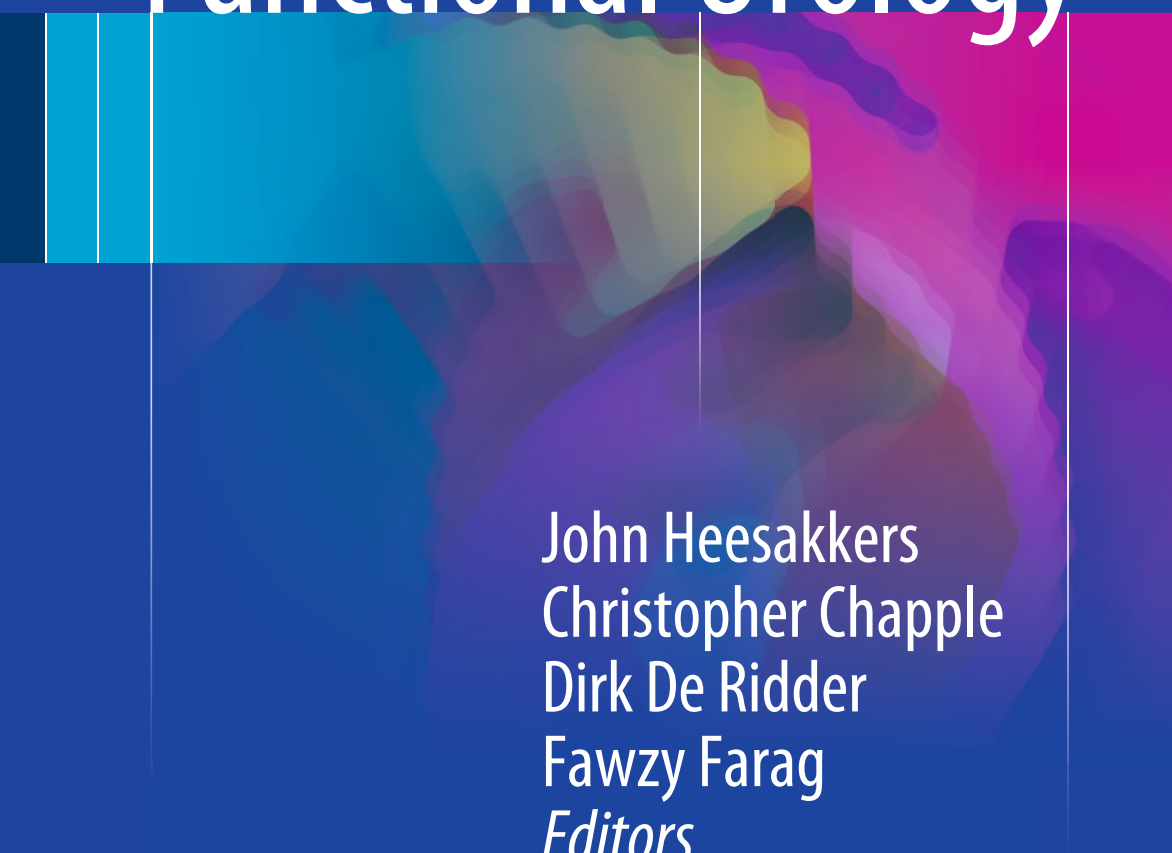
Practical Functional Urology



John Heesakkers
Christopher Chapple
Dirk De Ridder
Fawzy Farag
Editors

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Editors
John Heesakkers
Radboud University Medical Center
Nijmegen
The Netherlands

Dirk De Ridder
University Hospitals KU Leuven
Leuven
Belgium

Christopher Chapple
The University of Sheffield
The Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS
Foundation Trust
Sheffield
UK

Fawzy Farag
Sohag University Hospital
Sohag
Egypt

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Foreword

I was told that a preface to a book should serve as a tantalizing appetizer, so one might reasonably ask the questions: Why dine here? Why another book on lower urinary tract functional disorders and why should I have this one? The busy clinician has a practice that encompasses many issues relating to adult LUT dysfunction, with which he/she has some familiarity but about which he/she would like to be able to consult a "companion" for easy-to-find confirmation or guidance. Such a companion should cover symptomatology, necessary evaluation, differential diagnosis, pathophysiology, and solutions in a practical, concise, and readable way, i.e., "just the facts." This book was very ably designed by experienced specialists to fill this need. It is not over-scienced or over-referenced. The printed version should fit in a pocket of a white coat and a digital version on a pocket communicator with quick access.

Necessary anatomy and physiology and fundamentals of evaluation are covered, followed by a brief but detailed (enough-to-understand and treat) treatise on virtually every subject that falls under the rubric of lower urinary tract dysfunction, urinary infection, pelvic prolapse, and erectile dysfunction. Additionally, there is a chapter on practical catheter management. All in all, the goals are successfully achieved.

Alan J. Wein, MD, PhD(hon), FACS
Founders Professor & Chief of Urology
Director, Urology Residency Program
Penn Medicine
Perelman School of Medicine
University of Pennsylvania Health System
Perelman Center for Advanced Medicine, USA

Preface

We are very happy to present to the reader the first edition of the book Practical Functional Urology. We as editors had the feeling that a book was needed that compiled many practical issues that we, as functional urologists, deal with every day in clinical practice. Clinical functional urological practice has a very broad scope of topics ranging from neurourological pathologies to male LUTS or nocturia. Much has been written and published about all functional urological topics, quite often from a scientific point of view. Many of the participating authors of this book contributed to science in Functional Urology. The aim of this book is to give practical insight and advice about functional urological topics. The underlying guidelines

from among others EAU, AUA, ICUD and NICE serve as the framework and basement for clinical practice. Based on the guidelines the various topics are assessed from a practical point of view. In every chapter is explained how diagnostics and treatments are dealt with clinical practice. The chapters end with tips and trics, dos and donts and points of interest. The hope is that this will help the reader in his daily clinical activities. We also tried to avoid big references parts but changed that by a only a few references for further reading that are thought to be key publications by the writers of the chapter. We want to thank all the authors for their effort and contribution and Springer for supporting this important project.

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Contributors

Frank Van der Aa, MD, PhD Department of Urology, University Hospitals Leuven, Leuven, Belgium

Maarten Albersen, MD, PhD Department of Urology and Andrology, University Hospitals Leuven, Leuven, Belgium

António Avelino, MSc, PhD Department of Experimental Biology, Faculty of Medicine of the University of Porto, I3S and IBMC of University of Porto, Porto, Portugal

Truls E. Bjerklund Johansen, MD, Dr. Med. Sci. Oslo University Hospital, Oslo, Norway

Institute of Clinical Medicine, University of Aarhus, Aarhus, Denmark

Hendrikje M.K. van Breda, MD Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

Shirley Budd, MSc SEQOL Wiltshire, Swindon, UK

Tommaso Cai, MD Department of Urology, Santa Chiara Regional Hospital, Trento, Italy

Antonio Carbone, MD Department of Sciences and Medico-Surgical Biotechnologies, Sapienza, University of Rome, Rome, Italy

David Castro-Diaz, MD, PhD Department of Urology, Universidad de La Laguna/ Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain

Christopher Chapple, BSc, MD, FRCS (Urol), FEBU, DHC Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

Jean-Nicolas Cornu, MD, PhD, FEBU Tenon Hospital, Hôpitaux Universitaires Paris-EST, Assistance publique Hôpitaux de Paris, Université Pierre et Marie Curie Paris 6, Paris, France

Elisabetta Costantini, MD Urology and Andrology Clinic, Department of Surgical and Biomedical Science, University of Perugia, Perugia, Italy

Francisco Cruz, MD, PhD Department of Renal, Urologic and Infectious Disease, Faculty of Medicine of the University of Porto, I3S and IBMC of University of Porto, Porto, Portugal

Marie-Astrid Denys, MD Nopia Research Group, Department of Urology, Ghent University Hospital, Ghent, Belgium

Roger Dmochowski, MD, MMHC, FACS Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

Marcus J. Drake, MA, DM, FRCS(Urol) School of Clinical Sciences, University of Bristol, Bristol, UK

Karel Everaert, MD, PhD Nopia Research Group, Department of Urology, Ghent University Hospital, Ghent, Belgium

Magnus Fall, MD, PhD Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, Göteborg, Sweden

Fawzy Farag, MD, PhD Department of Urology, Sohag University Hospital, Sohag, Egypt

Radboud University Medical Center, Nijmegen, The Netherlands

Antonella Giannantoni, MD, PhD Department of Urology, University of Perugia, Perugia, Italy

An-Sofie Goessaert, MD Nopia Research Group, Department of Urology, Ghent University Hospital, Ghent, Belgium

Hashim Hashim, MBBS, MRCS, MD, FEBU, FRCS (Urol) Bristol Urological Institute, Southmead Hospital, Southmead, UK

John Heesakkers, MD, PhD Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

Odunayo Kalejaiye, MBBS, BSc, FRCS(Urol) Southmead hospital, Bristol, UK

Bristol Urological Institute, Southmead Hospital, Southmead, UK

Melissa Kaufman, MD, PhD Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

Thomas M. Kessler, MD Neuro-Urology, Balgrist University Hospital, Zürich, Switzerland

