomes. This is particularly pertinent when, as is usually the case, the outcomes are positively associated with one another. While there are alternative procedures that improve this deficiency, none of them are entirely satisfactory [26]. It is emphasized that whatever strategy is adopted to deal with multiple testing, the major errors are to rely solely on p-values rather than present CIs as well, to over-simplify the presentation of p-values to just “NS” or “p<0.05” rather than to quote the actual p-values, and above all to report selectively the results of significance tests.

Another example of a “multiplicity” is where there are more than two treatment groups, e.g., when different doses of a drug are being investigated or when more than one ‘active’ procedure is being compared with placebo [26]. Similar issues to multiple testing of different outcomes are involved here, but there are a greater variety of commonly used procedures available to deal with the central concern of finding a difference purely by chance. Standard methods for dealing with this multiple comparisons problem include the procedures attributed to Tukey, Newman-Keuls and Dunnett [71].

More complex primary analyses adjust for baseline measurements and potentially important prognostic variables (including but not exclusively those that were unbalanced at randomization). They may also involve adjustments for center effects and the investigation of differential treatment effects across centers in multi-center trials [27]. The correct approach for continuous outcome variables is to use the (regression-based) technique known as the analysis of covariance [26, 52]; the equivalent approach for binary outcomes is to use logistic regression. A commonly employed alternative for continuous outcome variables is to analyze simple change scores from baseline to follow-up (either in absolute or percentage terms), but for reasons of both bias and precision this is inferior to regression methods [26, 52]. It is good practice to present both the (unadjusted) simple intention-to-treat results alongside those from the regression methods. In any case, the results from alternative analyses such as these should be compared in a sensitivity analysis of the conclusions [27].

Secondary analyses of trial data include per-protocol analyses with adjustments using regression methods for pertinent process measures such as degree of compliance with the allocated treatments. Secondary analyses also include planned subgroup analyses, such as the investigation of different intervention effects across age, ethnic, or disease severity groups. Subgroups should be analyzed by using appropriate interaction terms in regression models [33, 52]. Using interaction terms rather than performing repeated, separate, subgroup-specific analyses considerably reduces the risk of false positive findings [72, 73]. Subgroup analyses should be carried out sparingly, specified in advance (preferably with a clinical rationale), and above all should not be reported selectively [33, 72, 74]. This last point relates not just to subgroup analyses but to all stages of reporting randomized trials. Pre-specification of the primary outcomes and clear statements about all the outcomes considered is essential to avoid selective reporting. The large volumes of data accumulated in major multicenter RCTs almost guarantee that something “significant” can be identified by “data-mining”. If not identified by the investigators as an a priori item of interest such findings should be viewed with great skepticism.

**k) Reporting of randomized controlled trials**

The CONSORT statement is specifically designed to provide standards for reporting RCTs [33, 49]. It includes a 22 item checklist (**Figure 2**) of critical items that should be included by authors preparing...
manuscripts. Adherence to these guidelines and the use of flow diagrams in particular is associated with improved quality in reporting of RCTs [79]. Errors in presentation of statistical information are extensively covered in many textbooks [20, 64]. This section will emphasize the most important points on reporting of RCTs, to ensure an objective and comprehensive presentation of the trial itself, and also to facilitate any subsequent synthesis of research evidence including formal meta-analyses of RCTs. Meta-analyses are themselves the subject of separate reporting guidelines, the QUORUM statement [76]. However, such guidelines are not a panacea [40]; deficiencies in reporting are still common [75].

The CONSORT statement recommends clear statements about the objectives of the trial, intended study population, and planned comparisons. Subgroup or covariate analyses should be clearly specified and justified. The method of randomization should be stated, as should the unit of randomization; in most cases, this will be the individual participant but occasionally an aggregate group of subjects will be allocated jointly in a cluster randomized design [25]. Cluster randomized designs are also now the subject of separate reporting guidelines [77], and involve particular complications in terms of data analysis [78]. For all trials, specifications for the sample size calculation (primary outcomes, target differences, etc.) should be stated and justified. In addition, the precision actually obtained in a study must be presented. This requires confidence intervals as well as the observed p-values, at least for primary outcomes but preferably for all outcome variables.

The principal confidence intervals should be for comparisons between the groups, rather than for differences in the outcomes within the trial groups [20, 26]. Results should include a trial flow diagram, with numbers and reasons for the exclusion of eligible subjects, the number randomized, and subsequent losses to follow-up [34]. Protocol deviations should be described and explained [52]. Finally, the discussion should include a brief summary of the trial’s findings, possible explanations for the results, interpretation of the findings in light of the literature, limitations of the trial including internal and external validity, and the clinical and research implications of the study [33].

Full disclosure also mandates that the manuscript includes statements defining the role of the sponsors
in the study, the role of the authors and their relationships to the sponsors and other relevant parties, and the registration of trial.

I) Conclusions

In conclusion, it is crucial that those intending to embark on research into incontinence plan the details of the study in advance. Many of the decisions to be made involve statistical issues; therefore it is vital that someone with relevant expertise is involved from the outset. Statistics has been described as a combination of mathematics, logic and judgment [26], and this applies to all phases of RCTs. Naturally, formally qualified biostatisticians are not the only professional group with the necessary expertise to address these issues, particularly since in the planning of studies the above three characteristics are probably stated in increasing order of importance. Furthermore, the benefits of such expertise will only fully be derived if the individuals are involved on an ongoing basis in the conduct of the trial. This is equally true of all the disciplines relevant to studies of health care technology and organization, including social scientists and health economists as well as statisticians and clinicians. Increasingly, the major funding bodies and international journals expect a sufficiently multidisciplinary team to carry out and report on health services research. If for no other reason than because of their central position in influencing the purchasing and provision of health care, this is especially important for randomized controlled trials. As noted in the Ethical Issues of Research section, planning is essential and it is ethically important when conducting human subject research. The study should be well planned, scientifically sound, with the ability to be completed, a reasonable assumption new knowledge will be provided at the end of the study and published to advance scientific knowledge [79, 80]

Recommendations on Study Conduct and Statistical Methods

- The role of quality RCTs as providing the strongest level of evidence in incontinence research should be fully acknowledged by researchers, journal reviewers, and editors. HIGH
- Careful attention to the planning and design of all research, especially RCTs, is of the utmost importance. HIGH
- Appropriate expertise in biostatistics and clinical trial design should be employed at the design phase of a RCT and thereafter on an ongoing basis. HIGH
- The design, conduct, analysis and presentation of RCTs must be fully in accordance with the CONSORT guidelines. HIGH

- The design, conduct, analysis and presentation of observational studies should follow STROBE guidelines. HIGH
- The design, conduct, analysis and presentation of meta-analyses should follow QUORUM guidelines. HIGH
- Reporting studies of diagnostic tests, including urodynamics, should follow the STARD statement guidelines. HIGH

4. OUTCOMES RESEARCH IN LUTS INCLUDING INCONTINENCE

An outcome is a specific result or effect that can be measured [81]. Careful selection of outcome measures that are valid and clinically relevant is intrinsic to the success of research; no single measure can fully express the outcome of an intervention. While every clinical trial must focus on a few primary endpoints, complete collection and reporting of data is essential to progress in understanding and treating disease. It is good to know that a drug or procedure appears to be “safe and effective”. It is better to know that treatment A is superior to treatment B, and by how much. It is ideal to understand why one treatment is better than another—to understand why a treatment works for a particular patient and not for another. Understanding at this level requires simultaneous consideration of outcomes, anatomic and physiologic variables. This degree of detail is often not obtained and is only rarely reported. Reports tend to concentrate on success or failure in achieving the primary endpoint (e.g., cure of stress incontinence); however, to understand outcomes, detailed data is needed on improvement and deterioration in anatomy, symptoms, lower urinary tract function, complications of the intervention, and the effect on quality of life.

The importance of using validated outcome measurements cannot be overstated. The tool must accurately measure what it intends to measure and must be reliable, i.e., it must measure outcome in a way that is consistent and dependable. Whenever possible, select a tool that has already been validated in a population similar to the one to be studied (for example, the age, education/language level and gender should be similar). An instrument that is appropriate for a young or middle-aged population may not be appropriate for older patients whose attention span and eyesight require a short questionnaire in a large font; similarly, scores written for an educated, English-speaking population may not be appropriate for a population for whom English is not the first language. Some LUTS-related instruments have already been validated in multiple languages [82-85]. These tools are optimal when studying populations who speak and read a variety of languages.
If there is no relevant, validated tool available, consider consulting an expert to get assistance with the validation process. Only as a last resort should a tool be used that has not been validated as this diminished the impact of the results. Consideration should also be given to whether the score is gender-specific or gender-neutral. Most validated LUTS outcome measures are gender-specific to target specific gender-related conditions, but for broader population studies, a gender neutral instrument is preferable.

In order to fully understand the outcome of an intervention data is needed far beyond the primary outcome measure. Change in anatomy, symptoms, and lower urinary tract function as well as complications, side effects, and impact on quality of life may influence the interpretation of a trial and may inform as to how an intervention produces an effect. It is also important to select instruments that provide enough data to give clarity without overwhelming the subject and swamping the investigator with irrelevant detail. Perceptions of the patient and clinician concerning outcome, which may be contradictory, must be reported. It is no longer enough for the physician to say treatment was successful; the patient must also have a voice. It is also useful to report the patients’ expectations, because a patient considers the trade-offs between symptom improvement, adverse events, and effects on daily life when assessing overall treatment benefit [86], which may influence the outcome of a study [87]. The following recommendations are adapted from the ICS Standardization Committee [11]

a) Baseline data:

b) Observations:
1. Patient’s observation/Subjective measures
2. Clinician’s observation/Objective measures
c) Tests
1. Quantification of symptoms—bladder diary and pad tests
2. Urodynamics
d) Follow-up
e) Quality of life measures
f) Socioeconomics

a) Baseline clinical and demographic data:

A complete demographic description of the study participants, essential for allowing comparison of studies among jurisdictions, includes [88]

- Age
- Race/ethnicity
- Gender
- Body mass index (height and weight)
- For women—obstetric history, including parity and menopausal status
- Smoking status
- Co-morbidities such as cardiovascular, respiratory and neurologic conditions and diabetes
- Medication use, including naturopathic medicines (e.g. herbs and botanicals [11]), dietary supplements (e.g., vitamins, minerals, fatty acids or amino acids [12] and other alternative treatments
- Past surgical history
- Level of education
- Mental and physical status
- Prior treatment for pelvic floor disorders, including behavioural, pharmacological and/or surgical interventions

Obstetric and gynecologic history is important in women. Recommendations for minimum data collection are made in the proceedings of the NIH Terminology Workshop for Researchers in Female Pelvic Floor Disorders [88]. While few trials will be large enough to analyze the effect of these demographic factors on outcome, the potential future use of meta-analysis makes a complete database valuable.

b) Observations:

1. Participants’ observations and Subjective measures

Validated patient completed symptom questionnaires and other validated instruments are recommended for all trials for LUTS and incontinence (see report from Committee 5). In addition to specific symptoms, the respondent’s overall opinion of the condition should be included. Different methods to obtain this measure include: a question with a forced choice, a graded response, a statement with a Likert scale agree-disagree response, and a statement with a visual analog graded scale response. An ideal instrument would record all symptoms related to the lower urinary tract and relevant associated organ systems. At a minimum, this would comprise:

- Storage symptoms
  - Incontinence, stress induced
  - Incontinence, urgency induced
  - Incontinence, other
  - Frequency and nocturia
  - Urgency
- Voiding/emptying symptoms
- Protection (e.g., pad use)
- Coping measures
• Pain
• Sexual function
• Bowel function

Items of great value in interpreting study results beyond the basic effect on patient symptoms include:
• Patient expectations of treatment
• Patient goals for treatment
• Quality of life

Measures should include the frequency of the symptom (e.g., daily urgency incontinence), the severity of the symptom (e.g., pads are saturated) and the impact or bother produced by the presence of the symptom (e.g., much greater for the individual who works in a public setting). There is no one instrument covering all of these areas which has established methodological reliability. Therefore, researchers should clearly describe their instrument and procedure and provide reliability data or indicate their absence. As there is no one universally accepted, ‘ideal’ instrument, trials are often conducted using multiple instruments to assess different domains. For a detailed discussion of available instruments see the report of Committee 5.

2. CLINICIAN’S OBSERVATION AND OBJECTIVE MEASURES

A detailed assessment of function and a complete description of anatomy complement the patient’s observations and subjective reporting. In some cases these measures could be the primary endpoint (physical exam assessment after prolapse repair or decrease in detrusor leak point pressure in neurogenic bladder patients) but in many other cases they provide important information about why interventions succeed or fail. Functional data, primarily urodynamic, are usually included in the evaluation of lower urinary tract disorders along with an investigation of possible anatomic changes in the lower urinary tract and its supporting structures. There are a few condition specific recommendations for evaluating male anatomy in the literature, such as those for urinary incontinence, recommended by the Urodynamics Society [100]. For women, the Pelvic Organ Prolapse Questionnaire - (POP-Q) is recommended

1 The POP-Q (Pelvic Organ Prolapse Questionnaire) provides a descriptive and quantifying system for the relative position of the organs within the pelvis and an objective system for staging pelvic prolapse. The system, adapted from several classifications by Baden and Walker [101], arose from the efforts of the International Continence Society Committee on Standardisation of Terminology, Subcommittee on Pelvic Organ Prolapse and Pelvic Floor Dysfunction, in collaboration with the American Urogynecologic Society and the Society of Gynecologic Surgeons [102] to develop a terminology standardization document.

2 The POP-Q descriptive system allows the clinician to quantify precisely a woman’s pelvic support without assigning a severity value, to make accurate, site-specific observations of the stability or progression of prolapse over time, and to accurately describe outcome of surgical repair. The system uses six reference points (Figure 3) and a three-by-three grid (Figure 4) for recording a quantitative description of pelvic organ support.

3 The POP-Q descriptive system uses the hymen as the best available fixed point of reference that can be consistently and precisely identified. Six points, two on the anterior vaginal wall, two in the superior vagina, and two on the posterior vaginal wall, are located with reference to the plane of the hymen. The anatomic position of the six points are recorded as cm above or proximal to the hymen (negative number), or cm below or distal to the hymen (positive number), with the plane of the hymen recorded as 0.

**Recommendations on Observations During Incontinence Research**

- One or more validated symptom instruments should be selected in advance of the clinical trial and then administered during the initial phase of the trial to define the baseline symptoms of the population. HIGH
- Observations of anatomy should be recorded using standardized, reproducible measurements. HIGH
- Pelvic muscle and voluntary sphincter function should be reported using a quantifiable scale. HIGH
- All observations should be repeated after intervention and throughout a minimum one-year follow-up, and their relationships with primary clinical outcome measures analyzed. HIGH
- Complications of the intervention should be reported. HIGH
Figure 3: Six sites used for pelvic organ support quantitation (points Aa, Ba, C, D, Bp, and AP), genital hiatus (gh), perineal body (pb) and total vaginal length (tvl). From: Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey PK, Shull BL, Smith, ARB. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996: 175(1): 10-17.

c) Tests

1. Quantification of Symptoms—Bladder Diary and Pad Tests

The diary (micturition time chart, bladder diary, or frequency-volume chart) is a self-monitored record of selected lower urinary function that is kept for a specific period of time. Recorded data may include fluid intake, voiding frequency (diurnal and nocturnal), frequency of incontinence episodes by type, pad use, and voided volumes. Urinary diaries are important in the evaluation of LUTS because they document functional bladder capacity, diagnose diurnal and nocturnal polyuria, and diagnose fluid restriction that may affect continence or other LUTS. The diaries measure what actually happens to the patient in day-to-day life in a way that no test or questionnaire can reproduce. Voided volumes provide additional insight into cause and effect. Diaries range from the very simple micturition time chart (frequency of voiding and incontinence episodes), to the complex bladder diary, which may include fluid intake, voiding frequency (diurnal and nocturnal), frequency of incontinence episodes by type, pad use, causes of incontinence, and voided volumes. Incontinence studies often use the number of incontinence episodes recorded in the diary as the primary endpoint. While this may provide a measurable endpoint, it does not provide the information necessary to interpret the data completely.

The accuracy of a diary is dependent on proper training of the subjects. Reproducibility depends on the parameters used and improves with the number of days that self-recording is obtained. Diaries are reliable for assessing the number of incontinent episodes [103,104]. Longer diaries are more reliable but have decreased subject compliance [104,105]. The length and degree of detail should be determined by the study design and specific requirements for data. Reliability and validity data for specific diaries should be provided if available, or their absence indicated [106,107]. The period of time the diary was used should be noted [108].

The pad test quantifies incontinence; therefore it can provide a key link in understanding outcome. A patient who experiences a decrease in the number of incontinence episodes from four to two per day may not be satisfied if the volume of urine loss is high. Similarly, cure of incontinence may not have a great impact on a patient with trivial volume of urine loss at baseline, particularly if any adverse effect is experienced with treatment.

Pad tests can be divided into short-term or provocative tests, generally performed under standardized conditions as in the 20-minute to 1-hour office tests [109], and long-term tests, generally performed at home over 24 to 48 hours [110,111]. 24-hour pad tests are reliable instruments for assessing the amount of urinary loss [112,113]. The longer pad tests are primarily used for research because of their complexity and the time required to complete them. Increasing the test duration to 48 or 72 hours increases reliability but decreases compliance [114]. For short-term tests, the experimental conditions must include standardized bladder volumes and the physical tasks must be described in detail. Instructions for pad tests have to be followed explicitly to ensure reproducibility.

2. Urodynamics

Urodynamics should be included in research where there is need to document physiologic measures of storage or emptying function. When urodynamics are incorporated, it is important to document equipment, conditions, and concurrent tests [88,115,116], including:

- Hardware and software
- Calibration
- Size of catheters
- Type of infusant and rate and temperature of infusion
- Patient position
- Specific annotations
- Lay language bladder sensation parameters
- Visual Leak point pressure techniques
- Modifications for prolapse
- Data recording
- Use of concurrent EMG and position of electrodes.

Measures of bladder sensation, capacity and urodynamic diagnoses should be made in accordance with current definitions as specified by the ICS Good Urodynamic Practices document [117]. Please refer to Chapter 6 for further discussion on the conduct of urodynamic investigations.

The tests are performed at entry and at conclusion of the study when used as primary or secondary outcome measures. In other instances, urodynamic studies might only be performed at the outset of a study as a means of defining the patient population and/or determining parameters that predict response to treatment. There is a great need for high quality, hypothesis driven research into the utility of using urodynamic studies to define patient populations or risk groups within clinical trials. Urodynamic studies are costly and greatly increase the complexity and expertise required to perform clinical trials. At this time urodynamic studies have not been proven to have adequate sensitivity, specificity or predictive value to justify routine use of testing as entry criteria or outcome measures in clinical trials [118-122]. Participants should generally not be stratified by urodynamic diagnosis; rather, more studies should be performed to define specific urodynamic parameters.
that predict outcome. There is evidence that urodynamics have a role in predicting outcome for some [123-124], but not all LUTS-related conditions [125, 126]. Valuable insights into the limitations of pre-operative urodynamic testing have been provided by the SISTEr trial [127] and the CARE trial [128]. The ongoing TOMUS trial comparing synthetic midurethral slings also employs blinded preoperative urodynamics and will further explore the utility of such investigations.

It would be ideal to use urodynamic studies routinely to accurately characterize baseline lower urinary tract function and dysfunction and the change after treatment. However this is impractical in most RCTs and unnecessary to answer the basic questions involved. At the same time, urodynamic tests are among the best tools currently available to understand the basic physiology and mechanisms of disease; these tests must somehow play a role in research. While routine incorporation of urodynamic testing is not warranted in clinical research, hypotheses driven inquiries aimed to refine the studies, define the utility of specific tests in different patient populations, and to develop new and better tools are needed.

Procedures for performing urodynamic studies must be carefully standardized in trials to ensure that consistent techniques are used for different subjects; this is particularly critical for different centers in a multicenter study. The exact same technique must be used at baseline and follow-up. Studies with urodynamic endpoints require an evaluation of whether or not the study reproduces the symptom under investigation. In multicenter studies investigator bias can be minimized by using a third party assigned to read the urodynamic tracings that have been annotated according to the agreed-upon definitions.

Recommendations on tests used in incontinence research

- Clinical trials of incontinence and LUTS should include frequency-volume charts as an essential baseline and outcome measure. HIGH
- The diary should include measured voided volume for at least one day. HIGH
- Pad tests should be considered in clinical trials whenever feasible. HIGH
- In all trials employing urodynamics, standardized protocols (based on ICS recommendations) should be defined at the outset. In multicenter trials, urodynamic tests should be interpreted by a central reader to minimize bias unless inter-and intra-rater reliability has already been established. HIGH

d) Follow-up

Minimal standards for evaluation of treatment outcomes in urinary incontinence have been presented in a report developed by a committee of the Urodynamic Society and approved by both the American Urologic Association and the Society for Urodynamics and Female Urology [129]. In addition to standard pre- and post intervention evaluation, they recommend evaluation of surgical, prosthetic, and implant therapies no less often than 1 to 3 months and 12 months after treatment, and thereafter at yearly intervals for as long as possible. Although early follow-up can provide important insights about outcomes, particularly adverse events, a great deal more emphasis needs to be placed on long-term effectiveness. Outcome reporting for surgery and some other interventions should begin at one year minimum (not mean) follow-up for all subjects.

The method by which follow-up data is collected should be specified, e.g., prospective questionnaires or retrospective chart review. Individuals collecting data should be identified, e.g., clinician or independent research nurse. The interval between the time of evaluation and the last treatment should be specified. The exact type of data collected at each time point in follow-up should be defined at the study’s outset. A minimum data set to be collected at each post-treatment interval includes: the total number of subjects evaluated versus the number of subjects actually enrolled in the study, and the total number of subjects lost to follow up and the reasons why they were lost. Indications for retreatment and the time interval since the last treatment should be specified. Efficacy assessment should be done at a specific time interval after the last treatment. The protocol should further specify the criteria by which treatment success or failure is determined.

Recommendations for follow-up

- More long-term follow-up is needed in all types of incontinence research. Conversion of RCTs to registries using structured annual follow-up with validated instruments is recommended whenever feasible. HIGH

e) Quality-of-life measures

Health related quality of life (HRQOL) refers to an individual’s perceptions of the effect of a health condition and its treatment on quality of life [130]. Primary domains of HRQOL include physical, psychological and social functioning; overall life satisfaction and well-being; and perceptions of health status. Secondary domains include somatic sensations (symptoms), sleep disturbance, intimacy and sexual functioning, and personal productivity (e.g., household, occupational, volunteer, or community activities). It is important to know not only how successfully
treatments decrease the frequency of incontinence episodes, but also how a treatment affects a patient globally. The combination of HRQOL data and more traditional objective endpoints will allow us to understand the reasons behind our success and failures.

Three measurement approaches are commonly used to assess HRQOL: generic, condition-specific and dimension-specific. These instruments are explained in the report from committee 5. Here only a few aspects of relevance to research are touched upon. Generic HRQOL instruments such as the SF-36 are designed to be used across groups by having established age and gender norms. Condition-specific instruments such as the Leicester Impact Scale for lower urinary tract symptoms [131] are designed to measure the impact of a particular condition. These instruments tend to be more responsive than generic instruments in detecting treatment effects. Symptom scales are considered condition-specific; generally, these scales should include measurement of the presence of a symptom as well as the “bother” related to it. The majority of generic and condition-specific instruments are multidimensional, i.e., they measure more than one aspect of HRQOL.

Dimension-specific instruments, in contrast, are designed to assess a single component of HRQOL, such as sleep disturbance. A practical approach to assessing HRQOL is to combine a multidimensional generic and/or condition-specific instrument with dimension-specific instruments appropriate for the trial.

The selection of an HRQOL instrument should be defined by the purpose of the study. Descriptive epidemiological studies should consider both generic and condition-specific instruments. Intervention studies should include a condition-specific instrument. Dimension-specific instruments should be used when more detail about a specific subdomain of HRQOL is desired. Researchers should define HRQOL for their study, clearly describe their instrument(s) and data collection, and provide reliability data if available. Selected instruments should be reliable and sensitive. In adopting HRQOL instruments, results obtained in the study population should be compared with published norms. If a new instrument will be used in a study, adequate pretesting should be done to establish its clinimetric characteristics (e.g., reliability and sensitivity) and an established instrument should also be used to provide a comparison.

**Recommendations on Health Related Quality of Life in Incontinence Research**

- Research in incontinence and LUTS should include both generic and condition-specific validated HRQOL instruments whenever practical and appropriate. HIGH

- Changes in HRQOL after therapy should be considered in relation to changes in individual symptoms, and with physiologic and anatomic outcome measures. LOW

- Changes in HRQOL are an important secondary outcome measure for incontinence research - HIGH

**f) Cost Analysis**

The financial burden on the health care system, the patient and patient’s family of various treatment options makes cost an important outcome to measure. A full discussion of the economic impact of urinary incontinence is detailed in the report of committee 22. We recommend that cost analyses be planned with clinical studies whenever possible. Costs may be influenced by economic and political factors that are subject to change at any time; however, when basic units of work, time, and resources are carefully defined, models of costs remain useful even if market forces change in an unforeseen manner.

In health and medicine, economic analyses are descriptive and/or comparative. Descriptive data include the socioeconomic cost caused by the disease and its current treatment, whereas comparative data provide an economic evaluation of different treatment strategies and interventions where costs are compared to health outcomes.

There are several relevant types of cost analysis, some of which require a high level of expertise to conduct:

- **Cost of illness analysis** (COI) typically quantifies the burden of medical expenses (direct costs) and the resulting value of lost productivity (indirect costs) attributable to a specific condition such as an illness or injury [132].

- **Cost effectiveness analysis** (CEA) measures the costs and consequences of two or more diagnostic or treatment pathways related to a single common effect or health outcome. It then summarizes the results in ratios that demonstrate the cost of achieving a unit of health effect for different types of patients and for variations of the intervention [133].

- **Cost utility analysis** (CUA) is a form of cost effectiveness analysis in which particular attention is paid to the quality of health outcome related to treatment. In CUA, health effects are expressed in terms of quality-adjusted life years (QALYs) [107]. A QALY is a measure of health outcome that assigns to a given period of time a weighting that corresponds to the health-related quality of life during that period, and then aggregates these weights across time periods. The QALY is important because it considers both quantity and quality of life.
- **Cost benefit analysis** estimates the net social benefit of an intervention by comparing the benefit of the intervention with the cost, with all benefits and costs measured in dollars [134]. Health outcomes are converted into monetary values using “willingness to pay” (the value an individual would pay for reduction in illness severity) or “risk of death” or “human capital” methods (an individual’s value to society based on productivity or future wages) [135,136].

**Recommendations on Cost Analysis in Incontinence**

- Cost analysis should be incorporated into clinical studies whenever possible [137].

### III. RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS

#### 1. MEN WITH LUTS, INCLUDING INCONTINENCE

Four unique factors influence research on lower urinary tract symptoms in adult men:

- the confounding influence of the presence of the prostate
- the likelihood of bladder outlet obstruction (BOO)
- the rarity of sphincteric incontinence, and

the rarity of any kind of incontinence at all in young and middle aged men except under two special circumstances – neurogenic bladder and after treatment for prostate cancer.

The presence of the prostate complicates research because of its known effect in causing bladder outlet obstruction (with or without benign prostatic enlargement—BPE), its propensity for developing prostate cancer and the effects of treatment for both conditions, resulting in sphincteric incontinence (after prostate surgery) and incontinence due to detrusor overactivity (after radiation based therapies). Further, prostate size itself may influence outcomes in some therapies of urinary incontinence, for example the type of surgical intervention in men with prostatic obstruction and urinary incontinence. Overall, about 2/3 of men with LUTS have urethral obstruction and over 50 % have detrusor overactivity, although a much smaller number have urinary incontinence due to detrusor overactivity [138]. The rarity of incontinence in men suggests that gender specific bother and quality of life instruments will be necessary.

**a) The presence of the prostate:**

Aside from obstruction (see below), the prostate impacts on outcomes research in incontinence in three ways – prostatic size, the possibility of undiagnosed malignancy, and prior therapy (prostatic surgery and other therapies for BOO, BPE or prostate cancer). If prostate size is believed to be a variable that could affect outcomes, measurement of prostate volume should be made before and after treatment. The method used to measure volume and its reliability and validity should be provided if available or their absence indicated. Timing of post-treatment testing depends of the treatment’s mechanism of action, but of course, prostate volume should be measured at the same time as the primary outcome measurements for incontinence are determined. The association between outcome and change in prostate size should be reported. Consideration should be given to stratifying participants by prostate volume when there is suspicion that response to therapy may be size dependent.

Since the presence of undiagnosed malignancy might affect outcomes, participants should be screened for prostate cancer by digital rectal examination and measurement of serum PSA and appropriate disposition should be made based on the outcome of such testing. A careful history of past surgery and other treatment of BPE, BOO, and prostate cancer should be obtained and dealt with based on the inclusion and exclusion criteria for the study.

**b) Likelihood of bladder outlet obstruction (BOO):**

Insofar as about 2/3 of men with LUTS have BOO, it is important in any research protocol to screen for its presence. At the least, uroflow and measurement of post-void residual urine should be recorded pretreatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. While synchronous pressure-flow studies are generally desirable and should be included whenever feasible there should be a focus on hypothesis driven research that will refine our knowledge about the utility and cost-benefit of these studies. Results should be presented as stated in the ICS 1997 Standardization Report on Pressure Flow Studies of Voiding, Urethral Resistance and Urethral Obstruction.” Methods used for the assessment of bladder outlet obstruction should be stated and reliability and validity data should be provided if available or their absence indicated. Several pressure-flow nomograms have been proposed to diagnose obstruction in men so it is important to specify which if any nomogram is being used [139].

**c) The rarity of sphincteric incontinence:**

The rarity of sphincteric incontinence in men has one practical consequence – any man with sphincteric incontinence should undergo an exhaustive neurologic evaluation unless it is consequent to prostatic surgery or a neurologic condition known to cause sphincteric incontinence, such as a thoracolumbar neurologic lesion.
d) The relative rarity of incontinence other than post-micturition dribbling in young and middle aged men except as noted above:

Young and middle aged men only rarely have incontinence unless they have a neurologic condition, prior prostatic surgery or severe bladder outlet obstruction. With advancing age, there is a gradually increasing incidence of detrusor overactivity and incontinence. For this reason, it may be important to use gender and even age specific quality of life and bother scores when assessing these outcome measures.

Recommendations for Research in Men

- High quality, symptom and bother scores (e.g., IPSS, ICIQ-MLUTS, DAN-PSS) validated in men should be employed when assessing outcome in male incontinence research. HIGH
- Uroflow and measurement of post-void residual urine should be recorded pre-treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. MEDIUM
- Measurement of prostate size (or at least Prostatic Specific Antigen) should be performed before and after treatment (synchronous with other outcome measures) whenever prostate size is expected to change due to the treatment. HIGH
- Participants should be stratified by prostate size at randomization when size is considered to be a potentially important determinant of treatment outcome. LOW
- Further research in on the cost-utility of pressure-flow urodynamic studies and the ability to use such studies to define relevant subgroups of men who may respond differently to various treatments is desirable. LOW

2. WOMEN WITH LUTS AND INCONTINENCE

We concur with the 1997 Urodynamics Society recommendations for outcome research in women [15, 16]. We also refer to the ICS recommendations for outcome measures in women with lower urinary tract dysfunction [12] and the Proceedings of the NIH Terminology Workshop for Researchers in Female Pelvic Floor Disorders [88]. Unique factors influencing research on lower urinary tract symptoms in adult women include:

a) hormonal effects
b) obstetric history
c) pelvic organ prolapse
d) gender related outcome measures
e) sexual functioning

All of these potentially confounding variables can affect the outcome of treatment of incontinence.

a) Hormonal effects

Our knowledge of hormonal influences on the lower tract remains limited. Recent RCTs and prospective cohort studies have demonstrated that (HT) does not improve or may worsen incontinence [140-142]. It therefore seems appropriate that information about menstrual and hormonal status should be an integral part of the baseline history. Studies designed to examine the influence of hormones on incontinence should include menopausal status (premenopausal, postmenopausal without HT, post-menopausal with HT), whether or not oophorectomy has been performed, and the type, dosage and route of administration of HT if used.

b) Obstetric History

The unique influence of vaginal childbirth on the structure and function of the female pelvis remains incompletely understood. That childbirth may lead to incontinence and pelvic organ prolapse is indisputable; the potential effect of childbirth on treatment of incontinence has yet to be determined. The need for basic clinical data on the study population and the specific aims of each study will determine the level of detail obtained for obstetric history. Potentially confounding variables include: number and route of deliveries (vaginal/Cesarean), use of forceps or suction devices, infant birthweight, duration of second stage of labor, use of midline versus mediolateral episiotomy, obstetric analgesia, and obstetric complications such as lacerations and fistulae.

c) Pelvic Organ Prolapse

The effect of pelvic organ prolapse on lower urinary tract function remains controversial and understudied. It has been suggested pelvic organ prolapse may affect lower urinary tract function in at least four ways. It may cause urethral obstruction, it may mask sphincteric incontinence, it may cause urgency and urgency incontinence, and/or it may diffuse pressure transmission, making it more difficult to void by abdominal straining. Some of these effects may be immediately reversible with reduction of the prolapse. For all of these reasons, it is essential to include assessment of pelvic organ prolapse in incontinence research. Methods used for the assessment of pelvic organ prolapse should be stated and reliability and validity data should be provided if available or their absence indicated; the Pelvic Organ Prolapse Quantification System (POP-Q) [9] is recommended as discussed by committees 5 and 15. Further, whenever prolapse is present, instruments for assessing incontinence and LUTS should be reported with the prolapse reduced and again at its full extent whenever possible. In either event, prolapse should be graded at the same time as the outcome assessment for incontinence and LUTS is performed.
The degree of urethral mobility is considered an etiologic and prognostic factor in women with urinary incontinence, although its precise role has not been defined. At present, there is neither a well accepted method of assessment nor a classification system. Common methods of assessment include measurement of the Q-tip angle (cotton swab test), magnetic resonance imaging, ultrasound, and cystogram. In the absence of a classification system, it is recommended that data be presented as a continuum, such as the Q-tip angle, not as a dichotomous normal versus abnormal classification, at least until the terminology is better defined. Methods used for the assessment of urethral mobility should be stated and reliability and validity data should be provided if available or their absence indicated.

d) Definition of Outcomes Measures for LUTS & Incontinence

Treatment of urinary incontinence in women may have broad ranging effects on lower urinary tract function, prolapse, sexual function, and bowel function. It is therefore important that a broad perspective of outcome be presented. The NIH Terminology Workshop for Researchers in Female Pelvic Floor Disorders recommendations [88] for stress incontinence treatment define outcomes as cure/improved/failed in terms of incontinence symptoms, signs, and testing, but also in terms of associated symptoms and unwanted (side) effects resulting from an intervention, after return to baseline activities and medications.

The strength of the definitions proposed by NIH is the amalgamation of subjective and objective measures as well as the recognition of the potential adverse effects of incontinence therapy. However, there is as yet little experience with this system. Although these recommendations advance the concept of global pelvic floor evaluation and emphasize the interrelatedness of pelvic organ function, there are limitations in compressing such broad outcome measures into only three categories. It is still critical to know whether a treatment corrects the intended problem. For example, if an operation reliably cures stress incontinence but causes dyspareunia, it may be more useful to report that there is a high cure rate plus a high complication rate. It may not be appropriate to report a woman cured of stress incontinence as failed if she develops urinary tract infections or a rectocele several years later. While appropriately emphasizing the significance of complications and adverse events, this system does not provide a means to fully express such complex outcomes. It also leaves a rather broad range of “improved” patients that must be further defined; when complete cures are relatively uncommon, this may diminish the impact of the outcome. In any case, if these definitions are not adopted it is still imperative that researchers specify the outcome measures that will be used to define cure, failure, and improvement in the materials and methods section. Further, possible (and likely) discordant outcomes should be described and categorized. For example, a woman might state that she is cured of incontinence, have a negative pad test and diary, yet stress incontinence might be demonstrated on a stress test with a full bladder.

An alternative view of a global outcome measure has been described [143]. Here, incontinence is first assessed and the patient declared cured, improved or failed based on outcome measures derived from the criteria listed below. If the patient is not cured (i.e. dry) the reasons ascribed are defined as sphincteric incontinence, detrusor overactivity incontinence, extraurethral incontinence (fistula) or incontinence of undetermined etiology. The system can be used for studies of both stress and urgency incontinence. Once incontinence status has been determined, other LUTS should be described using LUTS outcome instruments. In all instances, methods used for the assessment of incontinence and LUTS should be stated and reliability and validity data should be provided if available or their absence indicated. In such a scheme, incontinence could be cured yet the patient might experience de novo or persistent LUTS that mitigate against the patient considering herself cured or improved. Examples of outcome instruments that take these objective, semi-objective and subjective measures into account are the SEAPI-QMM system [144] and the Simplified Urinary Outcome Scores [145].

Outcomes for detrusor overactivity should be defined separately for symptoms, as described above, and for urodynamic findings. Cure of detrusor overactivity is defined as the absence of involuntary phasic detrusor contractions on filling cystometry. Failure is defined as unimproved or worsened detrusor overactivity on urodynamics. Improvement has not been standardized and should be precisely defined for each study.

e) Sexual function

Urinary incontinence, LUTS and the treatment of these disorders all have potential effects on sexual function and yet little is known about the impact of incontinence treatment on sexual function. It is therefore appropriate that sexual function be considered one of the domains for investigation in all types of incontinence research. Validated instruments that deal with sexual function in women with LUTS and incontinence include the Incontinence Impact Questionnaire (IIQ) [143], the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) [146], and the ICIQ-FLUTSSex (http://www.iciq.net/ICIQ_Fluttssex.html).

A final issue relating to research methodology in female incontinence is defining the population for studies of stress incontinence. One group has described a clinical algorithm that might be used to select patients without urodynamic testing [147].
Representative samples of well-defined target populations are necessary in different care settings including the community (independent and home-bound), acute inpatient, and nursing home or institutionalized (bedfast and non-bedfast). Well-conducted data collections are important to provide careful measurement of a wide variety of potential risk factors and a large sample to allow for statistical adjustment for multiple potential confounding variables to identify independent risk factors for incontinence. Cross-sectional studies are efficient to determine prevalence and identify potential risk factors while longitudinal studies are needed to estimate incidence, understand the natural history, and to define causality of risk factors. There have been few longitudinal studies of incontinence in this group. Unfortunately, most prior studies were small, did not differentiate functional or cognitive impairment, and failed to identify medical conditions or medication use. Most of the analyses were not adjusted for potential confounding variables as mentioned or age, body weight, parity, etc. It is important to include previously reported risk factors and potential risk factors. Validated instruments should be used when available. Otherwise, a detailed description of how the risk factor was measured is required to assess how well the variable represents the area of interest. In the frail elderly, important variables include:

- Demographic information: Advancing age, white race, and women [142, 149-151] are associated with an increase risk of incontinence and each of these variables should be adjusted for in most analyses.
- Reproductive History: Childbirth is an established risk factor for incontinence [152,153] and it is reasonable to collect data on the number of births. However, in women over 60 years of age, as chronic medical illnesses become more prevalent and impact incontinence, risk profiles change and parity may not remain a significant risk factor [151, 154-156]. Prior hysterectomy has also been suggested as a potential risk factor for incontinence in older women [157, 158].
- Medical Conditions: Medical conditions related and unrelated to the lower urinary tract have been shown to increase the risk of incontinence in older women and are especially important to assess in the frail older population [151,154-156].
- Medication Inventory: Certain medications may exacerbate incontinence and therefore a complete medication inventory is essential [158-161].
- Physical function: Mobility is often impaired in the frail elderly and impacts urinary control [163], therefore mobility should be assessed using validated instruments such as the Bartel Orcats or ADL scales [163, 164]. Data on walking aids or wheelchairs, gait speed, and manual dexterity may also be collected.

3. FRAIL OLDER AND DISABLED PEOPLE

We agree with recommendations for outcome research in frail older people as reported in the ICS Subcommittee on “Outcome Measures for Research of Lower Urinary Tract Dysfunction in Frail Older People” [14]. In addition, please refer to the full report of Committee 11 regarding conservative treatment in the elderly. Frailty is defined as “a state of reduced physiological reserve associated with increased susceptibility to disability [148].” There is a wide variation in functional capacity within this definition ranging from those requiring some assistance with activities of daily living to those suffering from dementia and severe physical handicaps. Consequently, the frail older population is a heterogeneous group residing in a broad range of care settings, with multiple medical conditions related and unrelated to the lower urinary tract, and often on numerous medications. There are a number of unique and pertinent research issues for this population.

a) Prevalence, natural history, and risk factors

There remains a paucity of research on the prevalence and incidence of urinary incontinence to assess the burden of disease in the frail older population. This information is vitally important to estimate health care costs and direct resource planning. Less information is available on risk factors and this lack of established risk factors limits preventive efforts and highlights the need for increased epidemiologic research.
• Cognitive function: Cognitive function impairment and/or dementia increase the risk of incontinence [162]. The Mini-Mental Status Scale Examination [165] assesses global cognitive function and the Confusion Assessment Method (CAM) [166] is a standardized assessment for delirium. A battery of neuropsychological tests to measure subtle impairments in cognitive function include the Buschke Selective Reminding Test (verbal learning and memory) [167], the Digit Symbol (incidental memory, visual scanning and motor speed) [168], and the Trails A (attention and visual) [169].

• Environmental factors: In the frail elderly, environmental factors may also contribute to incontinence: toilet access, the usual continence care available in the facility, and a description of caregivers and their training may be useful.

b) Outcome measures

An outcome measure should be reproducible (test-retest), accurate (sensitive and specific), feasible (balance of risks, costs, acceptability, ease of use), and sensitive to change over time. Additionally, the outcome measure should be clinically relevant and meaningful. It must be acknowledged that almost all outcome measures used in the study of incontinence that have been shown to be reliable and valid in the community dwelling population require separate validation for use with the frail elderly. Whatever outcome measures are chosen should be described in terms of applicability to the frail elderly.

Commonly used self-reported measures of frequency of urinary symptoms, severity, or level of bother may not be possible in the cognitively impaired frail elderly patient. Similarly, voiding diaries that have been shown to be valid and reliable in assessing urinary frequency, nocturia, and incontinence episodes by type [114, 107,169,170] may not be feasible or reliable. Motivated and trained staff, caregivers, or family members may be able to adequately collect diary data; however, this has not been validated.

In nursing home or inpatient settings, wet checks by staff at set intervals have been used in a number of studies. There are limitations to the measurement including visually determining what is “wet” because of new absorbent materials and staff reports not always being reliable or valid, due to underreporting [162, 171]. To overcome the limitation of defining wetness and underreporting, 24-hour pad weighing tests [172, 173] may be used. Pad weighing tests and wet checks are feasible and can provide important outcome data if staff are well trained and checks are often [174]. The usefulness of cystometry, simple or complex, as an outcome measure in the frail elderly remains unclear. Cystometry is invasive, difficult to perform, has poor reproducibility, and has not been shown to be clinically useful by demonstrating the improved outcomes in randomized controlled trials [172, 175]. A post-void residual volume is useful as a screening tool prior to an intervention that may exacerbate urinary retention (pharmacologic or surgical). It is also a useful outcome measure of adverse events in intervention studies by demonstrating the development of urinary retention. It is easily performed by ultrasound or catheter and has been shown to be reproducible and accurate [176-180].

Although a primary outcome is needed for sample size estimation, it is useful to have several outcome measures that assess different aspects of urinary incontinence. Evaluation of incontinence bother and effect on quality of life is pertinent to the patient and may also be important from the perspective of the staff, caregivers, and family members.

New outcome measures specific to the frail older population such as increased socialization or decreased caregiver burden need to be developed. Having multiple outcomes can provide a more detailed description of the effect on urinary incontinence.

c) Intervention trials

Prior to initiation of pharmacologic or surgical intervention trials in the frail elderly, careful consideration of the risks and benefits is important because of the increased risk of adverse side effects or events. In addition to the urinary incontinence outcome measures mentioned above, extensive outcome measures that will detect adverse effects from the intervention are important to demonstrate that the beneficial effect of the intervention outweighs the adverse events.

For example, in trials of new medications, using a battery of neuropsychological tests to measure subtle impairments in cognitive function would be important, but thus far have not been adequately used. In intervention trials of new medications or operations, clinically significant outcome measures (global patient satisfaction with improvement, and consideration of staff, caregiver, and family satisfaction perspectives) that demonstrate substantial effect sizes (clinical significance) rather than “statistically significant” improvements are particularly important in the frail elderly.

d) Conclusion

Research methodology for studying incontinence in the frail and housebound elderly is fraught with pitfalls. This has compromised the usefulness of past research. There is a great need for validation of practical and useful outcome measures that will allow meaningful results to be obtained. In addition, an understanding is required of the importance of defining clinical rather than statistical significance.
Recommendations for Research in Frail Older and Disabled People

- There is a need for validation of all instruments and procedures used in incontinence research for the population of frail elderly as well as development of new study measures in multiple domains of incontinence. These measures need to be evaluated for reproducibility, accuracy, feasibility, and effects on clinical decisions and outcomes. HIGH

- Clinically important outcome measures, and relationships of outcome to socioeconomic costs, are essential to establishing the utility of treating urinary incontinence in this population. HIGH

4. INCONTINENCE IN CHILDREN

The conduct of clinical research in children is generally more difficult than in adults. However, the need for quality clinical research in children has been emphasized in an official report from the United States National Institutes of Health (NIH) from March 1998, published in response to statements from the 1996 U.S. Congress Appropriations committees calling for increased and improved funding of pediatric medical research. The document [181] sets forth the policy and guidelines on the inclusion of children in research involving human subjects that is supported or conducted by the NIH. The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children. The document points out that, “The policy was developed because medical treatments applied to children are often based upon testing done only in adults, and scientifically evaluated treatments are less available to children due to barriers to their inclusion in research studies”. The American Academy of Pediatrics has reported that only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials performed in a pediatric population and a majority of marketed drugs are not labeled for use in pediatric patients. Many drugs used in the treatment of both common childhood illnesses and more serious conditions carry little information in the labels about use in pediatric patients. It is the stated policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. Appropriate exceptions are listed in the document. The specific responsibilities of all involved parties—principal investigators, institutional review boards, involved institutions, peer review groups, and the NIH—are detailed. Finally, and perhaps most importantly, the document describes levels of risk and the corresponding nature of assent required for participation in research studies. All clinical investigators who work with children should be familiar with the contents of this NIH document.

Four overriding issues separate pediatric research from the general recommendations. First, physiology varies widely within the group referred to as “children”, differs from adults, and changes with time. Because children are growing, any treatment, especially pharmacological and surgical therapy, may affect them profoundly in the long term. This is particularly true of the immature brain, nervous system and other incompletely developed systems. Second, compliance with therapy is more complicated as children may depend on caregivers to administer treatment in many studies. Third, reporting of symptoms and outcomes may be difficult. The child may be unable or unwilling to respond. Symptoms reported by a caregiver may not be interpreted in the same way as the child. Finally, the issue of informed consent becomes even more complex with children.

The pediatric population is not a homogenous group; neonates, infants, pre-pubescent children, and adolescents clearly differ physiologically and psychologically. The effect of illness and the treatment of that illness must be carefully studied in each age group. Studies should be robust enough to allow for evaluation of varying age groups when relevant. Urinary incontinence in children falls into four main categories: neurogenic (myelomeningocele and other less common neurogenic etiologies), pure nocturnal enuresis, detrusor overactivity, and dysfunctional voiding without neurologic disease. This issue of age groups is most crucial in children with myelomeningocele. These children are often on medication beginning at a very young age and continuing for many years; the long-term safety of medications in children must be established in all age groups. Therapy for other causes of incontinence in children tends to start at a later age, by which time size is the main difference between children. We recommend that clinical studies have long-term (five years or more), open label extension arms to monitor safety, particularly focusing on normal growth and development and the effects on treatment of liver and central nervous system function. Most importantly for incontinence studies, normal maturation may significantly enhance or obscure response to an intervention.

Assessment of compliance with therapy is always difficult, and even more so with children. Compliance with voiding diaries, a significant issue in the adult population, may be even more problematic with children. Children may “act out” and refuse medications or other treatments. Children may be willing to comply with instructions from one parent or caregiver but not another. Personal problems of the caregiver may dramatically affect the child’s compliance with a
treatment protocol. We can only recommend that this potential problem be recognized and given even more attention than in trials with adults. Adequate support to the family member consenting to the trial may aid in compliance with treatment. Specific compliance issues should be identified whenever possible. If a treatment is not accepted by either the adult or the child (e.g., tablet size too large, taste of the medicine not acceptable, behavioral treatment schemes too rigid), then it cannot be effective in practice, no matter how theoretically beneficial it may be.

The NIH document details appropriate levels of consent required based on the risks inherent to a particular study. Depending on the age of the child, consent may be given by the parent in a purely surrogate role or the child may participate to some degree in the process. However, true informed consent of the subject is not possible in the vast majority of cases when children are involved. We recommend that an effort be made to include the child in the discussion of the trial with age-specific language and illustrations when appropriate. It is important to include the primary care giver, when the consenting adult will not be administering the treatment. Such complex relationships exist where childcare is shared amongst more than one adult, or where an employee for the purposes of childcare exists, either inside or outside the home. While children should always be offered the standard of care when such exists, so few treatments have ever been studied properly in children that there are many areas in which no treatment can properly be called “safe and effective”.

Outcome measures are not as well developed in children as in adults. Validated, age-specific symptom and disease-specific quality of life instruments must be developed for the pediatric population. Early efforts in this area have been reported for dysfunctional voiding [182] and daytime incontinence [183]; much more work remains to be done. Invasive urodynamics can rarely be used (except in the neurogenic population), as parents will not allow repeated instrumentation of the child. The reproducibility of urodynamic investigations in children is still under investigation.

**Recommendations for Research in Children**

- Long-term follow-up is of critical importance in the pediatric population in order to ascertain the effect of a treatment on normal growth and development. **HIGH**
- Research is needed to develop standardized outcome measures including validated, age-specific symptom and disease-specific quality of life outcome measures. **MEDIUM**
- We support the NIH statement calling for increased clinical research in children. All investigators that work with children should be aware of the details of the document and particularly the issues surrounding informed consent. **MEDIUM**

5. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION (NLUTD)

In the past, renal failure was a leading cause of death in the spinal cord injured population and a feared complication of many neurologic conditions. Modern neurorehabilitative care is generally successful in maintaining renal function and preventing other upper urinary tract complications, affording social continence, and advancing independence in self-care. Lifelong urological follow-up is mandatory and there are many areas for further research to improve the lives of these patients. These recommendations add to the General Recommendations above and focus on the specific characteristics of the neurogenic patient. Specific discussion of treatment in the neurogenic population is contained in reports from committee 10. Statistical methods and research outcomes are applicable as described in the general recommendations. Emphasis should be given to:

- classification of the neurogenic patient
- the specifics of history and evaluation, necessary for research studies
- the urodynamic evaluation, which is the key investigational tool in the evaluation of this specific, complex and difficult patient population

**a) Classification**

Classification of NLUTD has three primary aims—to aid in discriminating or identifying an unknown underlying neurological disease process, to characterize the nature of the dysfunction so as to develop a treatment plan, and to assess the risk of secondary effects (e.g. on the upper tract) which may influence the necessity and aggressiveness of treatment. The latter two are clearly relevant to research in neurogenic incontinence and must be reflected in study design and patient description.

It is difficult to find a classification system of NLUTD as a base for research that is satisfactory for each of the three aims. The published systems have been reviewed in detail [184]. Both the disease process and the site of the neurologic lesion(s) are relevant in the study of NLUTD, yet even this information is inadequate to predict the functional characteristics for an individual patient. There is no one method that meets the broad needs of classification in this group. Typical or classic cases are often well described but
it is especially difficult to describe mixed and incomplete lesions. Thus, classification systems necessarily oversimplify or become extremely cumbersome. Finally, it must be acknowledged that the complexity of neurologic diseases and variations in individual behavior almost always call for a customized approach to therapy, further complicating research in the neurogenic patient. All of these factors complicate study design as it becomes difficult to create workable inclusion and exclusion criteria that apply to other than a narrow segment of the neurogenic population. Ideally a broad population of potentially relevant participants would be enrolled in research studies with full characterization of both the neurologic condition and the nature of the lower urinary tract dysfunction so as to allow for subgroup analysis.

b) History and evaluation

Study planning is best undertaken with the cooperation of urologist, neurologist, and other clinicians, who have a specific interest and special training in the neurogenic patient. Baseline data collected by history in subjects with neurogenic lower urinary tract disorders should include:

- bladder volumes by diary or examination (maximum voided or catheterized volume, post voiding residual urine, total capacity);
- mechanism of bladder evacuation: normal or volitional, reflex evacuation, spontaneous involuntarily, Credé, sterile intermittent catheter (SIC), clean intermittent catheter (CIC), intermittent catheter by second person, suprapubic or urethral catheter;
- use of external appliances (e.g., diaper or pad use, condom catheter, urethral catheter, suprapubic tube);
- the typical time span of continence (continence interval) following last bladder evacuation and maximal continent bladder volume.
- bowel function, sexual function, and specific neurologic deficits

Issues such as mobility, independence in activities of daily living, cognition, skin breakdown and faecal impaction frequently become relevant in this population compared to neurologically intact individuals. Standardized disability scales would be useful in clinical trials.

c) Urodynamics

In contrast to the general recommendations, baseline urodynamics are required for research studies of neurogenic incontinence. Because the nature of the lower urinary tract dysfunction cannot be accurately predicted, based on the history and physical findings, urodynamic classification is mandatory. Neurogenic disorders commonly cause complex and generalized lower tract dysfunction, often with combined bladder and urethral sphincter abnormalities. In addition, data should be collected on symptoms and the underlying neurologic disease. While urodynamic classification alone is suboptimal, it is clearly preferable to classification by symptoms or disease alone (e.g., a study involving subjects with neurogenic detrusor overactivity and coordinated sphincters will be easier to interpret than one of neurogenic urgency incontinence or multiple sclerosis).

Urodynamic studies in neurogenic disorders are qualitatively different compared to non-neurogenic disorders. For each subject, bladder function, sphincter function, and the coordination between the two must be fully described. In addition to the usual data on unstable contractions during the filling phase, compliance is also of major importance. Elevated detrusor leak point pressure predicted upper urinary tract deterioration in a small group of children with myelomeningocele [185]; non-compliant filling is presumed to be important in all neurogenic patients although complete evidence is lacking. Detailed analysis of voiding dynamics becomes more important (e.g., simultaneous pves/pabd during voiding, voiding time, shape of the Pdet and Q curves) because of the possibilities of functional obstruction and impaired contractility, which are uncommon outside of the neurogenic population. Because the detrusor and sphincter may be dyssynergic, assessment of sphincteric activity is particularly relevant. This may be accomplished by surface electromyography of the pelvic floor, needle electrodes, fluoroscopy, ultrasound, or direct measurement of urethral pressure. Videourodynamic studies are generally considered to be the gold standard for evaluation of LUT function in the neurogenic population.

Recommendations for Research in Neurogenic Lower Urinary Tract Dysfunction

- Detailed urodynamic studies are required for classification of neurogenic lower urinary tract disorders in research studies because the nature of the lower tract dysfunction cannot be accurately predicted from clinical data. Videourodynamic studies are preferred but are not mandatory. MEDIUM
- Change in detrusor leak point pressure should be reported as an outcome for spina bifida subjects and others with non-compliant filling. MEDIUM
- An area of high priority for research is the development of a classification system to define neurogenic disturbances. Relevant features could include the underlying diagnosis, the symptoms, more precise documentation of the neuromuscular lesion by clinical neuromy- siologic testing, and the nature of the urodynamic abnormality. LOW
6. FAECAL INCONTINENCE

Men and women with urinary incontinence frequently have coexistent problems with the posterior compartment, such as faecal incontinence, faecal urgency, constipation, chronic pain (such as levator syndrome or proctalgia fugax), solitary rectal ulcer syndrome, or rectal prolapse. Discussion of all these conditions is beyond the scope of this committee (see Chapters 16 & 17 for more detail), which will focus on research methodology in the study of faecal incontinence.

Faecal incontinence has been among the least studied of all pelvic floor disorders. There is a high degree of coexistence of urinary symptoms and faecal incontinence [186]; this warrants focusing more attention to comprehensive evaluation and management of pelvic symptoms. Many definitions for faecal incontinence have been created for use in clinical research, but there is still no consensus on a single instrument or group of instruments that is ideal for the assessment of outcomes, although the ICIQ-BS (bowel symptoms) is now available (see Chapter 5). Therefore, the following comments are by necessity non-prescriptive; we anticipate that future research findings will guide the development of more specific recommendations.

For the purposes of this discussion, faecal incontinence includes impaired ability to control either stool (liquid or solid) or gas. It is important to emphasize that faecal incontinence is a symptom and, as such, must be measured through subjective assessment [187]. The subjective evaluation of faecal incontinence in clinical research requires measurement of at least two aspects of the condition: severity and impact. Severity can be assessed by either grading scales or summary measures [188-190], and includes a component of frequency of episodes over a specified period of time.

Faecal urgency, while not an integral part of the definition of faecal incontinence itself, may have a marked impact on quality of life as patients restrict their activities to avoid faecal incontinence [190]. The impact of faecal incontinence is best measured by disease-specific quality of life instruments [191, 192]. The need for one standardized system of evaluation and quantitation of symptoms (which may include questionnaires, diaries, and quality of life assessment) is a high priority for further research in this field. The lack of standard accepted tools affect the study of this disorder. In past years and in one recent RCT on sacral nerve stimulation for severe faecal incontinence (193), the Wexner’s incontinence score [194] and the faecal incontinence quality of life index (FQIL) [195] have gained broad recognition. However, other tools such as the Manchester Health questionnaire [196] and the Faecal incontinence severity index (FISI) [197] are popular as well.

In contrast to urinary incontinence, the objective demonstration of faecal incontinence is not a component of current definitions. Because patients can significantly alter their lifestyle to avoid an accident, the physician needs to understand the patient’s symptoms and how it affects their life through a detailed history. Physical examination should include screening for pelvic organ prolapse (in some studies such as surgical studies of faecal incontinence, the standardized quantification system for staging of prolapse [9] should be used); rectal examination; assessment of pelvic muscle function; and screening pelvic neurologic examination. Other specific test results are not included in the definitions.

However, certain tests may be useful in identifying different subcategories of faecal incontinence, such as a specific sphincteric defect versus generalized atrophy. If any component of anorectal anatomy or function could reasonably be expected to change with treatment, consideration should be given to performing such tests before and after intervention. For example, if anal ultrasonography is used to detect sphincter defects preoperatively, it would be beneficial to obtain anal ultrasound postoperatively as well, to study the association between anatomic change and change in subjective assessment (i.e., symptoms).

In defining the impact of interventions on faecal incontinence, cure is defined as complete resolution of the symptom. Failed treatment ( persistence or recurrence) is defined as no improvement or worsening of symptoms. Without evidence, improvement cannot be specifically defined at this time but may include a favorable change in symptoms related to severity or impact or both.

Simply reporting a statistically significant average improvement in grading or summary scores in a group of subjects is not very informative; measuring within-patient change is more informative as to the true impact of the intervention. Like for urinary incontinence, it is important at the outset to establish some goals and expectations. Realistically, improvement in quality of life is a far more likely outcome than perfect continence. Further research is needed to develop clinically meaningful levels of improvement after intervention.
The authors found that 90% of the subjects meeting the NIDDK criteria [202]. Pain) and exclusion criteria that serve to create a consensus conference resulting in a research definition for research studies. In 1987 the NIDDK sponsored the definition of BPS/IC and the appropriate population database suggests that the prevalence of symptoms in women and 8-41 per 100,000 men [199]. The same database suggests that the prevalence of symptoms of BPS/IC is between 6.2% and 11.2% for women and 2.3-4.6% for men [201]. It is clearly an important problem for which a great deal more research is needed. The report of committee 19 reviews the knowledge base for this disease in detail.

There continues to be considerable controversy over the definition of BPS/IC and the appropriate population for research studies. In 1987 the NIDDK sponsored consensus conference resulting in a research definition of interstitial cystitis [201]. The definition encompasses inclusion criteria that describe the syndrome (centered on cystoscopic findings and the presence of pelvic pain) and exclusion criteria that serve to create a relatively homogeneous patient population. One study examined the performance of the NIDDK criteria [202]. The authors found that 90% of the subjects meeting NIDDK criteria were felt to have interstitial cystitis by experts. However, over 60% of participants diagnosed with interstitial cystitis by the same experts did not meet the strict criteria. Therefore, the use of the strict NIDDK criteria may exclude 2/3 of appropriate subjects and diminish the impact of trials because the patient population is not representative of the BPS/IC population at large. Such criteria could also select for patients with more severe/chronic disease who may be less likely to respond to intervention. It has been suggested [204] that very inclusive criteria be used in BPS/IC trials to improve the generalizability of results.

In 2002 the ICS defined “painful bladder syndrome” as, “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology” [204]. Cystoscopic findings were not part of this definition. It is further proposed that, “interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features”. This issue may not easily be settled as there appear to be markedly different worldwide perceptions as to the true nature of BPS/IC as manifest by willingness of different investigators to make the diagnosis [205]. For now, it would appear that there is much to be gained from trials with both inclusive and restricted entry criteria and there will be some that will be most appropriate for each strategy. Ultimately, identifying clinically significant patient phenotypes through biomarkers (e.g., antiproliferative factor and associated bladder growth factors), cystoscopic findings (ulcers and objective inflammation), associated diseases (autoimmune disorders), or associated pain syndromes (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome) may be useful in defining homogeneous and biologically meaningful patient populations for research.

Once the population to be studied is decided there has been considerable progress in defining appropriate methods of conducting clinical trials. Key clinical trial design issues have been reviewed [203]. TheInterstitial Cystitis Collaborative Research Network (ICCRN, http://porter.cceb.upenn.edu:7778/servlet/page?pageid=234,238&_dad=portal30&_schema=PORTAL30), a group funded by the NIDDK, is composed of 10 centers in North America and a Data Coordinating Center. The ICCRN has completed randomized clinical trials using both oral [204] and intravesical agents [206]. These provide excellent templates for the investigator in the planning phase of a project. A first of its kind, double blind clinical trial of newly diagnosed, previously untreated patients, evaluating the effects of amitriptyline has recently been completed. This trial will also add to our knowledge of the treated natural history of the disease in a unique population of IC patients. A pilot study suggested that pelvic floor physical therapy may be an effective treatment for urologic pelvic pain [206] and

### 7. BLADDER PAIN SYNDROME (INCLUDING INTERSTITIAL CYSTITIS)

The prevalence of Bladder Pain Syndrome (including interstitial cystitis) (BPS/IC) has been estimated at 52 to 67 per 100,000 adult women in the United States [198]. However, more recent work suggests that the prevalence of the diagnosis in a managed care practice is somewhere between 45 and 197 per 100,000 adult women and 8-41 per 100,000 men [199]. The same database suggests that the prevalence of symptoms of BPS/IC is between 6.2% and 11.2% for women and 2.3-4.6% for men [201]. It is clearly an important problem for which a great deal more research is needed. The report of committee 19 reviews the knowledge base for this disease in detail.

There continues to be considerable controversy over the definition of BPS/IC and the appropriate population for research studies. In 1987 the NIDDK sponsored consensus conference resulting in a research definition of interstitial cystitis [201]. The definition encompasses inclusion criteria that describe the syndrome (centered on cystoscopic findings and the presence of pelvic pain) and exclusion criteria that serve to create a relatively homogeneous patient population. One study examined the performance of the NIDDK criteria [202]. The authors found that 90% of the subjects meeting NIDDK criteria were felt to have interstitial cystitis by experts. However, over 60% of participants diagnosed with interstitial cystitis by the same experts did not meet the strict criteria. Therefore, the use of the strict NIDDK criteria may exclude 2/3 of appropriate subjects and diminish the impact of trials because the patient population is not representative of the BPS/IC population at large. Such criteria could also select for patients with more severe/chronic disease who may be less likely to respond to intervention. It has been suggested [204] that very inclusive criteria be used in BPS/IC trials to improve the generalizability of results.

In 2002 the ICS defined “painful bladder syndrome” as, “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology” [204]. Cystoscopic findings were not part of this definition. It is further proposed that, “interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features”. This issue may not easily be settled as there appear to be markedly different worldwide perceptions as to the true nature of BPS/IC as manifest by willingness of different investigators to make the diagnosis [205]. For now, it would appear that there is much to be gained from trials with both inclusive and restricted entry criteria and there will be some that will be most appropriate for each strategy. Ultimately, identifying clinically significant patient phenotypes through biomarkers (e.g., antiproliferative factor and associated bladder growth factors), cystoscopic findings (ulcers and objective inflammation), associated diseases (autoimmune disorders), or associated pain syndromes (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome) may be useful in defining homogeneous and biologically meaningful patient populations for research.

Once the population to be studied is decided there has been considerable progress in defining appropriate methods of conducting clinical trials. Key clinical trial design issues have been reviewed [203]. The Interstitial Cystitis Collaborative Research Network (ICCRN, http://porter.cceb.upenn.edu:7778/servlet/page?pageid=234,238&_dad=portal30&_schema=PORTAL30), a group funded by the NIDDK, is composed of 10 centers in North America and a Data Coordinating Center. The ICCRN has completed randomized clinical trials using both oral [204] and intravesical agents [206]. These provide excellent templates for the investigator in the planning phase of a project. A first of its kind, double blind clinical trial of newly diagnosed, previously untreated patients, evaluating the effects of amitriptyline has recently been completed. This trial will also add to our knowledge of the treated natural history of the disease in a unique population of IC patients. A pilot study suggested that pelvic floor physical therapy may be an effective treatment for urologic pelvic pain [206] and...
this is being examined in a larger trial of women with BPS/IC. There is general agreement that the primary outcome must be patient driven and the ICCRN has used the Global Response Assessment. The Global Response Assessment asks subjects to rate their symptoms, as compared to baseline, on a seven-point centered scale: markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, and markedly improved. Typically those responding as moderately or markedly improved are considered responders. A full spectrum of objective and subjective secondary endpoints will be required to fully characterize the treatment effect. However, not only changes in symptoms themselves but also bother of the symptoms and its impact on health related QOL should be focused on for outcome measurement. Special consideration should be given to examination of specific subgroups such as patients with Hunner’s ulcers, newly diagnosed patients, and male patients. As mentioned in the ICCRN trials above, attention should also be paid to the duration of symptoms prior to initiating a given therapy and to the number of prior unsuccessful treatments.

**Recommendations for Research in Bladder Pain Syndrome and Inter-stitial Cystitis**

- The patient population for BPS/IC trials must be carefully defined; improved diagnostic criteria such as biomarkers are needed. When appropriate, broader entry criteria should be used to reflect the full spectrum of the BPS/IC patient population. MEDIUM
- Study design should incorporate outcomes that are most relevant to these patients and should be standardised. LOW
- The primary endpoint of BPS/IC trials should be patient driven and the Global Response Assessment is recommended. A wide spectrum of secondary endpoints will be useful in defining the effect of treatments. MEDIUM

**8. PELVIC ORGAN PROLAPSE**

For the purposes of this discussion, pelvic organ prolapse includes anterior vaginal prolapse (previously known as cystocele), apical or uterine prolapse, posterior vaginal prolapse (previously known as rectocele), enterocoele, and perineal descent; it does not include rectal prolapse. Ideally, for clinical research purposes, prolapse would be defined by three components: (1) by the presence and severity of symptoms, with some indication of bother or impact on quality of life; (2) by signs obtained at physical examination; and (3) by testing, depending on specific study goals. However, singly or in combination, all three components are severely limited in their capacity to distinguish “normal” from “abnormal” regarding prolapse.

Most pelvic symptoms are highly nonspecific and do not show strong associations with the location (anterior, apical, or posterior compartment) or stage of prolapse [207-208]. One exception to this is the patient’s awareness of an actual bulge or protrusion, which has high positive and negative predictive values for Stage III or IV prolapse (but not the affected compartment of prolapse). As a consequence, specific symptoms cannot currently be required in the definition of prolapse (with the possible exception of tissue protrusion). By the same token, the resolution of specific symptoms cannot be required in the definition of “cure” after treatment; however, surgeons should state which symptoms (other than the local bulge) that he/she plans/hopes to cure/improve. Nevertheless, it is essential to include a comprehensive survey of pelvic symptoms to be able to describe what symptoms are present at baseline and which symptoms change with treatment. For example, the Pelvic Floor Distress Inventory (PFDI) includes subscales on prolapse, urinary function, and coloanal function; its companion, the Pelvic Floor Impact Questionnaire, surveys the degree to which symptoms impact quality of life [209]. These condition-specific instruments are relatively new and, although validated, have not yet been shown to be sensitive to change with treatment; however, their comprehensiveness makes them attractive for inclusion in studies where women may have or develop different pelvic floor disorders. Sexual function should be specifically assessed, especially in studies of surgical treatment for prolapse. The ICI questionnaire, the ICIQ-VS (vaginal symptoms), is one instrument that covers all of these areas of interest although experience with its use is limited.

Unfortunately, the relationship between symptoms and anatomy as measured by the POP-Q are poorly understood. The point at which symptoms may be attributed to the anatomical prolapse is not known. The POP-Q system is a validated, quantitative system with excellent inter- and intra-rater reliability. It includes measurement in centimeters of six vaginal sites relative to the hymen, plus three other measurements for total vaginal length, perineal body, and genital hiatus [9] as described in Outcomes section above.

Other measurements have not been standardized, such as assessment of urethral mobility (e.g., estimation on physical exam, cotton swab testing, perineal ultrasound, lateral cystogram), identification of paravaginal defects and perineal descent, pelvic muscle assessment, and pelvic imaging (e.g., defecating proctography, static or dynamic pelvic magnetic resonance imaging). Detailed descriptions of their measurement should be included if they are used. Data should be presented as a continuum, not as a dichotomy of “normal” versus “abnormal” until those terms are clearly defined by evidence of clinical relevance.

At the time of the 1999 NIH Terminology Conference
permanent synthetic mesh for prolapse repairs has for example, the dramatic increase in use of meshes, is also not known, and is discussed further in Chapter 15.

Although clinical experience strongly supports that prolapse develops gradually over years, it is not known whether Stage II prolapse predicts future support loss or, if it does, in how many women and over what time course. This is particularly controversial in choosing a cutoff for what constitutes clinically significant persistent or recurrent prolapse after surgical treatment. The location of prolapse is important in this choice as well. While both Stage II anterior and apical vaginal prolapse may be asymptomatic, most surgeons would not be willing to accept Stage II apical prolapse as a successful surgical treatment, yet Stage II anterior (or posterior) asymptomatic vaginal prolapse is often considered to be acceptable. While planning clinical trials, the goal of the surgical treatment (restoration to Stage 0, restoration to Stage 1, etc. with or without symptoms) should be clearly specified. Durability of all types of prolapse surgery requires longitudinal, long-term follow-up, which is generally not available in the current literature. The utility of supplementary materials, e.g. synthetic and biologic meshes, is also not known, and is discussed further in Chapter 15.

Primarily due to lack of evidence, prolapse is not currently defined based on specific test results. We recommend that further research be performed to investigate the usefulness of various tests (for example, imaging by X-ray contrast, ultrasound, MRI) in determining definitions and outcomes of prolapse treatment. In a specific study, if an aspect of anatomy will be directly influenced by surgery, it may be reasonable to perform imaging before and after surgery to assess whether any change seen on imaging is correlated with changes in symptoms and physical findings.

We recommend that interventional studies in POP employ both anatomic (POP-Q) and functional outcomes whenever possible. It is equally important that adverse events/treatment complications be reported in detail. For example, the dramatic increase in use of permanent synthetic mesh for prolapse repairs has created the possibility of new and delayed complications. These risks were highlighted by the United States Food and Drug Administration in a recent bulletin (http://www.fda.gov/cdrh/safety/102008-surgicalmesh.html). In particular, reoperations to excise mesh or granulation tissue, whether performed in the office or hospital, dyspareunia, and partner sexual pain “hispärenia” should be reported. Finally, key factors to patient satisfaction must be identified in order to develop better patient driven outcome measures. Goal achievement appears to be one such promising area of research in understanding outcomes after POP surgery. (Hullfish 2004 and Mahajan 2006)

9. NOCTURIA

While nocturia has often been viewed as just one of the manifestations of lower urinary tract dysfunction, there has been a recent appreciation that it is an important independent symptom that does not “belong to” another clinical problem. Waking at night to void can be the result of abnormal fluid intake or other behavioral issues, cardiac conditions, peripheral venous disease, and sleep disorders as well as lower urinary tract dysfunction. This complexity makes clinical research in nocturia very difficult; the fact that the condition is affected by so many different issues mandates a multidisciplinary research team. Although nocturia is one of the most bothersome of symptoms there has been little progress in treatment of nocturia outside of studies in pediatric nocturnal enuresis. On the other hand, major contributions to the understanding of nocturia and the methodology for research in nocturia have been made that should facilitate future research. The 2002 ICS Standardization sub-committee report on nocturia should greatly facilitate research efforts; it defines the relevant terms, introduces a flow-chart for evaluation, and presents tables of the causes for the various subtypes of nocturia [211]. Potential investigators should carefully review this document in the planning stage of research.

One major randomized controlled trial in adults was identified in a literature search. It found that desmopressin was significantly more effective than
placebo in reducing nocturia in a population of adult women with at least two voids per night [212]. Other studies suggest that celecoxib (213) and melatonin or other hypnotics [214] may benefit certain patients.

**Recommendations for Research in Nocturia**

- Population or community based research is needed to define the epidemiology of nocturia and how the symptom relates to normal aging. MEDIUM
- Clinical research in treatment of nocturia should begin with classification of subjects by frequency volume chart categories—polyuria, nocturnal polyuria, and apparent bladder storage disorders. If desired, those with low bladder capacity can be further divided into those with sleep disturbances and those with primary lower urinary tract dysfunction. HIGH
- The impact of nocturia on falls and fractures deserves further investigation MEDIUM

**IV. CONSIDERATIONS FOR SPECIFIC TYPES OF INCONTINENCE RESEARCH**

**1. BEHAVIORAL AND PHYSIOTHERAPY TRIALS**

Non-pharmacologic, non-surgical treatments for incontinence comprise a wide variety of tools often grouped under the name of behavioral treatment. Although these treatments are generally very safe and applicable to most incontinent patients, there should be no compromise in the quality of clinical research. Treatment may be time consuming for both patient and therapist and should not be suggested without a reasonable hypothesis and sufficient evidence.

The type of therapy must be defined with sufficient detail for other investigators to reproduce the study. The type of behavioral therapy should be clearly stated, including the duration of the total treatment period, duration of each treatment session, and number of treatment sessions. The time between qualification for study entry and start of therapy must be specified. Any devices used must be properly described. The background and training of the therapist should be defined. All instructions, training, and educational materials given the subjects should be reproduced or referenced. A complete description of all differences in the experience of the treatment and control groups should be provided.

As in other studies, the study population should be characterized. The usual clinical outcome measures suffice. In order to progress in our understanding of these treatments it is important to consider clinical outcome alongside physiologic changes. If the intervention is intended to increase the strength of pelvic floor muscle contraction, this should be measured and correlated with continence.

Outcome measures to assess effects on other related organ systems (e.g., gastrointestinal and sexual functioning) should also be considered, as well as possible adverse outcomes.

It is important to distinguish between **specific and non-specific** effects, such as improvement related to the extra attention of the therapist, leading to a gain in motivation, confidence, etc. The goal is to isolate what a particular therapy achieves on its own. However, in behavioral therapy, the non-specific effect is widely considered to be an essential, desirable and important part of the effect of the therapy. It therefore needs to be evaluated along with the specific effect.

Carefully designed randomized controlled studies should allow separation of specific and non-specific effects. This is particularly important with techniques such as electrical stimulation and biofeedback where particular instrumentation or equipment may be credited with results that could be due to the efforts of the therapist. Recent studies using a standardized self-help booklet are commended as important steps in defining this issue [215,216].

There have been many trials of various physical therapies and these are summarized in Chapter 12; there have been relatively fewer regarding the many behavioral issues suggested to affect incontinence. It can be difficult to perform double-blind studies of behavioral technique.

Clinicians and subjects often cannot be blinded. In quality assessment of studies, double blinding is often one of the criteria of methodological quality. It may not be reasonable to demand double-blinding in all behavioral studies, or, if double blinding is not accomplished, to consider such research less valuable. It is more realistic to demand the ‘most optimal and possible level of blinding’.

A relevant control group is established, allocation to treatment groups is concealed, as many persons as possible are blinded (in particular, those individuals recording outcome measures), and appropriate measures surrounding this issue are discussed in the manuscripts. A recently completed trial studying obese women with urinary incontinence undergoing a weight loss program—the Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial—presents a model of high quality work in behavioral therapy.
Recommendations for Behavioral and Physiotherapy Research

- There is a great need for long term data to define the durability of effect for all conservative treatment modalities in all population groups. HIGH
- Intervention protocols must be detailed to the degree that the work can easily be reproduced. HIGH
- A structured examination of pelvic floor neuromuscular function should be included before and after treatments that are aimed at pelvic muscle training. HIGH
- More work is needed to separate the specific and non-specific effects of treatment. MEDIUM
- Consider a variety of methodologies in development, evaluation, and interpretation of these interventions. MEDIUM

2. DEVICE TRIALS

In the United States, devices for urinary incontinence are regulated by the Center for Devices and Radiological Health (http://www.fda.gov/cdrh), a branch of the United States Food and Drug Administration (FDA). Although urethral devices and bulking agents differ considerably in risks to research subjects, they are grouped together for the purpose of FDA regulation. Requirements for the protection of human subjects are appropriate for the study of these treatments, yet other devices used in incontinence therapy may elude careful scrutiny. For example, materials for reconstructive surgery are primarily approved based on biocompatibility testing. However, implantation in less than a sterile environment (e.g. vagina), placement during concomitant operations (e.g. hysterectomy, prolapse repair) and effects of biofilms adjacent to the urinary tract could pose unique conditions with subsequent complications in the long term. Very little is known about the effectiveness of such devices at the time of approval.

Detailed guidelines for studies on intra-urethral urethral bulking agents were published in 1995 [217]. Guidelines for implantable devices such as used for neuromodulation fall under different criteria. Guidelines for engineered tissues and cell therapy are evolving. Neuromodulation therapies and would be evaluable in the context of all population groups. MEDIUM

1. Inclusion in trials has been limited to subjects with “urinary incontinence due to ISD (intrinsic sphincter deficiency), as evidenced from urodynamic studies or radiographic assessment”. While the basic concept of ISD is understood, there is no consensus on its definition for clinical care or research and little evidence for use of specific tests such as the abdominal leak point pressure in defining eligibility for research or clinical care.

2. The potential study population should be defined as broadly as is reasonable in include the majority of patients who could potentially benefit from such therapies and would be evaluable in the context of a clinical trial.

3. The recommendations for urethral inserts and injectable urethral bulking agents could be refined and separated in appropriate areas as injections represent a different level of risk.

4. The Stamey grading scale (0-3) for stress urinary incontinence has been recommended as the primary outcome measure. There is little evidence that this measure is as valid or reliable as other measures such as voiding diaries, pad tests, and leak point pressure measurements.

5. The need for follow-up beyond one year in all areas, to include: effectiveness, adverse events including retreatment, and patient satisfaction.


An important area of concern in device studies is patient recruitment procedures. We strongly support reporting according to the CONSORT guideline, including the flow diagram (Figure 2) for subject enrollment and follow-up. Subjects should be enrolled in a manner that minimizes selection bias. The protocol should detail the procedure by which consecutive patients meeting the inclusion criteria are selected. All situations in which a patient meets the inclusion/
exclusion criteria but is not offered enrollment by the investigator should be documented. The number of patients who decline enrollment should be stated, along with the reasons. There should be a complete accounting of all participants in the study including the reasons for subject withdrawal.

**Recommendations for Research in Incontinence Devices**

- Safety and serious side effects of incontinence devices must be completely defined with adequate follow-up, especially for use of implantable devices and biologic materials, so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, prospective, multicenter prospective cohort studies when RCTs are not feasible. HIGH
- Physiologic testing such as urodynamics should be considered, in addition to survey instruments, to substantiate the proposed biologic effect of devices especially when a placebo or sham is not available. MEDIUM
- Clear, updated guidelines for each of the categories of new devices should be developed that protect patient safety while promoting research in a practical manner. LOW
- Patients deserve complete information about implantable devices when considering surgical therapy. New devices may be introduced into the market with no or minimal track record of safety and efficacy for the proposed use. In such cases it may be best to have separate surgical consents for the operation and use of the new device. LOW

**3. PHARMACOTHERAPY TRIALS**

Drug trials are necessary so that new drugs can be clinically and scientifically evaluated for quality, efficacy and safety [219-224]. Since the 1960's administrative bodies such as the Food and Drug Administration have required that new pharmaceuticals undergo controlled investigations to establish efficacy. The specific stages of development and of study design have been discussed in detail in section IIB. Many large RCTs have been conducted in recent years and incontinence research has generally benefited from the attention to the field and emphasis on valid outcomes. As the financial backing of the pharmaceutical industry has been largely responsible for this research, new conflicts of interest and problems have arisen due to the changing economics. As stated in a joint editorial endorsed by members of the International Committee of Medical Journal Editors, "published evidence of efficacy and safety rests on the assumption that clinical trials data have been gathered and are presented in an objective and dispassionate manner. We are concerned that the current intellectual environment in which some clinical research is conceived, study subjects are recruited, and the data analyzed and reported (or not reported) may threaten this precious objectivity" [225]. Several of these issues are discussed in Section V3 below.

Although many RCTs have been published in recent years on pharmacotherapy for urinary incontinence a great deal more remains to be learned. The trials have almost all been limited to 8-12 weeks of treatment giving very little information about long term safety and efficacy of drug therapy. Studies have typically been performed in isolation, i.e. drug vs. placebo, as opposed to a real life scenario where drug therapy is combined with behavioral and pelvic floor therapy. There is less than adequate information about special patient groups—men, children, neurogenic patients, and especially the frail elderly. Because incontinence creates such an impact on the older population, good studies to define the utility and safety of drug therapy are greatly needed in this group. There are many practical concerns in employing pharmacotherapy, particularly regarding long term use of medication. The BE-DRI Study [226] from the Urinary Incontinence Treatment Network, is a good example of a trial designed to optimize use of medical therapy. It showed that combining behavioral therapy with pharmacotherapy did not improve patient’s likelihood of discontinuing drug treatment.

An issue of special relevance in trials of pharmaceutical agents (although germane to other treatment modalities) is the controversy regarding placebos in clinical trials. Regardless of whether a drug is effective or not, simply giving a drug to a patient may produce a beneficial response. To assess if a drug has an effect over and above the placebo response, it is usually tested against an inactive substance (placebo). In incontinence, the placebo effect may be quite large, anywhere from 30-50% in recent published studies. To account for this, investigators and regulators have generally demanded a placebo arm in most clinical trials of medication. On the other hand, the Helsinki Agreement (1989) states that "far from being useful, a placebo is unethical: in any medical study every patient including those in the control group, if any, should be assured of the best proven diagnostic and therapeutic method". Clinicians need to know how a new drug compares with established treatment. The FDA does not require placebo-controlled trials of drugs for approval. However, the sponsor will generally prefer to compare the drug with a placebo and not with a competitor, since it is usually easier to detect a difference between treatment and no treatment, compared to two active treatments. For drugs in that same class that are already available, an active control agent should be used whenever possible. In addition, comparator trials of behavioral therapy versus drug or device versus drug are lacking, as are combination
studies. Combination studies are especially relevant since such strategies are common in clinical practice despite the absence of data. Researchers must carefully consider these issues in designing a relevant, ethical study.

**Recommendations for Pharmacotherapy Trials**

- Every consideration should be given to making sure that the interests of the subjects are kept at the forefront in designing safe, ethical research. In urinary incontinence, safe and effective conservative therapy is available for the vast majority of patients. In most trials, comparison should be with "standard therapy" rather than placebo/no treatment. This approach respects practical patient management where placebo is not an option. HIGH

- As effective drug therapy is available for most forms of incontinence comparator arms are recommended for most trials. Claims of superiority of drugs even within the same class are unfounded in the absence of randomized comparator trials. HIGH

- Very little is known about the safety, efficacy and tolerability of drug therapy beyond 12 week trials. A concerted effort is needed to create this type of information base. Long-term follow-up of RCT cohorts in an observational cohort is recommended HIGH

**4. SURGICAL TRIALS**

Standards for surgical trials are detailed in recommendations from the CONSORT Organization (http://www.consort.org), ICS, SUFU, and the AUA [12-17]. We support the adoption of these standards by clinical and basic science researchers, the peer review process, specialty and sub-specialty organizations, the health care industry, regulatory agencies and ultimately by clinicians. While discussion of surgical therapy for incontinence mainly applies to females with stress incontinence, most of these points are equally applicable to males undergoing surgery for post-prostatectomy incontinence and related problems (and females undergoing surgery for repair of pelvic organ prolapse). Unique research issues for surgical research using observational studies and randomized controlled trials will be presented and insights from other surgical specialties will be discussed.

**a) Observational studies**

Observational studies are important major sources of descriptive data to understand the patterns of use for surgical procedures and of factors that influence these patterns. A few observational studies that included representative samples with well-conducted data collections have been reported and will serve as examples for future research.

Cross-sectional studies of surgical procedures by type can provide estimates of prevalence, variation by age, race, and region as well as morbidity and mortality. Using the US National Hospital Discharge Survey, it has been determined that incontinence operations have increased in frequency over time, are the third most common surgery in women, that there are large regional and racial differences in the rates of incontinence surgery, and morbidity and mortality are low [227,228]. This type of information raises important health policy questions regarding physician practices, patient preferences for incontinence treatment, and differential access to and the utilization of care. In another large US national cross-sectional study, participants reported satisfaction with surgery even if they had not achieved complete continence, demonstrating the importance of patient reported outcomes [229].

The largest prospective cohort study published to date included all women undergoing the three most common operations for stress incontinence at 18 representative hospitals in the United Kingdom [230]. A variety of measures of incontinence, symptom severity, symptom impact and complications were used, and participants were followed for 1 year. Overall, 87% of the women reported some improvement in incontinence one year after surgery, but only 28% reported complete continence [21, 231, 232]. This prospective cohort demonstrated that it is possible to collect standard data on multiple outcomes of surgery for stress incontinence to provide women with better information on the likely outcomes and effectiveness of the procedure in community practice. Lessons learned from this study will drive improvements in surgical research in incontinence as discussed below.

**b) The importance of surgical randomized controlled trials**

Observational studies can also provide important information for designing and selecting potential randomized clinical trials. The randomized controlled trial is the accepted "gold standard" for research of treatment effects. However, case series are far more common in the surgical literature, especially for new "innovative" surgical procedures. This is true despite the fact that case series cannot account for selection bias on the part of both the patient and surgeon, non-reporting bias of failures or loss to follow-up, lack of long-term follow-up, and provide the lowest level of evidence for treatment effects. In all surgical specialties, there has been growing concern regarding the limited number of randomized controlled trials for surgical procedures, poor methodological standards in those that have been performed, and a perception that surgeons are reluctant to rigorously test new surgical interventions [233-236]. A number of reasons
for the paucity of surgical trials have been suggested including the lack of a regulatory board similar to the Food & Drug Administration responsible for the development of new medications [165]. Surgeons can therefore perform new procedures with little or no limitations from hospital or ethics committees and without any substantive trials [234]. In the United Kingdom, the National Institute of Health and Clinical Excellence’s (NICE www.nice.org.uk) Interventional Procedures Advisory Committee, which analyzes all new procedures and seeks to provide commissioners and providers of health care with objective guidance, regarding their value, with respect to safety and efficacy.

The importance of surgical randomized controlled trials was demonstrated in a sham trial of arthroscopic surgery for osteoarthritis of the knee, one of the most widely used orthopedic operations. Numerous uncontrolled case series had reported substantial pain relief after arthroscopic surgery. The trial provided strong evidence that the surgical procedure was no better than the placebo procedure [238].

There have been few methodologically rigorous randomized trials of surgical procedures for incontinence. In reviewing the literature to prepare the 1997 AUA Guidelines for surgical treatment of stress incontinence, 943 studies identified but there were only 11 randomized controlled trials [239]. Overall, the randomized trials were considered of poor quality because they had few participants and were underpowered to detect small differences between groups, lacked blinding of the participants and/or individuals assessing the outcomes, and had short follow-up. It is particularly important that operations for incontinence undergo methodologically rigorous randomized trials because surgery is elective and non-emergent, the effect difference between two techniques will be at best modest, and patients as well as surgeons need accurate data to make informed choices using risk and benefit data to compare operations [240,241]. It has also been suggested that the first anti-incontinence procedure provides the highest success rate and subsequent procedures have a far higher failure and complication rate [239]. The last decade has brought us several new trials with strong methodology, as discussed below.

The Urinary Incontinence Treatment Network is one example of a multi-center consortium created to conduct randomized controlled clinical trials enrolling patients with urinary incontinence. The UITN, established by the U.S. National Institutes of Health in 2000, consists of 9 recruiting centers and a data coordinating center. The clinical expertise includes a mixture of urology and urogynecology specialists. The first clinical trial undertaken by the Network compared standardized forms of the Burch colposuspension (Tanagho modification) and the autologous rectus fascia sling procedures for overall treatment success and stress urinary incontinence success at 24-month post-operatively (the trial is known as the Stress Incontinence Surgical Treatment Efficacy Trial or SISTEr) [243]. A second trial, the Behavior Enhances Drug Reduction of Incontinence, BE-DRI tested whether the addition of behavior treatment to tolterodine therapy will increase the number of patients who can discontinue tolterodine therapy and sustain a significant reduction of incontinence. The work of this and other cooperative groups will inform surgical practice to a much greater degree than historical literature that was primarily composed of single institution case series.

c) Surgical trial methods

“Surgeons should realize that using the right tools for clinical research is comparable to selecting and using the right instruments for an operation.” [243]

To ensure surgical trials are relevant and credible, detailed information about the study design is essential [233]. Reports of randomized trials should follow the current CONSORT flow diagram [30]. In order to understand how surgical results can be generalized to the population at large it is critically important that researchers carefully record the number of patients with incontinence who were not offered enrollment in the trial and those who refused to participate as well as the reasons for each. All participants should undergo a comprehensive baseline evaluation as discussed in the general recommendations and baseline comparability of the intervention groups should be demonstrated using descriptive statistics. The randomization technique must be clearly described to confirm random allocation and that none of the study team has influenced the assignment, resulting in selection bias.

Differential drop out after randomization can introduce bias. In the largest and most methodologically sound randomized controlled trial to date comparing the tension-free vaginal tape (TVT) and colposuspension (referred to as the UK TVT RCT), a large number of women withdrew from the colposuspension arm after randomization [244,245].

The loss of participants after randomization introduced bias in favor of the TVT because the drop outs had less severe incontinence resulting in the colposuspension group having more severe incontinence. It has been suggested that participants were only willing to continue if they were randomized to the “new and better” TVT procedure [245,246]. Accounting for subjects “lost to follow-up” must also be detailed as per the CONSORT flow diagram. In the UK TVT RCT, drop out after surgery was similar for both procedures. In contrast, the UITN study discussed above had no drop outs with 850 participants randomized in the operating room at the time of surgery [242].
The surgical procedure should be described in such detail that it could easily be reproduced in another study. Standardization of the procedure may vary depending on the research question [247]. Trials where the surgical technique is tightly controlled (i.e. small number of highly skilled surgeons) are analogous to medical trials where only compliant patients are randomized, reflecting efficacy of the procedure in an ideal setting. If the surgical procedure is less controlled, it may be more generalizable to a mixture of skill level among surgeons in the community, and so reflect effectiveness of the procedure in usual practice [240].

Masking of participants as to their assigned intervention and those assessing the outcome is particularly important for surgical trials for incontinence because there may be enthusiasm by the patient or surgeon for a new procedure, many outcomes are based on the patient's own assessments such as symptom and quality of life scores, and the intervention is primarily for improvement of symptoms [249]. In the previously mentioned UK TVT RCT, neither the participants nor the staff collecting the post-operative assessments were blinded and this may have resulted in a biased assessment of the outcome.

It is unfortunately clear that much remains to be done to improve the quality of the surgical literature in incontinence and LUTS. Using a standardized evaluation form based on the CONSORT statement published in 1996, 152 reported RCTs were identified in the Urology literature across 4 leading urology journals between 1996 and 2004 [251]. The most prevalent topic was voiding dysfunction (38%) and only 40% of the studies reported information about funding, of which 63% was from industry support. Although progress was identified in sample size justification and randomization implementation, reporting of these key methodological criteria remained consistently below 50% in 2004. The authors recommended more graduate and postgraduate education be offered in trial design to improve on RCT reporting. Another article by the same group, “Evidence based clinical practice: a primer for urologists”, is recommended as an excellent reference. [252].

d) Outcomes of UI

Surgical outcomes are discussed in detail in Chapters 13 & 14 as well as in the specific patient groups discussed above and will not be repeated here. The key issues are that validated outcome measures should be decided in advance and data collected prospectively, as well as throughout the study.

e) Development & assessment of new surgical procedures

Surgical research presents unique challenges to efforts at optimizing patient care. It is important to create a pathway for real advances while simultaneously protecting patient safety. It would be desirable to have RCTs of all operations for incontinence; while one may argue that resources are inadequate it is also very costly to introduce ineffective or unsafe procedures without proper research. When new procedures are substantially different from prior operations there should be a broad based preliminary exploration leading to a comparative trial if warranted. At the same time, many minor modifications of surgical procedures are inappropriate for randomized trials and if required, surgical progress would be slowed [253].

It has been argued that the first patient in whom a procedure is performed should be randomized [234, 250]. Alternatively, it has been suggested that case series for new procedures are allowed until the procedure finds its intended use and to avoid doing studies while those performing the procedures are on the “learning curve”. Typically, new surgical procedures for incontinence have been reported as case series [108, 254]. Not only do surgical case series provide the lowest level of evidence for treatment effects, case series may be “harmful”. An accumulation of “positive” case series may present a premature certainty about benefits of a procedure and make it even more difficult to perform randomized trials [233,240]. Influential members of the surgical community may endorse a new procedure and if the procedure is considered better it may be difficult to get surgeons and patients to randomize or a trial may appear to be unethical with a “proven” procedure [233, 234, 255].

For new surgical procedures, important issues of adequate informed consent and conflicts associated with incentives for developing, starting and using new procedures have been raised. Informed consent for a new procedure must include:

• acknowledgement that the procedure is new and has not been shown to be more effective than a traditional approach
• discussion of potential complications, especially any integrally related to the procedure or device
• disclosure that information on complications are limited, and
• disclosure that the long-term benefits are unclear [254].

Incentives for adopting new procedures prior to sufficient evidence can arise from self-interest by attracting patients to one’s practice, industry marketing, and patient desire for “cutting edge” techniques. Industry sponsorship or a surgeon’s financial interest must be disclosed.

It has been recently suggested that innovations in maternal-fetal surgery be conducted in centers of excellence, evaluated as research, and that randomized controlled trials are necessary before...
procedures become available outside the research setting or are integrated into clinical practice [256]. This recommendation is based on the premise that evidence is critical to ensuring that promising therapies are in fact safe and efficacious. [256]. Unfortunately, clinical trials and systematic analysis of outcomes have not preceded integration of new surgical therapies for incontinence into clinical practice [21, 239, 254, 257].

On the other hand, organizations and treatment networks have been established to address many issues related to surgical interventions. Examples include the UK National Institute of Clinical Excellence (NICE www.nice.org.uk), the Australian Safety and Efficacy Register of New Interventionsal Procedures-Surgical (ASERNIP-S www.surgeons.org/asernip-s), and the US treatment networks: Urinary Incontinence Treatment Network (UITN http://www.niddk.nih.gov/patient/uitn/uitn.htm) for the NIDDK and the Pelvic Floor Dysfunction Network (PFDN). The NICE and ASERNIP-S provide systematic reviews of new operations, assessment of effectiveness, and recommendations that the technique has sufficient data for widespread use, or that the techniques appear unsafe, or that further audit/research are required before its widespread usage. The UITN and PFDN were established to provide the infrastructure for multicenter large randomized controlled trials for incontinence and prolapse.

The PFDN is a multicenter network in the United States, supported by the National Institute of Child Health and Human Development, one of the institutes of the NIH. Started in 2001, the network has seven clinical sites and a data coordinating center, with the primary goal of performing clinical trials related to the prevention, evaluation, and treatment of pelvic floor disorders in women, including pelvic organ prolapse, and urinary and faecal incontinence as well as other abnormalities of the lower urinary and gastrointestinal tracts. The Colpopexy and Urinary Reduction Efforts (CARE) trial studied 322 women to test whether the addition of Burch colposuspension prevents postoperative stress incontinence when continent women with advanced prolapse undergo abdominal sacrocolpopexy [259]. It was stopped early due to a lack of benefit from the prophylactic incontinence procedure. Interestingly, the urodynamic analysis showed that demonstration of stress incontinence, by any method of prolapse reduction predicted postoperative stress incontinence, regardless of whether or not a Burch suspension was performed.[260] Other studies are either underway or have finished enrollment including:

- a cohort study of 900 primiparous women after their first birth, determining the prevalence and incidence of faecal and urinary incontinence among women who did and did not have an anal sphincter laceration at vaginal delivery, compared to women delivered by cesarean without labor; comparing symptoms, physical examination, and imaging (pelvic magnetic resonance imaging and endoanal ultrasound) in 255 women after vaginal delivery with and without anal sphincter laceration and in women after cesarean delivery without labor
- the OPTIMAL trial (sacrospinous ligament fixation versus uterosacral vaginal vault suspension with and without perioperative behavioral therapy/pelvic muscle training)
- the OPUS trial (vaginal prolapse repair with or without concomitant TVT procedure to address the issue of surgical stress incontinence prophylaxis).