Aqsa Khan, MD Department of Urology, New York University, New York, NY, USA

Tricia L.C. Kuo, MBBS, MRCS, MMed, FAMS Department of Urology, Singapore General Hospital, Singapore, Singapore

Jan Moritz Laturnus,

Martina D. Liechti, PhD UCL Institute of Neurology, London, UK

Scott MacDiarmid, MD, FRCSC Department of Urology, Alliance Urology Specialists, University of North Carolina, Chapel Hill, NC, USA

Stephen Mock, MD Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

Franca Natale, MD Department of Urogynecology, San Carlo-IDI Hospital, Rome, Italy

Victor Nitti, MD Department of Urology, New York University, New York, NY, USA

Matthias Oelke, MD, FEBU Department of Urology, Hannover Medical School, Hannover, Germany

Nadir Osman, MBChB (Hons), MRCS Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

Giovanni Palleschi, MD Department of Sciences and Medico-Surgical Biotechnologies, Sapienza, University of Rome, Rome, Italy

Jalesh N. Panicker, MD, DM, FRCP Department of Uro-neurology, The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, London, UK

Antonio Luigi Pastore, MD Department of Sciences and Medico-Surgical Biotechnologies, Sapienza, University of Rome, Rome, Italy

Massimo Porena, MD Department of Urology, University of Perugia, Perugia, Italy

Silvia Proietti, MD Humanitas Clical and Research Centre, Rozzano, MI, Italy

W. Stuart Reynolds, MD Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

Dirk De Ridder, MD, PhD Department of Urology, UZ Leuven Campus Gasthuisberg, Leuven, Belgium

Julian Shah, FRCS Institute of Urology and University College London Hospitals, London, UK

Karl-Dietrich Sievert, MD, PhD, FACS, FRCS Department of Urology and Andrology, SALK University Clinic and Parccelsus Private Medical University (PMU), Salzburg, Austria

Tufan Tarcan, MD, PhD Department of Urology, Marmara University School of Medicine, Istanbul, Turkey

Stefan De Wachter, MD, PhD, FEBU Department of Urology, University Hospital Antwerpen, Edegem, Belgium

Emmanuel Weyne, MD Department of Urology and Andrology, University Hospitals Leuven, Leuven, Belgium

Chapter 1
Basic Principles

António Avelino, Francisco Cruz, Jalesh N. Panicker, and Martina D. Liechti

The present review highlights the morphology and neurophysiology, as well as the pharmacology, of the lower urinary tract (LUT).

The central element of the LUT is a reservoir, the urinary bladder, which stores and periodically eliminates urine. To perform this function, an efficient coordination is needed between storage and voiding mechanisms. During the storage phase, the bladder wall must accommodate a relatively high volume of urine at low pressure and the bladder outlet must remain closed by the urethral sphincter. Naturally, this coordination is carried out by a neural control system present in the brain, the spinal cord, and the peripheral ganglia.

A. Avelino, MSc, PhD
Department of Experimental Biology, Faculty of Medicine of the University of Porto, I3S and IBMC of University of Porto, Porto, Portugal
e-mail: aavelino@med.up.pt; cruzfjmr@med.up.pt

F. Cruz, MD, PhD (✉)
Department of Renal, Urologic and Infectious Disease, Faculty of Medicine of the University of Porto, I3S and IBMC of University of Porto, Porto, Portugal
e-mail: aavelino@med.up.pt; cruzfjmr@med.up.pt

J.N. Panicker, MD, DM, FRCP (✉)
Department of Uro-neurology, The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, London, UK
e-mail: j.panicker@ucl.ac.uk

M.D. Liechti, PhD
UCL Institute of Neurology, London, UK

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LUT: Anatomy

The bladder wall is formed by a mucosal and a muscular layer, surrounded by a serosa. The mucosa is lined by a stratified epithelium, the urothelium, comprising three layers: a basal cell layer, an intermediate layer, and an apical layer of umbrella cells. The lamina propria contains several cell types including fibroblasts, mast cells, sensory nerve endings, and myofibroblasts (also referred to as interstitial cells; see below). It is also rich in afferent and efferent nerve endings, vascular and lymphatic vessels, collagen and elastic fibers, and more or less well-defined smooth muscle fascicles [1].

The detrusor muscle is composed of three layers of smooth muscle. They are typical smooth muscle cells, without particular features that distinguish them from those found in other viscera. The cells of the outer and inner layers tend to be oriented longitudinally and those of the middle layer circularly. In the human detrusor, bundles of muscle cells of varying size are surrounded by connective tissue rich in collagen. Those muscular bundles vary extensively in size. In the human detrusor they are large, often a few millimeters in diameter, and composed of several smaller sub-bundles.

The Urothelium

The major (and classical) function of the urothelium is to act as a barrier to block the passage of substances excreted in the urine into the bladder wall. The urothelium is a transitional-type epithelium, containing three layers of cells: a basal cell layer, an intermediate layer, and a superficial layer containing hexagonal cells (umbrella cells). The latter have particular characteristics that concur to the barrier function of the urothelium. Among them, they have specialized membrane lipids, uroplakin-rich asymmetric unit membranes, and a plasmalemma with stiff plaques. Uroplakins are transmembrane proteins that further reduce the permeability of the urothelium to small molecules like water, urea, and protons and can be used as a differentiation marker of umbrella cells. To reduce intercellular movement of molecules, occludin- and claudin-rich tight junctions connect the lateral membrane of superficial cells. The luminal membrane of umbrella cells is covered by a glycosaminoglycan (GAG) layer that further reinforces the barrier function and seems to have antibacterial and anti-adherence properties. The origin of the GAG layer is still not clear, with at least part of it being synthetized by the kidneys to increase surface area. Fusiform or discoidal-shaped cytoplasmic vesicles docked in the apical cytoplasm fuse with the apical membrane, thereby increasing the luminal area. The presence of SNARE proteins essential for exocytosis was recently reported in urothelial cells and one of its isoforms (SNAP23) is extremely abundant in umbrella cells (Fig. 1.1).

While the urothelium has been historically viewed primarily as a barrier, it is becoming increasingly appreciated as a responsive structure capable of detecting

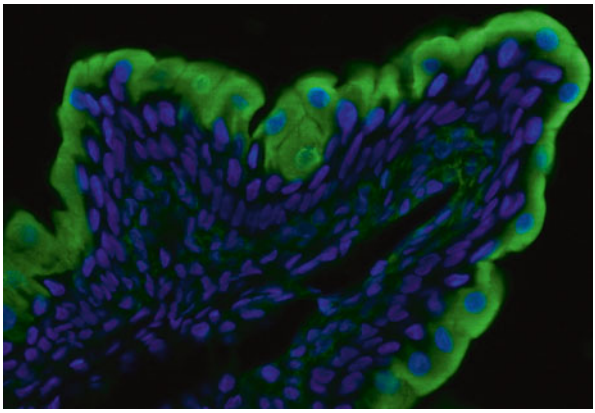

Fig. 1.1 Guinea pig urothelium stained for SNAP23 (*green*) and nuclei (*Blue*). Umbrella cells are strongly labeled. Lamina propria can be seen in faint green (*background*) (Avelino et al. 2015)

Table 1.1 Receptors and signaling molecules present in the urinary bladder

Receptor/channel/signaling molecule	Location	Neurotransmitter/agonist/stimulus
Receptors		
Cholinergic muscarinic (M2, M3)	D, U, S	Acetylcholine, muscarine
Cholinergic nicotinic	U, S	Acetylcholine, nicotine
Adrenergic alpha	U, D, S	Norepinephrine; epinephrine
Adrenergic beta	U, D, S	Norepinephrine; epinephrine
Degenerin/ENaC	U, S	Amiloride, mechanical
Neurotrophins (trkA; p75; trkB)	U, D, S	NGF, BDNF
Bradykinin receptor [1, 3]	U, D, S	Bradykinin
Tachykinin receptor [1–3]	U, D, S	Substance P, neurokinin A
Estrogen receptor	U, D, S	Estradiol
Proteinase-activated receptor	U, D, S	Thrombin; trypsin
TRPV1	U, S	Heat (43 °C), low pH, anandamide, vanilloids
TRPV2	U, S	Noxious heat (53 °C)
TRPV4	U, S	Cell stretch, moderate heat (24 °C), 4 alpha-PDD
TRPM8	U, S	Cold (8–28 °C), menthol, icilin
TRPA1	U, S	Cinnamaldehyde, mechanical
P2X	U, D, S	ATP
P2Y	U, D	ATP; UTP; ADP
P1	U, D	Adenosin
Cannabinnoid [1, 3]	U, D, S	Anandamide; cannabinoids
VEGF receptor	U, D, S	Vascular endothelial growth factor

Note: the order of the initials in the table indicates relative (decreasing) expression
U urothelium, *D* detrusor muscle, *S* sensory afferents

physiological and chemical stimuli and able to release a significant number of signaling molecules Thus, urothelial cells display a number of properties similar to sensory neurons and can use several signal-transduction mechanisms that perform an intricate cross talk with primary afferents located in the sub-urothelium. Urothelial cells express receptors for bradykinin, neurotrophins, as well as purinergic, cholinergic, adrenergic, and protease-activated receptors. Amiloride/mechanosensitive Na+channels and several transient receptor potential channels are also found in the urothelium (Table 1.1). In addition, urothelial cells can release neurotransmitters and signaling molecules such as nitric oxide, ATP, acetylcholine, prostaglandins, substance P, and neurotrophins (Table 1.1) that influence the excitability of suburothelial afferent nerves. Mediators released by urothelial cells may eventually act indirectly on suburothelial myofibroblasts (also referred to as "interstitial cells") that lie in close proximity to afferent nerves. Thus, it is believed that urothelial cells and myofibroblasts can participate in sensory mechanisms in the urinary tract in an autocrine/paracrine way.