To make ethical and evidence-based progress in surgical knowledge for incontinence, a new paradigm to balance surgical innovation and research is essential. Cooperative collaboration of investigators and possibly industry, a preliminary phase to develop new procedures and training, prospectively collected comprehensive data, and ongoing assessment as to the need for randomized controlled trials has been suggested [254]. Strong position statements have been issued by individuals [261,262] and organizations [263] regarding the marketing of new procedures and the legal/ethical implications for physicians. Registries have been suggested to track complications and their management but they can fall short by lack of denominator information and incentivization in reporting. It has regrettably become easier to try new surgical procedures in women with stress urinary incontinence without much knowledge of their effectiveness or potential complications than to develop a new drug and receive FDA clearance. Although the FDA has a reporting site (MAUDE), it has remained vastly under-utilized. As stated by Dr Ostergard in his article’s concluding comments: “…do not let industry control how we practice medicine.” As surgeons, we have the opportunity and responsibility to improve our understanding of surgical interventions and improve patient care.

**Recommendations for Surgical Trials**

- The safety and serious side effects of new operations must be completely defined with adequate follow-up so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, independent, prospective, multicenter cohort studies when RCTs are not practical. HIGH
- Valid informed research consent is required in all trials of surgical interventions, which is separate from the consent to surgery. HIGH
- We recommend ongoing research into the usefulness of pre- and post-operative urodynamics in surgical trials. One of the primary...
It is appreciated that both device and surgical research trials present significant challenges to trial design. Although decades of experience have refined the conduct of drug trials the absence of comparable robust device and surgical trials derives from these design challenges. Table 2 lists adherence to Design criteria between Behavioral, Drug, Device and Surgical Trials as specified in General Recommendations for Clinical Research in Incontinence. The net result of failure to adhere to these principles may be that the efficacies of the latter two approaches for urinary incontinence are over-estimated. By analogy to intervention trials for pain, the more invasive the

<table>
<thead>
<tr>
<th>Design Issue</th>
<th>Behavioral</th>
<th>Drugs</th>
<th>Devices</th>
<th>Surgery</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>Sometimes</td>
<td>Often</td>
<td>Rare</td>
<td>Rare</td>
<td>Biases may not be eliminated in device or surgery if patient aware of treatment</td>
</tr>
<tr>
<td>Parallel</td>
<td>Sometimes</td>
<td>Often</td>
<td>Rare</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Crossover</td>
<td>Rare</td>
<td>Sometimes</td>
<td>Never</td>
<td>Never</td>
<td>Unable to un-do procedure</td>
</tr>
<tr>
<td>Placebo/sham</td>
<td>Rare</td>
<td>Often</td>
<td>Sometimes</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Run-in period</td>
<td>Often</td>
<td>Often</td>
<td>Sometimes</td>
<td>Never</td>
<td>Including the 5-10% of subjects who would drop out for failure to meet inclusion criteria will favor device, surgery</td>
</tr>
<tr>
<td>Single institution</td>
<td>Often</td>
<td>Sometimes</td>
<td>Often</td>
<td>Usually</td>
<td>Reporting a surgeon’s results could influence</td>
</tr>
<tr>
<td>Multi-institution</td>
<td>Sometimes</td>
<td>Often</td>
<td>Sometimes</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Single Blinded</td>
<td>Never</td>
<td>Sometimes</td>
<td>Never</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Double Blinded</td>
<td>Never</td>
<td>Often</td>
<td>Never</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>Rare</td>
<td>Often</td>
<td>Never</td>
<td>Never</td>
<td>If assume those lost to follow-up are failures, results when not included biased in favor of treatment</td>
</tr>
<tr>
<td>Per protocol</td>
<td>Rare</td>
<td>Rare</td>
<td>Often</td>
<td>Often</td>
<td>Efficacy at last follow-up fails to allow durability assessment</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Months</td>
<td>Weeks</td>
<td>Months</td>
<td>Months</td>
<td>Durability questioned with behavioral and procedures</td>
</tr>
<tr>
<td>Equivalence trial</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Devices/surgery enrolled after behavioral/drug therapies</td>
</tr>
</tbody>
</table>

5. SUMMARY OF SPECIFIC TYPES OF TRIALS

It is appreciated that both device and surgical research trials present significant challenges to trial design. Although decades of experience have refined the conduct of drug trials the absence of comparable robust device and surgical trials derives from these design challenges. Table 2 lists adherence to Design criteria between Behavioral, Drug, Device and Surgical Trials as specified in General Recommendations for Clinical Research in Incontinence. The net result of failure to adhere to these principles may be that the efficacies of the latter two approaches for urinary incontinence are over-estimated. By analogy to intervention trials for pain, the more invasive the

• Long-term follow-up of RCT cohorts in an observational cohort is recommended HIGH
• There needs to be a standardized procedure for classifying adverse events (e.g., Dindo) HIGH

research goals should be to collect data to determine the predictive value of urodynamic testing prior to intervention for stress urinary incontinence. Other important areas include the utility and performance of urodynamics for continent women undergoing pelvic organ prolapse repair. HIGH

• Reports of successful treatment should be limited to subjects with a minimum (not mean) of one year follow-up and should include a patient perspective measure. Specific assumptions about subjects lost to follow-up should be stated; last observation carried forward may not be the most appropriate method of handling this data as most patients lost to follow-up should be considered to have failed treatment. HIGH
• Randomization for surgical trials should occur at the time of surgery to minimize drop-outs and switch of procedure HIGH
treatment, the greater the placebo effect and desire by the patient to self report better outcomes. For urinary incontinence, like pain, this is especially relevant in that even purported “objective” outcomes of diary and pad tests rely on patient reporting and can be circumvented.

V. ETHICAL ISSUES IN INCONTINENCE RESEARCH

1. GENERAL CONCEPTS
This section will highlight the important aspects of the Introduction to Responsible Conduct of Research from the US Office of Research Integrity (ORI) [277] on planning, conducting, and reporting human research. It is beyond the scope of this section to review the rules of conducting human subject research in depth and extensive coverage is available elsewhere [263-267] Responsible conduct of animal research will not be covered and can be found at the National Institutes of Health, Office of Laboratory Animals Welfare (http://grants2.nih.gov/grants/olaw/olaw.htm). International rules of human research were first presented in the Nuremberg Code [268] and later the Helsinki Code. [269]

All investigators should understand the difference between “research” and “practice”. Research is defined as “systematic investigation designed to develop or contribute to generalizable knowledge” [270] and participants accept risks to advance scientific knowledge and to benefit others [271]. Practice is directed toward benefiting the individual patient [272].

The 3 primary guiding ethical principles for human research as outlined by the 1979 Belmont Report on “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” [273] are:

1. Respect for Persons that includes informed consent without undue influence
2. Beneficence to maximize benefits and reduce risks to the subject
3. Justice that the benefits and risks be distributed fairly (i.e. not only using people without access to health care, prisoners, or those impaired).

a) Respect for Persons

Research protocols are required to be approved by an Institutional Review Boards (IRB). IRB’s can adequately evaluate consent forms, however IRB’s have been criticized because they lack the resources to review the scientific merit/design or monitor if the research is being carried out as designed. For these reasons, IRB approval should be regarded only as a minimal ethical standard for research. Ultimately it is the responsibility of the investigator to ensure the research is ethically acceptable [272].

b) Beneficence

The primary concern of the investigator should be the safety of the research participant and careful consideration of the risk/benefit ratio; this includes an ongoing responsibility to monitor research and medical literature as the research proceeds. The investigator needs to critically consider within the expert medical community if there is clinical equipoise for the proposed interventions in their trial [274]. Is one treatment no better than another? Are the research risks reasonable in relation to anticipated benefits? It is the responsibility of the investigator to ensure risks are minimized and potential benefits enhanced as well as that the knowledge gained outweighs the risks [275]. Of note, invalid research cannot be ethical no matter how favorable the risk–benefit ratio for study participants [263].

c) Justice

Justice is of particular concern in Phase I testing of pharmaceutical agents and in early investigation of surgical devices/implants. Payment offered for participation in such drug trials may be extremely attractive to poor and disenfranchised subjects. Early device studies may target countries with lax regulatory environment even if there is little intent to market the device there in the long term.

As pointed out in the ORI Introduction to Responsible Conduct of Research, although the rules set by the investigator’s institution and/or government are important, they are often set at a minimum standard, and it is the personal responsibility of the investigator to strive for a higher standard of conduct [277]. The rules for research need to be supplemented with good judgment and a strong sense of personal integrity. A simple test was recommended for the investigator to use when resolving an ethical research dilemma: “Imagine what you are preparing to do will be reported the next day on the front page of your local newspaper. If you are comfortable having colleagues, friends, and family know what you did, chances are you acted responsibly”.

2. PLANNING

As noted in the section on the Study Conduct and Statistical Consideration, planning is essential and it is ethically important when conducting human subject research. Minimal criteria for an ethical study are:

• the study is well planned and scientifically sound,
• the study is feasible with a realistic chance to be completed,
• there is a reasonable assumption that new knowledge will be provided at the end of the study, and
3. FINANCIAL CONFLICTS OF INTEREST

Many investigators are involved in testing new drugs or devices developed by industry. Especially in the US, proceeds from clinical trials (primarily pharmaceutical but also surgical and device trials) have become an increasingly important supplement to clinician income. Clinical research, previously limited to a few academic institutions, is now spread through all segments of the medical community. While this may improve the variety of patient representation in studies, it also makes safeguarding the rights of research subjects more difficult. Competition for revenue from research, aggressive advertising for research subjects, and dependence of clinicians on income from pharmaceutical companies are trends that bear close attention.

It is acceptable for investigators to receive contracted financial support to perform this research and a principled partnership between industry and investigators is essential if we are to preserve medical progress [278]. Financial conflict of interest policies have been developed due to ethical concerns about potential biases that may influence trial design, conduct, over interpretation of positive results or not publishing negative results [272; 279]. It is important that investigators do not receive money directly from industry sponsors but rather through a research contract. Most quality peer-review scientific journals require a declaration of conflict of interest. While declaration does not in and of itself eliminate bias, allowing the audience to evaluate potential biases is a step toward retaining trust. Although there is no one definition, significant financial conflict has been defined as [277].

1. additional earnings in excess of $10,000 a year outside of a research contract
2. equity interests in excess of 5 percent in an entity that stands to benefit from the research

These guidelines are inadequate and arbitrary—5% of an entity could vary from an inconsequential amount to many millions of dollars, others have argued that any financial reimbursement is too much [281]—but as yet there is no other commonly adopted definition. Ideally, the focus would not be on specific rules but on the constant obligation to consider ethics in all phases of research.

An investigator’s institution may have additional definitions and reporting requirements for financial conflict of interest disclosures. There are many potential relationships between physicians and industry; it is preferable that the nature of the relationship and its financial magnitude if any, be fully defined rather than categorized (i.e. “consultant”) so that the reader can appropriately assess the actual and potential conflict of interests.

4. CONFLICT OF INTEREST IN CONDUCTING AND REPORTING RESEARCH, AUTHORSHIP

a) Conducting Research

The investigator has an ethical responsibility to take responsibility for all aspects of the research, ensuring that the work is done rigorously and to maintain the integrity of the research [272]. Prior to participant enrollment, the International Committee of Medical Journal Editors (ICMJE) recommends information about trial design be placed into an accepted clinical trials registry [281]. A clinical trial is considered “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Registration is required if investigators wish to publish in an ICMJE journal. It is felt that public registration of trials increases the probability of the results being published. Additionally, in human research, data management is key to providing valid research. Clinical data management includes accurate recording of data, data systems, and appropriate statistical methods (See Study Conduct and Statistical Consideration, Section II 3 above), as well as data protection and storage. [282].

As discussed previously, a plan for statistical analysis and publication should be established in the design phase. This inherently implies, and it should be made explicitly clear, that the data belongs to the investigators and there is an expectation that the results will be published regardless of the outcome. All data must be made available to the writing team; summary tables alone are not acceptable. Similarly, the goal of the publication should be to present the data in the most transparent means possible so that the readers can reasonably draw their own conclusions.

Depending on the study and most often in randomized controlled trials, a data safety monitor (DSM) or data safety monitoring board (DSMB) is important to evaluate the study on an ongoing basis to determine early evidence of significant harm or benefit [283, 284]. Depending on the size, complexity, and risks of a trial, the DSMB is comprised of experts needed to monitor interim data to ensure the safety of the participants. A priori stopping rules or boundaries are established to assess if the study should continue or be terminated due to futility (no conclusion will be drawn due to low enrollment, few outcome events, or high drop out rates etc.), reaching an endpoint, or identifying increased risks. [272]. Further details on statistical issues for DSMB’s are included in the Study Conduct and Statistical Considerations section.

b) Reporting Research

Clear guidelines for authorship have been established by medical journals [285]. Beginning with the research contract, authorship rules should be established
according to accepted guidelines. In general, authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

For multi-center trials, a Publication Committee should be established to develop guidelines on: membership (chair, representatives of principal investigators, and a limited number of representatives of a sponsoring company; if the principal investigators are not adequately trained in statistical methods, independent statisticians should also be included); publication & presentation proposal rules and reviews; authorship requirements; disclosure of author conflicts of interest (financial & personal); defined period of sponsor review (30-60 days); and disclosure of use of scientific writers. There has been growing concern that industry sponsored studies have contributed to the proliferation of guest authorship (only minor contributions to a manuscript and perhaps only contributed by providing participants) and ghost authorship (those who have provided substantially to the manuscript for example employees or writing consultants of a pharmaceutical company) [286].

c) Useful Websites

- The National Reference Center for Bioethics Literature (http://bioethics.georgetown.edu/nrc/index.htm)
- International Bioethics Organizations Database (http://bioethics.georgetown.edu/databases/Organizations/index.htm)
- International Committee of Medical Journal Editors (http://www.icmje.org)

Recommendations for ethical research

It is the personal responsibility of investigators to maintain the highest level of ethical research as outlined in the above section. We recommend:

- Clinical trials should be registered and results should be published regardless of outcome. HIGH
- All authors should be able to accept responsibility for the published work and all potential conflicts of interest should be fully disclosed. HIGH
- Continuity in clinical direction from design through authorship is mandatory. Investigators should be involved in the planning stage and a publications committee should be named at the beginning of the clinical trial. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals, from the International Committee of Medical Journal Editors should be followed. HIGH

Authorship requires:

1) Substantial contributions to conception and design or acquisition of data or analysis and interpretation of data,
2) Drafting the article or revising it critically for important intellectual content,
3) Final approval of the version to be published

• Authors should provide a description of what each contributed and editors should publish that information. HIGH
• Authors should have access to all raw data from clinical trials, not simply selected tables. HIGH
• The funder should have the right to review manuscripts for a limited period of time prior to publication but the manuscript is the intellectual property of its authors, not the funder. HIGH

VI. CONCLUSIONS

The goal of this Consultation has been to examine and classify data in order to determine the level of evidence that supports our care of incontinent patients. The goal of this Committee has been to provide a roadmap for the investigators who will produce the high quality research for the next Consultation. Ultimately, good research is credible. Credibility creates impact and generates strong recommendations. Credible research draws others to follow and expand on the work while simultaneously guiding clinical care of patients. Unfortunately, it is clear that much of the published work in incontinence has not been of high quality and thus has not effectively changed patient care. However this can be remedied in the future for, in most cases, the failure has been due to preventable deficiencies in planning and data collection.

The Committee has emphasized that all quality research, be it prospective or retrospective, clinical or preclinical, begins with detailed planning—establishing a clear and relevant hypothesis, developing a trial of appropriate magnitude to accept or reject the hypothesis, and defining methods of adequate sensitivity and specificity to produce credible data. If investigators will work together in true multidisciplinary teams, following the methodology presented here, we will make great strides in the care on incontinent people throughout the world.
121. Rahmanou P, Chalita C, Kulinskaya E, Khullar V. Reliability testing of urodynamics, pressure flow studies and cough leak point pressure in women with urodynamic stress incontinence with and without detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Feb 5 [Epub ahead of print]


206. Fitzgerald, MP 2009 in press


210. Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z; 037


271. Institute of Medicine. Responsible research: a systems approach to protecting research participants.


276. Responsible Conduct of Research from the US Office of Research Integrity (ORI) (http://ori.hhs.gov/)

277. Responsible Conduct of Research from the US Office of Research Integrity (ORI) (http://ori.hhs.gov/)


A Brief History of Urinary Incontinence and its Treatment

Chairman

DIRK SCHULTHEISS  (Germany)
# CONTENTS

<table>
<thead>
<tr>
<th>I. INTRODUCTION</th>
<th>VI. SURGICAL TREATMENT:VESICOVAGINAL FISTULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. EARLY REPORTS ON URINARY INCONTINENCE FROM ANTIQUITY TO THE 18th CENTURY</td>
<td>VII. SURGICAL TREATMENT:STRESS URINARY INCONTINENCE</td>
</tr>
<tr>
<td>III. CONSERVATIVE TREATMENT</td>
<td>VIII. INJECTION THERAPY</td>
</tr>
<tr>
<td>IV. EXTERNAL DEVICES</td>
<td>REFERENCES</td>
</tr>
<tr>
<td>V. “ELECTROTHERAPY“</td>
<td>CORRESPONDENCE</td>
</tr>
</tbody>
</table>
A Brief History of Urinary Incontinence and its Treatment

DIRK SCHULTHEISS (GERMANY)

I. INTRODUCTION

Ancient reports on urinary incontinence are rather rare and mainly address cases of extraurethral incontinence (e.g. due to a fistula acquired during childbirth) or overflow incontinence (e.g. in males with urinary retention or after spinal cord injury). In later centuries several authors dealt with the problem of postoperative incontinence after perineal lithotomy. Defined surgical techniques for the cure of urinary incontinence were not introduced before the 19th century. First this was limited to fistula repair but at the end of the 19th century new procedures for stress incontinence were introduced and became standard clinical procedures. Other modern techniques, like artificial sphincters or electrostimulation, were alternatives developed in urology in the second half of the 20th century.

II. EARLY REPORTS ON URINARY INCONTINENCE FROM ANTIQUITY TO THE 18TH CENTURY

In contrast to frequent diseases like bladder stones, urinary retention and urinary fistula, descriptions of urinary incontinence and its treatment are rarely mentioned in early medical writings. Associated with the above listed entities only a few episodes of overflow incontinence and extraurthral incontinence are reported. On the other hand the use of different catheters for the relief of urinary retention is described in many early cultures [1, 2].

The first sources dealing briefly with urinary incontinence are Egyptian manuscripts from the 2nd millennium B.C.: the „Papyrus Smith“ [3] and the „Papyrus Ebers“ [4]. In the 31st case of the „Papyrus Smith“ incontinence resulting from spinal injury is described as followed: “...if thou examinest a man having a dislocation in a vertebra of his neck, shouldst thou find him unconscious of his two arms and his two legs on account of it, while his phallus is erected on account of it and urine drops from his member without his knowing it ...” [3, 5]. The „Papyrus Ebers“ consists of a collection of about 900 recipes for the treatment of a wide variety of partly poorly defined diseases. Among them one can find remedies “to remove the urine which runs to often” and “to remove constant running of the urine” [4, 6, 7]. Furthermore these Egyptian sources already mention devices for the collection of urine in males and also pessaries for women.

An examination of the mummy Henhenit (about 2050 B.C.) by D. E. Derry in 1935 revealed a large vesicovaginal fistula which is most likely due to a birth trauma as it was accompanied by a laceration of the perineum [8, 9].

Greek medicine was dominated by the outstanding work of Hippocrates (460-377 B.C.) who was writing extensively about the diseases of the urinary tract. Despite his discussion on perineal lithotomy he also dealt with the management of urinary incontinence [7, 10].

Giving a detailed description of the technique of perineal lithotomy the Roman author Aulus Cornelius Celsus (25 B.C.-50 A.D.) emphasized the importance of a wide incision that allows extraction of the stone without further uncontrolled rupture of the surrounding tissue, as this would increase the danger of urinary fistula [7].

Claudius Galen (129-201 A.D.) from Pergamon was one of the first do undertake physiological experiments on the lower urinary tract and postulated that micturition is conducted by contraction of the abdominal muscles. Concerning the causes of urinary retention he differentiated clinically between paralysis of the bladder after spinal injury and subvesical obstruction due to bladder stones [7, 11].

Even from the standpoint of medical sciences the Middle Ages represent a dark period for Europe. At this time the ideas of Greek and Roman authors were preserved and tradicted by Arabian medicine, as e.g. in the writings of Avicenna (930-1037 A.D.), until they were finally rediscovered by European scientist of the Renaissance.
Today we are highly impressed by the studies of Leonardo da Vinci (1452-1519), who performed several dissections on human bodies and over a period of about 25 years created a large anatomical work including the lower urinary tract. In his drawings of the bladder he is mainly presenting an open and funnel-shaped bladder neck and only in some of them he is indicating a circular structure at the bladder neck, the internal sphincter (Figure 1), which he describes as followed: "...and how the gate of the bladder is shut." or "...muscles which open and close the passage of the urine into the mouth of the bladder neck." On the other hand he is not aware of the contractile power of the detrusor muscle and does not mention the problem of urinary incontinence. As Leonardo failed to finish his studies and publish them in the form of a textbook on anatomy his work is only of medico-historical interest and did not influence the scientific development at his time [12].

Ambroise Paré (1510-1590), the most famous surgeon of the Renaissance, also showed great interest in the urinary tract and was one of the first to resect "carnosities" of the urethra with sharp sounds. He described the alterations caused by subvesical obstruction and realized the mechanism of synchronized sphincter relaxation and detrusor contraction during micturition. Figure 2a shows one of the first illustrations of a urinal for incontinent males. Another instrument facilitates urination in the standing position after loss of the penis (Figure 2b): "Those that have their yards cut off close to their bellies, are greatly troubled in making urine, so that they are constrained to sit downe like women, for their ease. I have devised this pipe or conduit ... that must be applied to the lower part of the os pectinis ... serving instead of the yard in making of water, which therefore wee may call an artificiall yard." [13]

Wilhelm Fabricius Hildanus (1560-1634) provided a modified urinal for the treatment of incontinence in his work "De ardore et incontinentia urinae, et nova inventione instrumenti, quo inter deambulandum coligitur" consisting either of glass or the bladder of a pig that was attached to the body by straps (Figure 3) [14].

In his book "Chirurgie", which was edited several times between 1718 and 1779, the German Lorenz Heister (1683-1758) dedicated two chapters on male and female incontinence: "Wenn Manns- und Frauen-Personen den Urin nicht halten können" [15]. In his opinion bladder stones or paralysis of the bladder sphincter are the two reasons for incontinence in males. The first has to be treated by lithotomy whereas the second is cured by "Nerven-stärckenden Medicamenten" (nerve-strengthening drugs).

Besides the use of a urinal as described by Paré or Fabricius Hildanus he suggested a penile clamp (Figure 4a) that was covered with leather and removed by the patient at the time of micturition. With reference to his colleague Winslow, Heister designed a belt that produces perineal compression to the bulbular urethra (Figure 4b). He saw no effective treatment for female urinary incontinence but mentioned a vaginal pessary, formed like a ring, in this case compressing the female urethra.
III. CONSERVATIVE TREATMENT

Empiric therapy with a variety of different recipes was used since antiquity and was for the most part effective on the lower urinary tract due to antidiuretic, cholinergic and anticholinergic ingredients. Some examples from the medical literature of the 18th and 19th century are ergotamine, chloral hydrate, opium ( Laudanum), colchicine, strychnia and atropine ( belladonna) [16, 17]. One of the first modern milestones in pharmacotherapy are the works of Samuel Hahnemann (1755-1843). In his books „Reine Arzneimittellehre” (1833) and “Die chronischen Krankheiten, ihre eigentümliche Natur und homöopathische Heilung” (1835) he already differentiated correctly the different types of urinary incontinence and suggested an adequate medical therapy [18, 19].

Hydrotherapy was a major aspect of mechanical therapy using cold water baths, hypogastric douches, aromatic baths and vaginal douches [16].

In 1762 T. Dickson applied blisters to the area of the os sacrum for reflectory therapy of urge incontinence [20]. One of the first bladder distensions for successful cure of the same disease in elderly patients was performed by J. Rhodes in 1858 using a mixture of carbonic acid gas with chloroform [21].

Another alternative were the sacral epidural injections of Fernand Cathelin (1873-1960) from the Hôpital Necker in Paris. Before 1903 he used saline or cocaine solutions for the treatment of different forms of urinary incontinence ( Figure 5 ) [22]. One year later M. Babinski reported on successful therapy of neurogenic bladder dysfunction with lumbar puncture and drainage of cerebrospinal fluid [23].

IV. EXTERNAL DEVICES

Some early examples of urinals and external compression instruments have been presented above. Compared to the devices listed in a medical catalogue from 1906 ( Figure 6 ) we recognize the same principles improved by new materials like India rubber [24]. The „Appliance for Amputation of Penis” seen on the upper part of this figure is designed for micturition in the standing position, an aspect of quality of life in male patients that was already addressed with the “artificiall yard” of Ambroise Paré (compare Figure 2b). Comparable to these devices the use of vaginal pessaries also has a long tradition in the treatment of female incontinence as mentioned above [25]. In 1826 T. Brown designed a sophisticated self-retaining instrument made from ivory that fitted anatomically to the female urethral orifice and avoided urinary
leakage. A removable stopper at the end of the hollow device allowed controlled emptying of the bladder without removing the whole device [26].

The idea of perineal compression, as introduced by Heister, was revived as lately as 1960 by S. A. Vincent, using an air-inflatable cushion that was fixed to the perineum with a special belt and expanded manually via bellows to obstruct the male bulb urethra (Figure 7) [27].

External devices of all kind have been perfected in our century [25] and were even partly replaced by modern surgery and its advances in continent urinary diversion, a development that will not be outlined any further in this chapter [see 7, 28].

A final remark addresses the cultural aspect of urinals and urine receptacles in the history of mankind. Although chamber pots ("matula") are described in antiquity, the daily use of a urine collecting receptacle (e.g. "bourdaloue") was only introduced in the late Middle Ages and early Renaissance [29].

With the development of electro-physiology in the 19th century the application of direct or alternating current for bladder dysfunction became of therapeutic interest. Robert Ultzmann (1842-1889) from Vienna mentioned three indications in his outstanding book „Die Krankheiten der Harnblase“ from 1890 for the use of electricity in the treatment of „Neurosen oder Neuropathien der Harnblase“: acquired paralysis of the detrusor or sphincter vesicae in adults and idiopathic enuresis in children [30]. The catheter-like electrode ("Rheophor") was introduced either into the bladder (for stimulation of the detrusor muscle) or into the prostatic urethra (for stimulation of the sphincter muscle). Therapy of enuresis in children was suggested with a rectal electrode. Earlier experiments of electrotherapy for incontinence had been undertaken by Nardin in 1864 and were the basis for Ultzmann’s work [31].

In 1898 L. Frankl-Hochwarth and Otto Zuckerandl (1861-1921) published their experience with local electrotherapy in nervous diseases of the bladder [32] and „Blasendiathermie“ with vaginal or rectal sounds was still used in hypertonic conditions of the detrusor in 1930 by Josef Kowarschik form Vienna [33]. Modern concepts of electrostimulation of the pelvic floor with so-called plug electrodes were finally initiated by B. R. Hopkinson and R. Lightwood in the 1960ies [34].

A different approach is the permanent intracorporeal implantation of stimulating electrodes or even complete stimulator systems [overview in 35]: For the treatment of detrusor hypocontractility mainly in spinal cord injured patients W. H. Boyce sewed stimulating electrodes directly onto the bladder in 1954 [36]. A direct stimulation of insufficient sphincteric muscles was tried by K. P. S. Caldwell in 1963 [37]. Another 4 years later T. Burghel attached stimulators to the pelvic splanchnic nerves [38] and H. N. Habib to segmental sacral nerves in patients with spinal cord injuries [39]. Finally the development of the first system for long-term spinal anterior root stimulation, tested in animals in 1969, and the first clinical implantation of such a system in a human being in 1976 by Giles S. Brindley represents the beginning of modern neurostimulation and neuromodulation in urology [35].

In the second half of the 19th century the introduction of antisepsis and asepsis as well as anaesthesia revolutionized modern surgery. With respect to urinary incontinence this activity was mainly restricted to the surgical correction of vesicovaginal fistulas in the beginning, i.e. extraurethral or extraanatomic incontinence [40]. First efforts were made by Franz C. Naegle from Heidelberg in 1812 who experimented with transvaginal closure of fistulas in human corpses [41]. Many well-known surgeons, as G. Dupuytren, J.
Figure 6: Several urinals from the catalogue of Down Bros., London (1906) [24]
M. Delpech, C. F. Lallemand and J. J. de Lamballe, followed this example over the next few decades [9].

In 1845 Johann Friedrich Dieffenbach (1792-1847), founder of modern plastic surgery, described the disease of urinary fistula, mainly arising from a birth trauma in younger women, and its social consequences for the patient in the following words:

“A vesico-vaginal fistula is the greatest misfortune that can happen to a woman, and the more so, because she is condemned to live with it, without the hope to die from it; to submit to all the sequelae of its tortures till she succumbs either to another disease or to old age. There is not a more pitiable condition than that of a woman suffering from a vesico-vaginal fistula. The urine constantly flowing into the vagina, and partially retained there, and heated, runs down the labia, perineum, and over the nates and thighs, producing a most intolerable stench. ... The husband has an aversion for his own wife; a tender mother is exiled from the circle of her own children. She sits, solitary and alone in the cold, on a perforated chair. This is not fiction, but naked truth; and the cure for such an evil is the prize for which we labor.” Although he contributed many aspects to fistula surgery he still emphasized that the results of the treatment were still poor at his time and that only very few advances had been achieved [40, 42].

Only 2 years later Gustav Simon (1824-1876) presented another milestone of fistula surgery, the so-called “German method” with a double row of sutures, one of the whole thickness of the bladder and the other one of the vaginal tissue [46a]. Moreover Simon suggested the “kolpokleisis” in which the vagina is completely closed below the level of the vesicovaginal fistula, a method that did not find wide acceptance (Figure 9) [46b].

As late as 1890 Friedrich Trendelenburg (1844-1924) finally published the first transvesical approach for fistula repair. In the same paper he introduced the operating position that is still named after him in our days [47].

In the very same year, 1845, the American James Marion Sims (1813-1883) performed his first surgery for transvaginal fistula repair in three black slaves. The owners lent Sims the three women for the period of treatment and they lived in a small hospital shack behind his house and office. His early techniques were obviously not to successful as 42 surgical procedures are reported on those three women over the next four years. Finally he succeeded with his special technique using silver wires for closure of the defect (Figure 8), published in 1852 [43], and therefore he is known to us as the founder of urinary fistula surgery. Seen from the ethical standpoint the circumstances of his early clinical research remain controversial [40, 44, 45].
Today extraurethral urinary incontinence due to complications during childbirth is hardly seen in western countries any longer, but is still a major medical problem in many developing countries with low standard obstetric care [48].

In contrast to the above outlined methods for fistula surgery the operative treatment of stress urinary incontinence developed far later and the reports mentioned before 1900 never became standard of therapy. One of these very early reports came from Frank in 1882, who was an assistant doctor of the well-known German surgeon Bernhard Bardenheuer (1839-1913) from Cologne [49].

In 1881 Frank had operated a 37 year old woman transvaginally by excising a wedge-shaped piece from the posterior urethral wall from the external orifice to a point 1 cm before the bladder neck, including the vaginal and urethral mucosa, (distance e to c on Figure 10). Furthermore he resected a part of the vaginal wall at the level of the bladder neck (area a, b, c, d on Figure 10). The defect was then closed with transverse sutures so that the passage of a 9 French catheter was just possible. The patient was continent at the time of control 4 months later.

Similar methods were reported by F. Winckel from Munich a few years later, who had performed the operation in two sessions in 1881/1882 [50], and by B. S. Schultze in 1888 [cited in 16]. Apposition of the urethral walls by flattening of the outer end of the urethra was suggested by Karl Pawlik (1849-1914) from Vienna (later Prague) in 1883 [cited in 16, 51]. He achieved this by drawing the external orifice of the urethra forward to the clitoris and sharply to each side and fixing it in that position with sutures. R. Gersuny from Vienna performed the first torsion of the urethra in 1888 and published this technique as an improvement of Pawlik’s method one year later [51]. In each session he dissected the entire urethra beginning from the external orifice to the bladder neck and twisted it to one direction before suturing it in the new position. In his first patient he operated three times within two months making a torsion of the urethra of 180°, 90° and again 180° (total of 450°). 5 months later the patient reported a lasting success of this treatment, although micturition time was up to 4 minutes for a volume of half a litre of urine.

VII. SURGICAL TREATMENT: STRESS URINARY INCONTINENCE
Comparable methods of urethral torsion and transfer of the urethral orifice towards the clitoris followed by Alfred Pousson and by Joaquin Albarrán (1860-1912), both in 1892, and E. C. Dudley three years later [cited in 16].

The first surgical technique that became a routine clinical procedure was initiated by the uro-gynecologist Howard A. Kelly (1858-1943) from Baltimore in 1900. It consisted of anterior colporraphy and plication of the bladder neck with deep mattress sutures. In 1914 Kelly presented the first detailed analysis and follow-up of twenty patients [16], a milestone in the history of urogynecology and standard of care for the next 60 years [52].

In two male patients with postoperative incontinence after perineal urethral and prostatic surgery a combined procedure through a transvesical and perineal approach was performed by Hugh H. Young (1870-1945), also from Baltimore, in 1907 and 1916. In the first step the interior of the bladder was exposed, the mucosa of the trigone denuded and finally the bladder wall was plicated with deep sutures that were inserted with a special boomerang needle holder (Figure 11a). The result of this plastic operation upon the internal bladder sphincter is shown in Figure 11b. In the second part of the operation periurethral scar tissue was resected via a perineal incision before plicating the remaining tissue of the external urethral sphincter [53].

Another principle, that is still one of the most common procedures for female stress urinary incontinence in our days, is the use of a retropubic sling made from different materials. The first method was described by D. Giordano in 1907 by using the gracilis muscle [54]. He detached the muscle from the thigh and translocated it retropubically as a sling around the urethra.

Three years later R. Goebell performed a sling operation with the pyramidalis muscles in two girls [54]. He separated the muscles from the fascia and postulated an active muscular closure effect on the urethra. Paul Frangenheim (1876-1934) used the same muscles together with the onlying fascia in 1914 [56] and Walter Stoeckel (1871-1961) suggested the combination of this muscle-fascia sling, as shown in Figure 12, with a transvaginal muscular plication of the bladder neck in 1917 [57]. This procedure is known as the Goebell-Frangenheim-Stoeckel operation in clinical terminology.

Another modification is the pubo-vaginal sling with bilateral stripes of the rectus fascia described by Albert H. Aldridge in 1942 [58] and later by Terence Millin (1903-1980) [59]. Both of them attached the sling to the rectus muscle and, besides from the mere suspension effect, they also expected an active closure during contraction of the rectus muscles.

Several perineal procedures were suggested using muscles that are anatomically in close relation to the urethra. The first one was introduced by J. B. Squier in 1911 who took parts of the levator ani muscle [60]. In 1926 C. L. Deming again used the gracilis muscle

Figure 11: Transvesical approach, denudation of the trigone and deep sutures of the bladder wall (a) for plication of the internal bladder (b) in male patients with postoperative urinary incontinence according to Hugh H. Young (1907 and 1916) [53]
and in 1936 Oswald S. Lowsley (1894-1955) provided a method with the ischiocavernous muscle.

Figure 13 shows a modified technique of Albert Vergés-Flaqué and Oswald S. Lowsley from New York in 1951 [63]. They separated the outer parts of the anal sphincter and formed a sling around the bulbar urethra in 7 males suffering from postoperative or posttraumatic incontinence.

Cystourethropexy and colposuspension, as it is still used today in urogynecology, was introduced by V. F. Marshall, A. A. Marchetti and K. E. Krantz in 1949 [64] and J. C. Burch in 1961 [65]. As a minimal invasive procedure A. J. Pereyra inaugurated vaginal needle suspension in 1959 [66] and T. A. Stamey first introduced cystoscopic control for this type of operation in 1973 [67].

The variety of different techniques that have been developed for urinary diversion, not only in cancer surgery but also as an ultima ratio for the treatment of urinary incontinence, are not discussed in detail in this chapter. It is worth while mentioning that first attempts were already undertaken in the 19th century. As early as 1864 Baker Brown created an artificial channel under the pubic bone that allowed the permanent introduction of a catheter and D. C. Rutenberg closed the urethra and performed a vesico-abdominal fistula in 1875 for the cure of urinary incontinence [cited in 16]. Several techniques of ureter-bowel implantation were established in clinical practice before the turn of the last century in patients with bladder ectrophy, vesicovaginal fistula or after cystectomy [see overview in 7, 28].

VIII. INJECTION THERAPY

Periurethral paraffin injection for compression of the urethra and cure of urinary incontinence was first suggested at the end of the 19th century by R. Gersuny from Vienna [cited in 57]. H. A. Kelly discussed the danger of embolism after injection of these unabsorbable foreign bodies and pointed out that this treatment only showed a temporary improvement of symptoms [16]. A further report came from B. C. Murless in 1938, who injected cod liver oil (sodium morrhuate) into the anterior vaginal wall [68]. Since 1953 several authors presented endoscopic transurethral injection with sclerosing agents, mostly containing paraffin, like Dondren® [see overview in 69].

The intraurethral injection of polytetrafluoroethylene (Teflon) was first described in 1973 by Victor A. Politano [70] and Soloman Berg [71]. In 1989 the use of collagen by Linda M. Shortliffe [72] and the injection of autologous adipose tissue by A. S. Gonzalez de Gariby followed [73]. Silicone was not used before the 1990’s.

IX. ALLOPLASTIC SPHINCTER

The oldest device for external compression of the male urethra is the penile clamp [15]. It was brought into use again by J. H. Cunningham as an helpful instrument for performing retrograde urethrography, a radiographic method that was introduced by him into urology in 1910, and is still named after Cunningham today [74].

The first artificial sphincter that was designed as an inflatable circular cuff and applied to the male urethra by surgical means was created by Frederic E. B. Foley (1891-1966) from St. Paul, Minnesota and published in 1947 [75]. This ingenious urologist is best known for the improvement of the principles of the transurethral balloon catheter and played a major...
role in the introduction of commercially manufactured balloon catheters in the 1930's [2]. Figure 14a shows the operative steps of dissecting the corpus spongiosum from the corpora cavernosa and closure of the skin around these two separated structures. After wound healing the external cuff of the urinary sphincter ("pneumatic clamp") was put around the urethra, that was now completely covered with skin, and inflated or deflated manually via a pneumatic piston (Figure 14b).

It was not before the 1960's that first operations with completely implantable devices were undertaken [see overview in 76]. In 1961 J. L. Berry provided perineal acrylic implants producing a permanent compression on the bulbar urethra [77]. The silicone-gel-prosthesis of Joseph J. Kaufman from 1973 was based on the same concept [78]. M. Rosen from Australia developed an inflatable urethral compression prosthesis in 1976 [79] and Udo Jonas in 1983 an internal penile clamp, that was implanted at the penoscrotal angle and opened for micturition by external pressure through the skin from both sides [80].

In June 1972 F. Brantley Scott, together with William E. Bradley and Gerald W. Timm, implanted the prototype of the so-called "Scott-sphincter" in a 45 year old woman [81].

Finally, 25 years after Foley's publication, the idea of an inflatable cuff for the treatment of stress urinary incontinence had been adopted again and became a standard clinical procedure.
Figure 14 a: In- or deflation of a cuff via pneumatic piston. Surgical dissection of the corpus spongiosum
REFERENCES

<table>
<thead>
<tr>
<th>Page</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.</td>
<td>Brown T: Case of incontinency of urine, with the description and figure of an instrument by which it was relieved. Edinburgh Med Surg J 1826; 26: 279.</td>
</tr>
</tbody>
</table>

CORRESPONDENCE

Dirk Schultheiss, M.D.
Consultant Urologist and Andrologist
Chairman, History Office, European Association of Urology (EAU)
Private Dermatological and Urological Office Baier Foundation and Department of Urology
Protestant Hospital Gießen
Friedrichstr. 21 D-35392 Gießen
Email: dirk.schultheiss@urologie-giessen.de
INDEX

Indexer: Dr Laurence Errington
www.errington-index.demon.co.uk

Figures and tables are comprehensively referred to from the
text. Therefore, significant material in figures and tables
has only been given a page reference in the absence of their
concomitant mention in the text referring to that figure.
Abbreviations: AI (or FI), anal (faecal) incontinence; EMG,
electromyography; LUT, lower urinary tract; LUTS, lower
urinary tract symptoms; POP, pelvic organ prolapse; QoL,
quality of life; SUI, stress urinary incontinence; UI, urinary
incontinence. UK and not US spellings have been used
throughout the index, although the text uses both.

A
Aδ fibres/axons, 176, 636
abdominal approach see transabdominal approach
abdominal examination, females with UI, 342
abdominal leak point pressure, 419
abdominal massage aiding defaecation, 868-9
spinal cord injury, 907
abdominoperineal resection of rectum, 802, 918
absorbent products (pads) for FI, 1530, 1556
odour control, 1627
absorbent products (pads) for UI, 1538-57
capacity and user requirements, 1544
categories, 1538-40
changing frequency, 1623, 1625
evaluation of different bodyworn designs, 1550-4
females with light UI, 1527, 1544-6
general recommendations on selection, 1556-7
for light UI
females, 1527
males, 1528, 1546-8
materials, 1540-4
measuring usage, 336
for moderate/heavy UI
females, 1528
males, 1529
ACET study, 647
acetaminophen, chronic pelvic pain, 1490
acetohydroaxmic acid, 1597
acetylcholine, 128, 131, 639-41
detrusor overactivity and, 263, 639-41
urothelial stretch and, 118
see also muscarinic receptors; nicotinic receptors
acetylcholinesterase inhibitors see cholinesterase inhibitors
Acticon Neosphincter®, 1396, 1398
actin in detrusor contraction, 121
activities of daily living and frailty, 964
acupuncture
male UI, 1093
nocturnal enuresis, 724
adenosine receptors, 131-2
adenosine triphosphate see ATP
ADH see vasopressin
adherence (compliance)
children, 1741-2
electrical stimulation, 1067
pelvic floor muscle training, 1044-5, 1045-6, 1047, 1651
adhesives, tissue, non-obstetric fistulas, 1249
adjuvant radiotherapy in prostate cancer, 1139
adrenoceptor(s) (and adrenergic nerves/innervation), 129
adverse urinary effects in older people of drugs acting at, 310, 311
bladder wall/detrusor, 123
as novel molecular targets, 140
α-adrenoceptor, 126, 129
bladder, 126, 129, 202
urethral, 127
urethral and anal rhabdosphincters and, 194
α-adrenoceptor agonists/stimulants, SUI, vs pelvic floor muscle
training, 1051
α-adrenoceptor antagonists, 657
multiple system atrophy, 884-5
neurogenic UI, 824-5
children, 743
older people, adverse urinary effects, 311
overactive bladder symptoms/detrusor overactivity, 657
overactive pelvic floor, children, 739
overflow incontinence, 676
β-adrenoceptor, 140-1
β3-adrenoceptor, 123, 658
agonists, 140, 141
overactive bladder symptoms/detrusor overactivity, 657-8
SUI, 673-4
antagonists, SUI, 673
bladder, 129
as novel molecular targets, 140-1
urethral, 127
advanced glycation end-products, 134
advanced practice nurses, 1655
collaboration with physicians in care of frail elderly, 1004
advocacy, continence, 1652-8
aesthetics, pads, 1557
aetiology (incl. risk factors/pathogenesis), 1667-8
AI/FI, 74-9, 137, 286, 354, 861-3, 877-922, 1323-41, 1364-7
children, 764
frail elderly, 1362, 1364-7
neurogenic, 861-3, 877-922, 1338-9, 1365-6
obstetric factors see childbirth
physical examination in determination of cause, 354-5
bladder dysfunction see bladder dysfunction
bladder pain syndrome, 222, 1469-71
constipation, older people, 1356
enuresis/wetting
day, 45-6
night, 41-2
fistulas see fistulas
POP see pelvic organ prolapse
UI (in general), 1667-8
frail elderly, 965-75, 1009, 1739-40
men see males
neurological, 69, 799-802, 877-922
in primary prevention, 1667-8
research recommendations, 93
women, 55-61, 83
see also pathophysiology
afferents see sensory (afferent) nerves/neurones
African-American women see black and African-American women
aganglionosis, colonic (Hirschsprung’s disease), 138
age (and aging)
AI/FI risk and, 74, 1330
bowel, 1363-4
of child, effects of incontinence and its treatment related, 1741
LUT changes with, 965-70
nocturnal enuresis prevalence and, 39-40, 41
non-neurogenic detrusor overactivity and, 260-1
outcome of female UI treatment related to
bladder training, 1078
electrical stimulation, 1066-7
pelvic floor muscle training, 1054-5
outcome of male UI treatment related to, bladder training,
1092-3
pharmacology and, 981-3
POP and, 283
surgical management of, 1275
anal sphincter, external (EAS; anal rhabdosphincter), 285, 614-16
anal canal, 139
anal sphincter (both muscles or unspecified), 285-6, 475, 612-16
anal plug, 869, 1530, 1612, 1615-16, 1617, 1618
anal incontinence
anal electrical stimulation, 1359, 1360
incisions (sphincterotomy), FI risk, 1338
obstetric trauma, 288, 612
surgery see surgery
anal stool bag, 1614, 1617, 1618
analgesia/analgesic drugs
pelvic organ prolapse surgical outcome related to, 1276
pelvic organ support-related see pelvic organs
angiotensin-converting enzyme inhibitors, 310, 311
anismus, 499
anorectal incontinence, elderly, 1366
treatment, 1371-2
anorectoplasty, posterior sagittal, 1153
anorectum, 137-40, 285-6, 289-90, 474-502
anaemia and POP, 1096, 1097
anaesthesia see general anaesthesia; local anaesthesia; regional anaesthesia
anal canal, 139
bulk-enhancing agents injected into, 1403-5, 1408
length of high-pressure zone, 481
pressure and its measurement see manometry; pressure sensation see sensation
anal electrical stimulation, 1359, 1360
anal incontinence see faecal incontinence
anal plug, 869, 1530, 1612, 1615-16, 1617, 1618
anal pouch, 1530, 1614, 1617, 1618
anal sphincter (both muscles or unspecified), 285-6, 475, 612-16
anatomy, 285-6, 475
artificial see artificial anal sphincter
digital examination, 355
endurance and fatigability assessment, 485-6
in etiopathogenesis of FI, 288
functional assessment, 475
imaging, 612-16
obstetric/childbirth-related trauma, 291-7, 612, 1334-7
dynamic methods of assessment, 487
instrumental delivery, 297-8
recognised, 295-7
repair, 295-7, 1390
unrecognised/occult, 291-5
physiology, 137, 139, 285-6, 475
pressure studies see manometry
repair see surgery
anal sphincter, external (EAS; anal rhabdosphincter), 285, 614-16, 1353-9
anatomy, 475
EMG, 497, 501, 527, 529, 532
in neuropathic patients, 866
vector manometry compared with, 486
imaging of abnormalities, 614-16
innervation, 188-92
neurophysiological tests, 496-8
obstetric trauma, 288
assessment, 487
pharmacology, 194-7
physiology, 475
repair see surgery
aneurysm see aneurysm
anaesthesia
sinus see sinus
sensational see sensation
sensation
spinal cord injury, prophylactic, 904
with indwelling catheters, 1595-6
with neurogenic detrusor-sphincter dysfunction, 743-4
diarrhoea associated with use in older people, 1366
with indwelling catheters, 1595-6
antibiotic-impregnated catheters, 1593, 1594
prophylactic, 818, 1593, 1594, 1595, 1602-4
therapeutic, 1595-6
with spinal cord injury, prophylactic, 904
anti-blow off features, sheaths, 1558
anticholinergics see antimuscarinics
anticonvulsants, chronic pelvic pain, 1491
antidepressants, 660
bladder pain syndrome, 1482-3
chronic pelvic pain, 1491
diarrhoea-associated FI, 1351
neurogenic UI, 821-2
nocturnal enuresis, 723
overactive bladder symptoms/detrusor overactivity, 660
SUI, 674-5
antidiarrhoeal drugs, 1350-1
antidiuretic hormone (ADH) see vasopressin
antiepileptics (anticonvulsants), chronic pelvic pain, 1491
antihistamines, bladder pain syndrome, 1483
anti-incontinence devices see continence devices
anti-kinking/twisting features
drainage bags, 1562
sheaths, 1558
antimuscarinics (anticholinergics), 639-52
enuresis, 736-40
day and night-time, 729, 736-40
night-time, 722, 771
mechanism of action, 639-41
mixed smooth muscle relaxants and, 653
neurogenic bladder, 821
as bladder relaxants, 821
in Parkinson’s disease, 888
in spinal cord injury, 903
neurogenic detrusor-sphincter dysfunction in children, 742, 743, 744
older people (incl. frail persons), 681-2, 990-4
adverse effects, 308, 310, 681-2, 982-3
for nocturia, 1000
recommendations, 1008
overactive bladder symptoms/detrusor overactivity, 639-52
pharmacology, 641
rationale for use, 639, 640
urge UI, 645, 681-2
antiproliferative factor and bladder pain syndrome, 1470, 1478
antiglycereics, in chronic pelvic pain, 1490
anti-twisting features see anti-kinking features
anus
anatomy and function, 285-6
benign conditions associated with FI, 354
endovascular cushions, 286
fissure, chronic, 486
imperforate see imperforate anus
stimulation with water streams see water
see also anorectum; perianal examination and entries under anal; transanal
APCAB (Asia Pacific Continence Advisory Board), 1658
apnoea, sleep see sleep apnoea
apomorphine, 887
aponeurotic bladder neck slings, neurogenic LUT dysfunction, 846-7
apoptosis, detrusor smooth muscle cells, 148
appendix
for antegrade continence enema, 1407
for continent urinary diversion, 856
appliances see continence devices
aprepitant, 671-2
AQoL (Assessment of Quality of Life), 1696
Arabian medicine, 21
areflexia
detrusor see underactive bladder/detrusor
urethral sphincter see underactive urethral sphincter
L-arginine, bladder pain syndrome, 1485
Argus sling, 1130-1, 1137
arousal (from sleep), children
infants, 704
nocturnal enuresis and, 42, 717-18
alarm facilitating arousal see enuresis alarm
arousal training, 724, 770
see also waking
artificial anal sphincter, 1396-8, 1408
neurogenic FL, 875-7
artificial bladder (prosthetic bladder), child, 750
artificial bowel sphincter, 1398
artificial urethral/urinary sphincter (=AUS), 845, 847-9, 1160-8
availability and cost, 1160
children, 751, 754
complications see safety
component durability, 1164-5
historical accounts, 29-30
men, 29-30, 1134-5, 1160-8
consensus protocol on follow-up, 1168
diagnostic evaluation of UI after placement, 1165-7
indications, 1161
post-prostatectomy (for benign disease), 453, 1134-5
post-prostatectomy (for cancer), 453, 1134-5
post-radiotherapy, 1139
technique, 1161-3
women, 29-30, 1255
ascending pathways/tracts, bladder control, 207
ASCRS (American Society of Colon and Rectal Surgeons) FQIQL scale, 1402
ASERNIP-S (Australian Safety and Efficacy Register of New Interventional Procedures - Surgical), 1754
Asia Pacific Continence Advisory Board (APCAB), 1658
Asian and Asian-American women, epidemiology
PO: 83-4
UI, 53
Asociacion de Enfermedades Uroginecologicas, 1681
assessment (evaluation) of patients and their conditions, 331-412
bladder pain syndrome, 1474-9, 1494-8, 1501, 1502, 1503, 1503-5
outcome, 1498-501
childhood enuresis and UI, 706-12
day and night time enuresis, 728, 767-8
nocturnal enuresis, 719-21
continence products, 1524
FI see faecal incontinence fistulas
non-obstetric, 1248-9
obstetric, in developing world, 1429-35, 1453
frail elderly, 975-7, 1005-7, 1009
nocturia, 1000
of outcome see outcome
UI
children see subheading above
frail elderly see subheadings above
initial, 333-53
patient-reported outcome, 364-7, 377-403
post-fistula repair, 1448-9
preoperative, men, 1124-6, 1169
see also diagnostic tests; history-taking; investigations; physical examination
Assessment of Quality of Life, 1696
Association for Continence Advice (ACA), 1682
Association National de Ostomizados e Incontinentes (Spain), 1681
Associazione Italiana Donne Medico, 1681
ASTRA (anterior transsphincteric transanal surgical approach) to rectourethral fistula repair (ASTRA), 1158
astrocytes, spinal cord, 183
ATP, 118, 123
K+ channel gating by, 122
purinoceptors and, 123, 130, 174, 178-9
and non-neurogenic detrusor overactivity, 262-3
as urethelial stretch-released factor, 118
atrial natriuretic hormone and nocturia in the frail elderly, 999
atrophic vaginitis, 309
atrophy, urethral, with artificial urinary sphincter, 1163-4, 1167-8
atropine (hyoscyamine), overactive bladder symptoms/detrusor overactivity, 643, 822
intravesical, 822-3
attention and modulation of brain responses to visceral stimuli, 232
attention deficit hyperactivity disorder (ADHD)
daytime wetting and, 763-4
nocturnal enuresis and, 762-3
augmentation cystoplasty see cystoplasty
Australia
continence awareness/promotion/services, 1648-9, 1650-1, 1680
continence nurse advisors, 1654
professional education, 1660
referral centres, 1655
Continence Foundation of, 1655
family doctor education in, 1660
Australian Safety and Efficacy Register of New Intervventional Procedures - Surgical, 1754
Austria, continence organisation, 1680
authorship, guidelines for, 1757-8, 1758
auto-augmentation (bladder/detrusor myectomy or myotomy), 1149
child, 749
detrusor overactivity, 1240
men, 1149
neurogenic LUT dysfunction, 854
autografts, for suburethral sling, 1216
autoimmune mechanisms in bladder pain syndrome pathogenesis, 1470
automatic bladder see reflex bladder
autonomic nervous system, 797
bladder, 198-200, 200-2
in bladder pain syndrome aetiology, 1470-1
dysfunction and neuropathy
in diabetes mellitus, 1339
in Guillain-Barré syndrome, 911
leading to FI, 289, 1339
tests (in generalised neuropathy), 537
functional testing, 536-7
hyperreflexia/dysreflexia
with catheters, 1607
with digital rectal stimulation, 868
with sacral anterior root stimulation, 840
see also enteric nervous system; ganglia; parasympathetic nervous system
autonomous hypothesis of spontaneous detrusor activity, 125
autoplasty, vesical, 1446-7
average volume voided, measurement, 336
Avicenna, 21
axon(s) (nerve fibres)
 C- see C-fibres/axons
terminal, bladder, 200
azathioprine, bladder pain syndrome, 1484