Examples of this phenomenon are well documented: distension of the bladder causes ATP release from urothelial cells that consequently stimulates P2×2/P2×3 receptors in suburothelial sensory; stimulation of urothelial cells with the vanilloid receptor agonists capsaicin and RTX increases their intracellular calcium and evokes transmitter (nitric oxide and ATP) release. It is noteworthy to mention that in aged mice, increased levels of ATP are released in the bladder lumen, resulting in increased primary afferent activity, suggesting that aging results in aberrant urothelial function.

Interstitial Cells

Interstitial cells of Cajal, ICC-like cells, or myofibroblasts found in the urinary bladder resemble the interstitial cells of Cajal (ICC) of the gastrointestinal tract. After some debate, there is some consensus that these cells should be referred as interstitial cells of Cajal (ICC) or just as interstitial cells (IC).

Based on their location within the bladder wall, several subgroups of IC have been identified. ICC of the lamina propria are stellate-shaped cells that have been found to be extensively linked by gap junctions. Detrusor IC are elongated non-networked cells arranged in circular, longitudinal, and oblique orientation, on the boundary of smooth muscle bundles; see Fig. 1.2. They make close structural connections with nerves, but the origin of the nerve fibers (afferent or efferent?) was never determined.

Ultrastructurally, IC of the lamina propria present the characteristics of the classical gut myofibroblasts. These include bundles of fine cytoplasmic filaments, dense bodies, linear arrays of subsurface vacuoles, and the presence of an interrupted basal lamina. In the detrusor, electron microscopy studies showed that interstitial cells have flattened, dendritic-like processes, forming a branching network around individual muscle fascicles. In the cell soma and cytoplasmic processes, mitochondria, rough endoplasmic reticulum, and Golgi apparatus were observed, as well as intermediate filaments. Gap junctions and close appositions were described, but not specialized contacts with smooth muscle.

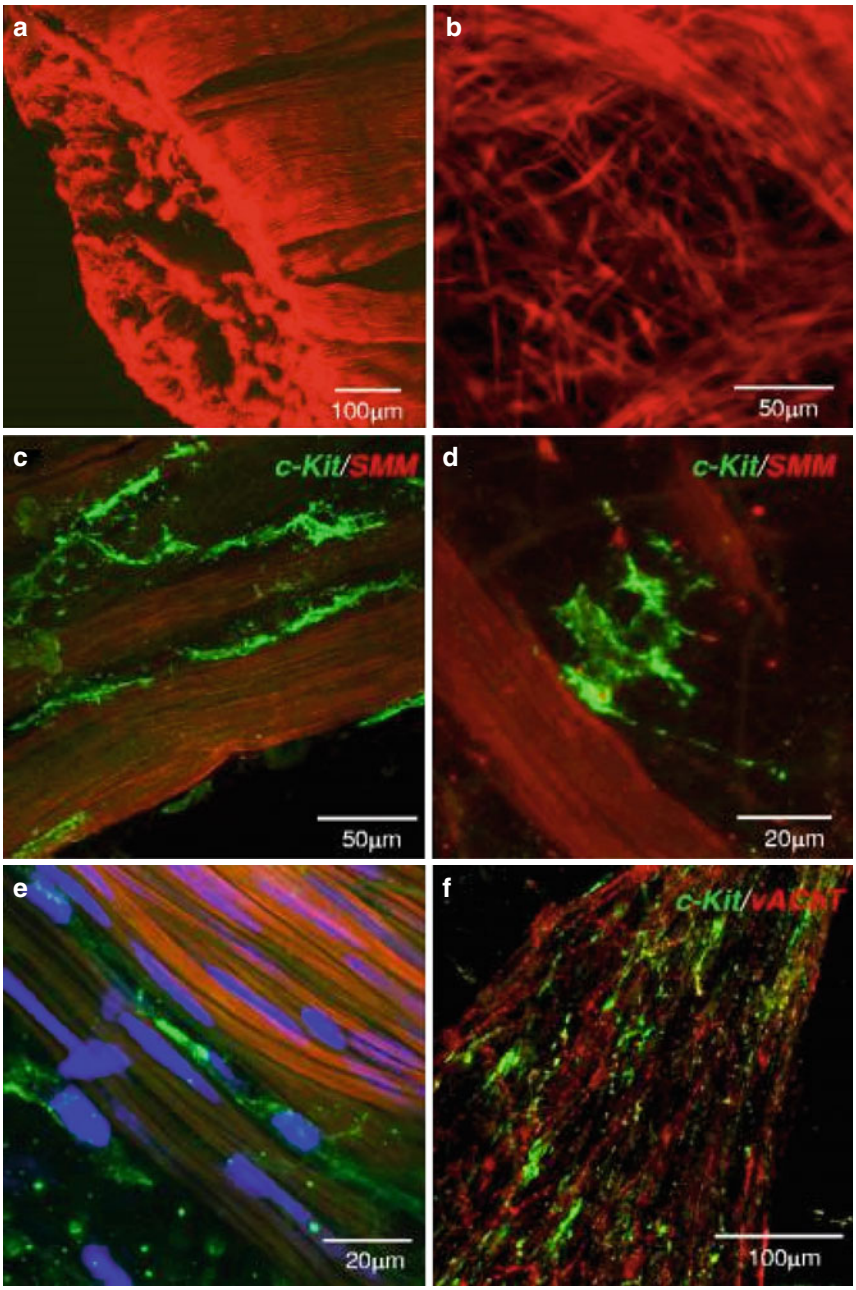

Fig. 1.2 Human detrusor ICC. (**a**) human detrusor labeled with anti-SM myosin (*SMM*). (**b**) At mucosa-detrusor interface, SMC were arranged in loose network, which was organized into distinct bundles in detrusor muscularis. (**c**–**e**) Representative human detrusor colabeled with anti-SM myosin and anti-*KIT* (*green* areas). Elongated, branched *KIT*-positive ICC track SM bundles and occupy spaces between bundles with obvious spiky morphology. (**e**) Nuclei counterstained with 4,6-diamidino-2-phenylindole (*blue areas*). (**f**) Detrusor ICC (*green areas*) associated with vAChT nerves (*red areas*) (From Johnston et al. *J Urol*. 2010;184:370–7)

IC can be detected by immunostaining for the intermediate filament, vimentin. A subpopulation of these cells, in addition, also expresses the tyrosine kinase receptor, KIT. Some data is available regarding the functional role of IC in overactive bladders, but the emerging picture is still not clear. Some reports showed that overactive human bladder tissues had upregulated numbers of IC and enhanced contractility, which was more sensitive to a tyrosine kinase inhibitor. On the other hand, C-kit immunoreactivity was similar in patients with neurogenic bladders and controls and remained unchanged after treatment.

IC form an heterogeneous population, with some cells responding to cholinergic stimulation (detrusor IC) whereas others (lamina propria IC) do not. In contrast, they respond to application of ATP with calcium inflow. In this way, they appear to be ideally placed to respond to ATP released from urothelial cells, providing a putative transduction signaling system between the suburothelial sensory fibers and the detrusor muscle. In addition, they may eventually contribute to myogenic activity (nerve-dependent or spontaneous) due to their syncytial-like network.

Detrusor Muscle

The smooth muscle cells of the detrusor muscle are not clearly arranged in distinct layers, but run in all directions, forming groups of small functional units, or fascicles. Here, individual cells are evenly separated by an approximately 200 nm thick space containing collagen fibrils attached to a basal lamina. Specialized junctions, like zonulae adherens, and areas of sarcolemma apposition can be found in contiguous cells. Connexin-rich gap junctions were described in normal detrusor human bladder biopsies. Experimental studies suggest that gap junctions may have an important role in detrusor function. In animals with bladder outlet obstruction

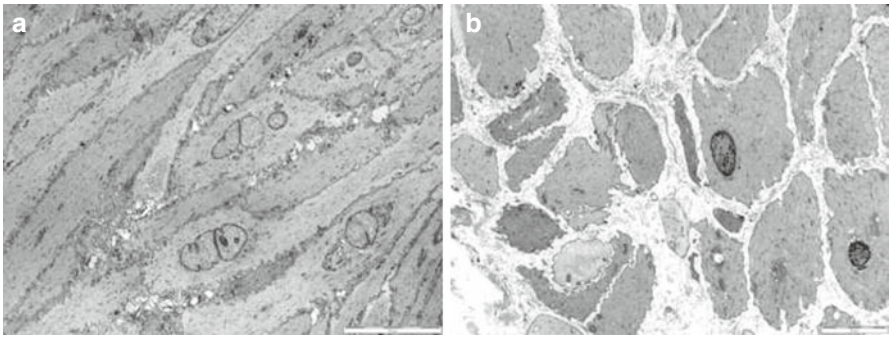

Fig. 1.3 (**a**) Normal detrusor. Normal detrusor myocytes are spindle-shaped mononuclear cells evenly aligned with minimal interstitial collagen and elastin in fascicles. (**b**) Ultrastructural features that correlated with each other and with poor postoperative voiding outcome were loss of fascicle arrangement, variable cell size, collagen in fascicles, and abnormal cell shape (From Blatt et al. *J Urol*. 2012;188:2294–9)

(BOO) leading to hypocontractility of the detrusor, connexin expression and the number of gap junctions were significantly reduced.