Bacille Calmette-Guérin instillation in bladder pain syndrome, 1487
baclofen, detrusor overactivity, 668-70
bacterial infections, urothelium in, 117, 171
see also antibiotics
bacteriuria, 337
asymptomatic, 338
children with neurogenic detrusor-sphincter dysfunction, 743-4
frail elderly, 468, 469, 970
indwelling catheters and, 1590, 1592, 1593
non-continent urinary diversion and, 859
spinal cord injury, 902
bags
interanal (stool bag), 1614, 1617, 1618
urine drainage see drainage bags
balloon systems/devices
anal pressure measurement, 475
external urethral sphincter dilatation, 837
of indwelling catheters
cuffing on deflation, 1600-1
filling solution, 1589
inflation failure, 1605
inflation leading to water loss from balloon over time, 1589
size, 1590
intravaginal, for resistance treatment, 1044
passive compression of urethra in men, 1131-3
rectum
compliance estimates, 494-6
distension, 488-9
expulsion test, 500
retention test, 493
sensitivity measurement, 488
see also double balloon urethrography
barrier function, urethelium, 170
barrier products, 1623, 1624
barrier products, 1623, 1624
Barrington’s nucleus, 209, 228
basal ganglia lesions, 800
Parkinson’s disease, 887
baseline clinical and demographic data, ICS Standardization Committee recommendations, 1730
baseline techniques in cognitive-behavioural therapy, 769
BBUS-Q (Birmingham Bowel and Urinary Symptoms Questionnaire), 394
BCG, intravesical/intramural, in bladder pain syndrome, 1487
BCSQ (Bladder Control Self-Assessment Questionnaire), 385
BE-DRI (Behavior Enhances Drug Reduction of Incontinence), 1752
bed sores (pressure ulcers), 1620-1
bedpads see underpads
bedpans, 1526, 1535-7
bedwetting see nocturnal enuresis
Behavior Enhances Drug Reduction of Incontinence (BE-DRI), 1752
behaviour
health and treatment-seeking see help-seeking behaviour
homeostatic emotions driving, 226-7
behavioural disturbances, 760-7
FI and, 764-6
subclinical, 766-7
behavioural therapies and modifications, 813-15
bladder pain syndrome, 1480
FI in children, 1349
frail elderly, 984-8
nocturia, 1000
recommendations, 1008
neurogenic UI, 812, 813-15
trials/research, 1748-9
Belgium, continence organisation, 1680
beneficence, 1756
Benefit, Satisfaction and Willingness Questionnaire (BSW), 383, 384
benign prostatic hyperplasia/enlargement/obstruction - BPH/BPE/BPO (and benign prostatic disease in general), 302-3, 969-70
age-related occurrence, 969-70, 983-4
drug therapy of frail elderly, 1001
nocturia, 263-4
prostatectomy for see prostatectomy
PSA levels in, 352
questionnaires, 379, 381, 396-7, 401
UI, 302-3
beta-adrenoceptors see adrenoceptors
bethanechol
supersensitivity test, 807-8
therapeutic use in detrusor areflexia, 825
frail elderly, 995
BFLUTS (Bristol female LUTS questionnaire), 377, 378
bias in trials, 1722
bilharziasis (schistosomiasis), contracted bladder, 746, 1151
bimanual examination in bladder pain syndrome, 1475
biofeedback (BF)
children, 770
day/night-time enuresis, 735
neurogenic detrusor-sphincter dysfunction, 743
FI, 1353-9, 1375-6
meningomyelocele, 915
men (post-prostatectomy), pelvic floor muscle training plus, 1085, 1085-7
with electrical stimulation, 1090
women/vaginal, pelvic floor muscle training plus alone, 1045, 1046-7, 1047, 1065
with electrical stimulation, 1065-6
biofilms, indwelling catheters, 1590-2
prevention, 1596-7
biomarkers, bladder pain syndrome, 1478
biomaterials for bladder augmentation, 854
biomechanical properties see mechanics
Bioplastique® see polydimethylsiloxane
biopsies, bladder pain syndrome, 1477
Birmingham Bowel and Urinary Symptoms Questionnaire (BBUS-Q), 394
birth see childbirth
BISF-W (Brief Index of Sexual Function for Women), 398
black and African-American women, epidemiology
POP, 83-4
UI, 53
bladder
afferent neurones see sensory nerves
agenesis, surgery, 745
in aging see older people
artificial see artificial bladder
augmentation see auto-augmentation; cystoplasty
automatic/reflex see reflex bladder
bladder/urinary tract infections, 1341
bilharzia/schistosomal scarring, 746, 1151
capacity see bladder capacity
compliance see compliance
control (of function), 207-21
disorders see bladder dysfunction
control (of function), children
CNS role, 726
normal development, 703-4
damage
endoplasmic reticulum stress-related damage, 148
traumatic see injury
denervating agents injected into, 838-9
women, 1238-9
distension (technique) see cystostension
duplication, surgery, 745
dysfunction see bladder dysfunction
efferent/motor pathways, 198-207
electrical stimulation see intravesical electrical stimulation
emptying
central control, 203
feeling of incompleteness, 335
peripheral control, 634
see also micturition
emptying, facilitation
with catheters see catheters
with drugs, 821, 824-5
with spinal lesions, 812, 898
with surgery, 833-8
emptying, impairment/failure
children, postoperative, 755
see also overflow UI; urine retention
endoscopy
diagnostic see endoscopy
resection performed via, 1237
epithelial Na+ channels, 144
exstrophy, 464
surgery, 745, 1142-5
filling
central regulation, 211
pressure-volume studies during see filling cystometry
fistula between vagina and see vesicovaginal fistulas
fistula repair using, 1446-7, 1447
function (in general)
alterations see bladder dysfunction
brain and, 207-21
control see subheading above
hypoxia see hypoxia
inflammation see bladder pain syndrome; schistosomiasis
interactions with other pelvic organs at efferent neural level, 203-5
irrigation in spinal cord injury, 904
morphological alterations in multiple sclerosis, 895
myectomy see autoaugmentation
neuroactive agents, 128-32
neurogenic see neurogenic LUT dysfunction
obstruction at outlet see bladder outlet obstruction
overactive see overactive bladder
preparation for enterocystoplasty, 849-50
pressure within see intravesical pressure
reconstructive surgery see cystoplasty
reflex see reflex bladder
sensations, 429
categorisation, 335
children (with enuresis), 712
in diabetes mellitus, 916-17
in spinal cord injury, 900-1
sensations, assessment in cystometry, 534
objective, 420
stones see stones
support/suspension, imaging (of normal and defective support), 552-3
surgery circumventing see urinary diversion
tissue-engineered see tissue engineering
training see bladder training
transient receptor potential cation channels, 146
trigone of, 125-6
botulinum toxin injection, 662
denervating agents injected through/below see denervating agents (subheading above)
underactive see underactive bladder
urine leakage see leakage
urine reflux into ureter see vesicoureteric reflux
volume
bladder pressure and relationship to, measurement see filling cystometry
pad test and, 619
residual see residual urine
weight, ultrasound, 563-4
see also entries under cyst-; intravesical; vesico-
Bladder and Bowel Health Foundation (UK), 1682
Bladder and Bowel Health website (Australia), 1649
bladder cancer
neobladder for, 1141
patient-reported outcome questionnaires, 401
risk
with enterocystoplasty, 853
with indwelling catheter use, 818, 1599-600
with multiple sclerosis, 895-6
with non-continent urinary diversion, 859
bladder capacity, 429
children, 704-5
maximum cystometric, 712
males, reduced, 1151, 1161
surgery, 1151, 1161
normal values, 429
bladder chart see frequency/volume chart
Bladder Control Self-Assessment Questionnaire (BCSQ), 385
bladder-cooling reflex see ice water/ test
bladder diary see frequency/volume diary
bladder dysfunction (abnormal function and functional changes)
bladder relaxants (incl. smooth muscle relaxants), 820, 821-2

bladder rehabilitation (urotherapy), children, 734-6, 769-71

bladder expression, 813-14

specific (classes of) drugs in neurogenic UI, 821-2

bladder neck (urethrovesical junction; bladder outlet) surgery (incl. reconstruction), 1141-2

bladder neck flaps for urethral reconstruction (with fistulas), 1446

bladder neck closure, 752

male, 609

interactions with other pelvic organs at efferent neural level, 203-5

mobility (and hypermobility), assessment, 342-3

needle suspension, 1202-3

obstruction see bladder outlet obstruction open, causes and imaging, 601-2

support devices/prosthesis, intravaginal, 1572-5

bladder outlet obstruction (outflow obstruction; BOO), 259-60

endoscopic evaluation

female, 607-8

male, 609

bladder outlet obstruction see bladder neck; bladder outlet obstruction

bladder outlet obstruction (outflow obstruction; BOO), 259-60

children, assessment, 712

endoplasmic reticulum stress involvement in damage caused by, 148

men

PSA levels and, 352-3

research, 1736

urodynamic studies, 450

neural mechanisms, 224-5, 259-60, 260

women, postoperative, 1234

bladder pain syndrome (BPS; interstitial cystitis), 222, 1459-518

bladder outlet obstruction see bladder outlet obstruction

bladder outlet obstruction (outflow obstruction; BOO), 259-60

children, assessment, 712

endoplasmic reticulum stress involvement in damage caused by, 148

men

PSA levels and, 352-3

research, 1736

urodynamic studies, 450

neural mechanisms, 224-5, 259-60, 260

women, postoperative, 1234

bladder-related complications, 1236

Bonferroni correction, 1727

Bonney's original stress test, 342

bladder wall anatomy, 116

biomechanical properties, 132-7

smooth muscle see detrusor

thickness, ultrasonography, 562-4

bleeding/haemorrhage, SUI surgery, 1233-4

blinding in trials, 1716, 1722

men, 1527, 1546-8

women, 1528, 1545-6

leg bags, 1561-2, 1562, 1563, 1564, 1565, 1566

urinals, 1567

men, 1529, 1567

women, 1567

bone-anchored procedures male sling

post-prostatectomy, 1130

post-radiotherapy, 1139

SUI, 1203

women, 1567

bones, 1259

bothersomeness in outcomes research, 1731

questionnaires, 377, 387, 388-9

ICI modular questionnaire, 371

Botox® see botulinum toxin A

botulinum toxin A (Botox® and Dysport® ), 661-6, 823-4, 1146, 1148

bladder emptying facilitated by, 825

in bladder pain syndrome, 1488

children, 664, 739, 743

in detrusor overactivity, 662-8, 1146

economic analysis, 666, 1699

in GI tract spasticity, 138

injection protocol, 662

mechanism of action, 661

in neurogenic LUT dysfunction, 823-4, 825

side-effects, 665-6

botulinum toxin B (Neurobloc® ), 666

bowel (intestine/lower GI tract), 137-40

afferent projections to spinal cord, 182-4

ageing, 1363-4

bladder reconstruction/augmentation using (enterocystoplasty), 849-53, 1160, 1239-40
calcium ion (and Ca$^{2+}$ channels), 118, 144
detrusor and, 122, 144
contraction of, 121, 122
as molecular targets (antagonists), 652
in bladder pain syndrome, 1486
novel agents, 144
older people, adverse urinary effects, 310, 311
urethral smooth muscle, 127
calcium ion-activated potassium channels (BKCa), 122, 129, 141, 142
calcium ions, 118, 144
Caucasian women, epidemiology
catheters, urinary tract (predominantly urethral), 815-20, 1576-612
rectal, 1530, 1612-14, 1616-17, 1617, 1618
anal manometry, 475-6
case series, 1716-17
care (continence)
education see education models, 1653-6
multidisciplinary see multidisciplinary care
organisations see organisations
quality see quality of care
seeking, behaviour related to see help-seeking behaviour
see also continence care; health care; routine care; treatment
CARE trial see Colpopexy and Urinary Reduction Efforts
caregivers
FI education, 1342-3, 1373
of frail elderly, 983
interventions with, 988-9
preferences for UI care, 979
in nursing homes, training, 1664
pads/absorbent products applied by, 1552-4
case series, 1716-17
catheters, anal manometry, 475-6
catheters, rectal, 1530, 1612-14, 1616-17, 1617, 1618
catheters, urinary tract (predominantly urethral), 815-20, 1576-612
choices, 1578
indwelling see indwelling catheters; suprapubic catheter
intermittent see intermittent catheterisation
condom see condom
in fistula repair, 1440, 1441, 1443
neurogenic UI, 812, 815-20
other care strategies compared with, 1606
overall recommendations, 1610-11
post-prostatectomy pelvic floor muscle training immediately after removal, 1083, 1084
quality of life, 817, 1606-7, 1612
self-management, 1609
spinal cord lesions see spinal cord lesions
in urodynamic studies
air-charged catheters, 419-20
children, 467
condom catheters, 421
influence on voiding, 430
Caucasian women, epidemiology
POP, 83-4
UI, 53
cauda equina lesions/injury, 799, 898-9
children, urodynamic studies, 461
conservative treatment, 812
cauda equina stimulation see sacral neuromodulation, anterior
cauda equina syndrome, 908-9
cause see aetiology
CCAAT enhancer-binding protein-homologous protein (CHOP), 148
cell(s)
for tissue-engineered graft generation, 150-1
functional control, 151
nutrient supply, 150-1
support mechanisms, 150
urothelial, in visceral sensation, 171-5
cell biology, lower urinary tract, 113-66
Celsus, Aulus Cornelius, 21
central nervous system (and central pathways), 207-21, 634
drugs acting on, in overactive bladder/detrusor overactivity, 670-2
imaging see neuroimaging
LUT function and role of, 207-21, 634
children, 726
nocturnal enuresis and, 717-18
see also brain; brainstem; spinal cord
cerebral cortex and bladder function, 207-21
cerebral palsy, 800
neurogenic detrusor-sphincter dysfunction, 741
urodynamic studies, children, 462
cerebral peduncular somatosensory evoked potentials, 535
cerebrovascular accident (CVA incl. stroke), 800-1, 862-3, 890-4
FI, 862-3, 893-4, 1339, 1365
UI, 454, 800-1, 890-3
frail elderly, 971, 973
prognostic value of UI, 973
cerebrovascular disease, detrusor overactivity, 258
cervical damage in obstructed labour, 1432
cetrorelix, 670-1
CHAMMP (Continence, History, Assessment, Medications, Mobility, Plan) tool, 1656
chance node (decision tree), 1692
change, responsiveness to, in questionnaires, 366-7
chemical stimuli, urothelial role in sensing of, 173-5
Child Behaviour Check List (CBCL), 761, 762, 763, 764, 765, 767, 767-8
childbirth (parturition incl. vaginal delivery), 264-71
FI after, 76, 288, 290-9, 354, 1334-7
delivery technique and, 297-8, 298
dynamic testing, 487
episiotomy and, 269-70, 298, 1337
training of health professionals about, 298-9
see also anal sphincter
fistulas associated with see fistula
patient-reported outcome assessment, 400
pelvic floor and effects of, 264-71
levator ani, 266, 267, 565-7, 586-8
MRI, 586-8
pathophysiological mechanisms of injury, 264-71
prolapse, 272-3, 586
ultrasound, 565-6
perineal trauma see perineum
POP associated with, 84-5, 282-3
services in developing world, 1656
UI related to, 55-7, 264-71, 272-3
pathophysiology, 264-71
prevention, 1036-42, 1668-9
research on, 93
stress, 264, 265-6, 267, 272-3
ultrasoundography, 570-1
see also Caesarean delivery; delivery; instrumental delivery; labour
children, 701-92, 1741-2
assessment/evaluation see assessment
bladder overactivity, prevalence, 74
bulking agents, 750-1, 843
classification of UI, 713
congenital/anatomic anomalies see congenital/anatomic anomalies
constipation see constipation
continence devices
FI, 1555-6, 1615-16
UI, 1555-6
digital rectal examination, 347
epidemiology of UI and enuresis, 38-46
behavioural disorders and, 761
day and night time enuresis, 38, 43-5, 727-8
nocturnal enuresis see nocturnal enuresis
FI, 764-6
assessment/investigations, 767
continence devices, 1555-6, 1615-16
management, 769-70, 770, 1349, 1406-7, 1408
parental impact, 766-7
psychological consequences, 764-6, 766
imaging, 709-10
intermittent catheterisation, 1579
management of UI, 718-26
non-pharmacological, 734-6
surgical, 744-59
neurogenic detrusor overactivity see neurogenic detrusor overactivity
normal (LUT) values, 704-6
parental impact, 766-7
psychological consequences of UI, 760-71
research see research
sexual abuse see sexual abuse
urodynamics see urodynamic studies
wetting see daytime and night-time wetting; enuresis; nocturnal enuresis
see also boys; girls; infants
cholinergic drugs, neurogenic UI, 825
cholinesterase inhibitors, UI risk
Alzheimer’s disease, 878
elderly, 682, 983
chondroitin sulfate, intravesical/intramural, in bladder pain syndrome
CHOP, 148
chronic pelvic pain see pelvic pain
cigarette smoking see smoking
cimetidine, bladder pain syndrome, 1483
cingulate gyrus and cortex, anterior (ACG), 217, 221
imaging, 606
circumcision, female, 1424
circumferential fistulas, 1445
cisapride in FI, 1352
neurogenic patients, 868
Parkinson’s disease, 890
clam cystoplasty, 849
clamps, penile, 1575, 1576
historical accounts, 29-30
cleaning/cleansing
commodities or bedpans, 1536
intermittent catheters, 1583-4
clenbuterol
overactive bladder, 658
SUI, 673
clinical data, baseline, ICS Standardization Committee recommendations, 1730
clinical trials see trials
clinicians observations in research, ICS Standardization Committee recommendations, 1731
cloacal nerve, dorsal, electrical stimulation, 535
cloacal extrophy, 745
Clostridium difficile-associated diarrhoea, 1347, 1366
management, 1372
coatings
for recurrent SUI, 1225
open, 1197-8
Burch see Burch colposuspension
cost-effectiveness compared to laparoscopic colposuspen
dion, 1208, 1698-9
Marshall-Marchetti-Krantz procedure vs, 1202
mid-urethral tapes vs, 1218
for recurrent SUI, 1225
sling procedures vs, 1212
rectus fascia sling vs, 1752
tension-free vaginal tape compared with, 1752, 1753
comfort
drainage bags, 1562
indwelling catheters, 1600
pads, 1556
commodities, 1526, 1535-7
communication, continence promotion programmes, 1649
community
absorbent bodyworn products in, evaluation, 1550, 1551
acute or subacute care to, 1656
fistula prevention in, 1436
comorbidity and pre-existing medical conditions
bladder dysfunction and, 225
FI associated with, 78, 1333-4, 1338-9, 1340, 1365-6, 1367-70
frail elderly with UI, 970-5, 983
research, 1739
role in management, 978, 1000
nocturnal enuresis and, 42
POP associated with see pelvic organ prolapse
see also cost of illness; disabilities
complementary and alternative medicine/therapy
females
POI, 1105, 1106
UI, 1079
FI, 1343
male UI, 1093-4
literature search strategies, 1108
compliance (distensibility)
bladder/detrusor, 132, 133, 428-9
child, 712
low drug therapy, 820, 821-2
normal values, 428-9
obstructed labour adversely affecting, 1430
rectal, assessment, 488, 493-6
compliance (with treatment) see adherence
complications, of procedures see safety aspects
compression devices, urethral (males) see males
computerised tomography (CT)
CNS, 605-7
upper urinary tract, 548
COMS (Continence Outcomes Measures) Dissemination Project
(Australia), 1649
concentric needle electromyography (CNEMG), 527-9
condom catheters (penile sheaths; uridomes), 421, 820, 1529,
1557-61
applications, 421
product categories and features, 1558
results, 1558-9
conduction see nerves
conduit urinary diversion see non-continent urinary
conflicts of interest
in conduct and reporting of research, 1757-8
financial, 1757
congenital/anatomic anomalies
anorectal see anorectum
CNS, 459-61, 741, 912-16
colonic aganglionosis (Hirschsprung’s disease), 138
LUT, 463-5
surgery, 745, 1153
connective tissue
diseases, and POP, 280
injury in childbirth, 266
in pregnancy, POP aetiology related to, 282
connexin, 124
conscious perception of input from body as aspects of homeostasis,
230-1
consent, informed see informed consent
conservative/medical management
FI, 1341-50, 1353-61
frail elderly, 1370-3
meningomyelocele, 914-15
neurogenic, 867-70
surgery with failure of, 871
fistulas in women, 1437-9
outpatient, economic analysis, 1700-2
research see research
surgical vs, decision tree, 1692
UI and LUT problems, 811-29, 1025-120
historical accounts, 23
men, 1082-95, 1108
neurogenic LUT dysfunction, 811-29
older people see older people trials see trials
women, 1027-82, 1107-8
women with non-obstetric fistulas, 1249
women with POP, 1095-107, 1108
see also specific methods
consistency, internal, questionnaires, 366
Consolidated Standards of Reporting Trials see CONSORT
CONSORT statement/guideline, 1718, 1726, 1727-8, 1749, 1751,
1752, 1753
flow diagram, 1726, 1728, 1749, 1752
constipation, 1334
assessment and quantification
children, 708
older people, 1367-9
children, 42, 765
with enuresis, 43
management, 770
quantification, 708
FI due to see overflow FI
neurological patients
dementias, 882-3
drug therapy, 868
spinal cord injury, 862
women with
effect of lifestyle interventions on UI in, 1033
POP and, 82, 283, 1096, 1097
content validity of questionnaires, 366
Contilife®, 378
continence
advocacy, 1652-8
age-related changes affecting, 966
awareness, promotion, 1645, 1646-58
preventive aspects, 1666-7
factors maintaining, 137
oestrogens, 676
males
mechanisms, 300-2
post-prostatectomy recovery, 306
organisations see organisations
POP surgery combined with treatment of, 1294-5
post-fistula closure, status, 1449
continence gap, 1448
in sneezing, neural mechanisms, 194
urethral reconstruction to achieve, child, 752-3
Continence Association
Danish, 1680
New Zealand, 1681
South Africa, 1682
continence care see care
Continence Care Pathways, 1662
continence centre (L-region), pontine, 212, 220
cortex (cerebral), correlation coefficient, 1694

coronary heart disease, 61

coordination training (in FI management), 1353

cooling test

Conveen Continence Guard, 1573, 1574

conus (medullaris) lesions, 799, 898-9

controlled studies and trials

Contrelle Activgard (Conveen Continence Guard), 1573, 1574

contraction, 637-8

Continence Society

Continence Outcomes Measures (COMS) Dissemination Project, 1649

Continence Promotion Committee (CPC) of ICS, 1657

continence reflex (guarding reflex), 189, 192, 197, 215

Continence Society

Hong Kong, 1680

Indonesian, 1680

Taiwan, 1682

continent urinary diversion, 855-7

child, 749

psychological consequences, 759

in extrophy-epispadias complex, 1144

neurogenic LUT dysfunction, 855-7

continuing medical education (CME), 1660, 1665

continuous UI, definition, 334

ConTIPI, 1574

contractile properties of LUT smooth muscle, 135-6

detrusor, 132

age-related changes, 967

changes in bladder outlet obstruction, 260

contraction, 637-8

detrusor (bladder) smooth muscle, 121-6, 637-8

physiology, 121-6, 132, 637-8

spontaneous, 123-5, 262-3

strength assessment in geriatric patients, 471

surgery increasing contractility, 838

external anal sphincter, voluntary, pressure on, 481-5

pelvic floor muscle

ultrasound assessment, 564-5

voluntary see pelvic floor muscle training

urethral smooth muscle, 127

neuronal control, 127

urethral sphincter see urethral sphincter

Contrelle Activgard (Conveen Continence Guard), 1573, 1574

controlled studies and trials

non-randomised, 1716

randomised see randomised controlled studies

comas (medullaritis) lesions, 799, 898-9

lesions, therapy, 812

Conveen Continence Guard, 1573, 1574

cooling test see ice water test

coordination training (in FI management), 1353

coronary heart disease, 61

correlation coefficient, 1694

cortex (cerebral)

bladder function and, 207-21

interceptive, spino-thalamic input to, 230

motor, spino-thalamic input to, 230

cost(s) (and economic/financial issues), 1685-712, 1735-6

analysis/measurement/determination, 1685-712, 1735-6

types, 1690-5

artificial urinary sphincter, 1160

barrier products preventing dermatitis, 1624

country-specific issues, 1689-90

FI, 1707-8

frail elderly UI treatment, 980-1

future research priorities, 1708-9

pads, 1557

washable, 1557

practical aspects of economic analysis, 1695-6

summary of recent economic analysis, 1697-704

women with UI, 62

outcome of surgery, 1254

see also funding; socioeconomic factors

cost-benefit, 1691, 1736

antimicrobial-impregnated catheters, 1594-5

frail elderly UI treatment, 980-1

sacral nerve stimulation in FI, 1402

cost consequence analysis, 1691

cost-effectiveness, 1691, 1695, 1735

botulinum toxin A in neurogenic detrusor overactivity, 666

surgical treatment of UI, 1208, 1697-8

cost minimisation analysis, 1690

cost of illness studies, 1687, 1687-8, 1690, 1735

FI, 1707

cost-utility analysis, 1691, 1696-7, 1735

cotton swab (Q-tip) test, 343, 343-4, 348, 1738

coughing, 60

smokers, 60

stress test (leak point pressure measurements), 433, 442, 443, 444

frail elderly, 977

in women after UI surgery, 1253

counselling, children, 769

CPC (Continence Promotion Committee) of ICS, 1657

cranberry supplement in UTI prevention, 904, 1597

with indwelling catheters, 1596, 1597

with intermittent catheters, 1582

creatinine, serum, measurement in men, 352

Crédé manoeuvre, 813-14

Crohn’s disease and FI, 1334

cross-infection risk, urine drainage bags, 1564-5

cross-sectional studies of surgery, 1751

cryoablation surgery of prostate, 1140

urethrorectal fistula after, 1153, 1155

culdoplasty, Mayo, 1286

cultural aspects

female UI, 47

nocturnal enuresis, 42

patient-reported outcome questionnaires, 367

Cunningham clamp, 1576

current perception threshold tests, neuroselective, in spinal cord injury, 901

cutaneous care/problems etc. see skin

cutaneous continent urinary diversion, 856

cyclo-oxygenase inhibitors see non-steroidal anti-inflammatory drugs

cyclosporine, bladder pain syndrome, 1483-4

cystectomy

radical, neobladder following see neobladder

subtrigonal, and cystoplasty in bladder pain syndrome, 1494

supratrigonal see supratrigonal cystectomy

and urethrectomy, urinary diversion with/without, in bladder pain syndrome, 1494

cystitis (bladder inflammation)
interstitial see bladder pain syndrome
reduced bladder capacity in, 1151
cystocele see vaginal wall prolapse, anterior
cystodistension (hydrodistension; overdistension), 1237-8
in bladder pain syndrome, 1477, 1502-3
in chronic pelvic pain, 1492
cystolysis, bladder pain syndrome, 1492
cystometric capacity, maximum, child, 712
cystoscopy, 419, 426-30
adjacents to, 440
bladder pain syndrome, 1475
bladder sensation assessment during, 534
filling see filling cystometry
frail elderly, 470, 471
neurogenic LUT dysfunction, 804-6
normal values, 426-30
spinal cord injury, 900
voiding, 419
cystopathy, diabetic, 916-17
cystoplasty (bladder reconstruction/augmentation/enlargement - reservoirs, pouches etc.), 747-50, 849-55, 1239-40
in bladder pain syndrome, 1493-4
children, 747-50
in neurogenic dysfunction, 458, 459
psychological consequences, 759
techniques, 748-9
in detrusor overactivity, 1239-40
complications, 1242
fistulas (non-obstetric), 1251
in neurogenic dysfunction, 849-55
children, 458, 459
see also auto-augmentation; neobladder
cystoscopy see endoscopy
cystotomy, continent, 855-6
cystourethrography, voiding (VCUG), 550
child, 710-11
with daytime and night-time wetting, 466
combined with urodynamics see videourodynamics
female, 551-7
methodology, 551-9
non-obstetric fistulas, 1248, 1249
urethral diverticulum, 1246
see also urethrography
men, preoperative, 1124
other imaging methods compared, 557, 593
cystourethroscopy, historical accounts, 29
cystourethroscopy see endoscopy
cytology, urine, males, 352
Czech Republic, continence organisation, 1680

D

Da Vinci, Leonardo, 22
Dacron®-reinforced silicon sling, 1212
Daily Living Self Management Project (Australia), 1697
Danish Prostatic Symptom Score (DAN-PSS), 377, 378
darifenacin, 648-50, 822, 1703
adverse effects, 649
elderly, 682, 994
economic analysis, 1703
elderly, 994
adverse effects, 682, 994
data
baseline clinical and demographic, ICS Standardization Committee recommendations, 1730
collection, in trials, mistakes, 1719
interpretation/analysis, 1725-7
intention-to-treat vs per-protocol approaches to, 1724-5
mistakes, 1719
quality, transient UI in older people, 309
Data Safety Monitoring Board, 1722, 1757
daytime and night-time wetting, co-existent (non-monosymptomatic nocturnal enuresis), 38, 43-5, 726-40, 761, 763-4
assessment, 728
causes/risk factors, 761
classification, 729-34
confounding factors, 728-9
epidemiology, 38, 43-5, 727-8, 761
prevalence, 727-8
therapy, 734-40
voiding cystourethrography, 466
daytime frequency (=frequency of daytime micturition), measuring, 336
daytime frequency (=frequent micturition), definition, 334-5
daytime wetting (diurnal enuresis), 763-4
bladder training, 1078
bowl problems and, association between, 43-5
night-time and see daytime and night-time wetting
risk factors and causes, 45-6
urodynamic studies, 465-6
DDAVP see desmopressin
deaths/mortalities
terocytecystoplasty, 850
obstetric fistula-related, 1446
SUI surgery-related, 1236
decision analysis, 1691-4
decision tree, 1692-3
decompression surgery, lumbar disc prolapse, 912
decubitus (pressure) ulcers, 1620-1
deep brain stimulation, 827-8
defaecating proctography see defaecography
defaecation (bowel/rectum evacuation)
assistive techniques, 868-9, 1349
forces, 500
inappropriate see faecal incontinence
physiology/mechanism, 137
reflex-triggered, 868
by mechanical stimulation, 867, 867-8
training, 1349
urgency see urgency
defaecography (defaecating/evacuation proctography), 612
in POP, 285
definitions and terminology, 334-5
bladder pain syndrome, 1461-2, 1464-6, 1503, 1745
enuresis, 38-46
nocturnal, 38-9, 713
in epidemiological studies, 38
differing/varying, 86-7, 93
female UI, 46, 47
FI, 1323
frailty, 964
male UI, 65
POP 80, 1746, 1747
storage symptoms, 334-5
degenerative joint disease, frail elderly, 971
defenibulation, 1424
delirium, older people, 309
delivery, fistula numbers per 1000 deliveries, 1426
see also Caesarean delivery; childbirth; instrumental delivery
Delorme procedure, 1307-8
dementia, 877-83
constipation and FI associated with, 882-3, 1338, 1365
caregiver education in prevention of, 1342-3
treatment, 1371
LUT problems/UI risk, 800, 877-82, 970-2
with cholinesterase inhibitors, 682, 983
men, 69
women, 59, 60
demographic data
baseline, ICS Standardization Committee recommendations, 1730
frail older and disabled people with UI/LUTS, 1739
demyelination
  in Guillain-Barré syndrome, 801, 909-11
  in multiple sclerosis, 801
denervation (pathological) see nerve injury
denervation (technique)
  in bladder pain syndrome, 1493
  in detrusor overactivity, 838-42
  women, 1238-9
Denmark, continence organisation, 1680
depression (and LUT dysfunction), 225, 1668
  spinal cord injury, 902
  SUI surgical outcome in, 1224
  UI risk, 60, 1668
  frail elderly, 971, 972-3
dermal collagen, porcine
desmopressin (dDAVP), 679-81
desipramine, bladder pain syndrome, 1483
descriptive epidemiology, 37
descending pathways/tracts
dermatomes, lower spine, 803
dermatology see skin
dermatomes, lower spine, 803
descending pathways/tracts
  anal and urethral rhabdosphincters and, 189
  homeostatic reflexes and feelings and, 231, 233-4
descriptive epidemiology, 37
desipramine, bladder pain syndrome, 1483
desmopressin (dDAVP), 679-81
  nocturia, older people, 1001
  nocturnal enuresis, 721-2, 771
  and alarm, 725
  non-responders, 725
detrusor (bladder wall smooth muscle)
  activation and contraction see contractile properties; contraction
  biomechanics, 132-7
  botulinum toxin A injection, 661, 662, 663
  compliance see compliance
  EMG in neurogenic LUT dysfunction, 808-9
  hyperreflexia see neurogenic detrusor overactivity
  ion channels, 122, 144
  myectomy/myotomy see auto-augmentation
  overactive see detrusor overactivity
  preoperative functional assessment, men, 1125
  relaxation, 123
  urethral sphincter contraction and, disorders of see detrusor-sphincter dysfunction; detrusor-sphincter dyssynergia
  strengthening surgery, 838
  underactive see underactive bladder
  urothelial/suburothelial interactions with, 120
  see also smooth muscle, bladder wall
detrusor overactivity (hyperreflexia), 429, 434-8, 639-72, 1145-9, 1237-45
  bladder training, 1075
  children, 726, 727, 730, 742
  neurogenic see neurogenic detrusor overactivity
  nocturnal, 717
  resistance to therapy, 744
  and underactive sphincters, 742, 744
definition of outcome in women, 1738
diagnosis, 434-40
  distinguishing and defining characteristics, 438-9
  drug therapy see drug therapy
electrical stimulation, men, 1088, 1089-90, 1149
electrical stimulation, women, 1060, 1061, 1062, 1063, 1064, 1065
  and/or pelvic floor muscle training, 1066
  filling cystometry, 434-6
  idiopathic, 664-5
  botulinum toxin A, 664-5
  men, management, 1145-9
  resiniferatoxin, 667-8
  incontinence due to, 434
  urodynamic studies, 434-5
  magnetic stimulation
  men, 1145
  women, 1065
  men, 1145-9, 1161
  electrical stimulation, 1088, 1089-90, 1149
  idiopathic, 1145-9
  men, surgery, 1149
  older men, 1138
  neural mechanisms, 222-4
  see also neurogenic detrusor overactivity
  non-neurogenic, 259-64
  in normal subjects, 429
  pathogenesis, 636
  and sphincter underactivity/areflexia, 812
  children, 742, 744
  conservative management, 812
  in spinal canal stenosis, 909
  SUI surgical outcome in patients with, 1226-7
  surgery, 1237-45
  complications, 1242-5
  denervation procedures, 838-42
  men see subheading above
  women, 1237-45
  urodynamic studies, 434-8
  men, 450-1
  therapeutic response prediction, 441-2
  see also overactive bladder
detrusor pressure measurement, neurogenic LUT dysfunction, 804
detrusor-sphincter dysfunction, neurogenic, children, 740-4
  children, 742
  EMG, 532
  spinal cord injury, 901
  treatment, 904
  surgery, 833
  urodynamic studies, 456
Deutsche Kontinenz Gesellschaft e.V., 1680
developing world
  obstetric fistula see fistula
  services in, 1656
development
  bladder/sphincter control, 703-4
  delayed
  and daytime enuresis, 45
  and nocturnal enuresis, 42
developmental reflexes in Alzheimer’s disease, 878
devices see continence devices
dextranomer-hyaluronic acid co-polymer see hyaluronic acid-dextransomer co-polymer
diabetes mellitus, 801, 916-17, 1667
  children, and nocturnal enuresis, 42
  FI, 917, 1339, 1365
  UI, 801, 916-17
  frail elderly, 971
  lifestyle management of weight, 1029
  risk, 1667
  risk, women, 58
Diablo™ , 836
diacylglycerol (DAG), 128, 129
diagnostic tests
  children, 707-12
  invasive, 710-12
  non-invasive, 707-10
  neurogenic FI, 864-6
  neurogenic UI see neurogenic LUT dysfunction
  screening tools see screening
  urodynamic studies as, 433, 434-40
  see also assessment; investigations
  diaphragm, chronic pelvic pain, 1491
  diaper(s)/briefs (adult/all-in-ones), 1540, 1553
  frail elderly, vs other methods, 979-80
  with superabsorbent polymers, 1621-3
  diaphragms, intravaginal bladder neck-supporting, 1572-3
The page contains a list of medical terms and concepts, mainly related to pelvic floor dysfunction and neurostimulation therapies. Some key terms and concepts include:

- **Electrical stimulation (and neuromodulation)**: Techniques used to treat pelvic floor disorders.
- **Elderly**: Population group often affected by pelvic floor issues.
- **Elastin**: Structural protein involved in vaginal and supportive tissues.
- **Dyspareunia**: Painful sexual intercourse.
- **Dysfunctional Voiding**: A type of urinary problem.
- **Dynamic Muscle Transposition (DST)**: A surgical technique for treating pelvic floor disorders.
- **Dysport**: A botulinum toxin used in medicine.
- **Duloxetine**: A medication used for various conditions.
- **Dry Bed Training**: A type of bladder training.
- **Dynamic MRI**: Imaging technique used in pelvic floor research.
- **Ectopic Ureterocele**: A birth defect involving the ureter.
- **Ectopic Ureter**: An abnormal ureter location.
- **Electrodiagnostic Tests**: Tests used to diagnose neurological disorders.
- **Electroencephalography (EEG)**: A test to record the electrical activity of the brain.

The page also includes references to various studies and treatments, such as:

- Recommendations for practice based on literature searches.
- Future research directions in pelvic floor disorders.
- Economic analyses of treatments for pelvic floor problems.