Innervation of the detrusor can be seen coursing the interstitium as Schwann cell-ensheathed axon bundles. Many axons form varicosities closely apposed to the muscle cells, forming neuroeffector junctions. Ultrastructural studies have shown that many of the varicosities are probably autonomic motor efferents, while others are undoubtedly primary afferents (Fig. 1.3).

Several bladder dysfunctions show ultrastructural changes in the detrusor. These are particularly evident in muscle cells and in the interstitium (Fig. 1.4). In overactive human bladders, a well-described disjunction pattern was recognized, consisting of widened spaces between cells, reduction of intermediate cell junctions, and increase of protrusion junctions and ultraclose cell abutments. In a recent study, the detrusor muscle of patients suffering from bladder underactivity subsequent to bladder outlet obstruction also showed morphological abnormalities. These consisted of variations in muscle cell size and shape, abnormal fascicle arrangement, and collagenosis, loosely corresponding to the myohypertrophy pattern originally described by.

The detrusor muscle contains receptors for numerous transmitters/modulators, released from nerves or generated locally. In humans the smooth muscle contraction is almost exclusively cholinergic. The predominant receptors for contraction are the muscarinic M_2 and M_3 receptors. In the normal human detrusor, the M_2 muscarinic receptor is more abundant, although the M_3 receptor is more relevant for detrusor contraction.

Muscarinic receptors are coupled to G proteins but with varying signal-transduction pathways. M_3 receptors couple to Gq/11, activating phosphoinositide

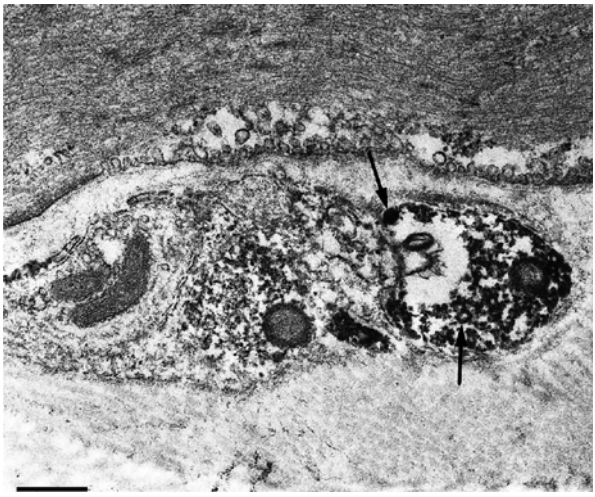

Fig. 1.4 Ultrastructural visualization of VR1 (presently know as TRPV1) immunoreactivity in nerve profiles found in the muscular layer. Immunoreactive varicosities lie in shallow grooves in the surface of smooth muscle cells. Small clear and large dense-core vesicles (*arrows*) can be seen (Adapted from Avelino et al. *Neuroscience*. 2002;109:787–98)

hydrolysis, leading to mobilization of intracellular calcium stores and causing a direct smooth muscle contraction. M_2 receptors couple to pertussis toxin-sensitive Gi/o, leading to inhibition of adenylyl cyclase activity. The most important receptor for relaxation is the β_3-adrenoreceptor. It is also coupled to a Gs protein, and its prototypical signaling pathway is activation of adenylyl cyclase to elevate intracellular cAMP concentrations. Sequentially, cAMP activates protein kinase A (PKA) decreasing intracellular calcium by stimulation of the sarcoplasmic reticulum calcium pump ATPase. Thus, in theory M_2 receptor activation oppose to sympathetically mediated smooth muscle relaxation, mediated by β_3-adrenoreceptor agonists. This forms the rationale for the therapeutical use of agents that block M3 receptors or drugs that activate the β_3-adrenoreceptor.

The other mechanisms that influence detrusor contraction are collectively known as non-adrenergic, non-cholinergic mechanisms. They involve mainly purinergic neurotransmission, but also nitric oxide release, neuropeptides, and prostaglandins.

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. The detrusor response to ATP seems to be mediated by activation of a ligand-gated cation channel (P2X receptor) that promotes the influx of extracellular Ca, whereas uridine triphosphate and adenosine act through G protein-coupled receptors (P2Y2 or P2Y4) to induce smooth muscle contractions via a phospholipase C/IP3 signaling pathway.

Although purinergic stimulation is considered to be the only minor contributor to normal bladder function in healthy humans, some studies show that this may not be true in abnormal conditions. The aging bladder seems to have a higher contribution of purinergic transmission. A significant positive correlation between age and purinergic neurotransmission, accompanied by a reduction of cholinergic neurotransmission, was detected in bladder strips of aging human bladders. Additionally, upregulation of purinergic activity through P2X receptors has been demonstrated in the bladder following chronic bladder outlet obstruction.

Nitric oxide (NO) has a strong role on the inhibitory non-adrenergic, non-cholinergic mechanisms. NO is generated by a reaction catalyzed by the enzyme NO synthase (NOS), of which three isoforms are currently known: neuronal NOS (nNOS), epithelial NOS (eNOS), and inducible/inflammatory NOS (iNOS). In a very convenient way, the three isoforms can be detected using NADPH histo- or immunohistochemistry. Using this approach, NO synthesis was identified throughout the bladder, in the detrusor muscle blood vessels, urothelium, nerves, and pelvic ganglia.

The most prominent effect of NO is its action on soluble guanylate cyclase, producing guanosine 3′, 5′- cyclic monophosphate (cGMP) and mediating relaxation of muscle. Accordingly, there is strong evidence that NO contributes to bladder reflex activity, since, e.g., the intravesical administration of the NO scavenger oxyhemoglobin induces bladder overactivity in experimental animals.

The effect of NO in bladder contraction opens a window of opportunity for the use of phosphodiesterase inhibitors, targeting a nitric oxide-cyclic guanosine monophosphate pathway, in the treatment of lower urinary tract symptoms.

Neuropeptides are abundant in the urinary bladder, but their functional role is far from being fully understood.

Tachykinins like substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are abundant in primary afferent nerves of the human bladder. Despite their afferent functions, peripheral release of these peptides seems to have an important role on detrusor function by inducing "neurogenic inflammation." Tachykinins bind to G-coupled receptors, and in the human bladder, NKA is the most potent tachykinin, through binding to the NK2 type.

Although detrusor smooth muscle contraction is normally triggered by the release of neurotransmitters, a certain degree of spontaneous activity is also present. Spontaneous contractile and electrical activities can be detected in isolated cells, bladder strips, or whole bladders. Spontaneous activity can affect the muscle from simple changes of tone to contractions involving several muscle bundles. Interestingly, spontaneous activity is increased in overactive bladders of experimental animals and patients. Recent reports showed that treatment of rat bladders with botulinum toxin, a neurotoxin that disrupts nerve vesicle exocytosis, abolished afferent and efferent nerve discharge without affecting spontaneous muscular activity.

Detrusor smooth muscle cells are electrically connected via gap junctions composed of the connexin subtype C×45. This fact may contribute to increased spontaneous activity, since gap junction blockers inhibit spontaneous contractions in animal models of overactive bladders. Furthermore, an increase of C×45 was reported in the detrusor muscle of patients with neurogenic detrusor overactivity and of patients with lower urinary tract symptoms (LUTS).

Innervation

Three sets of nerves (sacral parasympathetic, thoracolumbar sympathetic, and somatic nerves) innervate the bladder [2]. The nerves consist of efferent and afferent axons originating at thoracolumbar and sacral spinal levels. Parasympathetic efferent nerves contract the bladder while sympathetic efferent nerves relax the bladder and contract the urethra. Somatic efferent nerves contract the EUS. Sympathetic postganglionic efferent pathways in the pelvic and hypogastric nerves elicit similar effects in the bladder, for example, firstly, inhibition of the detrusor smooth muscle via release of noradrenaline from nerve terminals causing activation of ß-adrenoceptors and, secondly, excitation of the urethra via noradrenaline release and activation of urethral α_1-adrenoceptors

Parasympathetic preganglionic neurons are located in the intermediolateral gray matter (laminae V–VII) in the sacral segments of the spinal cord, whereas sympathetic preganglionic neurons are located in medial (lamina X) and lateral (laminae V–VII) areas in the rostral lumbar spinal cord. Intramural parasympathetic ganglion cells are present in the bladder wall of humans and some other species (curiously, are not present in the rat). The majority of the ganglia are small sized, containing one to six neurons, and typically stain for choline acetyltransferase (ChAT).

Afferent fibers project into Lissauer's tract in the lumbosacral spinal cord and extend through lamina I laterally and medially around the dorsal horn into deeper laminae (V–VII and X). Unmyelinated peptidergic bladder afferents project to spinal cord lamina I and non-peptidergic afferents project to spinal cord inner lamina II.

Myelinated Aδ-fibers are located primarily in the detrusor muscle layer, respond primarily to detrusor stretching during bladder filling, and convey sensations of fullness. These nerves enter the bladder through the neck and branch extensively, forming a rich plexus in the trigone. Unmyelinated sensory C-fibers are more widespread and reside in the muscle, close to the urothelium in the mucosa and directly adjacent to the urothelial cells. In some species, including humans, peptidergic afferent axons are also located in close proximity to intramural parasympathetic ganglion cells, where they participate in local reflex networks within the bladder wall.

Bladder afferent neurons display immunoreactivity for several neuropeptides, such as SP, CGRP, PACAP, leucine-enkephalin, galanin, and corticotrophin-releasing factor as well as nitric oxide synthase, glutamic acid, and aspartic acid. Co-expression of neuropeptides is highly prevalent, namely, of CGRP, SP, and PACAP. Several transient receptor potential channels, namely, the vanilloid receptor TRPV, are also highly expressed in primary afferent fibers [3].

The micturition reflex starts when stretch receptors in the bladder wall project sensory information regarding the degree of bladder distension via pelvic afferent nerve fibers to the spinal cord and convey this information to the pontine micturition center (PMC) and periaqueductal gray (PAG). During the initial part of the filling phase, afferent nerve firing is low, inhibiting the sacral parasympathetic nerves and exciting lumbar sympathetic preganglionic neurons. Stimulation of sympathetic neurons initiates the release of noradrenaline which acts on ß-adrenoceptors in the bladder detrusor muscle to cause relaxation of the muscle and acts on α-adrenoceptors on the urethral sphincter causing contraction of the sphincter muscle, promoting continence.

When the volume of the bladder nears the micturition threshold, afferent nerve signals produce nerve firing in the sacral parasympathetic pathways and inhibit the sympathetic and somatic pathways. Voiding of urine consists of two phases, firstly parasympathetically mediated relaxation of the urethral sphincter by nitric oxide as well as cessation of excitatory adrenergic and somatic inputs to the urethra and secondly the release of ACh which acts on muscarinic receptors on detrusor muscle by the parasympathetic nerves of the bladder, eliciting bladder contraction and urine flow.

Summary and Conclusions

This review pretends to stress the complexity of the mechanisms involved in an apparently simple voiding-filling cycle.

From its inner lining, the urothelium, to the outermost layer, the detrusor, a delicate balance of various inhibitory and excitatory pathways must exist. The molecular

cross talk between several structures is being further dissected every day, expanding knowledge and improving therapeutics.

Pelvic Neurophysiology

Jalesh N. Panicker and Martina D. Liechti

Introduction

Neurophysiology tests involve the recording of bioelectrical activity from muscles and the nervous system to investigate nerve functions. It is practical to distinguish recordings from muscle (electromyography, EMG) and tests of nerve and nervous pathway function (conduction studies). Although less widely available in functional urology, some neurophysiology tests may be useful in the assessment of patients with pelvic organ complaints.

Electromyography

Electromyography (EMG) is a diagnostic procedure to assess the integrity of muscle functions and their innervation. In this way, muscles that are difficult to test clinically can be investigated, for example, those of the pelvic floor. Kinesiological EMG recordings during specific tasks may be useful in specific situations, such as during biofeedback applications to address disturbances of pelvic floor muscles activity which enable patients to be actively involved in the treatment of their symptoms.

Pelvic floor EMG was first introduced as part of urodynamic studies to assess the extent of relaxation of the urethral sphincter during voiding, with the aim of recognizing detrusor-sphincter dyssynergia. For this purpose, either surface or needle electrodes may be used. The best signal is obtained using a concentric needle electrode (CNE), but the discomfort from the needle itself is likely to influence relaxation of the pelvic floor. Surface recording electrodes often provide sufficient information; however they also record EMG signals from other pelvic floor muscles. EMG allows an ongoing assessment of muscle activity during the entire urodynamics test; however the test is performed less often nowadays because of increasing availability of video-urodynamic investigations for diagnosing detrusor-sphincter dyssynergia.

However, CNE EMG studies of the external urethral and anal sphincter muscles, performed separately from urodynamics, have been proven useful to assess the integrity of the innervations to the pelvic floor. It provides information on insertion

activity, spontaneous activity, interference pattern, and motor unit potentials. The normal sphincter EMG shows continuous "tonic" activity at rest, which may be increased voluntarily or reflexly. The number of recorded motor units recorded depends upon the uptake area of the electrode. Using a CNE, activity from one to five motor units is usually recorded per site in the anal sphincter at rest. Electromyography has been used to demonstrate changes of reinnervation in the urethral or anal sphincter in a few neurological disorders. Well-established values exist for the normal duration and amplitude of motor units recorded from the sphincter muscles.

Sphincter EMG in the Evaluation of Suspected Cauda Equina Lesions

Lesions of the cauda equina are an important cause for pelvic floor dysfunction and patients present with lower urinary tract (LUT) dysfunction and often sexual and bowel dysfunction as well. Most often, EMG of the external anal sphincter demonstrating changes of chronic reinnervation, with a reduced interference pattern with fewer motor units and enlarged polyphasic motor units (>1 mV amplitude), can be found in patients with long-standing cauda equina syndrome. Though EMG may demonstrate pathological spontaneous activity 3 weeks or more after injury, these changes of moderate to severe partial denervation (i.e., fibrillations and positive sharp waves) often become lost in the tonically firing motor units of the sphincter.

Sphincter EMG in the Diagnosis of Multiple System Atrophy

Multiple system atrophy (MSA), a variant of Parkinson's disease, is a progressive neurodegenerative disease which often, particularly in its early stages, is mistaken for Parkinson's disease but is poorly responsive to antiparkinsonian treatment. Autonomic failure causing postural hypotension and cerebellar ataxia causing unsteadiness and clumsiness may be additional features. Urinary incontinence in both women and men occurs early in this condition, often appearing some years before the onset of obvious neurological features, and not uncommonly, patients may present to the urologist. Degenerative changes occur both in the brain and spinal cord resulting in LUT dysfunction. Neuropathological studies have shown that the anterior horn cells in Onuf's nucleus are selectively lost in MSA and this results in changes in the sphincter muscles that can be identified by EMG. The anal sphincter is once again most often studied and changes of chronic reinnervation in MSA tend to result in prolonged duration motor units and these changes can be detected easily (Fig. 1.5).

The value of sphincter EMG in the differential diagnosis of parkinsonism has been widely debated over the years. Technically, the MUPs recorded in MSA are quite prolonged and automated MUP analysis results in a tendency to chop up these long polyphasic MUPs into individual components. Thereby the late components might be missed when measuring the motor unit duration and the duration of the

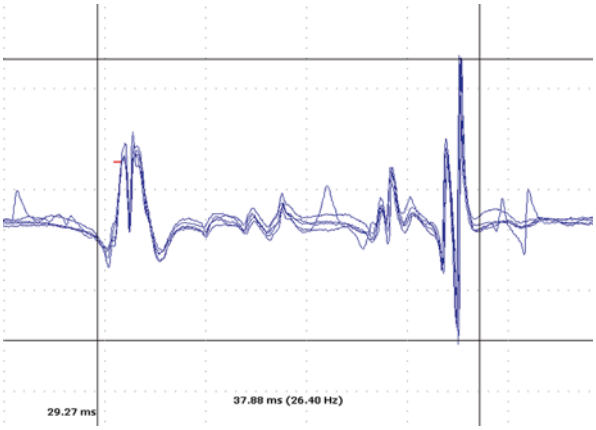

Fig. 1.5 Concentric needle EMG of the external anal sphincter from a 54-year-old gentleman presenting with voiding difficulties and incontinence on the background of a recent onset parkinsonism syndrome. Duration of the recorded motor unit is 37.9 ms, which is prolonged and suggests chronic reinnervation. The mean duration of MUPs during the study was 19 ms (normal <10 ms) and the EMG was compatible with a diagnosis of multiple system atrophy (gain 200 microvolts/division, sweep speed 10 ms/division)

MUP may be erroneously noted as being normal. It is advisable therefore to also identify MUPs manually when performing the EMG for a patient with suspected MSA to avoid this pitfall. Moreover, the EMG changes are not specific to MSA, and similar changes of chronic reinnervation may be found in long-standing Parkinson's disease, other parkinsonian syndromes such as progressive supranuclear palsy, dementia with Lewy bodies, and other neurodegenerative conditions such as spinocerebellar ataxia type 3 and following obstetric injury with sphincter damage and cauda equina damage. Nevertheless, a body of opinion exists that maintains that a highly abnormal result in a patient with mild parkinsonism is of value in establishing a diagnosis of probable MSA. A highly abnormal EMG in the absence of other obvious causes in a patient with suspected MSA in first 5 years is significant [4]. This correlation is important not only for the neurologist but also for the urologist, because inappropriate surgery for a suspected prostate enlargement as the cause for bladder troubles can then be avoided.