Various medical conditions and procedures are mentioned, such as detrusor overactivity, neurogenic injury, and bladder pain syndrome. The text also references specific therapies and treatments, indicating a comprehensive approach to pelvic floor management.
Frykman-Goldberg operation, 1308-9
fructose, dietary, 1347
frontotemporal dementia, 881-2
frontal lobe, in bladder control, 216-17
frequency/volume diary (bladder/voiding diary), 337, 1733, 1734
frequency/volume chart (bladder chart)
frequency (=frequent micturition), measuring, 336
Frank (German doctor in 1882), 27
France
frail elderly persons, 468-73, 961-1024, 1362-73
four-dimensional ultrasonography, 559
forebrain interoceptive representation, 231
forceps delivery, trauma, 297-8
force(s), defaecation, 500
footdrop, 1434
forceps delivery, trauma, 297-8
forebrain interoceptive representation, 231
four-dimensional ultrasonography, 559
frail elderly persons, 468-73, 961-1024, 1362-73
aetiology of UI, 965-75, 1009, 1739-40
assessment see assessment
definition of frailty, 964
FI, 1362-73, 1376
impact of UI on morbidity and institutionalisation, 964-5
LUT dysfunction, outcome measures, 1740
management of UI, 977-97, 1010-12
algorithm, 1010-12
factors in, 977-84
models of care, 1001-5
pharmacological see drug therapy recommendations, 1005-9
special issues, 983-4
surgical see surgery
nocturia see nocturia
prevention of UI, 1669-70
research see research
urodynamic studies, 468-73, 977
France
continence awareness and promotion, 1651
continence organisation, 1680
Frank (German doctor in 1882), 27
frequency (=frequency of micturition), measuring, 336
frequency (=frequent micturition)
daytime, definition, 334-5
see also urgency/frequency
frequency/volume chart (bladder chart)
children, 707-8
nocturnal enuresis, 719
frequency/volume diary (bladder/voiding diary), 337, 1733, 1734
children, 706, 707
neurogenic LUT dysfunction, 802
women, postoperative (after UI surgery), 1253
frontal lobe, in bladder control, 216-17
frontotemporal dementia, 881-2
fructose, dietary, 1347
Frykman-Goldberg operation, 1308-9

FSFI (Female Sexual Function Index), 397-8
full spectrum home training in nocturnal enuresis, 770-1
functional brain imaging, 583
bladder control studies, 216-20
visceral stimuli, 231-3
functional control of tissue-engineered grafts, 151
functional disorders of LUT see lower urinary tract dysfunction
functional FI, older people, 1365
functional impairment (mobility restriction; physical disability)
FI risk, 1331
research, 1739
UI risk
men, 69
older people, 311, 972, 973-5
women, 59, 64
functional incidental training, 986
functional outcome, enterocystoplasty, 853
functional status in FI, assessment, 354
functional UI, children
classification, 713
prevalence, 42-5
funding, fistula care in developing world, 1450

G

G-proteins and G-protein coupled receptors, 140, 142, 637
GABA (gamma-aminobutyric acid - and its receptors), 201
GABA receptors, 142, 194
agonists in detrusor overactivity, 668-70
urethral and anal sphincter, 194
GABA
bladder pain syndrome, 1481
chronic pelvic pain, 1491
UI, 671
α-galactosidase, oral, 1627
Galen, Claudius, 21
gamma-aminobutyric acid see GABA
ganglia, bladder, 198-200
gastric augmentation see stomach
gastrointestinal tract (gut)
brain interactions with, 225-34, 231-2
disorders, intestinal segment removal causing, 756
in FI, 285-90
lower see bowel
reconstruction using see neobladder
research recommendations, 151
see also specific regions e.g. bowel
Gellhorn pessary, 1102, 1103, 1104, 1105, 1106
gender (sex)
AI and, 74
care-seeking behaviour and, 1647, 1648
continence devices and, 1525
bodyworn absorbent, 1552
nocturnal enuresis and, 41, 715
see also females; males
general anaesthesia for POP vs local anaesthesia, 1707
general practitioners see primary care
genetic factors (in disease)
bladder pain syndrome, 1471
nocturnal enuresis, 714-15
POP, 83, 84, 280
UI, women, 61, 64, 65, 83
SUI, 275-6
genal herpes, 801
genitalia/genital organs
afferent projections to spinal cord, 182-4
female
injury in obstructed labour, 1431-3
mutilation, 1424-5
physical examination, 342
indwelling catheters, transurethral (and in general), 818-20
indwelling catheters, suprapubic, 819-20, 1578, 1588, 1589, 1606
Indonesian Continence Society, 1680
Indian Continence Foundation, 1680
India, obstetric fistulas
Indevus Urgency Severity Scale (IUSS), 389, 390
independence as factor with continence devices, 1525
incremental costs in SUI, 1701-2
Incontinence Screening Questionnaire (ISQ), 385
Incontinence QoL (I-QOL) index, 379, 390
Incontinence Outcome Questionnaire, 379
Incontinence Impact Questionnaire (IIQ) and IIQ-7, 379, 380
Incontinence Bothersome Scale (IBS), 378
Incontinence Action Group, 1660
incontinence
Inco Forum
inclusion criteria in trials, 1721-2
common mistakes, 1719
Inco Forum
Czech Republic, 1680
Poland, 1681
Slovakia, 1682
incontinence see faecal incontinence; urinary incontinence
Incontinence Action Group, 1660
Incontinence Bothersome Scale (IBS), 378
incontinence devices and products see continence devices
Incontinence Impact Questionnaire (IIQ) and IIQ-7, 379, 380
Incontinence Outcome Questionnaire, 379
Incontinence QoL (I-QOL) index, 379, 390
Incontinence Screening Questionnaire (ISQ), 385
incremental costs in SUI, 1701-2
independence as factor with continence devices, 1525
pads, 1557
Indevas Urgency Severity Scale (IUSS), 389, 390
India, obstetric fistulas
fistula centres, 1446
prevention, 1437
Indian Continence Foundation, 1680
Indian system/pouch/reservoir, child, 754
Indonesian Continence Society, 1680
indwelling catheters, suprapubic, 819-20, 1578, 1588, 1589, 1606
indwelling catheters, transurethral (and in general), 818-20, 1585-606, 1610
catheter characteristics, 1588-9
catheter maintenance solutions, 1598, 1602, 1604
catheter management strategies, 1600-2
catheter materials, 1589-90
in prevention of encrustation, 1596-8
catheter size, 1590
complications, 818, 1590-600, 1602-6
infections see urinary tract infections in spinal cord injury, 901
drainage bags, 1564-6, 1602, 1608
females, 1528
infection risk, 818, 1564-6
intermittent catheters compared with, 1584-5
long-term, 1578, 1585, 1587-8, 1599-600
males, 1529
neurogenic UI, 818-20
multiple sclerosis, 896
spinal cord injury, 903
prevalence of use, 1587
research priorities, 1611
safety aspects see safety aspects
short-term, 1578, 1585, 1587
in urodynamic studies, children, 467
user characteristics, 1587-8
infants (incl. neonates)
bladder/sphincter control, development, 703-4
intermittent catheterisation, 742
size (at birth), and FI risk, 1337
infections
urinary see urinary tract infections
urothelium in, 117
wound, in SUI surgery, 1236
see also antibiotics
infertility and obstetric fistulas, 1432-3
infibulation, 1424
inflammation
bladder dysfunction in, 222
in bladder pain syndrome aetiology, 222, 1469
in neighbouring pelvic organs, 203-5
prostate, age-related occurrence, 970
inflammatory bowel disease and FI, 1334
information, public, 1650-1
media in dissemination of, 1649-50
sources, 1680-3
see also education
informed consent (in trials), 1722
for new surgical procedures, 1753
Ingelman-Sundberg denervation, 1238-9
inheritance see genetic factors
Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), 1501, 1501
injection
botulinum toxin see botulinum toxin
bulking agents/biomaterials
anal canal, 1403-5, 1408
urethral/periurethral see bulking agents
denervating agents see bladder, denervating agents
injury (predominantly traumatic/mechanical)
bladder
in obstructed labour, 1429-30
in SUI surgery, 1232-3
brain, FI, 863, 1339
cauda equina see cauda equina lesions
childbirth-related see childbirth
fistula due to obstetric, 1422-5, 1429-31
rectourethral, 1153-4
iatrogenic see iatrogenic damage
levator ani, 583-6
ultrasound, 565-7, 571
nerve see nerve injury
pelvic floor see pelvic floor
renal, with obstructed labour, 1431
spinal see spinal cord lesions
ureteric, with obstructed labour, 1431
urethral
incontinence after, men, 1141-2
with indwelling catheters, 1599
with intermittent catheterisation, 1582-3
with obstructed labour, 1430-1
with SUI surgery, 1232
urothelial response to, 170-1
vaginal, with obstructed labour, 1431-2
Inko Forum, 1680
innervation see nerve supply
inositol trisphosphate (IP3), 128, 142-9
inserts
external (liners; shields), 1538-40
light UI, females, 1545, 1547
light UI, males, 1548, 1549
moderate/heavy UI, 1550, 1551, 1552, 1553
urethral, 1570-2
institutional care (elderly) see nursing home
instrumental delivery, 297-8
intravesical drugs and chemicals (transvesical instillation/injections), 822-4
atropine, 822-3
BCG, in bladder pain syndrome, 1487
botulinum toxin A, 661-2, 663, 665
in bladder pain syndrome, 1488
men, 1146
chondroitin sulfate, in bladder pain syndrome, 1487
DMSO in bladder pain syndrome, 1486-7
heparin, in bladder pain syndrome, 1487
hyaluronic acid in bladder pain syndrome, 1487
lidocaine, in bladder pain syndrome, 1487
in neurogenic LUT dysfunction, 822-4
nociceptin/orphanin FQ, 822
oxypurinol, 655, 822
in bladder pain syndrome, 1488
children, 743
frail elderly, 992
pentosan sulfate, in bladder pain syndrome, 1487
phenol, 1238
propapheine, 822
vaniloids, 666-8, 823
in bladder pain syndrome, 1487-8
spinal cord injury, 903-4
intravesical electrical stimulation (and neuromodulation), 24, 828-9
children, 743
in neurogenic FI, 869-70
meningomyelocele, 915
intravesical potassium chloride challenge, 1475-6
intravesical pressure (bladder pressure)
difference between urethral pressure and see urethral closure pressure
with involuntary leakage of urine see leak point pressure measuring, 419
urethral flow rate and, relationship see pressure-flow studies
see also filling cystometry
intrinsic sphincter deficiency see urethral sphincter
Introduction to Responsible Conduct of Research (US Office of Research Integrity), 1756
Introt, 1573-4
invasive diagnostic procedures, enuresis, 710-12
investigations (sophisticated testing), 413-630
correlation with symptoms in females, 340-1
fistula evaluation, 1435
see also diagnostic tests
ion channels, 145-9
detrusor, 122, 144
as molecular targets, 652-3
novel agents, 144-9
see also specific ions
IOQ (Incontinence Outcome Questionnaire), 379
IPSS (International Prostate Symptom Score), 351, 352, 386, 400
I-QoL (Urinary Incontinence QoL Scale), 379, 382
irritable bowel syndrome, 232, 233, 234
postpartum, 299
irritative agents, bladder, animal studies, 223
ischaemic heart disease, 61
ischio cavernous muscle, innervation, 188
isotopic scans, upper urinary tract, 549
ISQ (Incontinence Screening Questionnaire), 385
Israel
family physicians, 1656
National Center for Continence, 1655, 1681
Italian version of Female Sexual Function Index, 398
Italy, continence organisations, 1681
IUSS (Indevus Urgency Severity Scale), 389, 390
Kappa opioid receptor agonists, 181
Kegel’s exercises see pelvic floor muscle training
Kelly, Howard A, 28
Kerala, obstetric fistula prevention, 1437
KHQ (King’s Health Questionnaire), 380, 382
kidneys
  function
    intestinal reservoir effects on, 756-7
    paediatric neurogenic bladder and monitoring of, 744
    imaging, 546, 548, 549
  injury with obstructed labour, 1431
stones see stones
transplantation in myelodysplasia, 459
Kinesiological EMG, 529-31
King’s Health Questionnaire (KHQ), 380, 382
kinking of external continence devices
  see anti-kinking features
knowledge of nurses about incontinence, levels of, 1662-3
Kock pouch
  child, 754
  complications, 757
Kontinensoreningen (Danish Continence Association), 1680
Korea Continence Foundation, 1681
Kropp procedure, 845

L

L-region (continence centre), pontine, 212, 220
laboratory examination
  bladder pain syndrome, 1475
  nocturnal enuresis, 720-1
labour
  epidural analgesia, 268-9
  obstructed (and consequent injury and fistula development), 1422, 1429-34
  prevention of fistulas, 1436
second stage
  management affecting continence, 1668
  prolonged, FI risk, 1337
  see also childbirth
lactose, dietary, 1347
  intolerance (and lactase deficiency), 1347
  older people, 1366
lamina 1 afferents, 227, 228, 230, 231
language
  in questionnaires, 367
UI prevalence in women and, 47
laparoscopic surgery
  non-obstetric fistula, 1251
POP surgery, 1278
  colposuspension see colposuspension
sacrocolpopexy, 1286
ventral rectopexy, 1309
radical prostatectomy, 1128
laser surgery/resection
  prostate, and UI risk, 1136
urodynamic studies, 451
urethral sphincter, 837
latex catheters, 1589
laughter (giggle) incontinence, 732-3, 764
laundry facilities for continence devices, 1525, 1557
laxatives, 1352, 1375
  children with neurogenic detrusor-sphincter dysfunction, 743
  older people, 1371
  overuse, 1566
Le Fort colpocleisis, 1292
leaves/leafs, male (pouches), 1540, 1548, 1549
  leak point pressure, 432-4
abdominal, 419
  in coughing see coughing
  detrusor see detrusor leak point pressure
men, preoperative, 1124-5
reliability, 433-4
severity of UI and, correlation studies, 443
in SUI, influencing surgical outcome, 446, 1228
Valsalva, 274, 422, 432, 433, 443, 444, 446
leakage
  stools
    passive, 353
  products preventing or containing, 1612-18
  urine
    assessment with continence devices, 1533
    bladder pressure with involuntary leakage of see leak point pressure
    with pads, freedom from, 1552, 1556
learning disability/mental retardation, 800
FI risk, 1338
nocturnal enuresis and, 42
see also cognitive impairment
leaves/leafs, male (pouches), 1540, 1548, 1549
leg bags, 1561-2, 1562, 1563, 1564, 1565
Leicester Impact Scale (LIS), 380, 382, 1735
Leicester Urinary Symptom Questionnaire (LUSQ), 383, 385
length-tension relationship in LUT smooth muscle, 135
Leonardo da Vinci, 22
leucotomy and bladder control, 217
leukotriene antagonists, bladder pain syndrome, 1485-6
levator ani muscles, 582-3, 583-6
  female
    childbirth effects, 266, 267, 565-7, 586-8
    innervation, 184-8
    myorrhaphy, 1286
    pelvic organ prolapse and, 187-8
    racial differences, 588
    hiatus, size changes, imaging, 586
    innervation, 197
    female, 184-8
MRL, 582-3
  defects/injury and bulk, 583-6
  plate angle change, imaging, 586
  ultrasound of trauma, 565-7, 571
levator ani nerve, 184, 186
  continence in sneezing and, 194
levodopa, 887, 890
Lewy body dementia, 880-1
lidocaine, bladder pain syndrome, 1488
life expectancy, remaining, treatment of frail elderly and role of, 978
lifestyle
  continence devices, 1525
  pads, 1557
lifestyle interventions
  FI, 1341-3, 1374
  frail elderly, 984
  recommendations, 1007-8
  men, 1083-4
  future research directions, 1094
  literature search strategies, 1108
  recommendations for practice, 1094
  women with POP, 1095-7
  literature search strategies, 1108
  recommendations for practice, 1106
  women with UI, 1028-34
  future research directions, 1081
  literature search strategies, 1107
  recommendations for practice, 1079
ligaments (pelvic region)
  sacrospinous see sacrospinous ligament suspension
  uterosacral, suspension, 1280, 1286
limbic behavioural motor cortex, spino-thalamic input to, 230
liners see inserts
pathophysiology of UI, 299-308
pelvic trauma, 1141-2, 1169
physical examination, 351-2
digital rectal examination, 347, 351-2
post-void residual urine, determination, 339-40
sexual dysfunction
penile erection see erectile dysfunction
questionnaires in assessment of, 395, 396, 398-9
SUI see stress incontinence
surgery see surgery
urethral occlusion devices, external (compressive), 1575-6
historical accounts, 22, 24, 29-30
with sling, 1129-31
urethral occlusion devices, internal, adjustable balloons, 1131-3
urodynamic studies, 450-5
UII see urge UI
see also boys; gender
Male Urinary Symptom Impact Questionnaire, 380
Male Urogenital Distress Inventory (MUDI), 380
malignancy see cancer
Malone’s antegrade colonic enema see antegrade continence enema
Manchester Health Questionnaire, 394
mandelic acid, 1598
Manchester questionnaires, 385
Manchester Orthogeriatric Distress Inventory, 380
Manchester Overactive Bladder Questionnaire, 380
Manchester Physiological Aging Study (MPAS), 380
Manchester short form, 380
Manchester University Short Incontinence Questionnaire, 380
Manchester urinary assessment scale, 380
Manchester Health Questionnaire, 394
manometry, anorectal, 475-91, 501
devices, 475-6
multiple sclerosis, 898
Parkinson’s disease, 889
position, 476
resting pressure, 476-81
units of pressure in, 476
vector, 486-8
Markov model, 1693-4
Marshall-Marchetti-Krantz (MMK) procedure, 1198-202
marsupialisation, open and transurethral, 1247
Martius flaps/grafts, 1440, 1445, 1446
mass, body see body mass
massage see abdominal massage
mast cells in bladder pain syndrome, 1473
activation, 222, 1469, 1473
counting, 1477-8
male
females, 1567-75
light UI, 1527
males, 1575-6
historical accounts, 22, 24, 29-30
intra-urethral, 1131-3
light UI, 1528
moderate/heavy UI, 1529
mechanical failure of artificial urinary sphincter, 1164
treatment, 1168
mechanical stimulation
bowel evacuation triggered by, 867, 867-8
sacral reflexes on, 536
urothelial role in sensing, 173-5
mechanical trauma see injury
mechanics/biomechanics
bladder wall, 132-7
pelvic floor muscles
MRI assessment, 588
ultrasound assessment, 565
media in continence promotion, 1649-50
medial prefrontal cortex, 221
medial reticular formation, 211
medical conditions, comorbid/pre-existing see comorbid and pre-existing
medical education on incontinence, 1658-9
medical history
in FI aetiology, 354
taking see history-taking
medical management see conservative/medical management
medication see drug
Medizinische Gesellschaft fur Inkontinentenhilfe Österreich, 1680
medullary cone see conus lesions
megacolon, congenital (Hirschsprung’s disease), 138
membrane, ion channels, see specific ions
Memokath™, 836
men see males
meningomyelocele see myelomenigocele
menopausal/postmenopausal women, risk of UI, 60
HRT and, 57-8
menstrual pads, 1544, 1545, 1546, 1547
mental disorders see psychiatric and psychological disorders
mental retardation see learning disability
meperidine (pethidine), chronic pelvic pain, 1491
Mersiline® sling, 1215
MESA (Medical, Epidemiological and Social Aspects of Aging) questionnaire, 385
mesencephalon (midbrain) and bladder function, 202-14
meshes, synthetic
anterior wall prolapse, 1300-1
sacrocolpopexy, 1279
ultrasound aiding implantation, 571
metabolism, intestinal reservoir-related disturbances, children, 755-6
metabotropic receptors, 140-4
metalloproteinases, matrix (MMPs), 627, 628
methadone, chronic pelvic pain, 1491
methotrexate, bladder pain syndrome, 1485
methoxamine, 763
N-methyl-D-aspartate see NMDA
Mexico, continence organisation, 1681
microglia, spinal cord, 183
micturition, 209-13
central pathways controlling, 207, 209-11, 212-13, 214-17, 220, 231, 634
control, development, 703-4
frequency of, 212
dribbling after see dribble
frequency of see frequency
inappropriate see urinary incontinence
off-switching, 212
on-switching, 209-11
see also post-micturition; voiding
micturition reflex (bladder reflex; voiding reflex), 182-3
circuitry/pathways, 212-13, 215
supraspinal see supraspinal pathways
in non-neurogenic detrusor overactivity, changes, 260
ORL receptors and, 180, 181
suppression, 212-13
triggering (triggered reflex voiding), 811, 813
micturition time chart, see also frequency/volume chart
midbrain and bladder function, 202-14
midline fascial plication, 1290
midodrine, 672, 763
mid-urethral tapes see tension-free vaginal tape
Miniguard, 1569
minimal important difference of measure, 366-7
Minimally Clinically Important Change (MCID), women after UI surgery, 1254
minimally invasive surgery of non-obstetric fistulas, 1249
see also endoscopic surgery; laparoscopic surgery
misoprostol, bladder pain syndrome, 1486
Mitrofanoff procedure, child, 753-4
mixed (urge and stress) UI
muscle(s)
muscarinic (M) receptors (for ACh), 118, 120, 123, 128, 140, 149, 157-8
agonists
multiple system atrophy, 885
overflow incontinence, 676
antagonists see antimuscarinics
detrusor overactivity and, 262
as novel molecular targets, 140
spinal cord injury-related LUT problems and, 899
muscle(s)
bioelectrical activity recording see electromyography
denervation see denervation (technique); nerve injury
excision (myectomy) see autoaugmentation
primary disease, EMG, 531
see also pelvic floor muscle; skeletal muscle; smooth muscle

and specific named muscles
muscle relaxants see bladder relaxants
muscle transposition in FI (augmenting anal sphincter action), 1394-6
artificial anal sphincter compared with, 1398
dynamic/stimulated, 873, 1394-6, 1408
neurogenic FI, 873
non-stimulated, 873, 1394-6, 1408
MUSIQ (Male Urinary Symptom Impact Questionnaire), 380
myectomy, bladder see autoaugmentation
myelin loss see demyelination
myelinated afferents, 636
bladder, 176, 636
myelodysplasia (neural tube closure defects), 457-9, 740, 741, 912-16
myelomingocele (meningomyelocele), 460, 804, 805, 863, 912-16, 1741
FI, 863
neurogenic detrusor-sphincter dysfunction, 741
see also spina bifida
myocytes, trigone, 125, 126
myofascial release treatment, bladder pain syndrome, 1480-1
myofibroblasts, 118, 120
myogenic basis/hypothesis of spontaneous detrusor activity, 124, 262
myopathies, EMG, 531-2
myorrhaphy, levator, 186-7
myosin, in detrusor contraction, 121
myosin light chain kinase (MLCK), 121
myosin light chain phosphatase (MLCP), 121, 122
myotony, bladder see autoaugmentation

NAFC (National Association For Continence), 1646, 1647, 1650, 1658, 1682
National Association For Continence (NAFC), 1646, 1647, 1650, 1658, 1682
National Center for Continence (Israel), 1655, 1681
National Continence Management Strategy (NCMS), Australia, 1648-9
National Family Health Survey (India) and obstetric fistulas, 1437
National Health and Nutrition Examination Survey (NHANES) in
US, FI prevalence estimates, 1330
National Institute of Diabetes, Digestive and Kidney
Disorders/NIDDK (on bladder pain syndrome), 1462, 1464
classification, 1480
definitions, 1462, 1464
diagnosis/assessment, 1475, 1475-6
drug therapy, 1483, 1484
National Institute for Health and Clinical Excellence (NICE)
pharmaceutical therapy of overactive bladder, 1702
sacral nerve stimulation, 1244-5
on surgical interventions, 1752
new procedures, 1754
National Institutes of Health (NIH), research on incontinence in
children, 1741, 1742
National Men’s Continence Awareness Project (Australia), 1649
national organisations, 1657, 1658, 1680-3
National Overactive Bladder Evaluation (NOBLE), 349
National Pressure Ulcer Advisory Panel (NPUAP), 1620
natural history of UI in frail older and disabled people, research, 1739
NCMS (National Continence Management Strategy), Australia, 1648-9
Nd/YAG laser sphincterotomy, 837
NEAT device, 1571
needle EMG, 527-9
external anal sphincter, 497, 527, 529, 532
needle suspension (bladder neck), 1202-3
sling procedure vs, 1212
negative binomial distribution, 1694
Nelaton intermittent catheter, 1580
neobladder, orthotopic (reconstruction using other tissue e.g. gas
trointestinal segments), 150
for bladder cancer, 1141
nocturnal enuresis with, 454
tissue-engineered see tissue engineering
see also bowel, bladder reconstruction/augmentation using
neodymium/YAG laser sphincterotony, 837
neonates see infants
neoplasms see cancer; tumours
neosphincter, anal see artificial anal sphincter; muscle transposition
in FI
neostigmine in spinal cord injury, 907-8
nerve(s) (peripheral)
afferent/sensory see sensory nerves
conduction studies, 525, 809
correlation with biology, 525
neurogenic LUT dysfunction, 809
pudendal nerve see pudendal nerve conduction tests
see also neurography
efferent/motor see motor neurones
electrical stimulation (therapeutic) see electrical stimulation
neurophysiological studies see neurophysiological studies
nerve growth factor (NGF), 181
bladder dysfunction/disorders, 223
inflammatory, 222
Na+ channels resistant to, 182
nerve injury/lesions, peripheral (incl. denervation of pelvic floor),
799
in bladder outlet obstruction, 259-60
childbirth-related, 266, 290-1
FI due to, 290-1
concentric needle EMG, 528-9
conservative treatment, 812
iatrogenic, 802, 917-20
in obstructed labour, 1434
patient-reported outcome assessment, 400-1
in POP aetiology, 281
SUI surgery-related, 1235-6
see also neuropathy; reinnervated muscle
nerve roots, sacral see sacral nerve roots
nerve supply (innervation) to LUT, 634-6
anal rhabdosphincter, 188-92
anorectum, 137-8, 138-9, 286
bladder/bladder wall
bladder base and trigone, 126
detrusor contraction and, 123-4
denervation (technique) see denervation (technique)
lesions see nerve injury
levator ani see levator ani
urethra, 127
urethral sphincter see urethral sphincter
see also nervous system
nerve supply (innervation) to pelvic floor in FI pathogenesis, 289
nervous system, 167-253, 634-6, 797
autonomic see autonomic nervous system; parasympathetic
nervous system; sympathetic nervous system
central see central nervous system
enteric see enteric nervous system
regulation by, 167-253, 634-6
see also nerve supply and entries under neuro-
Netherlands (Holland)
continence organisations, 1681
costs, 1690
networking, continence organisations, 1658
neural pathways and control see autonomic nervous system; central
nervous system; enteric nervous system; nerve supply; nervous sys-
tem; parasympathetic nervous system; sympathetic nerv
ous system
nerve growth factor (NGF), 181
nerve injury/lesions, peripheral (incl. denervation of pelvic floor),
799
neural tube closure defects (myelodysplasia), 457-9, 740, 741
neuroactive agents, lower urinary tract, 128-32, 912-16
NeuroBloc® (botulinum toxin B), 666
neurogenic bladder see neurogenic LUT dysfunction
neurogenic detrusor overactivity, 258-9
children
botulinum toxin A, 664, 739
urodynamic studies, 456
drug therapy, 643-5, 820, 821-2
toxins, 661-8
pathophysiology, 258-9
urodynamic studies, 456
children, 457-62
distinguishing and defining characteristics, 438-9
neurogenic detrusor-sphincter dysfunction, children, 740-4
neurogenic FI (neuropathic FI), 861-77
aetiology, 861-3, 877-922, 1338-9, 1365-6
conservative management, 867-70
surgery following failure of, 870
epidemiology, 78, 861-3
management
conservative see subheading above
in specific neurological diseases, 878-922
surgical, 870-7
special diagnosis, 864-6
neurogenic hypotheses
bladder pain syndrome aetiology, 1470-1
spontaneous detrusor activity, 124
neurogenic inflammation and bladder pain syndrome, 222
neurogenic LUT dysfunction and incontinence (incl. neurogenic
bladder), 455-7, 799-861
children, classification, 713
classification, 1702-3
diagnostics and investigations, 802-11, 1743
imaging, 552
urodynamic studies see urodynamic studies
epidemiology and aetiology, 69, 799-802, 877-922
management, 1741
conservative, 811-29
surgery see surgery
research see research
neurogenic sphincter dysfunction or deficiency, drug therapy, 820,
824-5
neurography, sensory, 534
neuroimaging, 605-7
surgical, 870-7
bladder control studies, 216-20
functional see functional brain imaging
visceral stimuli, 231-3
neurokinins (NKs)
neurokinin A, 132, 179-80
neurokinin B, 132, 179-80
neurokinin receptors (and agonists/antagonists), 132, 179-80
NK-1, 132
NK-1 antagonists, 671-2
NK-2, 132, 179-80
NK-3, 179-80
neurological disorders/diseases, 793-960
AI/FI due to see neurogenic FI
bowel in see bowel
comorbid, frail elderly with UI, 970-2
minor, children, associated with day wetting, 45
UI due to see neurogenic LUT dysfunction and incontinence
see also central nervous system; nerve supply and entries under
neurogenic
neurological examination, female IU, 342
neurological injury see nerve injury
neuromodulation, electrical see electrical stimulation
neuromodulators in brainstem controlling bladder function, 213-14
neurones
afferent/sensory see sensory nerves/neurones
continence centre, in brain, 211
efferent/motor see motor neurones
'filling', in brain, 211
signalling see signalling
urothelial-neuronal signalling, 173
neuropathic analgesics, chronic pelvic pain, 1491-2
neuropathy, autonomic see autonomic nervous system
neuropathy, peripheral, 801
diabetic, 916
FIC risk, 1339, 1365
iatrogenic, 802, 917-20
neuropeptide(s), 132
neuropeptide Y (NPY), 199, 199-200, 200
neuropharmacology see drug therapy; pharmacology
neurophysiological studies and tests (incl. electrophysiology), 523-40, 808-11
biological correlates, 525-7
classification of tests, 525
evidence-based use, 537-8
in Fl, 496-8
neuropathic patients Non-continent cutaneous diversion, 865-6
methodological considerations, 526-7
in neurogenic LUT dysfunction, 808-11
spinal cord injury, 899-900
recommendations, 538-9
in research, usefulness, 538
tests used, see also specific tests
urethral function, 275
urethral sphincter see urethral sphincter
neurophysiology clinical see neurophysiological studies
research in see research
neuropathic dysraphism see spinal dysraphism
neurotism and SUI surgical outcome, 1224
neurotoxin see botulinum toxin A
neurotransmitters, 128-31
bladder, 200-2
in brainstem controlling bladder function, 213-14
urethral and anal rhabdosphincters and, 194-5
neurotrophins, 181-2
see also specific types
neurourology, 803
New Zealand Continence Association, 1681
county doctor services, 1656
newborns see infants
NGF see nerve growth factor
NHANES (US), FI prevalence estimates, 1330
NICE see National Institute for Health and Clinical Excellence
nicotine (from smoking), 1031
nicotine receptors, 131, 198
NIDDK see National Institute of Diabetes, Digestive and Kidney Disorders
nifedipine in bladder pain syndrome, 1486
right drainage bags, 1561, 1562, 1563, 1564, 1565
see also entries under nocturnal
NIH, research on incontinence in children, 1741, 1742
nitrergic (NOS-containing) mechanisms, 131
nitric oxide (NO), 126, 131, 179, 659
bladder base and trigone and, 126
bladder pain syndrome pathogenesis, 1471
urethral smooth muscle relaxation, 127
nitric oxide synthase, 131
NKs see neurokinins
NMDA (N-methyl-D-aspartate) receptors, 183
antagonists, in chronic pelvic pain, 1492
cerebrovascular accidents and LUT problems and, 891-2
urethral and anal rhabdosphincters and, 194
N-methyl-D-aspartate see NMDA
NO see nitric oxide
NOBLE (National Overactive Bladder Evaluation), 349
nociceptin/orphin FQ, 180-1
in neurogenic LUT dysfunction, 822
nociception see pain
NOCTOPUS programme, 680
nocturia (waking to void), 335, 1747-8
bladder training, 1078
definition, 335
drug therapy see drug therapy
frail elderly, 999-1001
recommended management, 1009
pathophysiology see pathophysiology
research, 1747-8
see also nocturnal diuresis; nocturnal frequency
Nocturia Quality of Life Questionnaire, 380
nocturnal detrusor overactivity, children, 717
nocturnal diuresis, older people, 311
see also nocturia; nocturnal frequency
nocturnal enuresis (bedwetting), 38-42, 466-7, 714-26, 761, 762-3, 769, 770
adult males, 454, 456
classification, 715-16
primary vs secondary, 715
definitions and terminology, 38-9, 714
diurnal and see daytime and night-time wetting
epidemiology incl. prevalence, 39-41, 714, 761
behavioural disorders, 762-3
gender and, 41, 715
management/therapy, 718-26, 763
evidence-based recommendations, 721-6
non-responders, 725
pharmacological see drug therapy
urotherapy, 769, 770
monosymptomatic (MNE), 38, 41, 714, 715, 715-16
pathophysiology, 716-18
non-monosymptomatic (NMNE), 38, 43-5, 715
risk factors, 41-2
severity, 714
urodynamic studies, 466-7
nocturnal frequency (frequency of night-time micturition), measurement, 336
nocturnal frequency, older people, drug therapy, see also nocturia;
nocturnal diuresis
nocturnal polyuria children, 716-17
measurement, 336
multiple system atrophy, 884
NOFUS (Norwegian Society for Patients with Urologic Diseases), 1681
non-blinded (unblinded) trials, 1716, 1722
non-compliance see compliance
non-continent (conduit) urinary diversion, neurogenic LUT dysfunction, 858-61
non-inferiority trials, 1717-18
non-neurogenic detrusor overactivity, 259-64
non-neurogenic LUT dysfunction in children, 730
non-parametric studies, 1725
non-randomised controlled trials, 1716
non-steroidal anti-inflammatory drugs (COX inhibitors;
prostaglandin synthase inhibitors; NSAIDs)
chronic pelvic pain, 1490
nocturnal enuresis, 723
overactive bladder symptoms/detrusor overactivity, 660-1
noradrenaline see norepinephrine
norephedrine (phenylpropanolamine; PPA), SUI, 672, 673
norepinephrine (noradrenaline), urethral and anal rhabdosphincters,
194
norepinephrine and serotonin reuptake inhibitors see serotonin and
norepinephrine reuptake inhibitors
normalised micturition frequency, measuring, 336
Norwegian Society for Patients with Urologic Diseases (NOFUS), 1681
NPUAP (National Pressure Ulcer Advisory Panel), 1620
N-Qol, 380
MTM (Inco) Forum, Poland, 1681
nucleus tractus solitarius (NTS), 210, 227, 228, 230, 231
nurse(s), 1652-3, 1661-3, 1704-6
advanced practice see advanced practice nurses
as continence advisors see continence nurse advisors
education/training, 1661-3
specialist, 1654-5, 1661-2, 1663
nurse practitioners, continence, 1652-3, 1663
Nurses Health Study, 678
physical activity in, 1030
nursing assistants and aides, 1664
nurture(s), 1652-3, 1661-3, 1704-6
as continence advisors see continence nurse advisors
education/training, 1661-3
specialist, 1654-5, 1661-2, 1663
nurse home (and other long-term care institutions for elderly), 1004-5
absorbent bodyworn products in, evaluation, 1550, 1551
AI/Fl in, 78, 1362
management, 1370-1
residency as risk factor, 1331
caregivers in, training, 1664
constipation in, 1365
costs of care, 1704-6
nocturia, drug therapy, 680
staff in, interventions with, 988-9, 1009
UI as risk factor for admission, 964-5
UI in women in, 51, 61-2
nutrient supply for tissue-engineered grafts, 150-1
nutritional factors see dietary factors
OAB-Q (Overactive Bladder Questionnaire), 381, 382
Short Form, 380, 382
OAB-S (Overactive Bladder Treatment Satisfaction Questionnaire), 383, 384
OAB-SS (Overactive Bladder Symptom Score), 385, 387
OAB-V8/OAB Awareness Tool, 383-4, 385
Obesity and overweight, 1667
female, 1028-9
as risk factor for POP, 283
as risk factor for UI (in general), 57, 64, 1028-9, 1667
SUI surgical outcome and, 1223-4, 1232
Fl and, 74-6, 1331
see also weight
OBJECT trial, 646
observation(s), in research, ICS Standardization Committee recommendations, 1730-1
observation techniques in cognitive-behavioural therapy, 769
surgery, 1751
observational studies, 1717
obstetrics see childbirth, pregnancy
obstruction (LUT), bladder see benign prostatic hyperplasia/enlargement/obstruction; bladder outlet obstruction; urethral strictures
occluding devices, 1567-72
extra-urethral
females, 1567-70
males see males intra-urethral
female, 1570-2
males, 1131-3
occupational risk factors, 1668
Fl, 1341
women, POP, 85, 1096
interventions related to, 1096
see also physical exercise
O’Connor repair, 1447
odds ratio, definition, 38
odour control products, 1626-8
Oestrogens, 676-8
continence mechanisms and, 676
deficiency, and overactive bladder, 261
POP risk associated with, 283
therapeutic use in incontinence, 676-8
frail elderly, 992, 994-5
tissue analysis, 628
UI aetiology, 57-8, 64
urethral smooth muscle relaxation and, 127
see also hormone replacement therapy; selective oestrogen receptor modulators
office evaluation
economic aspects, 1687, 1707
pad testing, 618-20
Office of Research Integrity (US), Introduction to Responsible Conduct of Research, 1756
older people/elderly, 961-1024, 1362-73
Al/Fl in, 1362-73, 1376
antimuscarinics see antimuscarinics
bladder, 965-8
dysfunction, 260-1
conservative treatment, 984-95
drugs see drug therapy
continence services, 1656
frail see frail elderly
LUT dysfunction, outcome measures, 1740
nocturia see nocturia
nursing homes see nursing home
patient-reported outcome assessment, 400
physiological/pathological changes, detrusor overactivity, 261
prevention of UI, 987, 1669-70
research see research
surgery see surgery
temporary incontinence, causes, 308-11
see also age
O’Leary-Sant (OLS) questionnaire, 1467-8, 1475, 1495, 1496, 1498
OLS (O’Leary-Sant) questionnaire, 1467-8, 1475, 1495, 1496, 1498
omentum grafts in non-obstetric fistula repair, 1251
one-hour pad test, 619-20
Onuf’s nucleus, 187, 194, 636
OPERA trial, 646, 654
operant behavioural strategies, 986
operating theatre time, fistula in developing world, 1450-1
opiate (opioid) receptor(s), agonists, 181
opioid receptor-like 1 receptor, 180-1
chronic pelvic pain, 1490-1
opioid receptor-like 1 receptor, 180-1
OPTIMAL trial, 1754
OPUS trial, 1754
organisations, continence, 1657-8
directory of, 1680
networking, 1658
ORL1 receptor, 180-1
orphanin FQ see nociceptin
Orr-Loygue rectopexy, 1309
orthopaedic trauma in obstructed labour, 1433-4
orthotopic neobladder see neobladder
outcome(s)
of catheterisation (intermittent vs indwelling), 1584
of conservative interventions for female UI, factors affecting
electrical stimulation, 1066-7
treatment, 1034
pelvic floor muscle training, 1054-5
scheduled voiding incl. bladder training, 1078-9
vaginal cones, 1058
of conservative interventions for male UI, factors affecting
electrical stimulation, 1091
pelvic floor muscle training, 1087
scheduled voiding, 1092-3
catheter-based intervention
external devices, 1532-3
internal devices (catheters), 1592-3
in economic analysis, 1695-6
in cost-utility analysis, 1696
in Fl intervention
- resting anal pressure and prediction of, 479-80
- sacral nerve stimulation, 1402
- voluntary squeeze pressure, 484

in frail elderly
- measures, 1740
- treated for UI, defining, 978
- functional, enterocystoplasty, 853
- measurement, 1729-36

LUTS, 1729-36
- MRI assessment of treatment outcome, 592-3
- patient-reported see patient-reported outcome assessment

sacral nerve stimulation, 1402

voluntary squeeze pressure, 484

in frail elderly
- measures, 1740
- treated for UI, defining, 978
- functional, enterocystoplasty, 853
- measurement, 1729-36

LUTS, 1729-36
- MRI assessment of treatment outcome, 592-3
- patient-reported see patient-reported outcome assessment

sacral nerve stimulation, 1402

voluntary squeeze pressure, 484

Urethral pain syndrome see bladder pain syndrome

LUT, 634
- bladder, 198
- bladder neck and base, 126
- urethra, 127
- see also autonomic nervous system

paravaginal defect repair, 1203, 1288-90

Pari, Ambroise, 22

parents, impact of UI/enuresis on, 766-7

parity and FI risk, 1334
and UI risk, 55

Parkinson’s disease, 863, 881, 886-90
- detrusor overactivity, 258
- FI, 863, 888-90
- multiple system atrophy and, differential diagnosis, 884
- UI and LUT dysfunction (in general) in, 454, 800, 881, 884, 886-8
- combined urodynamics and imaging, 552
- frail elderly, 971, 972
- urodynamic studies, 454-5, 472-3

Parrish, Joseph, 1462

parturition see childbirth

pathogenesis see aetiology
pathophysiology, 257-330
of FI, 799
older adults, 1363-4
of nocturia, 263-4
in the frail elderly, 999
of nocturnal enuresis, 716-18
of POP, 278-84
of UI see urinary incontinence
see also aetiology
patient(s)
adherence see adherence
assessment see assessment
FI risk factors related to, 1330-3, 1339
frail elderly, preferences for UI care, 979
history see history-taking
obstetric fistula risk factors (and prevention) related to, 1435
satisfaction with treatment see treatment
SUI surgery risk factors related to, 1231-2
in trials/research
informed consent see informed consent
observations, ICS Standardization Committee recommendations, 1730-1
Patient Global Impression of Severity and of Improvement (PGI-I and PGI-S), 388
Patient Perception of Bladder Condition (PPBC), 387, 388
patient-reported outcome (PRO) assessment, 363-412
for clinical trials and practice, 401-2
literature search strategy, 363
questionnaires see questionnaires
research recommendations, 403-4
types of PRO measures, 402-3
Patient Perception of Bladder Condition (PPBC), 387, 388
Patient Satisfaction Questionnaire (PSQ), 384
Pawlik, Karl, 27
PD-1151T, bladder pain syndrome, 1484
pelvic floor, 135
age-related changes, women, 968-9
anatomy, 184
obstetric, training of health professionals, 298-9
chronic stress, 283
electrical stimulation, 828
electromyography see electromyography
imaging in neurogenic FI, 865
innervation, in FI pathogenesis, 289
magnetic stimulation see magnetic stimulation
obstetrics and see childbirth; pregnancy in POP, associated conditions, 264-5
properties, 135
relaxation, MRI grading, 590-2
research recommendations, 197
surgery, ultrasound, 571
trauma
in men, incontinence after, 1141-2, 1169
in women, due to childbirth, 266-8
Pelvic Floor Distress Inventory (PFDI), 391-2, 1746
intravaginal rings and pessaries and, 1103
pelvic floor dysfunction/disorders
birth injury, 266-8
children, treatment, 739
detrusor overactivity, 261
FI relating to, 354
imaging see imaging
symptoms of, 341
Pelvic Floor Dysfunction Network (PFDN), 1754
Pelvic Floor Impact Questionnaire (PFIQ), 391-2, 1746
intravaginal rings and pessaries and, 1103
pelvic floor muscle (and pelvic organ-supporting tissues) deinnervation see nerve injury
electrical stimulation see electrical stimulation
EMG see electromyography
MRI, 579-82
neural control in females, 184-8
remodelling, in POP aetiology, 282
strength evaluation, 348
strength-increasing programmes, 1353
women, 1035-6
supraspinal activation, 193-4
tissue analysis, 627-9
ultrasound, 564-5
weakness and fatigue, definition, 348
pelvic floor muscle training/rehabilitation (PFMT; pelvic floor exercises), 1034-55, 1079-80, 1353-9
adherence (compliance), 1044-5, 1045-6, 1047, 1651
costs, 1689
in FI management, 1353-9, 1375-6
frail elderly, 985
men (incl. post-prostatectomy), 1083-6
combined with other treatments, 1085-7, 1090-1
compared with electrical stimulation, 1089
future research directions, 1095
literature search strategies, 1108
recommendations for practice, 1094
MRI assessment of outcome, 593
women, 1034-55, 1076, 1079-80, 1097-100
combined with other treatments, 1044-8, 1052-4, 1058, 1065-6, 1076
compared with other treatments, 1048-52, 1057, 1058
evidence for, 1036
future research directions, 1081
literature search strategies, 1107
pregnancy and postnatal period, 1036-42, 1079-80, 1668-9
preventive use, 1037, 1668-9
recommendations for practice, 1079-80
women with POP, 1097-100
future research directions, 1106
recommendations for practice, 1106
Pelvic Floor Netherlands, 1681
Pelvic Floor Patients Foundation, 1681
pelvic nerve afferents, electrical stimulation, 918-19
pelvic organ(s) (and tissues/viscera)
anatomical/structural aspects, 184, 278, 279, 1278-9
interactions at efferent neural levels, 203-5
quantifying support, 1731
sensation
brain circuits activated by, 231-3
urothelial cell role in, 171-5
see also specific organs
pelvic organ prolapse (POP), 80-6, 278-85, 344-7, 579-88, 589-92, 1095-7, 1273-320, 1706-7, 1737-8, 1746-7
aetiology/risk factors, 82-5, 274-84, 1096-7
levator innervation, 187-8
obstetric, 272-3, 586
related to choice of surgical route, 1295-300
classification/staging, 344-7, 1731
comorbid conditions, 85, 284-5
FI, 1333
UI see subheading below
definitions, 80, 1746, 1747
epidemiology, 80-6
research recommendations, 93-4
help-seeking behaviour, 88
imaging, 579-88
in grading of relaxation, 590-2
MRI, 579-88, 589-92, 593
quantitative assessment, 567-70
ultrasound, 567-70
management, 1095-107, 1273-320
anatomical aspects of surgical outcome, 1277
conservative, 1095-107, 1108
costs, 1698, 1706-7
MRI assessment of surgical outcome, 592
surgical see surgery
PTP (PTQ) implants, 1404
PTFE (polytetrafluoroethylene)
as bulking agent
anal canal, 1403
perurethral, 844
indwelling catheters, 1589
as mesh for sacrocolpexy, 1279
as sling, 1212-15
PSP (PTQ) implants, 1404
pubic pressure urinals, 1567
pubic symphysis
distance between urethral orifice and, 533
trauma in obstructed labour, 1434-3
public/consumer education and awareness, 1646, 1649-50, 1650-1, 1657-8
publications see literature
PubMed, neurogenic UI, 800
puborectalis muscle, 290, 475
anatomy and physiology, 475
FI and, 281-2
assessment of muscle function, 355
pubovaginal sling, historical accounts, 28
pudendal nerve, 186, 188
continence in sneezing and, 194
electrical stimulation of pudendal nerve afferents, 192-3
therapeutic use, 826, 830
injury see nerve injury
innervation by, 186, 188
anal and urethral rhabdosphincters, 188, 189
levator ani, 186, 188, 197
nucleus of (Onuf’s nucleus), 187, 194, 636
pudendal nerve conduction tests (incl. terminal motor latency/PDTRL), 532-3
FI investigation, 496-7, 501
postpartum, 290, 291
pudendal somatosensory evoked potentials, 535
puerperium see postnatal period
puerperium
pudendal somatosensory evoked potentials, 535
pudendal nerve conduction tests (incl. terminal motor latency/PDTRL), 532-3
FI investigation, 496-7, 501
postpartum, 290, 291
pudendal somatosensory evoked potentials, 535
puerperium see postnatal period
race/ethnicity
  FI risk and, 1331
  men, UI and, 65
  nocturnal enuresis and, 41
  women
  pelvic dimensions and, MRI studies, 588-9
  POP and, 83-4
  SUI surgical outcome, 1223
  UI and, 53, 64
radiation-induced conditions, pelvic
  cystitis and reduced bladder capacity, 1152
  FI, 354, 1338
  radiography, plain film, 551-9
  radionuclide scans, upper urinary tract, 549
  radiology see imaging
  radiotherapy, prostate cancer (and associated UI), 307-8, 452-3, 1138-40
  interstitial see brachytherapy
  prostate surgery and, 1151, 1153-60, 1169
  rectoanal inhibitory reflex, 498-9
  sacral see bulbocavernosus reflex; sacral reflexes
  spinal see spinal reflexes
  spinobulbospinal, 215
  urine storage, 192-4
referred pain
reflex(es), 525
  biological correlates with studies of, 525
  bladder cooling see ice water/ test
  bulbocavernosus, evaluation, 809
  continence/guarding, 189, 192, 197, 215
  developmental, in Alzheimer’s disease, 878
  homeostatic, 227-30, 231
  micturition see micturition reflex
  rectoanal inhibitory, 498-9
  sacral bulbocavernosus reflex; sacral reflexes
  spinal see spinal reflexes
random sampling, 1720
randomisation, 1720-1
randomised controlled studies (RCTs), 1716
  data analysis, 1725-6
  reporting, 1727-8
randomised control studies (RCTs), 1720
randomised controlled studies, 1716
  data analysis, 1725-6
  reporting, 1727-8
radiation therapy, prostate cancer (and associated UI), 307-8, 452-3, 1138-40
rectocele see vaginal wall prolapse, posterior
rectopexy, 1308-9
rectosigmoidoscopy, 355
rectourethral fistula, men, 1151, 1153-60, 1169
rectovaginal fistula, obstetric, 1433
  repair, 1447
rectum
  abdominoperineal resection, 802, 918
  accommodation and reservoir function, 289
  balloons see balloon systems as bladder reservoir, 747
  brain and, interactions, 226, 227, 231
  cancer, 918
  anal mucosal sensitivity following anterior resection, 491
  compliance, assessment, 488, 493-6
  continence devices, 1530, 1612-14, 1616-17, 1617, 1618
  cooling test, 499
  digital stimulation, 867-8
  distension, 286
  evacuation see defaecation; defaecography
  examination (incl. digital examination)
    bladder pain syndrome in men, 1475
    child, 347
    in FL, 355
    older people, 1369
    women, 347
  examination (incl. digital examination), male, 347, 348-9
  pelvic floor muscle training using feedback via, 1085
  irrigation with water, 869, 1349
  oxybutinin administration via, 655
  prolapse, 1307-9
  surgery, 1307-9
  vector manometry, 487
  prosthetic bowel sphincter implanted around, 1398
  sensation see sensation
  rectus fascia sling, 1211, 1212, 1215-16
  vs Burch colposuspension, 1752
real-time three-dimensional ultrasonography, 559
rectum
abdominoperineal resection, 802, 918
accommodation and reservoir function, 289
balloons see balloon systems as bladder reservoir, 747
brain and, interactions, 226, 227, 231
cancer, 918
  neurophysiological tests, 526
  urodynamic studies
  children, 467-8
  leak point pressure measurement, 433
  in neurogenic LUT dysfunction, 456-7
  urethral pressure measurements, 430-2
  reliability of patient-reported outcome questionnaires, 366
  Reliance device, 1571
  REMEE, 1130, 1131, 1137
remission, UI
  men, 65
  women, 53-5
  Renacidin, 1598
  renal problems/imaging/transplantation etc. see kidney
renography, 549
reporting of research
  conflict of interest, 1757-8
  randomised controlled studies, 1727-8
reproducibility
  anal manometry
  resting pressure, 476
  squeeze pressure, 482
  cystourethrogram, 555-7
  neurophysiological tests, 526
  pad testing, 610, 618-19, 620
  urodynamic studies, 423-7, 430-2