Sphincter EMG in the Investigation of Urinary Retention in Young Women

Isolated urinary retention in young women may occur where the neurological examination is normal and investigations such as MRI exclude a neurological cause for voiding dysfunction. A characteristic abnormality, however, can be found on urethral sphincter EMG, consisting of decelerating bursts (Fig. 1.6), a signal somewhat like myotonia, and complex repetitive discharges (Fig. 1.7). It has been proposed that this abnormal spontaneous activity results in impairment of relaxation of the urethral

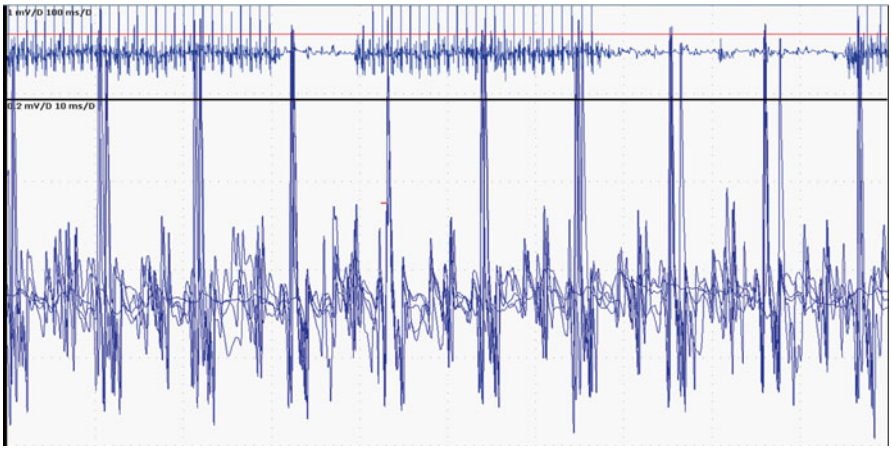

Fig. 1.6 Decelerating burst recorded during concentric needle EMG of the urethral sphincter in a young woman presenting with urinary retention (gain and sweep speeds provided in respective panels)

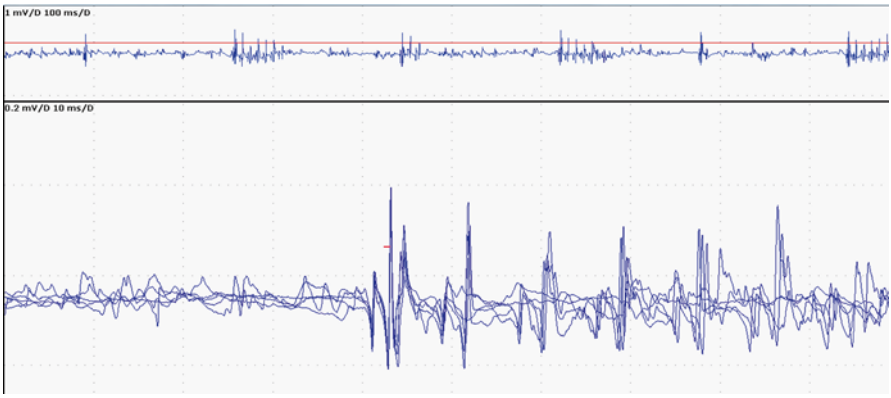

Fig. 1.7 Complex repetitive discharges recorded during concentric needle EMG of the urethral sphincter in a young woman presenting with urinary retention (gain and sweep speeds provided in respective panels)

sphincter, which may cause urinary retention in some women and obstructed voiding in others. This condition, nowadays known as Fowler's syndrome [5], is also characterized by elevated urethral pressures with values regularly in excess of 100 cmH_2O.

Sacral Reflexes

Mechanical, electrical, or magnetic stimulation in the perineal region can be used to elicit reflex responses from the perineal and pelvic floor muscles. The penilocavernosus reflex and anal reflex both involve the sacral (S2,3,4) roots and pudendal

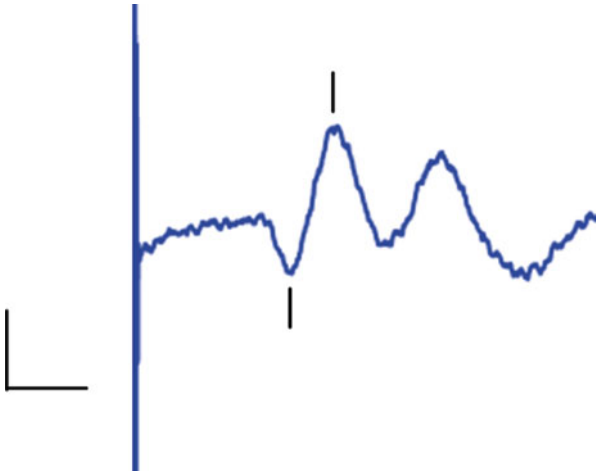

Fig. 1.8 Somatosensory evoked potential (SSEP) recorded at Cz-Fz during electrical stimulation (15 mA) of the dorsal penile nerve in a young man presenting with genital numbness. The P40 waveform was of normal latency

nerve in their reflex arc and are often elicited during the clinical examination. However, reflex responses are more accurately assessed and can be quantified when tested using neurophysiology tests.

Similar to the anal reflex, which is elicited by perianal stimulation and recording from the anal sphincter muscle, the penilo-cavernosus reflex, formally known as the "bulbocavernosus" reflex, assesses the sacral root afferent and efferent pathways. For the penilo-cavernosus reflex, the dorsal nerve of penis (or clitoris) is electrically stimulated and recordings are made from the bulbocavernosus muscle or external anal sphincter, usually with a concentric needle. In those patients in whom the reflex is difficult to elicit, double electrical stimuli should be used. A sacral reflex arc lesion should not be inferred by absence of a response if only single pulse is used for stimulation. This test is complementary to the clinically assessed response and the EMG examination of the pelvic floor muscles in patients with suspected peripheral nervous lesions. It may be of value in patients with bladder dysfunction suspected to be secondary to cauda equina damage or damage to the lower motor neuron pathway.

Evoked Potential Studies

The acquisition of somatosensory evoked potentials (SSEP) is a well-established method to assess afferent/sensory nerve fiber function from various parts of the body. Stimulation of a certain nerve or dermatome elicits SSEPs, which can be measured along the spinal cord or over the cortex providing characteristic latency and amplitude measures.

Pudendal SSEP are typically recorded from the scalp following electrical stimulation of the dorsal nerve of penis or clitoral nerve (Fig. 1.8) and are compared to tibial evoked potentials. SSEP may be abnormal when a spinal cord lesion is the cause of sacral sensory loss or neurogenic detrusor over activity; however, such

pathology is usually apparent from the clinical examination. Additional recordings over the cauda equina and lumbosacral cord help in localizing spinal lesions. Apart from its main application in intraoperative monitoring, normal pudendal SSEP can help to rule out a neurological cause in certain situations such as erectile dysfunction.

Similarly, though technically more demanding, LUT sensory evoked potentials can be obtained on stimulation of the bladder urothelium or urethra. Currently, these tests are limited to research applications, but considering the potential relevance for neurogenic LUT dysfunction, these tests need to be further developed for future clinical applications.

Motor evoked potentials (MEP) can be used to study efferent/motor pathways, which involve the stimulation of the motor cortex or spinal pathways and the recording from target muscles. While these tests can be useful to localize lesions in the central nervous system, they have a limited role in the investigation of pelvic floor problems.

Nerve Conduction Studies

Due to the limited accessibility in that area of the body, the only test of motor nerve conduction for the pelvic floor is the pudendal nerve terminal motor latency (PNMTL). The pudendal nerve is the most important motor nerve innervating the pelvic floor. The pudendal nerve is stimulated either per rectally or vaginally adjacent to the ischial spine using the St Mark's electrode, a finger-mounted stimulating device with a surface EMG recording electrode 7 cm proximal located around the base of the finger which records from the external anal sphincter. Prolongation was initially considered evidence for pudendal nerve damage, although a prolonged latency is a poor marker of denervation. This test has not proved contributory in the investigation of patients with suspected pudendal neuralgia and can currently only be interpreted in combination with the results of other tests.

Autonomic Function Tests

The tests mentioned so far are restricted to evaluating the somatic nervous system. Considering the significant proportion of autonomic innervation relevant for the sympathetic and parasympathetic control of sacral organ functions, appropriate function tests would be important. The only test available is the sympathetic skin response (SSR) which can be recorded from palms, soles, and perineal skin. Although the responses are easily habituated and highly dependent on individual as well as environmental factors, the latencies can typically be interpreted which can be used for the evaluation of LUT dysfunction and sexual impotence.

Conclusion and Outlook

Neurophysiological tests are important to better understand and diagnose the neurological cause for pelvic organ complaints, which is also helpful for the choice of treatment. Apart from EMG and reflex tests, which have a clear role in patients with suspected peripheral nervous system lesions, pelvic neurophysiology remains technically demanding and often test only a subset of nerves. However, these tests are useful as a research tool to understand the basis of LUT dysfunction, and it is anticipated that they will gain clinical relevance for diagnosis of LUT dysfunction and intraoperative applications in the future.