QoL see quality of life
Questionnaire for Urinary Incontinence Diagnosis (QUID), 386, 387
QUID (Questionnaire for Urinary Incontinence Diagnosis), 386, 387
QWB (Quality of Well-Being) Index, 1695-6
children, 467-8
neurogenic LUT dysfunction, 456-7
reproductive history (pregnancy/obstetric history), research relating to, 1737
frail older and disabled people, 1739
reproductive organs see genitalia/genital organs
reproductive performance and obstetric fistulas, 1432-3
research (incl. future/further research needs and recommendations), 1713-65
bladder pain syndrome, 1502-3, 1744-5
catheters
indwelling, 1611
intermittent, 817, 1611
children, 1741-2
continence devices (UI and FI), 1556
urodynamic studies, 468
conservative treatment
with continence devices see subheading below
men, 1094-5
women, 1081-2
continence awareness and promotion, 1651-2, 1658
continence devices, FI, 1618
children, 1556
continence devices, UI, 1749-50
absorbent products for light UI in females, 1546
absorbent products for light UI in males, 1548
absorbent products for moderate/heavy UI, 1554
adherence to trial design criteria, 1755
bodyworn urinals, 1567
children with UI and/or FI, 1556
comodes and bedpans, 1537
handheld urinals, 1535
mechanical devices for females, 1570, 1572, 1575
mechanical devices for males, 1576
penile sheaths, 1561
product evaluation methodology, 1531-3
underpads, disposable, 1555
underpads, washable, 1555
urine drainage bags, 1566-7
dementia and UI
Alzheimer’s disease, 879
frontotemporal dementia, 882
Lewy body dementia, 881
vascular dementia, 880
on economic analysis, 1708-9
endoscopy, 610
epidemiological, 92-4
FI, 93-4
POP, 93-4
UI, 64, 92-3
ethical considerations, 1756-8
FI, 1744-5
assessment of FI, 355
biofeedback and anal sphincter/pelvic floor training, 1359, 1375-6
bowel training, 1350, 1375
continence devices see FI (subheading above)
diet and fluid intake, 1348, 1375
drug therapy, 1352, 1375
electrical stimulation, 1360, 1376
epidemiological studies, 93-4
imaging, 616-17
lifestyle factors and education, 1343, 1374
in neurological disease see subheading below
older people, 1373
prevention of FI, 1341, 1374
QoL, 870
general recommendations, 1716-29
goals, 1715
imaging, 549
cystourethrography, 557
FI, 616-17
MRI, 594
open bladder neck and proximal urethra, 602
residual urine evaluation, 599
urethral diverticula, 604
LUT (in general), 151
LUTS (in general), 337, 1736-9
men, 1736-7
outcomes measurement, 1729-36
women, 1737-9
neurogenic UI, 1742-4
intermittent catheterisation, 817
neurological disorders causing see subheading below
triggered reflex bladder, 811
neurological disorders (FI or UI due to)
cerebral lesions and cerebrovascular accidents, 892
dementia see subheading above
in diabetes mellitus, 917
Guillain-Barré syndrome, 910-11, 911
HIV disease, 922
iatrogenic, 919
meningomyelocele, 914
multiple system atrophy, 885, 886
Parkinson’s disease, 888, 890
spinal cord injury, 904-5, 908
neurophysiological tests, 538
nocturia, 1747-8
odour control products, 1628
older people (incl. frail persons) with FI, 1373
with UI, 311, 1006-7, 1009-10, 1739
outcomes, 1658
LUTS, 1729-36
patient-reported outcome questionnaires, 403
pad testing, 623
pelvic floor, 197
pharmacotherapy see drug therapy
physical examination
females, 349
males, 353
POP, 1746-7
epidemiology, 93-4
treatment, 1310-11
post-void residual volume testing, 340
professional education, 1665
skin care products, 1626
surgery, 1751-5
adherence to trial design criteria, 1755
frail older people, 1740
men, 1170
in new procedures, 1753-4
women with POP, 1310-11
tissue replacement/engineering, 149-51
translational, 149
urinalysis, 338
urodynamic studies
air-charged catheters for pressure measurements, 420
children, 468
detrusor overactivity, 439, 441, 442
geriatric patients, 471, 473
men, 453-4
in neurogenic LUT dysfunction, 457, 1743
reproducibility of results, 426
in therapeutic response prediction, 442
women, 445, 446, 449-50
see also literature: trials
Resident Assessment Instrument and Resident Assessment Protocol, 1005
residential care see nursing home
residual urine (post-void; PVR), evaluation, 338-40, 562-4, 597-9
children, 709-10
imaging, 597-9
ultrasound see ultrasound
neurogenic incontinence
multiple sclerosis, 896
multiple system atrophy, 884
older people (incl. frail elderly), 469-70, 471, 472, 977
recommendations, 1011
women, 339
residual urine (post-void), elevated, frail elderly, 982
resiniferatoxin, 180, 1146
therapeutic use, 667-8, 823, 1147
bladder pain syndrome, 1487
men, 1146
respect for persons, 1756
responsiveness to change in questionnaires, 366-7
reticular formation, medial, 211
retrograde colonic enema, meningomyelocele, 914-15
retrograde sacral enema, meningo-myelocele, 191-19
retrograde sacral enema stimulation, 533
with posterior sacral rhizotomy, 840
bladder pain syndrome, 1488-9
children, 736
complications see safety aspects
in detrusor overactivity, 1149
FI, 1359, 1399-402, 1408
cost-benefit, 1402
mechanism of action, 1400
neurogenic see subheading below
outcome, 1400-2
patient selection and indications, 1399-400
safety, 1402
technique, 1399
neurogenic FL, 871-2
meningo-myelocele, 915
neurogenic LUT dysfunction, 829-32
hypotheses on mode of action, 829-30
posterior/dorsal, section see sacral rhizotomy
in spinal cord injury, 904
sacral parasympathetic nucleus (SPN), 198, 202
sacral reflexes, 525-6
see also bulbocavernous reflex
sacral rhizotomy, 839, 1239
combined with anterior root stimulation, 840
sacral spinal cord dysfunction, FI, 1366
sacral spine, imaging, 605
sacrocolpopexy, 1277, 1278, 1279-86
Burch colposuspension added to, 1754
outcomes, 1281-5
sacroperineo-sacroabdomino-perineal pull-through, 1153
sacrospinous ligament suspension or colpopexy, 1280, 1286, 1287,
1754
vs sacral colpopexy, 1707
safety aspects (incl. adverse effects and complications)
adjustable balloons (for urethral compression), 1133
antegrade continence enemas, 1407
artificial urinary sphincter, 1161-3
male sling, 1131
PROMP surgery
intermittent catheterisation
indwelling urethral catheters
indwelling suprapubic catheters, 819
urethral catheters see indwelling catheters
intermittent catheterisation see intermittent catheterisation
male sling, 1131
sacral rhizotomy (sacral nerve stimulation)
in FI, 1402
in UI, 1244
safety aspects (incl. adverse effects and complications)
adjunct treatment of complications, 1165-8, 1169-70
bladder reconstruction, 755-9
continence devices, 1750
cryosurgical ablation of prostate, 1140, 1141
drugs in older persons, 681-2, 982-3, 993, 994
fistula repair, 1448, 1452
indwelling suprapubic catheters, 819
indwelling urethral catheters see indwelling catheters
intermittent catheterisation see intermittent catheterisation
male sling, 1131
neuromodulation (sacral nerve stimulation)
in FI, 1402
in UI, 1244
monitoring, 1722
triggered reflex voiding, 811
urinary diversion
continent, 856
non-continent, 858-9, 859-60
see also drug-induced incontinence
saline 0.9% (catheter maintenance solution), 1598
saline retention test, 493
sampling methods/strategies, 1720
sample size considerations, 1723-4
in UI prevalence estimation, 47
satisfaction with treatment see treatment
scaffold for tissue-engineered grafts, 150, 750
scheduled voiding
men, 1092-3
future research directions, 1095
women, 1070-8
future research directions, 1082
literature search strategies, 1107-8
scheduled voiding, women, see also timed voiding
scheduled waking, 724
schistosomiasis (bilharziasis), contracted bladder, 746, 1151
Schweizerische Gesellschaft fur Blasenschwache (Switzerland), 1682
scintigraphy (isotope scans), upper urinary tract, 549
Scott intermittent catheter, 1580
screening for FI in high-risk groups, active, 1524
tools and questionnaires, 383-8
children, 767-8
scrotal approach, artificial urinary sphincter implantation, 1161-3
sex hormones/steroids in UI treatment, 676-9
urethral smooth muscle relaxation, 127
urethral, age-related changes, 968
urinary symptoms, 740
sexual dysfunction, 1738
assessmentevaluation for see sexual function/satisfaction mode of delivery and, 267
POP and, 285
surgical management of, 1276
SUI surgery-related, 1236
symptoms associated with, 341
sexual function/satisfaction, evaluation, 395-9
men, 395, 396, 398-9
questionnaires in, 371, 395-9
women, 395, 396, 397-8, 398, 399, 1738
sexual intercourse (coitus) pain in (dyspareunia), SUI surgery, 1236
urinary incontinence, 334
Sexual Quality of Life-Female Questionnaire (SQOL-F), 399

sex see gender
sex hormones/steroids
in UI treatment, 676-9
urethral smooth muscle relaxation, 127
see also oestrogen; progestogens
sexual abuse (children/women) fistula related to, 1424
urinary symptoms, 740
sexual dysfunction, 1738
assessmentevaluation for see sexual function/satisfaction mode of delivery and, 267
POP and, 285
surgical management of, 1276
SUI surgery-related, 1236
symptoms associated with, 341
sexual function/satisfaction, evaluation, 395-9
men, 395, 396, 398-9
questionnaires in, 371, 395-9
women, 395, 396, 397-8, 398, 399, 1738
sexual intercourse (coitus) pain in (dyspareunia), SUI surgery, 1236
urinary incontinence, 334
Sexual Quality of Life-Female Questionnaire (SQOL-F), 399

sexuality
catheters and, 1608
children with detrusor-sphincter dysfunction and, 744
SF6D, 1696
sheaths, penile see condom catheters
shields see inserts; pouches
shingles (herpes zoster), 921
Shy-Drager syndrome see multiple system atrophy
sigma-rectum pouch, child, 747
sigmoid resection with rectopexy, 1308-9
see also rectosigmoidoscopy; uterosigmoidostomy
sign(s), correlation with investigations in females, 340-1
signalling
neuronal spinal cord glia modulation of, 183-4
urothelial and, 173
urothelium/suburothelium, 117-19
neuronal and, 173
see also second messengers
significance (statistical), 1723, 1724
SII (Symptom Impact Index), 388
sildenafil, 659
silicone biomaterial injectable see polydimethylsiloxane® for slings, 1212
silicone indwelling catheters, 1589
silicone urethral inserts, 1570-2
silver alloy-coated indwelling catheters, 1586, 1589, 1593, 1594, 1597, 1601, 1602
Simon, Gustav, 26
Simon Foundation for Continence, 1683
Sims, Marion, 26
Singapore, Society for Continence, 1681
single blind trial, 1722
single fibre EMG, 529
single photon emission tomography (SPECT), CNS, 605-7
Soave (Sweden), 1682
SISTEr (Stress Incontinence Surgical Treatment Efficacy Trial), 1752
six transmembrane (6TM) family of receptors, 144-6
skeletal muscle
anal sphincter see anal sphincter, external
disease, EMG, 531-2
urethral see urethral sphincter, external
see also muscle
Skene AJC, 1462, 1463
skin
fistula between, and urethra, men, 1151-3, 1169
health (and continence products), 1618-26
pads, 1556
obstetric fistula-related injury, 1434
sympathetic response see sympathetic nervous system
urinary diversion to continent, 855-7
non-continent 860-1, 855-7
sleep, children
arousal from see arousal; waking
nocturnal enuresis and, 42
sleep apnoea
children, 42
frail elderly, 971
sling procedures (sub-urethral), 1211-17
children, 752
historical accounts, 28-9
materials, 1211-12, 1212-16
men
post-prostatectomy, 453, 1129-31, 1132, 1136-7
post-radiotherapy, 1139
neurogenic LUT dysfunction, 846-7
ultrasound, 571
women, 1211-17, 1289, 1290
Burch colposuspension vs, 1752
concomitant to other surgery, 1295
mid-urethral tapes vs, 1218
vaginal extrusion of sling material, 1235
Slovakia, continence organisation, 1682
slow stream, definition, 335
smells, masking products, 1626-8
smoking, 1031, 1668
as FI risk factor, 1341-2
as UI risk factor, 1668
women, 60-1, 1031
smooth muscle (LUT)
active properties, 135-6
anorectum, 138-9
bladder wall/detrusor see detrusor EMG, 537
urethral, 127
vaginal wall/supportive tissues, alterations in POP, 280-1
smooth muscle myosin (SM) in detrusor contraction, 121
smooth muscle relaxants see bladder relaxants
SNARES (soluble N-ethyl maleimide sensitive-factor attachment protein receptors), 661
sneezing, continence in, neural mechanisms, 194
Soave procedure, 1160
social consequences, obstetric fistula, 1429
social factors
nocturnal enuresis, 42
see also cultural aspects
Society for Continence, Singapore, 1681
Society of Urologic Nurses see specific Associates, 1683
socioeconomic factors, POP, 85
sociomedical factors, obstetric fistulas, 1426, 1428
sodium ion channels
epithelial, 144
non-neurogenic detrusor overactivity and, 260
NGF and TTX-resistant, 182
sodium pentosan polysulfate see pentosan polysulfate
solabegron, 658
solifenacin (YM905), 650-1, 822, 1703
economic analysis, 1702, 1703
frail elderly, 993-4
soluble N-ethyl maleimide sensitive-factor attachment protein receptors (SNAREs), 661
Solution G, 1598
Solution R, 1598
somatic motor system and somatic innervation, 636, 797
tests, 527-33
somatosensory evoked potentials, 534-5, 818
sonography see ultrasound
sorbitol, dietary, 1347
South Africa, Continence Association, 1682
South Korea, continence organisation, 1681
Spain, continence organisation, 1682
SPARC (suprapubic arc sling), 1218, 1219
specialists (and specialist centers)
in continence care
nurses, 1654-5, 1661-2, 1663
single specialist model, 1654
training of physicians, 1661
fistula care in developing world, 1450
referral, LUTS symptoms requiring, 337
SPECT, CNS, 605-7
SpediCath, 816
Spence technique, 1247
sphincter see anal sphincter; urethral sphincter
sphincteroplasty, anal, 1391-3, 1408
sphincterotomy
internal anal, FI risk, 1338
urethral, 833-8
dermoscopic, 833-5, 837
prosthetic, 835-7, 838
SPI (Symptom Problem Index), 388
spina bifida, 912-16
FI, 863
occult, 741
urodynamic studies, 458-9, 913
see also myelomeningocele
spinal anaesthesia, fistula surgery, 1439
spinal canal stenosis, 801, 908-9
spinal cord
different neurones, 182-4, 227
developmental abnormalities (myelodysplasia), 457-9, 740, 741, 912-16
efferent pathways to bladder, 198, 200-2
evoked potentials, epidural recording, 810
glial cells, 183-4
sacral see sacral spinal cord
see also ascending pathways; descending pathways
spinal cord lesions (incl. injury/SCI), 799, 801, 862, 898-908
catheters and, 1606-7
indwelling, 901, 903, 1606-7
intermittent, 902, 903
conservative treatment, 811-12
detrusor overactivity, 258-9
electrical stimulation with, 24
FI due to, 799, 862, 906-7, 1338-9, 1366
colostomy, 877
diagnosis, 864
patient-reported outcome assessment, 400-1

1860
storage dysfunction/failure, 222-4, 633, 636
storage (urine)
stools
stones (calculi/lithiasis), urinary (incl. kidney/bladder)
stomach, bladder reconstruction/augmentation using (gastrocysto-
stoma, continent
steroid hormone therapy in UI, 676-9
stents, urethral sphincter, 835-7, 838
stem cells, transurethral injection
spina
spinal dysraphism, 459-60
detrusor-sphincter dysfunction, 740
imaging, 605, 606
occult, 459-60
physical examination, 707
urodynamic studies, 459-60
spinal reflexes, 227-8, 803
anal and urethral rhadosphincters and, 189, 192
assessment, 803
lamina I afferent input to, 227
spinal urine-storage-reflex inhibitory center (SUSRIC), 192-4
spine
discs see intervertebral disc disease
imaging, 605-6
'spinning-top' configuration, 711
spinal reflexes, 215
spino-thalamic input
to interoceptive cortex, 230
to limbic behavioural motor cortex, 230
spine
sponge, intravaginal polyvinyl, 1574
spontaneously hypertensive rat, 223
SQOL-F (Sexual Quality of Life-Female Questionnaire), 399
squeeze pressure measurements (external anal sphincter), 481-5
SSI (Symptom Severity Index), 388
staff
health care see health care staff
nursing home see nursing home
staining with washable pads, faecal, 1557
Stamey grading scale, 1749
Stamey needle suspension/colposuspension, 1202, 1203, 1212, 1216
standard error of the coefficient, 1694
standard setting for nurses, 1662
Standards for Reporting of Diagnostic Accuracy (STARD), 545
STAR trial, 651
statistical analysis, 1694
trials, 1718-29
recommendations, 1729
stem cells, transurethral injection
post-radical prostatectomy, 1129
ultrasoundography-guided, 572
stents, urethral sphincter, 835-7, 838
steroid hormone therapy in UI, 676-9
stoma, continent
child, 754-5
complications
continent urinary diversion, 856
non-continent urinary diversion, 859
cutaneous site, 855-7
other types, 857
stomach, bladder reconstruction/augmentation using (gastrocysto-
plasty), 853-4
child, 748
malignancy complications, 758-9
stones (calculi/lithiasis), urinary (incl. kidney/bladder)
cystoplasty and, 757-8
indwelling catheters and, 1599
intermittent catheters and, 1583
multiple sclerosis, 896
non-continent urinary diversion and, 859
spinal cord injury, 901-2
vesicovaginal fistula-associated, 1430
stools see faeces
storage (urine)
capability, intravesical pressure measurements in assessment of,
419
peripheral control, 634
storage dysfunction/failure, 222-4, 633, 636
children
postoperative, 755
surgery, 745, 746
neural mechanisms, 222-4, 636
storage reflexes (urine), 192-4
storage symptoms, definitions, 334-5
strain-softening phenomenon, 134-5
straining (defaecation), chronic, 354
straining (voiding)
definition, 335
urethral axis during, 553
stratification/stratified sampling, 1721
stream
intermittent, definition, 335
slow, definition, 335
strength, pelvic floor muscle see pelvic floor muscle
strength-duration test, external anal sphincter, 497-8
Strengthening of the Reporting of OBservational studies in
Epidemiology (STROBE) statement, 92
stress
pelvic floor, chronic, 283
psychological, reduction in bladder pain syndrome, 1481
stress incontinence (SUI - females), 27-9, 1193-237, 1701-2
conservative treatment, economic analysis, 1700-1
definition of, 334
drug therapy, 672-5
hormonal, 676-7, 678
electrical stimulation in
men, 1088
women, 1060, 1061, 1062, 1063-4, 1065, 1066
EMG changes, 531-2
frail elderly, 470
imaging, 276-8
initial assessment, 342
magnetic stimulation in, 1065, 1069, 1070
mixed UI and see mixed UI
neural mechanisms, 224
obstructive causes/risk factors, 264, 265-6, 267, 272-3
pathophysiology, 271-8
pelvic floor muscle training, 1042, 1066
biological rationales for, 1034-5
recommendations for practice, 1080
pelvic floor properties and, 135
POP comorbid with, surgical considerations, 1228-9
POP surgery and prevention or treatment of, 1294-5, 1296-9
postoperative, in POP patients, 448
selection of treatment, leak point pressure in, 433-4
severity, assessment, 443-4
surgery, 842-9, 1193-237, 1701-2, 1751, 1754
complications, 1222, 1223, 1229-37
concomitant urethral diverticulectomy, 1246
confounding variables, 1220-8
economic analysis, 1697-8, 1701-2
historical accounts, 27-9
men, 1161
predicting failure, 446
for recurrence, outcome, 1224-6
in sphincteric incompetence, 842-9
trials, 1751, 1754
urgency after, 447
voiding difficulties after, 446-7
urodynamic studies, 442-8
with coexisting overactive bladder, 436
diagnostic and therapeutic vale, 433-4
leak point pressure, 433
women, 442-8
vaginal cones, 1080
stress incontinence (SUI - males)
drug therapy, 675
stem cell therapy, 572
Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr), 1752
stress response, endoplasmic reticulum, 146-8
stress testing (provocation tests)
in detrusor overactivity, 439-40
frail elderly, 977
women, 342
after UI surgery, 1253
Stress/Urge Incontinence Questionnaire, 390
stretch, urothelial response to, 117, 118, 120, 122, 134
strictures, urethral see urethral strictures
STROBE (Strengthening of the Reporting of OBservational studies in Epidemiology) statement, 92
stroke see cerebrovascular accident
subcortical areas in bladder control, 216-20
subjective measures in outcomes research, ICS Standardization Committee recommendations, 1730-1
subural lesion, 799
substance P (SP), 179, 182, 195, 202
subthalamic nucleus deep brain stimulation, 827
substance P (SP), 179, 182, 195, 202
subsacral lesions, 799
subjective measures in outcomes research, ICS Standardization Committee recommendations, 1730-1
superabsorbent polymers (SAPs), products with, 1540-1, 1621
SUIQ (Stress/Urge Incontinence Questionnaire), 390
sudocrem, 1624
sucralfate, diarrhoea-associated FI, 1351
Suby G, 1598
suburothelium, 116-20
suburethral tapes, 842-3
suburothelium, 116-20
detrssor interactions with, 120
signalling and secretory properties, 117-19
Suby G, 1598
superabsorbent polymers (SAPs), products with, 1540-1, 1621
suprapubic tapes, 842-3
suprapubic arc sling (SPARC), 1218, 1219
suprapontine lesions, LUT and bowel dysfunction due to, 799
detrusor overactivity, 258
suprapubic arch sling (SPARC), 1218, 1219
suprapubic catheters, 819-20, 1578, 1588, 1589, 1606
suprapubic urethral tapes, complications, 1231
suprasacral spinal lesions, 799
suprascapular lesions, LUT dysfunction, conservative management, 811
see also specific lesions
supraspinal pathways
pelvic floor muscle activation, 193-4
urethral and anal rhabdosphincter activation, 193-4
supraspinal reflexes, 227-8
lamina I afferent input to, 227
supratrigonal cystectomy
and cystoplasty in bladder pain syndrome, 1493-4
neurogenic UI, 850
supra-urethral meatus approach to diverticulum, 1247
surgeons
fistula
fistula, 1439-52, 1453
ethical considerations, 1451-2
in SUI surgery, experience affecting outcome or causing complications, 1228, 1231
AI/FI following, 78, 1337-8, 1340
for Hirschsprung’s disease, 1407
for AI/FI incontinence, 870-7, 1387-417
children, 1406-7, 1408
costs, 1708
history, 1389
in meningomyelocele, 915
neuropathic patients, 1387-417
anal sphincter (external/internal) repair/reconstruction, 1390-1, 1408
obstetric, 295-7, 1390
problems after, 616-17
secondary/delayed (= sphincteroplasty), 1391-3, 1408
bladder pain syndrome, 1492-4
children with FI, 1406-7, 1408
children with UI, 744-59
complications, 755-9
consensus statement, 759
indications, 746-7
detrusor overactivity see detrusor overactivity
dermatoscopy of LUT during, 609
fistulas (not specifically in women)
children, 1406-7
men, 1155-60
fistulas in women, non-obstetric, 1249-51
fistulas in women, obstetric primarily and incl. vesicovaginal fistula, 1439-52, 1453
complex, 1444-7, 1452, 1453
complications, 1448-50
ethical considerations, 1451-2
historical accounts, 24-7
repeat, 1449
simple, 1439-44, 1452, 1453
iatrogenic damage see iatrogenic damage
large bowel, resting anal pressure and prediction of outcome, 479-80
men, prostate, and associated UI see prostatectomy
men, for UI, 1121-90
evaluation before, 1124-6, 1169
new technologies, 1170
older people, 1137-8
post-prostatectomy in benign disease, 1136-7, 1169
post-prostatectomy in cancer, 1128-35, 1137-8, 1169
post-radiotherapy, 1139-40
tissue damage due to, 802, 918
neurogenic LUT dysfunction, 829-61
meningomyelocele, 913-14
new procedures, development and assessment, 1753-4
older people/frail elderly, 995-7, 1008-9
complications in SUI surgery, 1232
men, 1137-8
recommendations, 1008-9
research, 1740
pelvic floor muscle training vs, 1049, 1050, 1051
pelvic floor surgery
pelvic floor (in general), ultrasound, 571
pelvic organ (incl. vaginal) prolapse, 1273-320, 1706-7
augmenting materials, 1300-7
concomitant/combined procedures, 1293-300
economic analysis, 1698, 1706-7
efficacy of specific procedures, 1278-92
modifications to traditional methods, 1291
obliterative procedures, 1292
outcome see outcome
and pelvic floor muscle training, 1098-9, 1099, 1100
predicting SUI risk, 448
recommendations, 1309-10
reconstructive procedures, 1278-91
research, 1310-11
safety issues relating to route, 1278
selection of routes, 1277-8
previous (for UI) affecting SUI surgical outcome, 1224-6
in prostatectomised patients see prostatectomy
prostatic see prostatectomy
research see research
SUI see stress incontinence
women
obstetric fistula see subheading above
for POP, see subheading above
women, for UI in general, 1191-272
confounding variables, 1220-8
pelvic floor muscle training vs, 1049, 1050, 1051
SUI see stress incontinence
see also specific procedures
survey studies, UI
general problems with, 86
in women, 47
suspension systems, urine drainage bags, 1564
SUSRIC (spinal urine-storage-reflex inhibitory center), 192-4
Switzerland, continence organisation, 1682

Sweden

Enuresis Trial (SWEET) Group, 722
patient-reported outcome assessment in older patients, 400
Swedish Urotherapists, 1682
SWEET study, 722

Symptom Problem Index (SPI), 388

Symptom Impact Index (SII), 388

Symptom Severity Index (SSI), 388

T-shaped pads/diaper, 1542, 1553

T-tetradotoxin-resistant Na+ channels, 182

Tibial nerve stimulation, posterior, 826, 1402-3, 1408

Tic doloureux, 1462, 1463

Timms C3 penile compression device, 1576

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231

Thalamocortical relay units (ventromedial thalamic nuclei), 230, 231
transurethral resection of prostate (TURP) or incision (TUIP)
transurethral marsupialisation
transurethral injection of stem cells
transurethral holmium laser enucleation of the prostate (HoLEP)
transurethral catheters
transsphincteric incision to rectourethral fistula repair
transrectal prostatic hyperthermia
transrectal irrigation
transrectal high-intensity focused ultrasound
transrectal irritation
transanal approaches
transabdominal approach
tramadol
transient receptor potential (TRP) cation channels
transdermal oxybutinin
transcutaneous electrical stimulation
transcrotal approach, artificial urinary sphincter implantation
transcranial magnetic stimulation
transanal ultrasonography (EAUS)
transanal irrigation
transanal approaches
transanal injection of drugs/chemicals
transanal fistula repair (non-obstetric)
transanal fistula repair (obstetric)
trans-obturator slings (TOT)
transmembrane family of receptors
transitional epithelium
traditional birth attendants
transient overactivity
transient overactivity, 661-8
traditional birth attendants, 1656
training of professionals
transanal approaches
transabdominal approach

radiotherapy after, 1139
as risk factor for UI, 302-3, 308, 350, 452, 1135-6
urodynamic studies, 451
transvaginal approach
fistula (non-obstetric) repair, 1250-1
fistula (obstetric) repair, 1447
combined with abdominal approach, 1447
POP surgery, 1277-8
 augmenting materials, 1302
paravaginal repair, 1288, 1288-9
posterior vaginal wall prolapse, 1290-1
sacrocolpopexy, 1286
transversus abdominus contraction, pelvic floor muscle activated by, 1035
transvesical injection of drugs/chemicals
transurethral resection of prostate (TURP) or incision (TUIP)
endoscopic assessment of urethral sphincter following, 609
frail elderly, 997
pelvic floor muscle training after, 1087

old people (incl. frail persons), 985, 987, 989
tolterodine, 646-7, 1703-4
child, 738, 738-9
economic analysis, 1702-3
elderly (incl. frail persons), 993
adverse effects, 682, 983
neurogenic LUT dysfunction, 821
spinal cord injury, 903
topical skin care products, 1623
toxic agents in bladder pain syndrome aetiology, 1471
toxins, therapeutic use in overactive bladder symptoms/detrusor overactivity, 661-8

traditional birth attendants, 1656
training of professionals see health care staff
tramadol
chronic pelvic pain, 1491
UI, 671
transabdominal approach
fistula repair (non-obstetric), 1251
fistula repair (obstetric), 1446
combined with vaginal approach, 1447
POP surgery, 1277-8
paravaginal repair, 1288, 1288-9
posterior extension of colpocexy mesh, 1292
for rectal prolapse, 1307, 1308-9
sacrocolpopexy, 1286
transanal approaches
posterior vaginal wall prolapse repair, 1291
rectourethral fistula, 1157, 1158
transanal irrigation, 869, 1349
transanal ultrasonography (endoanal ultrasonography; EAUS), 480, 487, 498, 611, 614, 616
transcranial magnetic stimulation, 827
transcutaneous electrical stimulation
  of anterior sacral roots see sacral neuromodulation, anterior
  children, 735
  men, 1089
  frail elderly, 992
transient receptor potential (TRP) cation channels, 146, 174, 180
botulin toxin A and, 661
transient UI
  in older adults, 308-11
  in pregnancy, 264
transitional epithelium see urothelium
translational research, 149
transmembrane family of receptors
  seven (7TM), 140
  six (6TM), 144
transobturator slings (transobturator route of tape placement; TOT), 1130, 1137, 1218, 1219-20
complications, 1231, 1233, 1234
transplantation, renal, in myelodyplasia, 459
see also grafts
transrectal high-intensity focused ultrasound, 1140-1, 1155
transrectal irritation, 869, 1349
transrectal prostatic hyperthermia, 1154, 1155
transphincteric incision to rectourethral fistula repair
  anterior, 1158
  posterior, 1156
transurethral catheters see catheters
transurethral holmium laser enucleation of the prostate (HoLEP), 1136
transurethral injection of stem cells see stem cells
transurethral marsupialisation, 1247
transurethral resection of bladder in bladder pain syndrome, 1492
transurethral resection of prostate (TURP) or incision (TUIP)
edoscopic assessment of urethral sphincter following, 609
frail elderly, 997
pelvic floor muscle training after, 1087
24-hour production, measurement, 336

twin studies, POP, 84

twisting of external continence devices see anti-kinking features
two-hour pad test, 620

U-Control vzw, 1680

UDI (Urogenital Distress Inventory) and UDI-6, 382, 382-3, 387, 389, 390

UHII (Urinary Incontinence Handicap Inventory), 381

UIS (Urinary Incontinence Score), 381

UISS (Urinary Incontinence Severity Score), 381

UITN (Urinary Incontinence Treatment Network), 1752, 1754

UK see United Kingdom

ulcer(s), pressure, 1620-1

ulcerative colitis and FI, 1334

ulcerative colitis and FI, 1345

ultralife™, 835, 836

ultrasonography, 1716

ultrasonic cystography, 1722

ultrasonic, transrectal, 1140-1, 1155

ultrasound, anal (in FI), 486, 487

endoanal/transanal (EAUS), 480, 487, 498, 611, 614, 616

ultrasound, transrectal high-intensity focused, 1140-1, 1155

ultrasound, urinary tract (and pelvic floor and its dysfunction), 557, 559-77

bladder neck, 561-2

children, 709-10

cystourethrography compared with, 557

men, preoperative, 1124

obstetric patients, 565-6, 570-1

residual urine evaluation, 562-4, 598-9

children, 709

standardisation, 559-61

SUI real-time, 276-8

types, 559

upper urinary tract, 548

children, 709-10

urethra, 561

ultrastructure (electron microscopy), bladder

age-related changes, 967-8

in bladder pain syndrome, 1473

umbrella cells, 117, 170

unblinded (non-blinded) trials, 1716, 1722

uncoated intermittent catheters, 1580, 1581

underactive bladder/detrusor (areflexia)

child, 732, 742

behavioural disorders and, 764

management, 732, 735

with overactive/hyperreflexic sphincter, 812

child, 742

with underactive/areflexic sphincter, 742

underactive urethral sphincters (areflexia/incompetence)

children, 744

surgery, 745

and overactive/hyperreflexic detrusor see detrusor overactivity

surgery, 842-9

children, 745

and underactive detrusor, 742

undergraduate medical curriculum, incontinence, 1658-9

underpads (bedpads), 1540, 1543, 1554-5

disposable, 1554-5

reusable, 1555

unfolded protein response, 148

United Kingdom/Britain (UK)

continence organisations, 1682

guidelines for UI in, 1664-5

nurse continence advisors, 1654

nurse specialist education, 1662, 1663

United States (USA)

continence awareness promotion, 1651

continence organisations, 1682-3

economic analysis in, 1688-9

nurse specialist, 1654-5, 1661-2, 1663

Office of Research Integrity, Introduction to Responsible

Conduct of Research, 1756

routine care costs, 1700-1

University of Wisconsin IC Scale, 1495, 1496, 1498

unmyelinated afferents, 636

bladder, 176-7, 636

upper urinary tract

in bladder neck reconstruction for exstrophy and epispadias, fate, 1144

imaging, 546-610

children, 709-10

indications, 546-60

injury in obstructed labour, 1431

multiple sclerosis-associated complications, 896

in non-continent urinary diversion, complications, 859

UPS (Urgency Perception Scale/Score), 387-9, 390

UQ (Urgency Questionnaire), 381

urease inhibitors preventing catheter encrustation, 1597

ureter

bladder augmentation using (ureterocystoplasty)

child, 750

neurogenic LUT dysfunction, 853-4

ectopic ureter see ectopic ureter

injury

with obstructed labour, 1431

with SUI surgery, 1233

reimplantation (in enterocystoplasty), 850

urine reflux see vesicoureteric reflux

ureterectomy, ectopic, 464

surgery, 745

ureterostomy, cutaneous, 860-1

urethra, 127-32

afferent projections to spinal cord, 182-3

age-related changes, 968

anatomy and location/position

females, 271-2

females, childbirth effects, and effects on urinary continence, 272-3

studies of, 275

atrophy with artificial urinary sphincter, 1163-5, 1167-8

bulking agents in/around see bulking agents

compression (therapeutic in males) see males

construction/reconstruction (neourethra), 1446

child, 752

diverticula see diverticula

duplications, surgery, 746

enhancement surgery, child, 750

erosions

with artificial urinary sphincter, 1168

postoperative (for SUI), 1235

fistulas and the

surgical procedures, 1444-5, 1445-6

urethral catheterisation, 1440, 1441, 1443

see also rectourethral fistula; urethrocutaneous fistula; urethroperineal fistula

inclination, 553

injury see injury

innervation, 127

incontinence, 127

mobility and possible hypermobility, 274-8

assessment, 343, 344, 1738

SUI surgical outcome related to, 1222, 1228

occluding devices see occluding devices

occluding forces confounding SUI surgical outcome, 1228

physiology, 127-32

position see subheading above

prostatectomy-related injury see injury

proximal, and open bladder neck at rest, imaging, 601-2

role/function, direct studies, 274-5

smooth muscle, 127
urethral valves, posterior, 463-4
urethral strictures, 465
urethral sphincter dysfunction (incl. incompetence)
urethral sphincter, internal/proximal, 300, 301
urethral pressure profile (UPP) and its assessment, 419, 423
urethral pressure profile (UPP) and its assessment, 419, 423
urethral pressure reflectionometry, 422-3
urethral pressure, 422-3
urethral pressure, 422-3
closure pressure see urethral closure pressure
measurements/studies, 419, 422-3
reproducibility/reliability/normal values, 430-2
retrograde see retro-pressure pressure
urethral pressure profile (UPP) and its assessment, 419, 423
urethral pressure reflectometry, 422-3
urethral resistance studies, 275
urethral sphincter, external/distal (rhabdosphincter; urethral skeletal muscle), 128
areflexia see underactive urethral sphincters
artificial see artificial sphincter
bypass procedures, children, 746-7
contraction, detrusor relaxation and, co-ordination, abnormalities see detrusor-sphincter dysfunction; detrusor-sphincter dyssynergia
control, development, 703-4
EMG, 275
in multiple system atrophy, 884
in neurogenic LUT dysfunction, 808
in spinal urine-storage-reflex inhibitory center characterisation, 192-3
females, anatomy/location, 271
function, mechanism, 300-2
incompetence see underactive urethral sphincters
innervation, 188-92, 301
intrinsic sphincter deficiency (ISD), 273-8
concept of, 273-4
hypermobility vs, 274-8
urodynamics in the frail elderly, 470-1
neurogenic deficiency, drug therapy, 820, 824-5
neurophysiological studies, 275
EMG see subheading above
overactive see overactive urethral sphincters
pharmacology, 194-7
supraspinal activation, 193-4
surgery, 833-8
underactive see underactive urethral sphincters
see also vesicourethrocystic disorders
urethral sphincter, internal/proximal, 300, 301
urethral sphincter dysfunction (incl. incompetence)
men, rarity of UI due to, 1736
neurogenic see neurogenic sphincter dysfunction
paediatric/congenital causes, surgery, 745-6, 746
post-prostatectomy, 306-7, 1124
endoscopic assessment for, 609
urethral strictures, 465
with intermittent catheterisation, 1582-3
urodynamics in children, 465
urethral valves, posterior, 463-4
urethrectomy and cystectomy, urinary diversion with/without, in bladder pain syndrome, 1494
urethrocutaneous fistula, men, 1151-3, 1169
urethrography
diverticula, 603, 1246
positive-pressure, 550
see also cystourethrography
urethropelvic angle, 553
urethroperineal fistula, surgery, 1406-7
urethrocystitis, men, 1151, 1153-60, 1169
urethroscopy, Q-tip test and, 343
see also endoscopy
urethrovaginal fistula, non-obstetric, 1251-2
evaluation, 1248
repair, 1252
urethrovaginal angle, posterior, 553
urethrovaginal junction see bladder neck
urge FI, 353
Urge Impact Scale (URIS) and URIS-24, 390, 400
urge syndrome see overactive bladder
urge UI (UI; urgency UI), 448-9
children
behavioural disorders and, 764
urotherapy, 769
definition, 334
depression and see depression
detrusor overactivity and, association between, 436
drug therapy
antimuscarinics, 645
oestrogens, 677-8
frail older people, 469-70
gender and, see also men; women (subheadings below)
magnetic stimulation, 1069, 1070
men
conservative treatment, 1088
prevalence, 65
refractory, management, 1145-9, 1169
mixed SUI and see mixed UI
pathophysiology, 448-9
deficiency, 448-9
women, 448-9
electrical stimulation, 1060, 1061
pelvic floor muscle training, 1035, 1080
and POP, surgical considerations, 1229
urodynamic studies, 448
urgency (to defaecate)
FI risk related to, 1334
resisting, 1348-9
urgency (to urinate)
bladder training, 1078
definition, 334
drug therapy
antimuscarinics, 647, 649, 651
resiniferatoxin, 668
electrical stimulation, 1061, 1062
measurement, 336
measurement of impact of, 381, 387-9, 389, 390-1
postoperative, in SUI, prediction, 447
ure UI see overactive bladder
urgency/frequency (U/F), sacral nerve stimulation, 1242-4
Urgency Perception Scale/Score (UPS), 387-9, 390
Urgency Questionnaire (UQ), 381
Urgency Rating Scale (URS), 387-9, 390
urgency UI see urge UI
uridine triphosphate (UTP), 120
urindomes see condom catheters
urinals (devices), 23, 25, 1533-5
bodyworn see bodyworn continence devices
handheld, 1526, 1533-5
urinalysis, 337-8, 625-6
children, 707
males, 352
urinary diary see frequency/volume diary
urinary diversion
  in bladder pain syndrome, cystectomy and urethrectomy with/without, 1494
  continent see continent urinary diversion
  in detrusor overactivity, 1240
  in developing world (in fistula management), 1447-8
  with exstrophy/epispadias complex, 1144-5
historical accounts, 29
non-continent see non-continent urinary diversion
with rectourethral fistula, 1155
urinary incontinence (UI - major refs only)
aetiology see aetiology
artificial urinary sphincter complicated by, 1163
assessment see assessment
children see children
classification by symptoms, 336
conservative management see conservative/medical management
definition, 334
devices for see continence devices
drug therapy see drug therapy
epidemiology see epidemiology
episode frequency, assessment, 336
extra-urethral, endoscopy, 609
FL and, association, 1333
guidelines, 1664-5
help-seeking see help-seeking behaviour
historical perspectives, 19-34
imaging see imaging
impact and consequences, 61-2
LUTS with, urodynamic studies in men, 450-1
men see males
neurological causes see neurogenic LUT dysfunction and incontinence
obstetric see childbirth; pregnancy
odour control products, 1626
older people see frail elderly; older people
overactive bladder with (OAB bladder), 72
overactive bladder without (OABdry), 72
overflow, urodynamic studies, 456
pathophysiology, 257-78, 299-311, 799
  men, 299-308
  men, post-prostatectomy, 1128
women, 271-8, 448-9
women, post-fistula repair, 1448
POP comorbid with see pelvic organ prolapse
post-fistula repair, 1448-50
prevention see prevention
reflex see reflex bladder
screening tools, 383-8
severity see severity
surgery see surgery
transient see transient UI
types, 334
  continuous, definition, 334
  mixed see mixed UI
urinalysis, 337-8
women see females
see also stress incontinence; urge UI
Urinary Incontinence Handicap Inventory (UIHI), 381
Urinary Incontinence Score (UIS), 381
Urinary Incontinence Severity Score (UISS), 381
Urinary Incontinence Treatment Network (UITN), 1752, 1754
Urinary Incontinence-4 Questionnaire, 388
Urinary Sensation Scale (USS), 389, 390
urinary sphincter
artificial see artificial sphincter
natural see urethral sphincter
Urinary Symptom Profile (USP), 381
urinary tract, lower/upper see lower urinary tract; upper urinary tract
urinary tract infections (UTIs)
artificial urinary sphincter-related, 1168
bladder pain syndrome and
voiding, 1611-12
invaginated, for continent urinary diversion, 857
posterior urethral, 463-4
vanilloids, intravesical see intravesical drugs
vascular dementia, 879-80
vasculature see blood vessels
vasoactive intestinal polypeptide (VIP), 132, 200
vasopressin (ADH), 679
analouges see desmopressin
nocturnal release, children, 716-17
VATER association, 463
vector manometry, 486-8
ventouse delivery
ventrourodynamics (urodynamics + imaging incl. videocys
Vereniging Nederlandse Incontinentie Verpleegkundigen (VNIV),
verapamil, 652
ventromedial thalamic nuclei (VMpo), 230, 231
ventral sacral rhizotomy, 839
ventouse delivery
vector manometry, 486-8
viscera, pelvic
vesicovaginal fistulas, 24-7
vesical autoplasty, 1446-7
vesicophosphatic disorders in multiple sclerosis, 894-6
vesicostomy, 860
child, 754
vesicoureteric reflux
botulinum toxin A and risk of, 666
children, 464, 744
day and night time enuresis and, 728-9
spinal cord injury, 901
vesicovaginal entrapment, 733
vesicovaginal fistulas, 24-7
children, surgery see surgery
non-obstetric, 1247-52
aetiology, 1247-8, 1424
complicated, 1251
evaluation, 1248-9
treatment, 1249-51
obstetric (in developing world), 1430
combined with rectovaginal fistula, 1433
conservative management, 1437, 1438
reproductive consequences, 1432
surgery, 1446, 1447
see also fistulas (women)
videourodynamics (urodynamics + imaging incl. videocys
tourethrography), 440, 551-2
children (enuresis), 710, 711-12
urethral diverticula, 603
viscera, pelvic see pelvic organs
visceral pelvic fascia see fascia
visco-elasticity, LUT, 134
Visual Analogue Scale, symptoms in bladder pain syndrome, 1475
vitamin B12 deficiency, intestinal reservoir-related, 756
voided volume see volume
voiding
catheter influence on, in urodynamic studies, 430
cerebral control, 214-21
children
normal, 705
postponement see voiding postponement
children, dysfunctional, 39, 751-2
behavioural disorders and, 764
treatment, 731-2, 735, 770
disorders/dysfunction/difficulty, 633, 636
children see subheading above
neural mechanisms, 224-5, 636
in Parkinson’s disease, 887
postoperative (in SUI), affecting outcome, 1222, 1234-5
postoperative difficulties in SUI, 446-7
pressure, in children, normal, 706
pressure-flow studies see pressure-flow studies
reflex see reflex bladder
scheduled see scheduled voiding; timed voiding
symptoms, definitions, 445
triggered, 811, 813
see also micturition
voiding cystometry, 439
voiding cystourethography see cystourethography
voiding diary see frequency/volume diary
voiding postponement, 39, 732, 764
urotherapy, 769
voiding reflex see micturition reflex; reflex voiding
volume
bladder see bladder, volume
residual see residual urine
voided
average, measurement, 336
maximum, measurement, 336
nocturnal, measurement, 336
see also frequency/volume chart; frequency/volume diary
voluntary contraction of external anal sphincter, pressure on, 481-6
Vulnerable Elders Survey, 975, 976
vulval pain in bladder pain syndrome, 1475

W

waking
scheduled, 724
to void see nocturia
see also arousal
Waldeyer’s sheath, 125
washable continence products see reusable/washable continence
products
water
anal stimulation with water streams, 868-9
spinal cord injury, 907
barrier products preventing skin penetration by, 1623, 1624
transanal and transrectal irrigation with, 868-9, 1349
water-perfused catheter in anal manometry, 475-6
see also ice water test
water-tight fistula closure, 1440, 1443
waveform analysis in neurophysiological tests, 527
websites, education resources, 1658
weight
bladder, ultrasound, 563-4
body, 1667
women, POP related to, 1096, 1096-7
see also weight reduction
body, reduction, 1667
FI prevention by, 1341
women, 1028-9
pad see pads
see also obesity
weighted vaginal cones see vaginal cones
wetting see enuresis
white matter structural lesions, frail elderly, 972
WHO see World Health Organization
Winckel F, 27
women see females
Women’s Health Initiative (WHI), 677, 678
work see occupational risk factors
World Federation of Incontinent Patients, 1683
World Health Organization (WHO) on fistulas
Fistula Surgeons Experts Meeting in Geneva (2004), 1439-40
geographical distribution data, 1422
indicators for monitoring programmes, 1425
worldwide issues, see entries under international
wound infection in SUI surgery, 1236

X

X-ray radiography (plain films), 551-9
xenograft slings, 1216

Y

YIPS (York Incontinence Perceptions Scale), 381
YM178, 658
YM905 see solifenacin
yogurt, 1347
York Incontinence Perceptions Scale (YIPS), 381
York-Mason approach to rectourethral fistula, 1156
Young, Hugh H, 28

Z

ZD0947, 653
zinc cream BP, 1624
zirconium oxide beads, pyrolytic carbon coated (Durasphere), 1404
zoster, 921
Zuidex see hyaluronic acid-dextranomer co-polymer
INTRODUCTION

The 4th International Consultation on Incontinence met from July 5th – 9th 2008 in Paris and was organised by the International Consultation on Urological Diseases, in order to develop recommendations for the diagnosis evaluation and treatment of urinary incontinence, faecal incontinence, pelvic organ prolapse and bladder pain syndrome.

The recommendations are evidence based following a thorough review of the available literature and the global subjective opinion of recognised experts serving on focused committees. The individual committee reports were developed and peer reviewed by open presentation and comment. The Scientific Committee, consisting of the Chairmen of all the committees then refined the final recommendations.

These recommendations published in 2009 will be periodically re-evaluated in the light of clinical experience, technological progress and research.
CONTENTS

1. DEFINITIONS
2. EVALUATION
3. MANAGEMENT RECOMMENDATIONS

I. URINARY INCONTINENCE IN CHILDREN
II. URINARY INCONTINENCE IN MEN
III. URINARY INCONTINENCE IN WOMEN
IV. VESICOVAGINAL FISTULA IN THE DEVELOPING WORLD
V. PELVIC ORGAN PROLAPSE
VI. NEUROGENIC URINARY INCONTINENCE
VII. URINARY INCONTINENCE IN FRAIL OLDER MEN AND WOMEN
VIII. PAINFUL BLADDER SYNDROME, INCLUDING IC (PBS/IC)
IX. FAECAL INCONTINENCE
X. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

4. RECOMMENDATIONS FOR PROMOTION, EDUCATION, AND PRIMARY PREVENTION
5. RECOMMENDATIONS FOR BASIC SCIENCE RESEARCH
6. RECOMMENDATIONS FOR EPIDEMIOLOGY
7. RECOMMENDATIONS FOR CLINICAL RESEARCH
International Consultation on Incontinence Modular Questionnaire (ICIQ) - ICIQ UI SF(short-form)
Annex 1 : Bladder Charts and Diaries
1. Definitions

The consultation agreed to use the current International Continence Society definitions (ICS) for lower urinary tract dysfunction (LUTD) including incontinence, except where stated. These definitions appeared in the journal Neurourology and Urodynamics (2002; 21:167-178 and 2006; 25: 293) or can be viewed on the ICS website: www.icsoffice.org

The following ICS definitions are relevant:

1. Lower Urinary Tract Symptoms (LUTS)

LUTS are divided into storage symptoms and voiding symptoms.

Urinary incontinence is a storage symptom and defined as the complaint of any involuntary loss of urine. This definition is suitable for epidemiological studies, but when the prevalence of bothersome incontinence is sought, the previous ICS definition of an "Involuntary loss of urine that is a social or hygienic problem" can be useful.

Urinary incontinence may be further defined according to the patient’s symptoms:

- Urgency Urinary Incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.
- Stress Urinary Incontinence is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
- Mixed Urinary Incontinence is the complaint of involuntary leakage associated with urgency and also with effort, exertion, sneezing and coughing.
- Nocturnal Enuresis is any involuntary loss of urine occurring during sleep.
- Post-micturition dribble and continuous urinary leakage denotes other symptomatic forms of incontinence.

Overactive bladder is characterised by the storage symptoms of urgency with or without urgency incontinence, usually with frequency and nocturia.

2. Urodynamic Diagnosis

- Overactive Detrusor Function, is characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked.

The overactive detrusor is divided into:

- Idiopathic Detrusor Overactivity, defined as overactivity when there is no clear cause.
- Neurogenic Detrusor Overactivity is defined as overactivity due to a relevant neurological condition.

- Urodynamic stress incontinence is noted during filling cystometry, and is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction.

3. Bladder Pain Syndrome *

- Bladder pain syndrome is defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.

4. Pelvic Organ Prolapse

- Uro-genital prolapse is defined as the symptomatic descent of one or more of: the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Uro-genital prolapse is measured using the POPQ system.

- Rectal prolapse is defined as circumferential full thickness rectal protrusion beyond the anal margin.

5. Anal Incontinence *

- Anal incontinence, defined as “any involuntary loss of faecal material and/or flatus” and may be divided into:
  - Faecal incontinence, any involuntary loss of faecal material
  - Flatus incontinence, any involuntary loss of gas (flatus)

* To date, these definitions are not included in the current ICS terminology
The following phrases are used to classify diagnostic tests and studies:

- **A highly recommended test** is a test that should be done on every patient.
- **A recommended test** is a test of proven value in the evaluation of most patients and its use is strongly encouraged during initial evaluation.
- **An optional test** is a test of proven value in the evaluation of selected patients; its use is left to the clinical judgement of the physician.
- **A not recommended test** is a test of no proven value.

The recommendations are intended to apply to children and adults, including healthy persons over the age of 65.

These conditions are highly prevalent but often not reported by patients. Therefore, the Consultation strongly recommends case finding, particularly in high risk groups.