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Chapter 2
Pathology: Neurological Diseases

Thomas M. Kessler, Stefan De Wachter, and Marcus J. Drake

Introduction

The control of the lower urinary tract is a complex, multilevel process involving both the peripheral and central nervous system. Thus, lower urinary tract dysfunction (LUTD) is very common in neurological patients resulting from the profound alterations of lower urinary tract control caused by the underlying disease. It is of utmost importance not only to appropriately assess LUTD but also to understand the neurological cause, as it significantly influences the choice of treatment.

What Do the Guidelines Say?

According to the Guidelines on Neuro-Urology of the European Association of Urology (EAU), the aims of neuro-urological management include enhancing quality of life, preservation of upper urinary tract function, control of urinary tract infection and maintenance of a low-pressure bladder that is both continent and capable of emptying completely. Ideally these goals are achieved without an indwelling catheter or a stoma and in a manner that is socially and vocationally acceptable to

T.M. Kessler, MD (✉)
Neuro-Urology, Balgrist University Hospital, Zürich, Switzerland
e-mail: tkessler@gmx.ch

S. De Wachter, MD, PhD, FEBU
Department of Urology, University Hospital Antwerpen, Edegem, Belgium
e-mail: stefan.dewachter@ua.ac.be

M.J. Drake, MD, DM, FRCS(Urol)
School of Clinical Sciences, University of Bristol, Bristol, UK
e-mail: marcus.drake@bui.ac.uk

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the patient, whilst avoiding complications such as recurrent urinary tract infections, urethral strictures, calculus disease, hydronephrosis and renal failure.

History taking is the cornerstone of neurogenic LUTD assessment. It needs to gather information on congenital and neurological abnormalities, prior urogenital complications and treatments, medication and urinary tract, sexual, bowel, neurological and gynaecological function. Evaluation of lifestyle factors, such as smoking, alcohol or addictive drugs, and quality of life are also important, and attention should be paid to physical and mental handicaps.

Bladder diary is a highly useful tool in clinical practice as it provides an objective measure of lower urinary tract symptoms (LUTS) mirroring day-to-day reality. In contrast, the patients' symptoms often cannot be reproduced by clinical examination and urodynamics because of the extraordinary situation and the time limits of medical consultation.

Physical examination includes the abdomen, flanks and external genital organs, as well as sensation and reflexes in the urogenital area (Fig. 2.1). Anal sphincter and pelvic floor functions must be tested extensively. Urinalysis and urinary culture, blood chemistry (if not already performed by the referring physician), free uroflowmetry and post-void residual measurement, either by ultrasound or catheterisation, are part of a basic neuro-urological assessment.

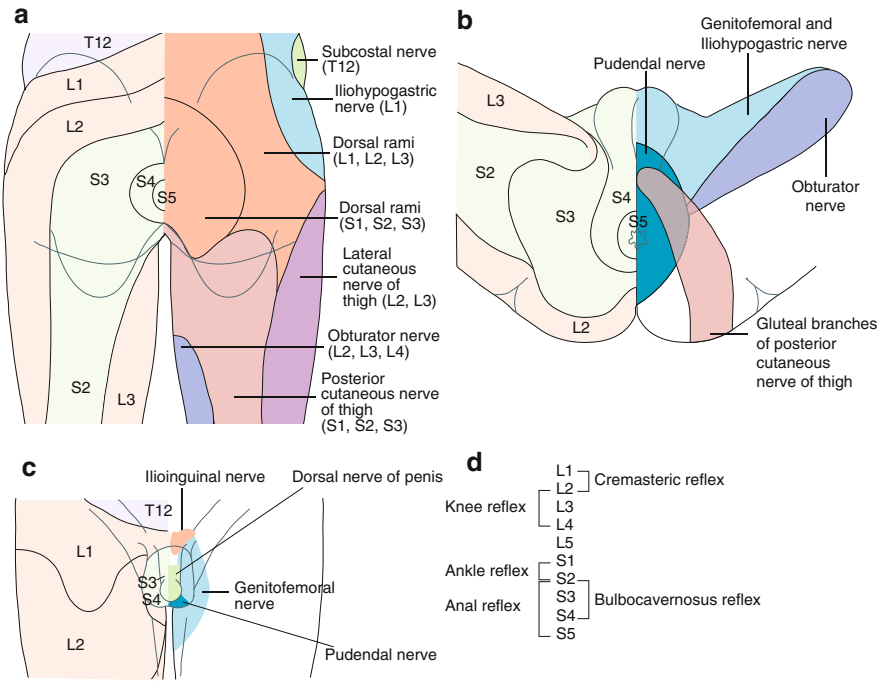

Fig. 2.1 Lumbosacral dematomes, cutaneous nerves, and reflexes. (Panicker JN et al. Lancet Neurol 2015)

Urodynamic investigation, with simultaneous fluoroscopic monitoring (i.e., video-urodynamics), is essential to assess detrusor and bladder outlet function, and it is crucial for clinical decision making. Generally accepted risk factors jeopardising the upper urinary tract are high detrusor pressure during storage phase due to low-compliance bladder and/or detrusor overactivity combined with detrusor sphincter dyssynergia, and urodynamic investigations are needed to identify these conditions.

Urethrocystoscopy (combined with bladder washing cytology if appropriate) is used if indicated to detect urethral and bladder pathologies, such as urethral stricture, urethral or bladder stones and bladder tumours, including carcinoma in situ.

Serum creatinine, cystatin c and corresponding estimations yield a reasonable estimation of renal function with minimal cost and inconvenience. Creatinine clearance provides a more accurate assessment but involves a 24-h urine collection to measure creatinine excretion. This may result in underestimation of renal function if the urine collection is incomplete. The most accurate measurement is isotopic glomerular filtration rate, especially when renal function is poor or with alterations of muscle mass (as is common in patients with neurological disease).

Clinical Practice

A very simple classification system for use in daily clinical practice is provided in (Fig. 2.2). Based on the dysfunction pattern, the appropriate therapeutic strategy to preserve both upper and lower urinary tract function, and to achieve or maintain urinary continence, is determined.

In patients with detrusor overactivity, the therapeutic concept is to convert the overactive detrusor into a normoactive or underactive one. Commonly, antimuscarinics are the pharmacological treatment of choice, but they have limited effectiveness and many patients discontinue their use due to adverse events. The beta-3 adrenergic agonist mirabegron has recently been introduced as an alternative to antimuscarinics for treatment of idiopathic overactive bladder, but research into its application in neurogenic LUTD has not been reported thus far. For refractory neurogenic detrusor overactivity, intradetrusor onabotulinumtoxinA injections are a highly effective, minimally invasive and generally well-tolerated treatment that improves health-related quality of life. In the case of failed onabotulinumtoxinA treatment, augmentation cystoplasty is a well-established treatment option but requires abdominal surgery with interposition of an intestinal segment (usually ileum) into the bladder and/or partial replacement of bladder by an intestinal substitute. In highly selected patients, cystectomy with continent or incontinent urinary diversion becomes necessary as a salvage procedure.

In patients with underactive/acontractile detrusor and/or with detrusor sphincter dyssynergia, intermittent self-catheterisation is recommended to assist bladder emptying. Passive voiding by abdominal straining (Valsalva manoeuvre) or, particularly, by suprapubic downwards compression of the lower abdomen (Credé manoeuvre) is

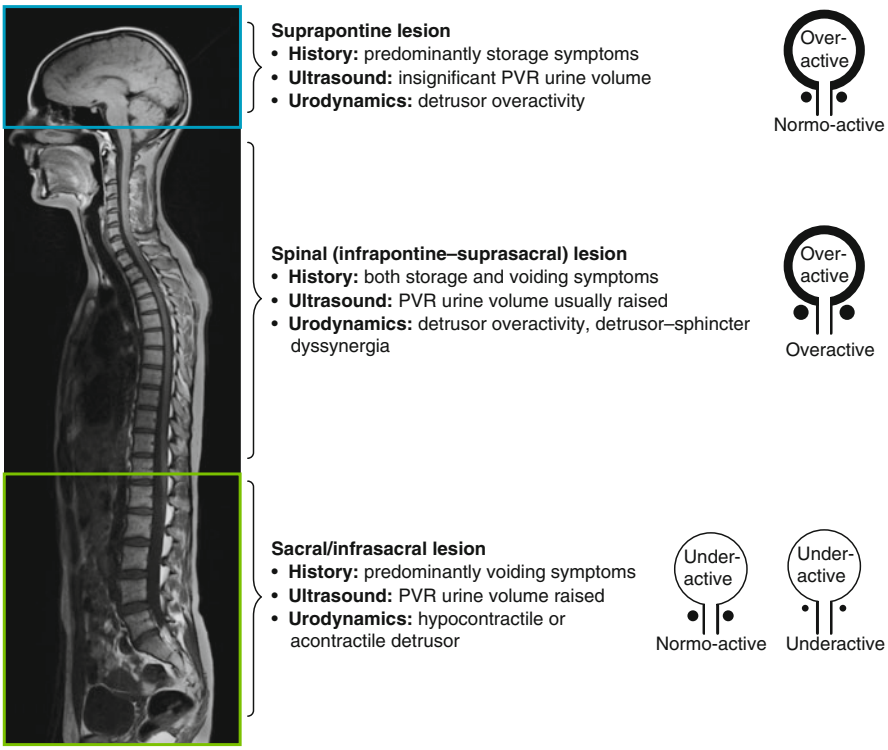

Fig. 2.2 Patterns of lower urinary tract dysfunction following neurological disease. (Panicker JN et al. Lancet Neurol 2015)

not recommended as it creates high, unphysiological intravesical pressure which puts the upper urinary tract at risk and causes compression of the urethra, i.e. a functional obstruction that leads to inefficient emptying. Nevertheless, some patients are not able and/or not willing to perform intermittent self-catheterisation, and therefore, an indwelling transurethral or suprapubic catheter is potentially the only alternative.