The main recommendations for this consultation have been abstracted from the extensive work of the 23 committees of the 4th International Consultation on Incontinence (ICI, 2008).

Each committee has written a report that reviews and evaluates the published scientific work in each field of interest in order to give **Evidence Based recommendations**. Each report ends with detailed recommendations and suggestions for a programme of research.

The main recommendations should be read in conjunction with the management algorithms for children, men, women, the frail older person, neurogenic patients, bladder pain, pelvic organ prolapse, and anal incontinence.

The initial evaluation should be undertaken, by a clinician, in every patient presenting with symptoms/signs suggestive of these conditions.

### 1. History and General Assessment

Management of a disease such as incontinence requires caregivers to **assess** the sufferer in a holistic manner. Many factors may influence a particular individual’s symptoms, some may cause incontinence, and may influence the choice and the success of treatment. **The following components of the medical history are particularly emphasized:**

**a) Review of Systems:**

- Presence, severity, duration and bother of any urinary, bowel or prolapse symptoms. Identifying symptoms in the related organ systems is critical to effective treatment planning. It is useful to use validated questionnaires to assess symptoms.
- Effect of any symptoms on sexual function: validated questionnaires including impact on quality of life are a useful part of a full assessment.
- Presence and severity of symptoms suggesting neurological disease

**b) Past Medical History:**

- **Previous conservative, medical and surgical treatment,** in particular, as they affect the genitourinary tract and lower bowel. The effectiveness and side effects of treatments should be noted.
- **Coexisting diseases** may have a profound effect on incontinence and prolapse sufferers, for example asthma patients with stress incontinence will suffer greatly during attacks. Diseases may also precipitate incontinence, particularly in frail older persons.
- **Patient medication:** It is always important to review every patient’s medication and to make an assessment as to whether current treatment may be contributing to the patient’s condition.
- **Obstetric and menstrual history.**
- **Physical impairment:** individuals who have compromised mobility, dexterity, or visual acuity may need to be managed differently

**c) Social History:**

- **Environmental issues:** these may include the social, cultural and physical environment.
• **Lifestyle**: including exercise, smoking and the amount and type of food/fluid intake.

**d) Other Treatment Planning Issues:**

• **Desire for treatment** and the extent of treatment that is acceptable.

• **Patient goals** and expectations of treatment

• **Patient support** systems (including carers).

• **Cognitive function**: all individuals need to be assessed for their ability to fully describe their symptoms, symptom bother and quality of life impact, and their preferences and goals for care, and to understand proposed management plans and to discuss, where appropriate, alternative treatment options. In some groups of patients formal testing is essential e.g. cognitive function testing for individuals for whom the clinician has concerns regarding memory deficits and/or inattention/confusion, and depression screening for individuals for whom the clinician has concerns about abnormal affect. Proxy respondents, such as family and carers, may be used to discuss history, goals of care, and treatment for individuals with dementia only if the individual is incapable of accurate reporting or weighing treatment decisions.

### 2. Physical Examination

The **more complicated** the history and the more extensive and/or invasive the proposed therapy, the **more complete** the examination needs to be. Depending on the patients symptoms and their severity, there are a number of components in the examination of patients with incontinence and/or pelvic organ prolapse.

**a) General status:**

• Mental status

• Obesity (BMI)

• Physical dexterity and mobility

**b) Abdominal/flank examination**: for masses, bladder distention, relevant surgical scars

**c) Pelvic examination:**

• Examination of the perineum and external genitalia including tissue quality and sensation.

• Vaginal (half-speculum) examination for prolapse

• Bimanual pelvic and anorectal examination for pelvic mass, pelvic muscle function, etc.

• Stress test for urinary incontinence.

**d) Neurological testing (see chapter on assessment)**

Neurological examination should be performed regardless of whether the patient is a child, a woman, a man, someone with neurological disease or a frail elderly person.

### 3. Urinalysis

In patients with urinary symptoms a **urinary tract infection** is a readily detected, and easily treatable cause of LUTS, and urine testing is highly recommended. Testing may range from dipstick testing, to urine microscopy and culture when indicated.

**Conclusion**

For simple treatments, particularly non-invasive and inexpensive therapies, management may start without the need for the further investigations listed below.

---

### II. RECOMMENDED FURTHER ASSESSMENT PRIOR TO, OR DURING, SPECIALIST ASSESSMENT

The tests below are recommended when the **appropriate indication(s) is present**. Some recommended tests become highly recommended in specific situations.

This section should also be read in conjunction with the relevant committee reports.

#### 1. Further Symptom and Health-Related QoL Assessment

In patients with **urinary symptoms** the use of a **simple frequency volume chart** or **bladder diary** (examples in Annex 1) is highly recommended to document the frequency of micturition, the volumes of urine voided, incontinence episodes and the use of incontinence pads.
The use of the highest quality questionnaires (Grade A, where available) is recommended for the assessment of the patient’s perspective of symptoms of incontinence and their impact on quality of life.

The ICIQ is highly recommended (Grade A) for the basic evaluation of the patient’s perspective of urinary incontinence; with other Grade A questionnaires recommended for more detailed assessment. Further development is required in the areas of pelvic organ prolapse, bladder pain syndrome and faecal incontinence, and for specific patient groups, as only Grade B questionnaires are currently available (see Appendix).

### 2. Renal Function Assessment

Standard biochemical tests for renal function are recommended in patients with urinary incontinence and a probability of renal impairment.

### 3. Uroflowmetry

Uroflowmetry with the measurement of postvoid residual urine is recommended as a screening test for symptoms suggestive of urinary voiding dysfunction or physical signs of POP or bladder distension.

### 4. Estimation of Post Void Residual Urine (PVR)

In patients with suspected voiding dysfunction, PVR should be part of the initial assessment if the result is likely to influence management, for example, in neurological patients.

### 5. Imaging

Although routine imaging is not recommended, imaging of the lower urinary tract and pelvis is highly recommended in those with urinary symptoms whose initial evaluation indicates a possible co-existing lower tract or pelvic pathology. Initial imaging may be by ultrasound, or plain X ray.

Imaging of the upper urinary tract is highly recommended in specific situations. These include:

- Haematuria
- Neurogenic urinary incontinence e.g. myelodysplasia, spinal cord trauma,
- Incontinence associated with significant post-void residual,
- Co-existing loin/kidney pain,
- Severe pelvic organ prolapse, not being treated
- Suspected extra-urethral urinary incontinence,
- Children with incontinence and UTIs, where indicated
- Urodynamic studies which show evidence of poor bladder compliance.

In anorectal conditions anal US or MRI prior to anal sphincter surgery is highly recommended, when obvious anatomic defects are not evident (cloacal formations). Defaecating proctography or dynamic MRI is recommended in suspected rectal prolapse which cannot be adequately confirmed by physical examination.

### 6. Endoscopy

Although routine cystourethroscopy is not recommended, LUT endoscopy is highly recommended:

- When initial testing suggest other pathologies, e.g. haematuria
- When pain or discomfort features in the patient’s LUTS: these may suggest an intravesical lesion
- When appropriate in the evaluation of vesicovaginal fistula and extra-urethral urinary incontinence (in childbirth fistulae, endoscopy is often unnecessary).

In anorectal conditions, proctoscopy or flexible sigmoidoscopy should routinely be performed in the evaluation of patients with faecal incontinence. Colonoscopy, air contrast barium enema or CT colography is highly recommended in the presence of unexplained change in bowel habit, rectal bleeding or other alarm symptoms or signs (see Basic Assessment chapter).

### 7. Urodynamic Testing

**a) Urodynamic evaluation is recommended**

- When the results may change management, such as prior to most invasive treatments for UI and POP
- After treatment failure, if more information is needed in order to plan further therapy.
- As part of both initial and long-term surveillance programmes in some types of neurogenic lower urinary tract dysfunction
- In “complicated incontinence” (for details please see relevant subcommittee reports).
b) The aims of Urodynamic Evaluation are

- To reproduce the patient's symptoms and correlate these with urodynamic findings
- The assessment of bladder sensation
- The detection of detrusor overactivity
- The assessment of urethral competence during filling
- The determination of detrusor function during voiding
- The assessment of outlet function during voiding
- The measurement of residual urine

These tests are recommended in the presence of unexplained diarrhoea or when Crohn's disease is suspected.

III. OPTIONAL DIAGNOSTIC TESTS

1. Additional Urodynamic Testing

**Video-urodynamics** may be useful in the management of UI in children, in patients who fail surgery and in some neurogenic patients, to obtain additional anatomical information. Both US and X-ray imaging can be used.

If a more detailed estimate of urethral function is required, then the following optional tests may give useful information:

- Urethral pressure profilometry
- Abdominal leak point pressures
- Video-urodynamics
- Electromyography

**If initial urodynamics have failed** to demonstrate the cause for the patient's incontinence then the following tests are optional:

- repeated routine urodynamics
- ambulatory urodynamics

2. Pad Testing

Pad testing is an optional test for the routine evaluation of urinary incontinence and, if carried out, a 24 hr test is suggested.

3. Neurophysiological Testing and Imaging

The information gained by clinical examination and urodynamic testing may be enhanced by neurophysiological testing of striated muscle and nervous pathways.

Appropriately trained personnel should perform these tests. The following neurophysiological tests can be considered in patients with peripheral lesions prior to treatment for lower urinary tract or anorectal dysfunction.

- Concentric needle EMG
- Sacral reflex responses to electrical stimulation of penile or clitoral nerves.

**Pudendal nerve latency** testing is **not recommended**.

**Further imaging of the central nervous system**, including spine, by myelography, CT and MRI may prove useful if simple imaging, for example by spinal X-rays in patients with suspected neurological disease, proves normal.

4. Further Imaging

**Cysto-urethrography**, US, CT and MRI may have an indication in case of:

- Suspected pelvic floor dysfunction
- Failed surgery, such as recurrent posterior vaginal wall prolapse or failed sling surgery
- Suspected fixed urethra

5. Cysto-urethroscopy

This is an optional test in patients with complicated or recurrent UI (e.g. after failed SUI surgery)

6. Anorectal physiology testing

**Anal manometry** is useful to assess resting and squeeze anal pressures.
3. Management Recommendations

The management recommendations are derived from the detailed work in the committee reports on the management of incontinence in children, men, women, the frail elderly and neurological patients, obstetric fistula, pelvic organ prolapse, bladder pain syndrome, and faecal incontinence. The management of incontinence is presented in algorithm form with accompanying notes.

The Consultation recognised that no algorithm can be applied to every patient and each patient's management must be individualised.

There are algorithms for

- I. Urinary Incontinence in Children
- II. Urinary Incontinence in Men
- III. Urinary Incontinence in Women
- IV. Obstetric Fistulae
- V Urinary Incontinence in Frail Older Men and Women
- VI. Urinary Incontinence in Neurological Patients
- VII Bladder Pain Syndrome
- VIII. Pelvic Organ Prolapse
- IX. Faecal Incontinence in Non-Neurological Patients
- X. Faecal Incontinence in Neurological Patients

These algorithms are divided into two for groups I to III, IX, XI and X: the two parts, initial management and specialised management require a little further explanation.

Although the management algorithms are designed to be used for patients whose predominant problem is incontinence, there are many other patients in whom the algorithms may be useful such as those patients with urgency and frequency, so-called "OAB dry".

The algorithms for initial management are intended for use by all clinicians including health care assistants, nurses, physiotherapists, generalist doctors and family doctors as well as by specialists such as urologists and gynaecologists. The consultation has attempted to phrase the recommendations in the basic algorithms in such a way that they may be readily used by clinicians in all countries of the world, both in the developing and the developed world.

The specialised algorithms are intended for use by specialists. The specialised algorithms, as well as the initial management algorithms are based on evidence where possible and on the expert opinion of the 700 healthcare professionals who took part in the Consultation. In this consultation, committees ascribed levels of evidence to the published work on the subject and devised grades of recommendation to inform patient management.

It should be noted that these algorithms, dated March 2009, represent the Consultation consensus at that time. Our knowledge, developing from both a research base and because of evolving expert opinion, will inevitably change with time. The Consultation does not wish those using the algorithms to believe they are “carved in tablets of stone”: there will be changes both in the relatively short term and the long term.

Essential components of basic assessment

Each algorithm contains a core of recommendations in addition to a number of essential components of basic assessment listed in sections I to III.

- General assessment
- Symptom assessment
- Assessment of quality of life impact
- Assessment of the desire for treatment
- Physical examination
- Urinalysis

Joint decision making

The patient’s desires and goals for treatment:

Treatment is a matter for discussion and joint decision making between the patient and his or her health care advisors. This process of
consultation includes the specific need to assess whether or not the sufferer of incontinence wishes to receive treatment and, if so, what treatments he or she would favour. Implicit in this statement is the assumption that the health care provider will give an appropriate explanation of the patient’s problem and the alternative lines of management, and the indications and the risks of treatment. The assumption that patients almost always wish to have treatment is flawed, and the need to consult the patient is paramount.

In each algorithm, treatments are listed in order of simplicity, the least invasive being listed first. This order does not imply a scale of efficacy or cost, two factors which need to be considered in choosing the sequence of therapy. The order is likewise not meant to imply a suggested sequence of therapy, which is determined jointly by the treating health care providers and the patient, considering all the relevant factors listed above.

In the initial management algorithms, treatment is empirically based, whilst, the specialized management algorithms usually rely on precise diagnosis from urodynamics and other testing.

The assumption is made that patients will be reassessed at an appropriate time to evaluate their progress.

◆ Use of Continence Products

The possible role of continence products should be considered at each stage of patient assessment, treatment and, if treatment is not (fully) successful, subsequent management.

- **Firstly**, intermittent catheterisation or indwelling catheter drainage often have a role to play in addressing urinary retention.
- **Secondly**, assisted toileting using such devices as commodes, bedpans, and handheld urinals may help to achieve dependent continence* where access, mobility and / or urgency problems under-mine a patient’s ability to maintain independent continence*, be it urinary and / or faecal.
- **Finally**, containment products (to achieve contained incontinence*) for urine and / or faeces find an essential role in enhancing the quality of life of those who:
  - Elect not to pursue treatment options
  - Are awaiting treatment
  - Are waiting for treatment to take effect
  - Are unable to be (fully) cured

Further guidance and care algorithms on which products might be suitable for a given patient are given in Committee 20.

1. **Initial management**

Children produce specific management problems for a variety of reasons: assessment requires help from their parents and carers; consent to treatment may be problematic; and cooperation in both assessment and treatment may be difficult.

Referrals for specialist treatment are recommended for a group of children who have complicated incontinence associated with:

- recurrent urinary infection
- voiding symptoms or evidence of poor bladder emptying
- urinary tract anomalies,
- previous pelvic surgery
- neuropathy

**Initial treatment is recommended for the remaining patients who have:**

- Nocturnal enuresis without other symptoms (mono-symptomatic enuresis).
- Daytime symptoms of frequency, urgency, urgency incontinence with or without night-time wetting

2. **Treatment**

- Initial treatment for *mono-symptomatic nocturnal* enuresis should include:
  - parental counselling and motivation
  - a choice between either alarm (Grade A) and anti-diuretic hormone analogues desmopressin (Grade A)*. It may be a parental choice if advantages and disadvantages are well explained.

- *Daytime incontinence* should be managed holistically including:
  - counselling, bladder training (timed voiding), behaviour modification and bowel management when necessary (Grade B).
  - antimuscarinics may be used if there are symptoms that suggest detrusor overactivity (Grade C).

Should initial treatment be unsuccessful for either enuresis or daytime symptoms, then after a reasonable period of time (8-12 weeks), referral for a specialist’s advice is highly recommended.

* A regulatory warning exists for the danger of overhydration in children on desmopressin.
Initial Management of Urinary Incontinence in Children

**HISTORY/SYMPOTOM ASSESSMENT**
- Nocturnal enuresis (monosymptomatic)
- Daytime ± Nighttime wetting ± Urgency / frequency

**CLINICAL ASSESSMENT**
- General assessment (see relevant chapter)
  - Physical examination: abdominal, perineal, ext. genitalia, back/spine, neurological
  - Assess bowel function -> if constipated, treat and reassess
  - Urinalysis ± Urine culture -> if infected, treat and reassess
  - Assess post-void residual urine by abdominal examination (optional: by ultrasound)

**PRESUMED DIAGNOSIS**
- Monosymptomatic Nocturnal Enuresis

**TREATMENT**
- Failure

**URGENCY INCONTINENCE**
- Bladder training
- Antimuscarinics
- Alarm
- Desmopressin

**RECURRENT INFECTION**
- Failure

**DYSFUNCTIONAL VOIDING**
- Any other abnormality detected e.g. Post void residual

**“Complicated” Incontinence**
- Associated with:
  - Urinary tract anomaly
  - Neuropathy
  - Pelvic surgery
  - Voiding (emptying) symptoms
  - Recurrent urinary infection

**SPECIALIZED MANAGEMENT**
I. CHILDREN

B. SPECIALIZED MANAGEMENT

Two groups of children with “complicated” incontinence should have specialist management from the outset.

- Children whose incontinence is due to, or associated with, urinary tract anomalies and neuropathy.
- Children without urinary tract anomalies, but with recurrent infection and, proven or suspected, voiding dysfunction.

Children who failed the basic treatment, but who have neither neurogenic nor anatomical problems, should also receive specialist management:

1. Assessment

As part of further assessment, the measurement of urine flow (in children old enough), together with the ultrasound estimate of residual urine and the upper urinary tracts is highly recommended.

Those who fail treatment and have neither neurogenic nor anatomical problems should be reassessed using micturition charts, symptom scores, urinalysis, Uroflowmetry and residual urine determination.

If there are recurrent infections, upper tract imaging and possibly a VCUG should be considered. However, endoscopy is rarely indicated.

Urodynamics should be considered:

- If the type and severity of lower tract dysfunction cannot be explained by clinical findings
- If invasive treatment is under consideration, for example, stress incontinence surgery or bladder augmentation, when there is sphincteric incompetence, or if there is detrusor overactivity.
- If upper tract dilatation exists and is thought to be due to bladder dysfunction.

Urodynamic studies are not recommended if the child has normal upper tract imaging and is to be treated by non invasive means.

Spinal Imaging (US/Xray/MRI) may be needed if a bony abnormality or neurological condition is suspected.

2. Treatment

The treatment of incontinence associated with urinary tract anomalies is complex and cannot easily be dealt with in an algorithm. In many children, more than one pathophysiology demands treatment. If there are complex congenital abnormalities present, the treatment is mostly surgical and it should be individualised according to the type and severity of the problem (please see Children's Committee Report).

Care should be given by specialist children’s nurses and therapists.

Initial treatment should be non-surgical.

- For stress urinary incontinence (SUI): pelvic floor muscle training (Grade C)
- For suspected detrusor overactivity (DO): bladder training and antimuscarinics (Grade C)
- For voiding dysfunction: timed voiding, biofeedback to teach pelvic floor relaxation, intermittent catheterisation (when PVR > 30% of bladder capacity). (Grade B/C)
- For bowel dysfunction: as appropriate

The child’s progress should be assessed and, if quality of life is still significantly impaired, or if the upper urinary tracts are at risk, surgical treatment is likely to be necessary.

If surgical treatment is required, then urodynamics is recommended to confirm the diagnosis.

- For SUI, sling surgery, bulking agent injection and AUS may be considered
- For DO/poor compliance, botulinum toxin * and bladder augmentation may be performed.
- If the child cannot do IC then a Mitrofanoff channel may be needed.

* At the time of writing, botulinum toxin is being used “off label” for refractory DO and must be used with caution.
Specialized Management of Urinary Incontinence in Children

**Expert History & Physical Examination**

- Urinalysis: if UTI, treat and reassess as appropriate
- Treat bowel dysfunction and reassess
- Renal / bladder ultrasound
- Assess Post void residual
- Flow rates ± electromyography
- Behavioral Evaluation

**Clinical Assessment**

- Timed voiding
- Pelvic floor relaxation ± biofeedback.
- Pharmacotherapy:
  - Antimuscarinics
  - α-blucers
- Intermittent cath.
- Bowel Management
- Antibiotic if infection

**Diagnosis**

- Incontinence without suspicion of urinary tract anomaly:
  - Urinalysis: if UTI, treat and reassess as appropriate
  - Treat bowel dysfunction and reassess
  - Renal / bladder ultrasound
  - Assess Post void residual
  - Flow rates ± electromyography
  - Behavioral Evaluation

- Incontinence with suspicion of urinary tract anomaly:
  - Consider:
    - Micturating cystogram
    - Renal scintigram
    - Urodynamics
    - Cystourethroscopy
    - Spinal imaging

**Treatment**

- Stress Urinary Incontinence:
  - Pelvic floor and muscle training

- Detrusor Overactivity / Poor Compliance:
  - Bladder training
  - Antimuscarinics
  - Bowel management.

- Voiding Dysfunction:
  - Timed voiding
  - Pelvic floor relaxation ± biofeedback.
  - Pharmacotherapy:
    - Antimuscarinics
    - α-blockers
  - Intermittent cath.
  - Bowel Management
  - Antibiotic if infection

- Anatomic Causes of Urinary Incontinence:
  - Correct anomaly (see: surgical treatment in children)

- Failure:
  - AUS
  - Sling
  - Bulking agent injection
  - Botulinum toxin
  - Bladder augmentation

- Mitrofanoff if IC fails
II. MEN

A. INITIAL MANAGEMENT

1. Initial Assessment should identify:

» **Complicated** incontinence group

Those with pain or with haematuria, recurrent infections, suspected or proven poor bladder emptying (for example due to bladder outlet obstruction), or incontinence following pelvic irradiation, are recommended for **specialized management**.

**Poor bladder emptying** may be suspected from symptoms, physical examination or if imaging has been performed by X-ray or ultrasound after voiding.

» **Four other main groups** of men should be identified by initial assessment as being suitable for **initial management**.

- Those with **post-micturition dribble** alone,
- Those with **overactive bladder** (OAB) symptoms: urgency with or without urgency incontinence, together with frequency and nocturia
- Those with **stress incontinence** (most often post-prostatectomy), and
- Those with **mixed** urgency and stress incontinence (most often post-prostatectomy)

2. Management

» For men with **post-micturition dribble**, this requires no assessment and can usually be treated by teaching the man how to do a strong pelvic floor muscle contraction after voiding, or manual compression of the bulbous urethra directly after micturition. (Grade B)

» For men with **stress, urgency or mixed** urgency / stress incontinence, initial treatment should include appropriate lifestyle advice, physical therapies, scheduled voiding regimes, behavioural therapies and medication. In particular:

- Lifestyle interventions (Grade D)
- Supervised pelvic floor muscle training for men with post radical prostatectomy SUI (Grade B)
- Scheduled voiding regimes for OAB (Grade C)
- Antimuscarinic drugs for OAB symptoms with or without urgency incontinence (Grade B) and the patient has no evidence of significant post-void residual urine
- **α**-adrenergic antagonists (a-blockers), can be added if it is thought that there may also be bladder outlet obstruction. (Grade C)

» **Should initial treatment be unsuccessful** after a reasonable period of time (for example, 8-12 weeks), **specialist advice** is highly recommended.

Clinicians are likely to wish to treat the **most bothersome symptom** first in men with symptoms of **mixed** incontinence.
Initial Management of Urinary Incontinence in Men

**HISTORY**
- Post-micturition dribble
- Incontinence on physical activity (usually post-prostatectomy)
- Incontinence with mixed symptoms
- Urgency / frequency, with or without urgency incontinence

**CLINICAL ASSESSMENT**
- General assessment (see relevant chapter)
- Urinary Symptom Assessment and symptom score (including frequency-volume chart and questionnaire)
- Assess quality of life and desire for treatment
- Physical examination: abdominal, rectal, sacral, neurological
- Urinalysis ± urine culture -> if infected, treat and reassess
- Assessment of pelvic floor muscle function
- Assess post-void residual urine

**PRESUMED DIAGNOSIS**
- STRESS INCONTINENCE presumed due to sphincteric incompetence
- MIXED INCONTINENCE (treat most bothersome symptom first)
- URGENCY INCONTINENCE presumed due to detrusor overactivity

**MANAGEMENT**
- Urethral milking
- Pelvic floor muscle contraction

**DISCUSS TREATMENT OPTIONS WITH THE PATIENT**
- Lifestyle interventions
- Pelvic floor muscle training ± biofeedback
- Scheduled voiding (bladder training)
- Incontinence products
- Antimuscarinics (OAB ± urgency incontinence) and α-adrenergic antagonists (if also bladder outlet obstruction)

**“Complicated” incontinence**
- Recurrent or “total” incontinence
- Incontinence associated with:
  - Pain
  - Hematuria
  - Recurrent infection
  - Prostate irradiation
  - Radical pelvic surgery

Any other abnormality detected e.g. significant post void residual

**SPECIALIZED MANAGEMENT**

Failure
The specialist may first reinstitute initial management if it is felt that previous therapy had been inadequate.

1. Assessment

- Patients with “complicated” incontinence referred directly to specialized management, are likely to require additional testing, cytology, cystourethroscopy and urinary tract imaging.

If these tests prove normal then those individuals can be treated for incontinence by the initial or specialized management options as appropriate.

If symptoms suggestive of detrusor overactivity, or of sphincter incompetence persist, then urodynamic studies are recommended in order to arrive at a precise diagnosis, prior to invasive treatment.

2. Treatment

When basic management has failed

and if the patient’s incontinence markedly disrupts his quality of life then invasive therapies should be considered.

- For sphincter incompetence the recommended option is the artificial urinary sphincter (Grade B). other options, such as a male sling, may be considered (Grade C).

- For idiopathic detrusor overactivity, (with intractable overactive bladder symptoms) the recommended therapies are bladder augmentation (Grade C) and neuromodulation (Grade B). Botulinum toxin continues to show promise in the treatment of symptomatic detrusor overactivity unresponsive to other therapies *

- When incontinence has been shown to be associated with poor bladder emptying and detrusor underactivity, it is recommended that effective means are used to ensure bladder emptying, for example, intermittent catheterisation (Grade B/C).

- If incontinence is associated with bladder outlet obstruction, then consideration should be given to effective treatment to relieve obstruction (Grade B). α-blockers and/or 5α-reductase inhibitors would be an optional treatment (Grade C). There is increased evidence for the safety of antimuscarinics for overactive bladder symptoms in men, chiefly in combination with an α-blocker (Grade B).

* Note: At the time of writing, botulinum toxin is being used “off-label”.

When basic management has failed

and if the patient’s incontinence markedly disrupts his quality of life then invasive therapies should be considered.
Specialized Management of Urinary Incontinence in Men

**HISTORY/SYMPOM ASSESSMENT**

- Post-prostatectomy incontinence
- Incontinence with urgency / frequency
- “Complicated” Incontinence:
  - Recurrent incontinence
  - Incontinence associated with:
    - Prostate or pelvic irradiation
    - Radical pelvic surgery

**CLINICAL ASSESSMENT**

- STRESS INCONTINENCE due to sphincteric incompetence
- MIXED INCONTINENCE Treat major component first
- URGENCY INCONTINENCE due to detrusor overactivity (during filling)

**DIAGNOSIS**

- Post-prostatectomy incontinence
- Incontinence with urgency / frequency

**TREATMENT**

- If initial therapy fails:
  - STRESS INCONTINENCE: Artificial urinary sphincter, Male sling (see chapter)
  - MIXED INCONTINENCE: ρ-blockers, 5ARI, Correct anatomic bladder outlet obstruction, Antimuscarinics (See note)
  - URGENCY INCONTINENCE: Intermitent catheterisation, Antimuscarinics

- If initial therapy fails:
  - Neuromodulation

- “Complicated” Incontinence:
  - Artificial urinary sphincter
  - Male sling
  - ρ-blockers, 5ARI
  - Correct anatomic bladder outlet obstruction
  - Antimuscarinics

- Consider:
  - Urethrocystoscopy
  - Further imaging
  - Urodynamics

- Correct anomaly
- Treat pathology

Consider:
- Urethrocystoscopy
- Further imaging
- Urodynamics

- Lower urinary tract anomaly/pathology

If initial therapy fails:
- Intermitent catheterisation
- Antimuscarinics
- Correct anomaly
- Treat pathology

If initial therapy fails:
- Neuromodulation

If initial therapy fails:
- Intermittent catheterisation
- Antimuscarinics
- Correct anomaly
- Treat pathology

If initial therapy fails:
- Neuromodulation

If initial therapy fails:
- Intermittent catheterisation
- Antimuscarinics
- Correct anomaly
- Treat pathology
III. WOMEN

A. INITIAL MANAGEMENT

1. Initial assessment should identify:

   ➤ “Complicated” incontinence group.
   Those with pain or haematuria, recurrent infections, suspected or proven voiding problems, significant pelvic organ prolapse or who have persistent incontinence or recurrent incontinence after pelvic irradiation, radical pelvic surgery, previous incontinence surgery, or who have a suspected fistula, for specialist referral.

   ➤ Three other main groups of patients should be identified by initial assessment.
   • Women with stress incontinence on physical activity
   • Women with urgency, frequency with or without urgency incontinence
   • Those women with mixed urgency and stress incontinence
   Abdominal, pelvic and perineal examinations should be a routine part of physical examination. Women should be asked to perform a “stress test” (cough and strain to detect leakage likely to be due to sphincter incompetence). Any pelvic organ prolapse or uro-genital atrophy should be assessed. Vaginal or rectal examination allows the assessment of voluntary pelvic floor muscle function, an important step prior to the teaching of pelvic floor muscle training.

2. Treatment

   ➤ For women with stress, urgency or mixed urinary incontinence, initial treatment should include appropriate lifestyle advice, physical therapies, scheduled voiding regimes, behavioural therapies and medication. In particular:
   • Advice on caffeine reduction (Grade B) and weight reduction (Grade A)
   • Supervised pelvic floor muscle training (Grade A), vaginal cones for women with stress incontinence (Grade B)
   • Supervised bladder training (Grade A) for OAB.
   • If oestrogen deficiency and/or UTI is found, the patient should be treated at initial assessment and then reassessed after a suitable interval. (Grade B).
   • Antimuscarinics for OAB symptoms with or without urgency incontinence (Grade A); duloxetine* may be considered for stress urinary incontinence (Grade B)
   Initial treatment should be maintained for 8-12 weeks before reassessment and possible specialist referral for further management if the patient has had insufficient improvement.
   Clinicians are likely to wish to treat the most bothersome symptom first in women with symptoms of mixed incontinence. (Grade C).

   ➤ Some women with significant pelvic organ prolapse can be treated by vaginal devices that treat both incontinence and prolapse (incontinence rings and dishes).

   * Duloxetine is not approved for use in United States. It is approved for use in Europe for severe stress incontinence (see committee report on pharmacological management for information regarding efficacy, adverse events, and ‘black box’ warning by the Food and Drug Administration of the United States).
Initial Management of Urinary Incontinence in Women

**HISTORY**
- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence / frequency with urgency

**CLINICAL ASSESSMENT**
- **Complicated incontinence**
  - Recurrent incontinence
  - Incontinence associated with:
    - Pain
    - Hematuria
    - Recurrent infection
    - Significant voiding symptoms
    - Pelvic irradiation
    - Radical pelvic surgery
    - Suspected fistula

**PRESUMED DIAGNOSIS**
- **Stress incontinence**
  - Presumed due to sphincteric incompetence
- **Mixed incontinence**
  - (treat most bothersome symptom first)
- **OAB - with or without urgency incontinence**
  - Presumed due to detrusor overactivity

**MANAGEMENT**
- **If other abnormality found e.g.**
  - Significant post void residual
  - Significant pelvic organ prolapse
  - Pelvic mass

**General assessment** (see relevant chapter)
- Urinary symptom assessment (including frequency-volume chart and questionnaire)
- Assess quality of life and desire for treatment
- Physical examination: abdominal, pelvic and perineal
- Cough test to demonstrate stress incontinence if appropriate
- Urinalysis ± urine culture -> if infected, treat and reassess
- If appropriate
- Assess oestrogen status and treat as appropriate
- Assess voluntary pelvic floor muscle contraction
- Assess post-void residual urine

**Stress incontinence**
- Life style interventions.
- Pelvic floor muscle training for SUI or OAB
- Bladder retraining for OAB
- Duloxetine* (SUI) or antimuscarinic (OAB ± urgency incontinence)

**Mixed incontinence**
- Other adjuncts, such as electrical stimulation
- Vaginal devices, urethral inserts

**SPECIALIZED MANAGEMENT**
- * Subject to local regulatory approval (see black box warning).
III. WOMEN

B. SPECIALIZED MANAGEMENT

1. Assessment

Women who have “complicated” incontinence (see initial algorithm) may need to have additional tests such as cytology, cystourethroscopy or urinary tract imaging. If these tests are normal then they should be treated for incontinence by the initial or specialized management options as appropriate.

(STD)

⇒ Those women who have failed initial management and whose quality of life is impaired are likely to request further treatment. If initial management has been given an adequate trial then interventional therapy may be desirable. Prior to intervention urodynamic testing is highly recommended, when the results may change management. It is used to diagnose the type of incontinence and therefore inform the management plan. Within the urodynamic investigation urethral function testing by urethral pressure profile or leak point pressure is optional.

⇒ Systematic assessment for pelvic organ prolapse is highly recommended and it is suggested that the POPQ method should be used in research studies. Women with co-existing pelvic organ prolapse should have their prolapse treated as appropriate.

2. Treatment

⇒ If urodynamic stress incontinence is confirmed then the treatment options that are recommended for patients with some degree of bladder-neck and urethral mobility include the full range of non-surgical treatments, as well as retropubic suspension procedures, (Grade A) and bladder neck/sub-urethral sling operations: (Grade A). The correction of symptomatic pelvic organ prolapse may be desirable at the same time.

⇒ For patients with limited bladder neck mobility, bladder neck sling procedures, (Grade A) injectable bulking agents (Grade B) and the artificial urinary sphincter (Grade B) can be considered.

⇒ Urgency incontinence (overactive bladder) secondary to idiopathic detrusor overactivity may be treated by neuromodulation (Grade A) or bladder augmentation (Grade C). Botulinum toxin can be used in the treatment of symptomatic detrusor overactivity unresponsive to other therapies (Grade C).*

⇒ Those patients with voiding dysfunction leading to significant post-void residual urine (for example, >30% of total bladder capacity) may have bladder outlet obstruction or detrusor underactivity. Prolapse is a common cause of voiding dysfunction.

* At the time of writing, botulinum toxin is being used “off-label” and with caution.
Specialized Management of Urinary Incontinence in Women

**HISTORY/SYMPTOM ASSESSMENT**
- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence with urgency / frequency

**CLINICAL ASSESSMENT**
- Assess for pelvic organ mobility / prolapse
- Consider imaging of the UT/pelvic floor
- Urodynamics (see notes)

**DIAGNOSIS**
- URODYNAMIC STRESS INCONTINENCE (USI)
- MIXED INCONTINENCE (USI/DOI) (Treat. most bothersome symptom first)
- DETRUSOR OVERACTIVITY INCONTINENCE (DOI)
- INCONTINENCE associated with poor bladder emptying

**TREATMENT**
- If initial therapy fails:
  - Stress incontinence surgery
  - bulking agents
  - tapes and slings
  - colposuspension
- If initial therapy fails:
  - Botulinum toxin
  - Neuromodulation
  - Bladder augmentation
- Correct anatomic bladder outlet obstruction (e.g. genito-urinary prolapse)
- Intermittent catheterization

“Complicated” incontinence:
- Recurrent incontinence
- Incontinence associated with:
  - Pain
  - Hematuria
  - Recurrent infection
  - Voiding symptoms
  - Pelvic irradiation
  - Radical pelvic surgery
  - Suspected fistula

Consider:
- Urethrocystoscopy
- Further imaging
- Urodynamics

Lower urinary tract anomaly/pathology
- Bladder outlet obstruction
- Underactive detrusor
- Correct anomaly
- Treat pathology
IV. VESICOVAGINAL FISTULA IN THE DEVELOPING WORLD

I. INTRODUCTION

• Obstructed labour is the main cause of vesicovaginal fistula in the developing world. The obstructed labour complex not only induces the vesicovaginal fistula and fetal death in most cases, but can also have urological, gynaecological, neurological, gastro-intestinal, musculoskeletal, dermatological and social consequences.

• Other aetiologies such as sexual violence or genital mutilation are less frequent. For these causes the general principles listed here should be adapted according to the patient’s need.

• Patients with vesicovaginal fistula should be treated as a person, and they deserve the right to adequate counseling and consent to the treatment they will eventually undergo, despite language and cultural barriers that may exist.

• Surgeons embarking on fistula surgery in the developing world should have appropriate training in that setting and should be willing to take on a long-term commitment.

• Prevention of fistula is the ultimate goal. Collaboration between fistula initiatives and maternal health initiatives must be stimulated.

II. ASSESSMENT

It is important to make a distinction between simple fistulae, which have a good prognosis, and complex fistulae, which have a less favourable outcome.

Careful clinical examination will allow the type of fistula to be determined, although no generally accepted classification system is available. Key items are the size and location of the fistula, the extent of the involvement of the urethra and the urethral closure mechanism, and the amount of vaginal scarring.

Associated pathologies should be actively searched for and should be taken into account in the treatment plan: all components of the ‘obstructed labour injury complex’ should be examined and defined.

III. TREATMENT

The treatment for vesicovaginal fistula is surgical. (Grade A)

➤ Simple fistula

A vaginal approach is preferred, since most simple fistula can be reached vaginally and since spinal anaesthesia carries less risk than general anaesthesia needed for an abdominal approach. A trained surgeon should be able to manage these simple fistula.

After wide dissection a tension-free single layer closure of the bladder wall and closure of the vaginal wall in a separate layer are advocated. A Martius flap in primary simple obstetric fistula repair is optional.

A care program for failed repairs and for persisting incontinence after a successful repair needs to be installed.

➤ Complex fistula

Complex fistulae should be referred to a fistula expert in a fistula centre. (Grade B)

In principle, most complex fistulae can be dealt with by the vaginal approach, but an abdominal approach may be needed in some cases (e.g. concommitant reconstructive procedures). Advanced training and surgical skills are prerequisites for treating this type of fistula.

If the urethra and/or the urethral closure mechanism is involved, a sling procedure, using an autologous sling, should be performed at the same time as the fistula correction. There is no place for synthetic sling material in this setting. (Grade B)

➤ After care

The majority of patients with a simple fistula will be cured after the repair. However, a proportion of them, and an even larger proportion of the patients after complex fistula repair, will remain incontinent. Depending on the local possibilities an after care program should be installed.
SURGICAL MANAGEMENT OF OBSTETRIC FISTULA

**HISTORY/SYMPOM ASSESSMENT**

**CONSTANT URINARY LEAKAGE**
- Single vesico-vaginal fistula
- No urethral involvement
- Fistula < 4 cm
- Acceptable vaginal access

**CONSTANT URINARY LEAKAGE AND/OR FECAL INCONTINENCE**
- Fistula > 4 cm
- Urethral involvement
- Intravaginal ureters
- Rectovaginal fistula
- Poor vaginal access
- Secondary fistula repair

**CLINICAL ASSESSMENT**

**SIMPLE FISTULA**
- Primary vaginal fistula repair by trained surgeon

**COMPLEX FISTULA**
- If urethral involvement with stress incontinence add autologous sling
- Refer to fistula specialist/ Fistula center

**DIAGNOSIS**

**TREATMENT**
Pelvic organ prolapse includes urogenital and rectal prolapse. Treatment for pelvic organ prolapse should be reserved for symptomatic women, except in rare, selected, cases.

1. ASSESSMENT

Symptom enquiry may reveal a variety of symptoms. Symptom severity may not correlate with the severity of the anatomic changes.

Physical examination should:
- define the severity of maximum anatomic support defect,
- assess pelvic muscle function and
- determine if epithelial/mucosal ulceration is present.

Post void residual should be measured; nearly all elevated post void residuals resolve with treatment of urogenital prolapse. Imaging of the upper tract is indicated when treatment of vaginal prolapse beyond the hymen is observation only (i.e. no pessary or surgery).

2. MANAGEMENT

- **Observation** is appropriate when medically safe and preferred by the patient (Grade C).

- **Pelvic floor muscle training may:**
  - reduce the symptoms of urogenital prolapse (Grade B), although topographic change is not expected
  - prevent or slow deterioration of anterior urogenital prolapse (Grade B)

- **Pessaries**, when successfully fitted, may improve protrusion symptoms (Grade B). Regular follow up is mandatory. **Support pessaries** that concurrently treat stress incontinence should be considered when appropriate.

- **Local oestrogens** may benefit hypoestrogenic women for the prevention and/or treatment of vaginal epithelial ulceration (Grade C).

- **Reconstructive surgery** should aim to optimise anatomy and function (see full text for grades of recommendation for specific surgical techniques). Pre and postoperative pelvic floor muscle training may promote quality of life and fewer symptoms after surgery for urogenital prolapse (Grade C).

- **Obliterative surgery** is reserved for selected women who agree to permanent vaginal closure (Grade B).
Management of Pelvic Organ Prolapse
(including urogenital prolapse, and recta prolapse)

HISTORY

- Bothersome pelvic organ prolapse
- Complex or recurrent prolapse

Symptoms Screening: assess bothersomeness, frequency and severity of urinary, ano-rectal, genital and sexual symptoms

- Urinary: PVR, cough stress test, urinalysis.
- Physical Examination: Sufficient to determine the site and severity of prolapse and detect other significant findings
  - Selective use of urodynamics when results would alter planned treatment
  - Selective use of upper tract imaging when observation is planned
- Ano-Rectal: Endoscopy, lower GI tract

CLINICAL ASSESSMENT

Investigation by specialist

DIAGNOSIS

UROGENITAL PROLAPSE WITH OR WITHOUT OTHER PELVIC SYMPTOMS

- observation
- lifestyle interventions
- pelvic floor muscle training
- pessary
- reconstructive surgery
- obliterative surgery

RECTAL PROLAPSE WITH OR WITHOUT OTHER PELVIC SYMPTOMS

- observation
- lifestyle interventions
- transperineal surgery
- transabdominal surgery

MANAGEMENT

Specialist management
VI. NEUROGENIC URINARY INCONTINENCE

A. INITIAL MANAGEMENT

I. STRONG GENERAL RECOMMENDATIONS

- Patients with known neurologic disease often need evaluation to exclude neurologic bladder, not only if symptoms occur, but as a standard diagnostic approach as **neurogenic bladder** has a high prevalence in this disease (for prevalence figures see chapter).

- A possible neurologic cause of “idiopathic” incontinence should always be considered. Diagnostic steps to evaluate this include basic assessments, such as history and physical examination, urodynamics and specialised tests.

- **Incontinence in neurologic** patients does not necessarily relate to the neurologic pathology. **Other diseases** such as prostate pathology, pelvic organ prolapse, et al might have an influence. These have to be ruled out.

- **Extensive diagnostic workout** is often useful and necessary only to tailor an individual treatment based on complete neurofunctional data. This may not be needed in every patient e.g. patients with suprapontine lesions or in patients where treatment will consist merely of bladder drainage due to bad medical condition or limited life expectancy.

- There is often a need to manage **bladder** and **bowel** together.

II. INITIAL ASSESSMENT

- The management of neurologic urinary incontinence depends on an understanding of the likely mechanisms producing incontinence. This can in turn depend on the site and extent of the nervous system abnormality.

- Therefore neurogenic incontinence patients can be divided into those having

- **peripheral lesions** (as after major pelvic surgery) including those with lesions of the cauda equina (eg. lumbar disc prolapse);

- **central lesions below the pons** (suprasacral infrapontine spinal cord lesions);

- **central lesions above the pons** (cerebro-vascular accidents, stroke, Parkinson’s disease).

- **History** and **physical examination** are important in helping distinguish these groups.

III. INITIAL TREATMENT

- Patients with **peripheral nerve lesions** (e.g. denervation after pelvic surgery) and patients with **suprasacral infrapontine spinal cord lesions** (e.g. traumatic spinal cord lesions) should get **specialised management** (A).

- Initial treatment for patients with incontinence due to **suprapontine pathology**, like stroke; need to be assessed for degree of mobility and ability to cooperate. Initial recommended treatments are behavioural therapy (C) and anti-muscarinic drugs for presumed detrusor overactivity (A). Appliances (B) or catheters (C) may be necessary for non-cooperative or less mobile patients.
Initial Management of Neurogenic Urinary Incontinence

HISTORY, level of lesion

- Suprapontine cerebral lesion (e.g. Parkinson’s disease, stroke, multiple sclerosis)
- Suprasacral infrapontine spinal cord lesion (e.g. trauma, multiple sclerosis)
- Peripheral nerve lesion (e.g. radical pelvic surgery) Conus/cauda equina lesion (e.g. lumbar disc prolapse)

CLINICAL ASSESSMENT

- Further history
- General assessment including home assessment
- Urinary diary and symptom score
- Assessment of functional level, quality of life and desire for treatment
- Physical examination: assessment of sensation in lumbosacral dermatomes, anal tone and voluntary contraction of anal sphincter, bulbocavernosus and anal reflexes, gait
- Urine analysis + culture (if infected: treat as necessary)
- Urinary tract imaging, serum creatinine: if abnormal: specialised management
- Post void residual (PVR) by abdominal examination or optional by ultrasound

This assessment will give basic information, but does not permit a precise neurourological diagnosis

PRESUMED DIAGNOSIS

- Stress urinary incontinence due to sphincter incompetence
- Urinary incontinence due to detrusor overactivity

MANAGEMENT

- Stress urinary incontinence due to sphincter incompetence:
  - Behavioural modification
  - External appliances

- Urinary incontinence due to detrusor overactivity:
  - With Poor bladder emptying (Significant PVR):
    - Intermittent catheterisation with or without
    - Antimuscarinics
  - With Negligible PVR:
    - Depending on cooperation and mobility:
      - Behavioural modification,
      - Antimuscarinics,
      - External appliances,
      - Indwelling catheter

Failure

Specialised management preferable for more "tailored" treatment
VI. NEUROGENIC URINARY INCONTINENCE

B. SPECIALIZED MANAGEMENT

I. ASSESSMENT

- Most patients with neurogenic urinary incontinence require specialized assessment: urodynamic studies are mandatory with videourodynamics if available.
- Upper tract imaging is needed in most patients and more detailed renal function studies will be desirable if the upper tract is considered in danger: high LUT pressure, UUT dilatation, recurrent or chronic upper tract infection, (major) stones, (major) reflux.
- In patients with peripheral lesions clinical neurophysiological testing may be helpful for better definition of the lesion.

II. TREATMENT

Also for specialized management conservative treatment is the mainstay (A). Management of neurogenic urinary incontinence has several therapeutic options. The algorithm details the recommended options for different types of neurologic dysfunction of the lower urinary tract. The dysfunction does not necessarily correspond to one type/level of neurologic lesion but must depend mostly on urodynamic findings. One should always ascertain that the used management is urodynamically safe (low pressure, complete emptying).

It is recommended to look at urinary and bowel function together if both systems are affected, as symptoms and treatment of one system can influence the other and vice versa (A).

As therapeutical approach can differ in various neurological diseases, the most prevalent diseases are discussed separately in the chapter

III. TREATMENT MODALITIES (often in combination)

- **Conservative**
  - Intermittent catheterization (A)
  - Behavioural treatment(C)
  - Timed voiding (C)
  - Ext. Appliances (B)
  - Antimuscarinics(A)
  - Alpha 1 blockers (C)
  - Intravesical electrical stimulation (C)
  - Bladder expression (B)
  - Triggered voiding (C)
  - Indwelling catheter (C)

- **Surgical treatment**
  - Artificial sphincter (A)
  - Bladder neck Sling (B)
  - Sub-urethral tapes (D)
  - Bulking agents (D)
  - Bladder neck closure (D)
  - Stents intraurethral (B)
  - TUI sphincter (B)
  - Botulinum toxin for: sphincter(C) detrusor (A)
  - Sacral deafferentation (B)
  - Sacral anterior root stimulator (B)
  - Enterocystoplasty (B)
  - Autoaugmentation (D)
Specialized Management of Neurogenic Urinary Incontinence

**LEVEL AND EXTENT OF LESION, HISTORY AND CLINICAL ASSESSMENT**

- Peripheral nerve lesion (e.g. radical pelvic surgery)
- Conus cauda equina lesion (e.g. lumbar disc prolapse)
- Suprasacral infrapontine spinal cord lesion (e.g. trauma, multiple sclerosis)
- Suprapontine cerebral lesion (e.g. Parkinson's disease, stroke, multiple sclerosis)

**SPECIALIZED ASSESSMENT**
- Urodynamic testing (consider the need for simultaneous imaging / EMG)
- Urinary tract imaging: if abnormal renal ultrasonography.
- Neurophysiological testing in peripheral lesions

**DIAGNOSIS**

- Stress UI due to sphincteric incompetence
- Incontinence associated with poor bladder emptying due to detrusor underactivity / sphincter overactivity
- UI due to detrusor overactivity

**CONSERVATIVE TREATMENT**

- Timed voiding
- Ext. Appliances
- Artificial sphincter
- Bladder neck Sling
- Sub-urethral tapes
- Bulking agents
- Bladder neck closure

- IC
- \(\alpha\)-1 blockers
- Intravesical ES
- Bladder expression
- Stents intraurethral
- TUI sphincter
- *Botulinum toxin to sphincter
- SDAF + IC
- SDAF + SARS

**SURGICAL TREATMENT**

- IC + AM
- Indwelling cath. + AM
- SDAF + IC
- SDAF + SARS
- Behavioural
- IC + AM
- Triggered voiding
- Indwelling cath. + AM
- Ext. Appliances + AM
- Botulinum toxin to detrusor
- Enterocystoplasty
- Autoaugmentation

**Stoma/diversion may be an option in selected cases**
Healthy older persons should receive the similar range of treatment options as younger persons, but frail older persons require a different approach addressing the potential role of comorbid disease, current medications (prescribed, over-the-counter, and/or naturopathic), and functional and/or cognitive impairment in UI. The extent of investigation and management should take into account the degree of bother to the patient and/or carer, goals for care, cooperation, and overall prognosis and life expectancy. Effective management to meet the goals of care should be possible for most frail elderly.

### I. HISTORY AND SYMPTOM ASSESSMENT

- **Active case finding and screening** for UI should be done in all frail older persons (Grade A). **History** should include comorbid conditions and medications that could cause or worsen UI. The physical should include rectal exam for faecal loading or impaction (Grade C), functional assessment (mobility, transfers, manual dexterity, ability to toilet) (Grade A), screening test for depression (Grade B), and cognitive assessment (to assist in planning management, Grade C). The mnemonic DIAPPERS (see algorithm) covers some of these comorbid factors, with two alterations: 1) **atrophic vaginitis** does not itself cause UI and **should not be treated for this purpose** (Grade B); and 2) current consensus diagnostic criteria for urinary tract infection (UTI) are poorly sensitive and specific in nursing home residents.

- The patient and/or carer should be asked about the degree of bother of UI (Grade B), goals for UI care (dryness, decrease in specific symtom[s], quality of life, reduction of comorbidity, lesser care burden) (Grade B), likely cooperation with management (Grade C), and the patient’s overall prognosis and remaining life expectancy (Grade C).

- **Urinalysis** is recommended for all patients, primarily to screen for hematuria (Grade C); treatment of otherwise asymptomatic bacteriuria/pyuria is not beneficial (Grade D), and it may cause harm by increasing the risk of antibiotic resistance and severe adverse effects, e.g., *Clostridium difficile* colitis (Grade C).

- **Utility of clinical stress test** in this population is uncertain (Grade D).

- **Wet checks** can assess UI frequency in long-term care residents (Grade C).

- **Post Voiding Residual volume** (PVR) testing is impractical in many care settings, and there is no consensus for the definition of "high" PVR in any population. Yet, there is compelling clinical experience for PVR testing in selected frail older persons with: diabetes mellitus (especially longstanding), prior urinary retention or high PVR; recurrent UTIs; medications that impair bladder emptying (e.g., opiates); severe constipation; persistent or worsening urgency UI despite antimuscarinic treatment; or prior urodynamic showing detrusor underactivity and/or bladder outlet obstruction (Grade C). Treatment of contributing comorbidity may reduce PVR. **Trial with catheter** may be considered for PVR > 200–500 ml if the PVR is felt to contribute to UI or frequency (Grade C).

- **Nocturia** Assessment of frail elders with bothersome nocturia should identify potential underlying cause(s) including nocturnal polyuria (by bladder diary [frequency-volume chart] or wet checks; oedema on exam) (Grade C) and primary sleep problem (e.g., sleep apnoea); low voided volumes (e.g., from high PVR).

### II. CLINICAL DIAGNOSIS

The most common types of UI in frail older persons are urgency, stress, and mixed UI. Frail elderly with urgency UI also may have detrusor underactivity and high PVR (without outlet obstruction), called detrusor hyperactivity with impaired contractility (DHIC). There is no evidence that antimuscarinics are less effective or cause retention in DHIC (Grade D).
III. INITIAL MANAGEMENT

- Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis (Grade C). In some frail elders the only possible outcome may be contained UI (managed with pads), especially for persons with minimal mobility (require assistance of ≥ 2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal UI.

- Conservative and behavioural therapy for UI include lifestyle changes (Grade C), bladder training for more fit alert patients (Grade B), and prompted voiding for frailer, more impaired patients (Grade A).

- For select cognitively intact patients, pelvic muscle exercises may be considered, but there are few studies (Grade C). Antimuscarinics may be added to conservative therapy of urgency UI (Grade A-C, depending on agent).

- Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction (Grade C). All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable.

- DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used (Grade A).

IV. ONGOING MANAGEMENT AND REASSESSMENT

Optimal UI management is usually possible with the above approaches. If initial management fails to achieve desired goals, next steps are reassessment and treatment of contributing comorbidity and/or functional impairment.

V. SPECIALIZED MANAGEMENT

If frail elderly have either other significant factors (e.g., pain, haematuria), UI symptoms that cannot be classified as urgency, stress, or mixed, or other complicated comorbidity which the primary clinician cannot address (e.g., dementia, functional impairment), then specialist referral should be considered. Referral also may be appropriate for insufficient response to initial management. Type of specialist will depend on local resources and the reason for referral: surgical specialists (urologists, gynecologists); geriatrician or physical therapist (functional and cognitive impairment); continence nurse specialists (homebound patients). Referral decisions should consider goals of care, patient/carer desire for invasive therapy, and estimated remaining life expectancy.

Age per se is not a contraindication to UI surgery (Grade C), but before surgery is considered, all patients should have:

- Evaluation and treatment for any comorbidity, medications, and cognitive and/or functional impairments contributing to UI and/or that could compromise surgical outcome (e.g., dementia that precludes patient ability to use artificial sphincter) (Grade C)

- Adequate trial of conservative therapy (Grade C)

- Discussion (including the carer) to insure that the anticipated surgical outcome is consistent with goals of care in the context of the patient’s remaining life expectancy (Grade C)

- Urodynamic testing, because clinical diagnosis may be inaccurate (Grade B)

- Preoperative assessment and perioperative care to establish risk for and minimise common geriatric post-operative complications such as delirium and infection (Grade A) and dehydration and falls (Grade C).
Management of Urinary Incontinence in Frail Older Persons

**Active Case Finding in Frail Elderly**
- Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text)
- Assess QoL, desire for Rx, goals for Rx, pt & caregiver preference
- Targeted physical exam including cognition, mobility, neurological and rectal exams
- Urinalysis
- Consider frequency volume chart or wet checks, especially if nocturia present

**URGENCY UI***
- Lifestyle interventions
- Behavioral therapies
- Consider addition and trial of antimuscarinic drug

**SIGNIFICANT PVR***
- Treat constipation
- Review medications
- Consider trial of alpha-blocker (men)
- Catheter drainage if PVR 200-500 ml, then reassess (see text)

**STRESS UI***
- Lifestyle interventions
- Pelvic floor muscle exercises

**If insufficient improvement, reassess for treatment of contributing comorbidity ± functional impairment**

**If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see text)**

---

**CLINICAL ASSESSMENT**
- Delirium
- Infection
- Pharmaceuticals
- Psychological
- Excess urine output
- Reduced Mobility
- Stool impaction and other factors
  Avoid overtreatment of asymptomatic bacteriuria

**CLINICAL DIAGNOSIS**
* Other

**HISTORY/SYMPTOM ASSESSMENT**

---

* These diagnoses may overlap in various combinations, e.g., Mixed UI, DHIC (see text)
Bladder Pain Syndrome (In the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis – ESSIC – definition is given along with a slight modification made at a recent international meeting held by the Society for Urodynamics and Female Urology – SUFU)

• ESSIC: Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent “urge” to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.

• Consensus Definition from SUFU International Conference (Asia, Europe, North America) held in Miami, Florida February 2008: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.

The scientific committee of the International Consultation voted to use the term “bladder pain syndrome” for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome. Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP), and focuses on the actual symptom complex. There is at this time no universally accepted nomenclature.

II. BLADDER PAIN SYNDROME (BPS)

1. NOMENCLATURE

Males or females with pain, pressure, or discomfort, that they perceive to be related to the bladder, with at least one urinary symptom, such as frequency not obviously related to high fluid intake, or a persistent need to void should be evaluated for possible bladder pain syndrome. The diagnosis of associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized “confusable” diseases that may explain the symptoms must be ruled out, for example UTI.

The initial assessment consists of a frequency-volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology and cystoscopy are recommended if clinically indicated. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and/or hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS. (Grade of recommendation: C).

III. INITIAL TREATMENT

• Patient education,
• dietary manipulation,
• non-prescription analgesics, and
• pelvic floor relaxation techniques comprise the initial treatment of BPS.
The treatment of pain needs to be addressed directly, and in some instances concurrent consultation with an anesthesia/pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome.

Treatment should be focused on the most bothersome or distressing symptoms(s).

➢ When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed,
  • oral medication,
  • intravesical treatment, or
  • physical therapy
  can be prescribed.

It is recommended to initiate a single form of therapy and observe results, adding another modality or substituting another modality as indicated by degree of response or lack of response to treatment. (Grade of recommendation: C).

4. SECONDARY ASSESSMENT

➢ If initial oral or intravesical therapy fails, or before beginning such therapy, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distension and possible bladder biopsy under anaesthesia.

Findings of detrusor overactivity suggest a trial of antimuscarinic therapy is indicated.

The presence of a Hunner’s lesion diagnosed at any stage in the evaluation suggests therapy with transurethral resection or fulguration of the lesion. Distension itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. (Grade of recommendation: C).

5. REFRACTORY BPS

➢ Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include neuromodulation, intravesical botulinum toxin, or newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anaesthesia pain clinic.

➢ The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream.
  • Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients.
  • Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series. (Grade of recommendation: C).
Bladder Pain Syndrome

SYMPTOM

Pain, pressure or discomfort perceived to be related to the bladder with at least one other urinary symptom (eg frequency, nocturia)

BASIC ASSESSMENT

- History
- Frequency / Volume Chart
- Focused Physical Examination
- Urinalysis, Culture, Cytology

"SIMPLE BPS" Conservative therapy

- Patient education
- Dietary manipulation
- Non-prescription analgesics
- Pelvic Floor Relaxation

FIRST LINE TREATMENT

"Complicated PBS"

- Incontinence
- Urinary infection
- Haematuria
- Gynecologic signs / symptoms

UTI

Consider:

- urine cytology
- further imaging
- endoscopy
- urodynamics

ABNORMAL

BPS : requiring more active intervention
when treatment response inadequate

Consider:

- Oral therapies
- Intravesical therapies
- Physical therapy

SECOND LINE TREATMENT

NORMAL

Improved with acceptable quality of life: Follow and Support

Consider:

- Cystoscopy under anesthesia with hydrodistention;
- Fulgeration of Hunner's lesion

THIRD LINE TREATMENT

Consider in context of clinical trial:

- Neuromodulation
- Botulinum toxin intramural
- Pharmacologic management

FOURTH LINE TREATMENT

- Urinary diversion with or without cystectomy
- Substitution cystoplasty

Consider:
Patients present with a variety of symptom complexes. As many people are reluctant to admit to symptoms of FI, it is important to proactively enquire in known high risk groups (such as women with obstetric injuries, patients with loose stool and neurological patients).

- **Serious bowel pathology** needs to be considered if the patient has symptoms such as an unexplained change in bowel habit, weight loss, anaemia, rectal bleeding, severe or nocturnal diarrhoea, or an abdominal or pelvic mass.

- **History** will include bowel symptoms, systemic disorders, local anorectal procedures (e.g. haemorrhoidectomy), childbirth for women, medication, diet and effects of symptoms on lifestyle.

- **Examination** will include anal inspection, abdominal palpation, a brief neurological examination, digital rectal examination and usually anoscopy and proctoscopy.

- **Two main symptoms are distinguished:** *urgency faecal incontinence* (FI) which is often a symptom of external anal sphincter dysfunction or intestinal hurry; and *passive loss of stool* may indicate internal anal sphincter dysfunction. Both urgency and passive FI may be exacerbated in the presence of loose stool.

---

**I. INITIAL ASSESSMENT**

Once local or systemic pathology has been excluded, *initial management includes*:

- Discussion of *options* with the patient
- Patient *information* and *education*,
- *Diet* and fluid advice, adjusting fibre intake (Grade A), and establishing a regular bowel habit with complete rectal evacuation and

- **Simple exercises** to strengthen and enhance awareness of the anal sphincter (Grade C).
- **Anti-diarrhoeal** medication can help if stools are loose (Grade B).
- **Irrigation** is helpful in a small number of patients (mainly neurological - Grade C).
- **Initial management can often be performed in primary care.** If this is failing to improve symptoms after 8-12 weeks, consideration should be given to referral for further investigations.

**III. INVESTIGATIONS**

A variety of anorectal investigations, including manometry, EMG, and anal ultrasound can help to define structural or functional abnormalities of anorectal function.

**IV. FURTHER MANAGEMENT**

- **BIOFEEDBACK**
  
  therapy is usually a package of measures designed to enhance the patient’s awareness of anorectal function, improve sphincter function and coordination and retrain the bowel habit (Grade C).

- **PRODUCTS**
  
  to manage severe faecal incontinence are ineffective in most cases.

- **SEVERE FAECAL INCONTINENCE**
  
  which fails to respond to initial management requires specialised investigations and a surgical opinion.

**V. SPECIAL PATIENT GROUPS**

The main chapter (refer to the book) also gives algorithms for the management of complex vesicovaginal fistulae and faecal incontinence in frail older adults. Committees 10 and 16 gives information on neurogenic FI.
Initial Management of Faecal Incontinence

Active Screening in High Risk Groups

Patient presents with FI

Basic assessment (history, examination, medication and diet review)

Take out of pathway:
- **Alarm signals**: referral for investigation
- **Impaction**: treat then evaluate
- **Surgical evaluation needed**: e.g. rectal prolapse, recent sphincter injury, recto-vaginal fistula, cloacal deformity

Address reversible risk factors e.g. Medication; toilet access; loose stools
- **Patient and / or carer education**
- **Bowel habit and training**
- **Manage constipation**
- **Diet (e.g. soluble fibre for loose stool)**
- **Medication (e.g. loperamide for loose stool)**
- **PFMT / anal sphincter exercises**
- **Adequate containment (e.g. pads or plugs) and practical management advice (Committee 20)**

If initial management fails to achieve adequate symptom relief consider:
- Diagnostic testing; Biofeedback; Irrigation

Surgical evaluation or symptom management if adequate relief not obtained from conservative management, depending on symptom severity and patient preference
The reader is referred to the relevant sections on "Dynamic Testing" and "Conservative Treatment for Faecal Incontinence." In general, patients referred for surgical management of faecal incontinence must either have failed conservative therapy or not be candidates for conservative therapy due to severe anatomic, physiologic or neurologic dysfunction.

Prior to surgical management of faecal incontinence, the morphological integrity of the anal sphincter complex should be assessed. This assessment is best performed with endoanal ultrasound (EAUS), though pelvic MRI may also be useful. Ancillary tests include anal manometry, electromyography (EMG), and defecography. [GRADE OF RECOMMENDATION C]

Patients with rectal prolapse, rectovaginal fistulae, and cloacas often have associated faecal incontinence. Initial therapy should be directed at correction of the anatomic abnormality (in the case of rectovaginal fistula or cloaca, this surgical repair may include overlapping sphincteroplasty.) If the patient has persisting faecal incontinence, he or she should undergo repeat assessment, including especially endoanal ultrasound.

Patients with sphincter defects of greater than 180° or major pereneal tissue loss require individualized treatment. In some cases, initial reconstruction can be performed. Should incontinence persist, alternatives include stimulated muscle transposition, artificial anal sphincter implantation, or sacral nerve stimulation. [GRADE OF RECOMMENDATION C]

Patients who remain incontinent following sphincteroplasty, repeat endoanal ultrasound should be undertaken to reassess the status of the repair. If there is a persisting sphincter defect, repeat sphincteroplasty can be considered. Alternatively, such patients can undergo individualized therapy, including sacral nerve stimulation. [GRADE OF RECOMMENDATION C]. For patients who remain incontinent despite an anatomically satisfactory sphincteroplasty, sacral nerve stimulation is recommended.

Patients who have failed sacral nerve stimulation can be considered for sphincteroplasty if a sphincter defect is present. Other alternatives include stimulated muscle transposition and implantation of an artificial anal sphincter. [GRADE OF RECOMMENDATION C]

Patients who fail surgical therapy for faecal incontinence, or who do not wish to undergo extensive pelvic reconstruction, should consider placement of an end sigmoid colostomy. [GRADE OF RECOMMENDATION C]. While this procedure does not restore continence, it does restore substantial bowel control and appears to improve social function and quality of life.

Individuals with severe spinal cord dysfunction (due, e.g., to injury or congenital abnormality) should be considered for an Antegrade Continence Enema (ACE) procedure or colostomy. [GRADE OF RECOMMENDATION C]
Surgical Management of Faecal Incontinence

Candidate for surgery for FI

EVALUATION
EAUS± Manometry, EMG, MRI, Defecography

Persistent Surgical treatment for anatomical abnormality

COMPLETE SPINAL CORD IMPAIRMENT

SPHINCTER DEFECT

None

< 180°

>180° or perineal tissue loss

Sphincteroplasty

Individualized treatment:
- Sphincteroplasty
- Muscle transposition
- Artificial sphincter
- Sacral nerve stimulation
- Biomaterial injection
- ACE
- Colostomy
- Conservative therapy

ACE Colostomy

Repeat EAUS

* = inadequate symptom relief
FI: fecal incontinence;
ACE: antegrade continence enema;
EAUS: endoanal ultrasonography;
EMG: electromyography;
MRI: magnetic resonance imaging
SNS: sacral nerve stimulation

SPHINCTER DEFECT

Sphincteroplasty

* = inadequate symptom relief
FI: fecal incontinence;
ACE: antegrade continence enema;
EAUS: endoanal ultrasonography;
EMG: electromyography;
MRI: magnetic resonance imaging
SNS: sacral nerve stimulation
Patients with known neurologic disease may present with symptoms related to neurologic bowel dysfunction – difficulty in defecation, constipation and faecal incontinence which disturb their activities of daily living and quality of life. Many have permanent impairments and functional limitations and disabilities, which are due to neurological deficits and complications.

**A. Initial management**

**I. Initial assessment**

- **History taking:** this includes
  - Neurological diagnosis and functional level;
  - Previous and present lower gastrointestinal (LGIT) function and disorders
  - Severity of neurogenic bowel dysfunction
  - Current bowel care and management including diet, fluid intake, medications affecting bowel functions
  - Co-morbidity / complication e.g., urinary incontinence, autonomic dysreflexia, pressure sores, sexual dysfunction
  - Patient's satisfaction, needs, restrictions and quality of life
  - Environmental factors and barriers and facilitators to independent bowel management.

- **Physical examination:**
  - Cognitive functions; motor, sensory and sacral reflexes – voluntary anal sphincter contraction, deep perianal sensation, anal tone, anal and bulbocavernous reflexes
  - Spasticity of the lower limbs
  - Abdominal palpation for faecal loading and rectal examination

**II. Basic investigations:**

- **Functional assessment:**
  - hand and arm use, fine hand use, mobility – maintaining body position, transfer and walking ability.

- **Environmental factors assessment:**
  - toilet accessibility; assistive devices for bowel care and mobility; carer’s support and attitude;

Stool exam, plain abdomen XRay

**III. Initial treatments**

- **Patient education and goals-setting** - complete defecation on a regular basis and faecal continence based on right time, right place, right trigger and right consistency
- **Adequate fibre diet and fluid intake**; appropriate trigger according to preservation of sacral (anorectal) reflex – digital rectal stimulation; suppository and enema; if no anorectal reflex, manual evacuation; abdominal massage can also be helpful
- **Prescribe medications** – stool softener, laxative, prokinetic agents, anti-diarrhea drugs as necessary
- Assistive techniques may be necessary for
  - defecation – irritation
  - for incontinence – anal plug.

The diagram does not apply to management in acute neurologic patients that need regular bowel emptying.
**Initial Management of Neurogenic Faecal Incontinence**

**HISTORY, level of lesion**
- Conus/cauda equina lesion (e.g. lumbar disc prolapse) Peripheral nerve lesion (e.g. radical pelvic surgery)
- Suprasacral spinal cord lesion (e.g. trauma, multiple sclerosis,)
- Suprapontine lesions (e.g. Parkinson)

**CLINICAL ASSESSMENT**
- History taking including diagnosis, pre-morbid bowel function and sensation and their disorders, current bowel and bladder programme, co-morbid diseases/disorders, QOL and needs
- Physical & neurological examination including cognitive function, voluntary anal contraction, sensation, sacral reflexes, per rectal examination, abdominal palpation for faecal impaction in the colon
- Functional assessment including hand and arm use, fine hand use, balance, transfer and walk
- Environmental factors assessment including toilet accessibility, assistive device, carer’s support and attitude
- Basic investigation: stool exam, plain film abdomen in selected patients (diarrhea, impaction not felt on rectal examination)

This assessment will give basic information but does not permit a precise diagnosis of neurogenic bowel dysfunction

**PRESUMED DIAGNOSIS**
- Incontinence due to sphincter incompetence
- Incontinence due to lack of cognitive function, sensory awareness disorders, unable to control by voluntary anal contraction
- "False incontinence" due to faecal impaction

**TREATMENT**
- Manual evacuation
- Assistive device – anal plug
- Digital rectal stimulation
- Chemical stimulant: suppository, mini-enema, stool softener, laxative; transanal/transrectal irrigation
- Faecal disimpaction

Patient education, adequate fibre diet and fluid intake; regular bowel care, preferable ± 3 times a week

Specialised management preferable for more "tailored" treatment
Some patients with neurogenic faecal incontinence will need specialized assessment, especially if initial management is unsuccessful to look for comorbidity and certainly before performing invasive treatment.

Do not assume that all symptoms are due to neuropathy, e.g. women with neurologic pathology might have had childbirth injury to the sphincter.

Special investigations: manometry, endoanal ultrasound, (dynamic) MRI, (needle) EMG. These specific bowel functional tests and electro-diagnostic tests must be considered optional as their value in neurologic pathology is not sufficiently demonstrated so far.

Management of neurogenic incontinence does not include very extensive treatment modalities and many conservative are still empirical.

Transanal irrigation (C)

Electrical stimulation sphincter, (C)

Percutaneous neuromodulation: further research is required.

Surgical management of neurogenic faecal incontinence has different options which need a very strict patient selection.

Antegrade Continence Enema ACE (C)

Graciloplasty (C)

Artificial sphincter (C)

Sacral Anterior Root Stimulation SARS (C)

Botulinum Toxin (C)

Neuromodulation (C)

It is recommended to look at urinary and bowel function together if both systems are affected, as symptoms and treatment of one system can influence the other and vice versa (A).

As therapeutical approach can differ in different neurological diseases, the most prevalent diseases are discussed separately in the chapter.
Specialised Management of Neurogenic Faecal Incontinence

**SPECIALIZED ASSESSMENT**
- Primary assessment, history, level and extent of lesion, clinical assessment
- Conus/cauda equina lesion (e.g. lumbar disc prolapse) Peripheral nerve lesion (e.g. radical pelvic surgery)
- Suprasacral spinal cord lesion (e.g. trauma, multiple sclerosis)
- Suprapontine lesions (e.g. Parkinson)

**DIAGNOSIS**
- Faecal Incontinence through loss of bowel sensation, sphincter deficiency or, severe rectum prolaps no anal control, comorbidity,
- Functional bowel testing / functional imaging
- Neurophysiological testing especially external anal sphincter needle electromyography, in addition to anorectal manometry, to identify or confirm neurogenic cause of faecal incontinence.

**CONSERVATIVE TREATMENT**
- Transanal irrigation
- Electrical stimulation sphincter,
- Percutaneous neuromodulation : further study

**SURGICAL TREATMENT**
- ACE
- Graciloplasty
- Artificial sphincter
- SARS
- Botulinum Toxin
- Neuromodulation

**Stoma/diversion may be an option in selected cases**

ACE = Antegrade Continence Enema
SARS = Sacral Anterior Root Stimulation

Faecal impaction
- Faecal disimpaction
  - Failure consider
  - Failure consider
4. Recommendations for Continence Promotion, Education and Primary Prevention

Continence promotion, education and primary prevention involves informing and educating the public and health care professionals that urinary incontinence and faecal incontinence are not inevitable, but are treatable or at least manageable. In addition, other bladder disorders such as bladder pain syndrome and pelvic organ prolapse can be treated successfully. Progress has been made in the promotion of continence awareness through advocacy programs, organization of the delivery of care, and public access to information on a worldwide basis. These have also been advocated in the education of professionals and primary prevention of mainly urinary incontinence. However, not much has changed in help-seeking behaviour for these disorders. This chapter updates previous International Consultation on Incontinence (ICI) chapters on three areas: continence promotion, education and primary prevention and the following are the recommendations in these individual areas.

### CONTINENCE AWARENESS AND PROMOTION

- Continence awareness should be included in any national advocacy program that is working towards an effective health literacy system, as it is consistent with and requires the involvement of many levels of educational, health-care, and community service providers. (Grade D)
- Continence awareness should be part of the main stream and on-going health education and advocacy programs with emphasis on eliminating stigma, promoting disclosure and help-seeking behaviour and improving quality of life. (Grade D)
- There is a need for research to provide higher level of evidence on the effectiveness of continence promotion programs to increase awareness, be it for primary prevention, treatment or management. (Grade D)
- There is a need for research on the most effective means to educate the public and professional groups on continence issues. (Grade D)

### CONTINENCE ADVOCACY

- Government support and co-operation are needed to develop services, and responsibility for this should be identified at a high level in each Health Ministry. Incontinence should be identified as a separate issue on the health care agenda. There is a need for funding as a discrete item and for funding, not to be linked to any one patient group (e.g. elderly or disabled), and should be mandatory. (Grade D)
- No single model for continence services can be recommended. Because of the magnitude of UI prevalence, detection and basic assessment will need to be performed by primary care providers. Specialist consultation should generally be reserved for those patients where appropriate conservative treatments have failed, or for specified indications. (Grade D)
- There is a need for research on patient-focused outcomes, should include evaluation of the outcomes for all sufferers who present for care, use validated audit tools/outcome measures and longitudinal studies of the outcomes of services provided. (Grade D)
- There is a need for cost-effectiveness studies of current services. (Grade D)

### PROFESSIONAL EDUCATION

- There remains a need for rigorously evaluated continence education programmes which adhere to defined minimum standards for continence specialists and, generalists, utilizing web-based and distance learning techniques alongside audit and feedback, train-the trainer models and leadership models as well as traditional methods. (Grade D)
- There is a need for research on the most effective means to educate professional groups on continence issues. (Grade D)

### PRIMARY PREVENTION

- Primary prevention studies efforts should be aimed at interventions to promote a healthy body weight to assist in the prevention of incontinence (Grade A).
- Primary prevention studies should not be limited to individual interventions, but also test the impact of population-based public health strategies (Grade C)
- PFMT should be a standard component of prenatal and postpartum care and to instruct women who experience incontinence prior to pregnancy PFMT (Grade C)
- Randomised controlled trials (RCTs) should be conducted to test the preventative effect of PFMT for men post-prostatectomy surgery (Grade B)
- Further investigation is warranted to assess the efficacy of PFMT and BT for primary prevention of UI in well older adults (Grade B)
5. Recommendations for Further Basic Science Research

1. Integrate data from reductionist experiments to formulate better systems-based approaches in the investigation of the pathology of the lower urinary tract (LUT), the genital tract (GT) and the lower gastro-intestinal tract (LGIT).

2. Generate and improve experimental approaches to investigate the pathophysiology of the LUT and LGIT by:
   - The development of fully characterised animals models
   - Use of human tissue from well-characterised patient groups

3. Encourage greater emphasis on basic research into our understanding of tissues receiving relatively little attention: ie the lower gastrointestinal tract; the bladder neck and urethra.

4. Generate a more disciplinary approach to investigate the function of the lower urinary tract through collaborations between biological, physical and mathematical sciences.

5. Increase interaction between higher education institutions (HEIs), industry and medical centres to encourage translational approaches to research.

6. Bring about a greater emphasis on the importance of research to medical trainees through:
   - establishing research training as a core component of medical training
   - increased access to support funds, especially scholarships and personal awards
   - organisation of focussed multidisciplinary research meetings, either stand-alone or as part of larger conferences
   - greater interaction between medical centres and HEIs

7. Increase emphasis on research into lower urinary tract and gastro-intestinal tract in HEIs through:
   - greater representation on grant-funding agencies
   - encouragement of submission to high impact-factor journals and recognition of research published in specialty journals
   - more integrated teaching and training opportunities

6. Recommendations for Further Research in Epidemiology

1. Longitudinal study designs are needed to estimate the incidence of urinary incontinence (UI), anal incontinence (AI) and pelvic organ prolapse (POP) and to describe the natural course of these conditions and to investigate risk factors and possible protective factors. In addition similar studies regarding other lower urinary tract symptoms (LUTS) should be initiated.

2. There is still little knowledge regarding prevalence, incidence, and other epidemiological data in developing countries. It is recommended that fundamental research regarding prevalence, incidence and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.

3. Some potential risk and protective factors deserve more attention. For example, the role of pregnancy and childbirth in the development of UI, AI and POP must be studied in a fashion that links population-based methods to clinical assessment of pregnancy, delivery and the birth trauma and follows women over many years. Such a design is necessary because the effect of pregnancy and childbirth may become clear only years later when the woman is older and because the woman will not then be able to report the exact nature of the tear and episiotomy, etc.

4. There should be more emphasis on the associations between UI, AI and POP and specific diseases like stroke, diabetes, and psychiatric diseases.

5. The variation of disease occurrence in groups of different racial origin yet similar environmental exposures, lend support to the presumed genetic influence on the causation of UI, AI and POP. This again provides circumstantial evidence for a genetic contribution to pelvic floor disorders since most of these studies have been unable to control for heritability in relation to the complex interaction of environmental factors.

6. The ethiology of UI, AI and POP is widely recognised to be multifactorial, yet the complex interaction between genetic predisposition and environmental influences is poorly understood. Genetic components require further investigation. Twin studies provide a possible means of studying the relative importance of genetic predisposition and environmental factors. By comparing monozygotic female twins with identical genotype, and dizygotic female twins who on average share 50 percent of their segregating genes, the relative proportions of phenotypic variance resulting from genetic and environmental factors can be estimated. A genetic influence is suggested if monozygotic twins are more concordant for the disease than dizygotic twins whereas evidence for environmental effects comes from monozygotic twins who are discordant for the disease.
7. Recommendations for Clinical Research Methodology

PART I: GENERAL RECOMMENDATIONS

I. RECOMMENDATIONS ON STUDY CONDUCT AND STATISTICAL METHODS

- Randomized controlled trials (RCTs) eliminate most of the biases that can corrupt research and provide the strongest level of evidence to direct clinical care. The primacy of RCTs in incontinence research should be fully acknowledged by researchers, reviewers, and editors.

- Careful attention to the planning and design of all research is of the utmost importance. This should begin with a structured literature review which should be described in the manuscript. High quality, systematic reviews on many topics in incontinence have been published by the Cochrane Incontinence Group (www.otago.ac.nz/cure) and provide a valuable starting point.

- The design, conduct, analysis and presentation of RCTs must be fully in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Statistical expertise is required at the start of the design of a RCT and thereafter on an ongoing basis.

- Equivalence trials are underutilized. Failing to find a difference between two treatments is not the same as proving equivalence if the correct design is not used.

- Inclusion and exclusion criteria inherently reflect a conflict between detecting a specific treatment effect and generalizability of the results. It is recommended that the study population in RCTs comprise a sample that is representative of the overall population. All patients who have the disorder in question, who could benefit from the treatment under investigation, and who are evaluable should be eligible. Exclusion criteria should be limited and related to clearly defined, supportable hypotheses.

II. RECOMMENDATIONS ON OBSERVATIONS DURING INCONTINENCE RESEARCH

- One or more high quality, validated symptom instruments should be chosen at the outset of a clinical trial representing the viewpoint of the patient, accurately defining baseline symptoms as well as any other areas in which the treatment may produce an effect. The objective severity and subjective impact or bother should be reflected.

- Whenever relevant, observations of anatomic support and pelvic muscle/voluntary sphincter function should be recorded using standardized, reproducible measurements.

- All observations should be repeated after intervention and throughout follow-up and their relationships with primary clinical outcome measures investigated. Most research follow-up has been inadequate in the past. Given the nature of the disorder, short term follow-up in incontinence trials should begin with all participants having reached one year.

III. RECOMMENDATIONS ON TESTS USED IN URINARY INCONTINENCE RESEARCH:

- Clinical trials of incontinence and LUTS should include a validated frequency volume chart or bladder diary as an essential baseline and outcome measure. Pad tests are a desirable adjunctive measure and should be considered in clinical trials when practical.

- Urodynamic studies have not been proven to have adequate sensitivity, specificity or predictive value to justify routine use of testing as entry criteria or outcome measures in clinical trials. Most large scale clinical studies should enroll subjects by carefully defined symptom driven criteria when the treatment will be given based on an empiric diagnosis.

- High quality, hypothesis driven research into the utility of using urodynamic studies to define patient populations or risk groups within clinical trials is greatly needed.
In all trials employing urodynamics, standardized protocols (based on ICS recommendations) are defined at the outset. In multicenter trials, urodynamic tests should be interpreted by a central reader to minimize bias unless inter- and intrarater reliability has already been established by standardized procedures within the trial.

High quality, gender specific quality of life and bother scores should be employed when assessing outcome in male incontinence research.

Uroflow and measurement of post-void residual urine should be recorded pre-treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. The value of invasive pressure-flow urodynamics in stratifying patients deserves further investigation.

Measurement of prostate size (or at least PSA, as a surrogate) should be performed before and after treatment (synchronous with other outcome measures) whenever prostate size is expected to change due to the treatment. Patients should be stratified by prostate size at randomization when size is considered to be a potentially important determinant of treatment outcome.

Specific information about the menopause, hysterectomy, and hormonal status, parity and obstetric history should be included in baseline clinical trial data

Strict criteria for cure / improve / fail should be defined based on patient perception as well as objective and semi-objective instruments such as validated questionnaires, diaries and pad tests.

“Clinically significant” outcome measures and relationships of outcome to socioeconomic costs are critically important to establishing the utility of treating urinary incontinence in the frail elderly.

Entry into RCTs should be defined by performance status rather than an arbitrary age limit.

Establishing the safety of incontinence treatment is even more important in the frail elderly than in other populations.

We support the NIH statement (http://grants.nih.gov/grants/guide/notice-files/not98-024.html) calling for increased clinical research in children. All investigators that work with children should be aware of the details of the document.

Long-term follow-up is of critical importance in the pediatric population with a primary focus of establishing safety of chronic treatments.

Detailed urodynamic studies are required for classification of neurogenic lower urinary tract disorders in clinical trials because the nature of the lower tract dysfunction cannot be accurately predicted from clinical data.

Change in detrusor leak point pressure should be reported as an outcome as appropriate, and can be considered a primary outcome for spina bifida patients.

An area of high priority for research is the development of a classification system to define neurogenic disturbances. Relevant features would include the underlying diagnosis, the symptoms, and the nature of the urodynamic abnormality.

Data should be collected on fecal incontinence whenever practical as part of research in urinary incontinence.

Well designed and adequately powered studies are needed to define best practice in investigation and for all treatment modalities currently available.

Further consideration should be given to new approaches and adoption of technologies/interventions that are of established value in treating urinary incontinence.
The patient population for BPS trials must be carefully defined. When appropriate, relaxed entry criteria should be used to reflect the full spectrum of the BPS patient population.

The primary endpoint of BPS trials should be patient driven and the Global Response Assessment is recommended. A rich spectrum of secondary endpoints will be useful in defining the effect of treatments.

Investigation of antiproliferative factor as an entry criteria for clinical research is desirable.

There should be a focus on patient reported outcomes with the goal of determining “clinically significant” prolapse. The implications of stage 2 prolapse in terms of natural history and treatment outcome are key issues.

Research is needed to define the epidemiology of nocturia and how the symptom relates to normal aging.

Clinical research in treatment of nocturia should begin with classification of patients by voiding diary categories, 24 hour polyuria, nocturnal polyuria, and apparent bladder storage disorders. If desired, patients with low bladder capacity can be further divided into those with sleep disturbances and those with primary lower urinary tract dysfunction.

Treatment protocols must be detailed to the degree that the work can easily be reproduced.

The highest practical level of blinding should be used.

More work is needed to separate the specific and non-specific effects of treatment.

Safety and serious side effects of new devices must be adequately defined with adequate follow-up, especially for use of implantable devices and biologic materials, so that risks can be weighed against efficacy. All new devices and procedures require independent, large scale, prospective, multicenter case series when RCTs are not feasible.

Valid informed research consent is required in all trials of surgical interventions, which is separate from the consent to surgery.

Reports of successful treatment should be limited to subjects with a minimum (not mean) of one year follow-up and should include a patient perspective measure. Specific assumptions about patients lost to follow-up should be stated; last observation carried forward is generally not the appropriate method of handling this data.

In urinary incontinence safe, effective non-invasive therapy is available for the vast majority of patients. Most trials should offer “standard therapy” rather than a pure placebo where efficacy is established.

Effective drug therapy is available for most forms of incontinence. Comparator arms are recommended for most trials.
Continuity in clinical direction from design through authorship is mandatory. Investigators should be involved in the planning stage and a publications committee should be named at the beginning of the clinical trial. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals, from the International Committee of Medical Journal Editors should be followed. Authorship requires:

- Substantial contributions to conception and design or acquisition of data or analysis and interpretation of data,
  - Drafting the article or revising it critically for important intellectual content,
  - Final approval of the version to be published
- Authors should provide a description of what each contributed and editors should publish that information.
- Authors should have access to all raw data from clinical trials, not simply selected tables

Clinical trial results should be published regardless of outcome. The sponsor should have the right to review manuscripts for a limited period of time prior to publication but the manuscript is the intellectual property of its authors, not the sponsor.

- All authors should be able to accept responsibility for the published work and all potential conflicts of interest should be fully disclosed.
Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth: DAY MONTH YEAR

2. Are you (tick one): Female Male

3. How often do you leak urine? (Tick one box)

   never 0
   about once a week or less often 1
   two or three times a week 2
   about once a day 3
   several times a day 4
   all the time 5

4. We would like to know how much urine you think leaks.
   How much urine do you usually leak (whether you wear protection or not)?
   (Tick one box)

   none 0
   a small amount 2
   a moderate amount 4
   a large amount 6

5. Overall, how much does leaking urine interfere with your everyday life?
   Please ring a number between 0 (not at all) and 10 (a great deal)

   0 1 2 3 4 5 6 7 8 9 10
   not at all a great deal

   ICIQ score: sum scores 3+4+5

6. When does urine leak? (Please tick all that apply to you)

   never – urine does not leak
   leaks before you can get to the toilet
   leaks when you cough or sneeze
   leaks when you are asleep
   leaks when you are physically active/exercising
   leaks when you have finished urinating and are dressed
   leaks for no obvious reason
   leaks all the time

Thank you very much for answering these questions.
The scientific committee which met at the end of the 1st ICI in 1998 supported the idea that a universally applicable questionnaire should be developed, that could be widely applied both in clinical practice and research.

The hope was expressed that such a questionnaire would be used in different settings and studies and would allow cross-comparisons, for example, between a drug and an operation used for the same condition, in the same way that the IPSS (International Prostate Symptoms Score) has been used.

An ICIQ Advisory Board was formed to steer the development of the ICIQ, and met for the first time in 1999. The project’s early progress was discussed with the Board and a decision made to extend the concept further and to develop the ICIQ Modular Questionnaire to include assessment of urinary, bowel and vaginal symptoms. The first module to be developed was the ICIQ Short Form Questionnaire for urinary incontinence: the ICIQ-UI Short Form. The ICIQ-UI Short Form has now been fully validated and published [2].

Given the intention to produce an internationally applicable questionnaire, requests were made for translations of the ICIQ-UI Short Form at an early stage, for which the Advisory Board developed a protocol for the production of translations of its modules. The ICIQ-UI Short Form has been translated into 30 languages to date. Two further, newly developed and fully validated, modules have been finalised since the third consultation and are now being incorporated into clinical practice and research, and translated accordingly for international use. The ICIQ-VS [7] provides evaluation of vaginal symptoms and the ICIQ-B [3] can be used to assess bowel symptoms including incontinence. Both questionnaires also provide assessment of the impact of these symptoms on quality of life (Table 1).

Where high quality questionnaires already existed within the published literature, permission was sought to include these within the ICIQ in order to recommend them for use. Eleven high quality modules have been adopted into the ICIQ which are direct (unchanged) derivations of published questionnaires (Table 1).

www.ICIQ.net provides details of the validation status of the modules under development for urinary symptoms, bowel symptoms and vaginal symptoms and provides information regarding the content of existing modules. Information regarding production of translations and the ICIQ development protocol is also available for those interested in potential collaborations to continue development of the project.
### Table 1. Fully validated ICIQ modules and derivation

<table>
<thead>
<tr>
<th>MODULES AVAILABLE FOR USE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICIQ – MLUTS (ICSmale Short Form [4])</td>
<td>Urinary symptoms (male)</td>
</tr>
<tr>
<td>ICIQ – FLUTS (BFLUTS Short Form [5])</td>
<td>Urinary symptoms (male)</td>
</tr>
<tr>
<td>ICIQ-VS [2]</td>
<td>Vaginal symptoms</td>
</tr>
<tr>
<td>ICIQ-B [3]</td>
<td>Bowel symptoms</td>
</tr>
<tr>
<td>ICIQ - UI Short Form [1]</td>
<td>Urinary incontinence short form</td>
</tr>
<tr>
<td>ICIQ – N (ICSmale [6]/ BFLUTS [7])</td>
<td>Nocturia</td>
</tr>
<tr>
<td>ICIQ – OAB (ICSmale [6]/ BFLUTS [7])</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>ICIQ – MLUTS Long Form (ICSmale [6])</td>
<td>Urinary symptoms long form (male)</td>
</tr>
<tr>
<td>ICIQ – FLUTS Long Form (BFLUTS [7])</td>
<td>Urinary symptoms long form (female)</td>
</tr>
<tr>
<td>ICIQ – LUTS qol (KHQ [8])</td>
<td>Urinary symptoms quality of life</td>
</tr>
<tr>
<td>ICIQ – Nqol (N-QOL [9])</td>
<td>Nocturia quality of life</td>
</tr>
<tr>
<td>ICIQ – OABqol (OABq [10])</td>
<td>Overactive bladder quality of life</td>
</tr>
<tr>
<td>ICIQ – MLUTSsex (ICSmale [6])</td>
<td>Sexual matters related to urinary symptoms (male)</td>
</tr>
<tr>
<td>ICIQ – FLUTSsex (BFLUTS [7])</td>
<td>Sexual matters related to urinary symptoms (female)</td>
</tr>
</tbody>
</table>

### REFERENCES

Three types of Bladder Charts and Diaries can be used to collect data:-

**Micturition Time Chart**
- times of voiding and
- incontinence episodes

**Frequency Volume Chart**
- times of voiding with voided volumes measured,
- incontinence episodes and number of changes of incontinence pads or clothing.

**Bladder Diaries**
- the information above, but also
- assessments of urgency,
- degree of leakage (slight, moderate or large) and descriptions of factors leading to symptoms such as stress leakage, eg. running to catch a bus
- time and location of leakage

It is important to assess the individual’s fluid intake, remembering that fluid intake includes fluids drunk plus the water content of foods eaten. It is often necessary to explain to a patient with LUTS that it may be important to change the timing of a meal and the type of food eaten, particularly in the evenings, in order to avoid troublesome nocturia.

The micturition time and frequency volumes charts can be collected on a single sheet of paper (Fig. 1). In each chart/diary, the time the individual got out of bed in the morning and the time they went to bed at night should be clearly indicated.

Each chart/diary must be accompanied by clear instructions for the individual who will complete the chart/diary: the language used must be simple as in the suggestions given for patient instructions. There are a variety of designs of charts and diaries and examples of a detailed bladder diary are given. The number of days will vary from a single day up to one week.

**INSTRUCTIONS FOR COMPLETING THE MICTURITION TIME CHART**

This chart helps you and us to understand why you get trouble with your bladder. The diary is a very important part of the tests we do, so that we can try to improve your symptoms. On the chart you need to record:-

1. When you get out of bed in the morning, show this on the diary by writing ‘Got out of bed’.
2. The time, eg. 7.30am when you pass your urine. Do this every time you pass urine throughout the day and also at night if you have to get up to pass urine.
3. Each time you pass urine, collect the urine in a measuring jug and record the amount (in mls or fluid ozs) next to the time you passed the urine, eg. 1.30pm - 320 mls.
4. If you leak urine, show this by writing ‘W’ (wet) on the diary at the time.
5. If you have a leak, please add ‘P’ if you have to change a pad and ‘C’ if you have to change your underclothes or even outer clothes. So, if you leak and need to change a pad, please write ‘WP’ at the time you leaked.
6. At the end of each day please write in the column on the right the number of pads you have used, or the number of times you have changed clothes.

When you go to bed at the end of the day show it on the diary - write ‘Went to Bed’

**INSTRUCTIONS FOR USING THE BLADDER DIARY**

This diary helps you and us to understand why you get trouble with your bladder. The diary is a very important part of the tests we do, so that we can try to improve your symptoms. On the chart you need to record:-

1. When you get out of bed in the morning, show this on the diary by writing ‘GOT OUT OF BED’.
2. During the day please enter at the correct time the drinks you have during the day, eg. 8.00am - two cups of coffee (total 400 ml).
3. The time you pass your urine, eg. 7.30am. Do this every time you pass urine throughout the day and night.
4. Each time you pass urine, collect the urine in a measuring jug and record the amount (in mls or fluid ozs) next to the time you passed the urine, eg. 1.30pm/320ml.
5. Each time you pass your urine, please write down how urgent was the need to pass urine:
   - ‘O’ means it was not urgent.
   - + means I had to go within 10 minutes.
   - ++ means I had to stop what I was doing and go to the toilet.
6. If you leak urine, show this by writing an ‘W’ on the diary at the time you leaked.
7. If you have a leak, please add ‘P’ if you have to change a pad and ‘C’ if you have to change your underclothes or even outer clothes. So, if you leak and need to change a pad, please write ‘WP’ at the time you leaked.
8. If you have a leakage please write in the column called ‘Comments’ whether you leaked a small amount or a large amount and what you were doing when you leaked, eg. ‘leaked small amount when I sneezed three times’.
9. Each time you change a pad or change clothes, please write in the ‘Comments’ column.
10. When you go to bed at the end of the day show it on the diary - write ‘Went to Bed’.
**Frequency - Volume chart - Standard Version - 7 days**

**Date** | **7:00 am** | **Mid-day** | **Midnight** | **6:00 am** | **Pads used**
---|---|---|---|---|---
16th April | Up 150 | 60 | 275 | 200 | 150 | Bed | 2.30 | 6.30 | 1
17th | Up 260 | 100 | 150 | 220 | 250 | Bed | 275 | 200 | 0
18th | Up 300 | 150 | 220 | 270 | 120 | Bed | 400 | 0
19th | Up 250 | 310 | 75 | 200 | 50 | 250 | Bed | 260 | 220 | 200 | 0
20th | Up 150 | 275 | 175 | 200 | 250 | Bed | 100 | Bed | 350 | 500 | 0
21st | Up 280 | 175 | 75 | 200 | 220 | Bed | 350 | 300 | 0
22nd | Up 150 | 150 | 290 | 200 | 150 | Bed | 350 | 4.30 | 1

**No. of drinks per day:** 7

---

**BLADDER DIARY**

**Detailed version - one day**

**Name:** Maria Schmidt | **Date:** 18th April 1998

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine passed</th>
<th>Urgency!</th>
<th>Leakage?</th>
<th>Comments</th>
<th>Drinks - time, type and amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:00 am</td>
<td>7:15</td>
<td>200</td>
<td>0</td>
<td></td>
<td>8:00 - 2 cups coffee</td>
</tr>
<tr>
<td></td>
<td>7:30</td>
<td>100</td>
<td>+</td>
<td></td>
<td>11:00 can coke</td>
</tr>
<tr>
<td></td>
<td>11:30</td>
<td>275</td>
<td>++</td>
<td>W</td>
<td>Wet pants</td>
</tr>
<tr>
<td>12:00 noon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30</td>
<td>150</td>
<td>+</td>
<td></td>
<td></td>
<td>12:30</td>
</tr>
<tr>
<td>3:00</td>
<td>220</td>
<td>0</td>
<td></td>
<td></td>
<td>2:30</td>
</tr>
<tr>
<td>3:45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7:30</td>
</tr>
<tr>
<td>5:30</td>
<td>175</td>
<td>0</td>
<td></td>
<td></td>
<td>6:00 pm</td>
</tr>
<tr>
<td>7:45</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td>9:00</td>
</tr>
<tr>
<td>9:30</td>
<td>175</td>
<td></td>
<td></td>
<td></td>
<td>1:00</td>
</tr>
<tr>
<td>10:30</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>3:30</td>
</tr>
<tr>
<td>12:00 midnight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>