In the case of stress urinary incontinence due to low bladder outlet resistance, electrical stimulation of the pelvic floor can help to restore urinary continence in patients with incomplete lesions. In some neurological patients, the implantation of a sub-urethral sling or an artificial urinary sphincter may become necessary. However, it needs to be considered that artificial urinary sphincters generally do not continue working indefinitely and may need to be replaced with increased risks for revision surgery.

Regular follow-up is essential since neurogenic LUTD is often unstable and symptoms might vary considerably even within a relatively short period. The EAU Guidelines on Neuro-Urology provide clear-cut grade A recommendations that any significant clinical changes should instigate further specialised investigation and that in high-risk patients, the upper urinary tract should be assessed at least every 6 months, physical examination and urinalysis should take place every year, and

urodynamics should be done at regular intervals. However, there is a complete lack of high-evidence level studies on which to base such recommendations. Thus, follow-up of the neuro-urological patient is more eminence- than evidence-based. There is no uniform follow-up, and a rather individualised, patient-tailored approach aiming to achieve an optimal quality of life and to protect the upper urinary tract is needed for this special population.

Spina Bifida

Background

Although spina bifida is one of the most common birth defects of the spine, the exact mechanisms resulting in closure or a dysraphic state are yet to be elucidated. Nevertheless, the aetiology of closure defects of the neural tube is supposed to be multifactorial, including both genetic and environmental factors. The deficit of folic acid in the early pregnancy period is a major risk; the role of folic acid in the prevention of neural tube defects has been established since the early 1990s. Maternal ingestion of 400 μg of folic acid per day in all women of child-bearing age can reduce the incidence of spina bifida by 50 %. In the United Kingdom and Ireland, the yearly prevalence of neural tube defects declined, predating any periconceptional folic acid supplementation policy initiatives from 4.5 per 1000 births in 1980 to 1–1.5 per 1000 in the 1990s.

In spina bifida patients, the neurological findings can vary from the most discrete deficit to a complete paraplegia potentially involving all levels of the spinal column. Most spinal defects occur at the lumbar spine with the sacral, thoracic and cervical areas, in decreasing order of frequency, less affected. Associated Arnold-Chiari malformation is seen in more than 80 % of spina bifida children mostly requiring ventriculoperitoneal shunt placement. Whilst the likelihood of bladder, bowel and pelvic floor dysfunction depends on the severity of the lesion, the pattern of the dysfunction is aligned to the localisation.

Neurogenic LUTD in children with spina bifida can lead to secondary upper urinary tract deterioration and often causes chronic urinary incontinence. The preservation of renal function is the primary goal in the neuro-urological management of spina bifida patients, but considering the impact on quality of life, efforts to promote urinary continence have become more and more important. Continence is associated with better self-concept, and incontinent girls are particularly at high risk for poor self-esteem. Urinary incontinence is a stress factor for these patients, and even a slight improvement in urinary continence means to these patients additional independence. Thus, reducing the frequency of incontinence or, even better, the achievement of continence is an important goal of urological medical care.

According to Verhoef et al., urinary and faecal incontinence is common in young adults with spina bifida (61 % and 34 %, respectively) regardless of bladder and bowel management they used. The majority of urinary and faecal incontinent patients perceived this as a problem (70 % and 77 %, respectively). Moreover, the

authors of this study found that patients with a level of lesion at L5 or above were far more likely to be urinary and faecal incontinent than those with a level of lesion of S1 or below. However, patients with a level of lesion at L5 and above were also more likely to perceive urinary incontinence as a problem. It is well known that urinary incontinence in these patients has an underlying component of detrusor overactivity and/or poor bladder compliance, which is more frequent in patients with intact or at least partially intact sacral reflexes, which are mostly present in lesions at L5 and above (suprasacral lesion). Remarkably, whilst in utero closure of spina bifida decreased rates of ventriculoperitoneal shunting and improved motor function, it seems not to be associated with a relevant improvement in lower urinary tract function compared to repair after birth.

Points of Interest

Although some authors have questioned the value of urodynamics shortly after birth and serially thereafter, most authors agree that early urodynamics are a prerequisite for an adequate treatment strategy.

The Innsbruck approach, based on more than 30 years of experience with spina bifida patients, is an early proactive conservative management which is the state of the art nowadays. This improves upper urinary tract function and reduces the need for surgery in patients with myelomeningocele in the long term. The initial evaluation consists of a history, neuro-urological examination (especially including bulbocavernosus reflex, anal reflex, anal sphincter tone), urinalysis, urine culture, sonography of kidneys and bladder, as well as (video-) urodynamics. Patients undergo initial evaluation as early as possible, ideally at the day of birth or within 2 weeks after closure of the spina bifida defect. Voiding cystourethrography and urodynamics are performed concurrently as video-urodynamics. Patients at risk for upper urinary tract damage (low bladder compliance, intravesical pressure >40 cmH_2O, detrusor sphincter dyssynergia) and those with abnormal findings on imaging studies (trabeculated bladder ± pseudodiverticula, vesico-uretero-renal reflux, dilated ureter, hydronephrosis, cortical thinning/scarring of renal parenchyma) undergo nuclear renal scan. Periodic reassessment with neuro-urological examination, urinalysis, urine culture, imaging studies and (video-) urodynamics are performed every 3–6 months up to age 2 and in yearly intervals thereafter.

Therapeutic strategies for treating neurogenic LUTD in spina bifida patients are in line with those of other neurological disorders mentioned above (see section "Clinical practice"). It should be considered, however, that latex allergy is very common in this population, and latex avoidance in children is strongly recommended as it seems also to prevent sensitisation to other allergens and allergic diseases which might be explained by the prevention of sensitisation spreading. In addition, due to the congenital nature of the disease, the patients cope since birth with the disability and spina bifida children have a lower self-concept than their peers with typical development, what may also become relevant for adolescence and adulthood.

Spinal Cord Injury

Background

Spinal cord injury (SCI) is a devastating event with far-reaching consequences for the individual's health and the family's economic and social future. It affects each year 15–40 new individuals per million in Western countries and will result in neurogenic LUTD in most of these patients. In the past, renal disease was responsible for more than 40 % of deaths following SCI. The introduction of intermittent self-catheterisation and the use of regular urodynamic investigations have since revolutionised the neuro-urological care of SCI patients. Hence, nowadays, urinary disease accounts for only about 13 % of deaths in SCI patients, and the most common cause of death now is related to pneumonia. It follows that adequate function of the urinary tract is essential to prevent morbidity and mortality in SCI patients.

Despite the fact that improved management of neurogenic LUTD has dramatically decreased morbidity and mortality in SCI patients, many important issues still remain. The patho-mechanisms involved in neurogenic LUTD are incompletely understood and many hypotheses established in animal models have not been proven in humans. Acute SCI lead to a state named "spinal shock": Muscles are generally in a flaccid state because of the loss of neurological reflexes, and urinary tract function is characterised by detrusor acontractility and urinary retention/voiding dysfunction. After a period of time of usually around 4–12 weeks, detrusor overactivity mostly combined with detrusor sphincter dyssynergia develops in the case of a suprasacral lesion (today the vast majority of SCI) as a result of reorganisation of neuronal circuitry. Disconnection from supraspinal centres means that voiding is not centrally driven but induced by volume-determined reflex detrusor connections. Detrusor sphincter dyssynergia may lead to high bladder pressures jeopardising the upper urinary tract. The emergence of these dysfunctional patterns is a complex, not yet fully understood process, but C-fibre-mediated spinal reflex pathways seem to be involved.

In contrast to chronic SCI, little is known about LUTD patterns during the acute phase of SCI, probably because urodynamic investigations are postponed to the chronic phase or are not performed at all, especially in patients with less well-pronounced neurological impairments. However, in a recent prospective study investigating neurogenic LUTD due to acute SCI (duration of injury less than 40 days), unfavourable urodynamic parameters, i.e. high-pressure system during storage phase, low-compliance bladder, detrusor overactivity, detrusor sphincter dyssynergia and vesico-uretero-renal reflux, were found in an unexpectedly high percentage of 60 % of the patients. Remarkably, ambulatory and nonambulatory patients had a similar risk of unfavourable measures so that same neuro-urological assessment including urodynamic investigations are strongly recommended in all acute SCI patients independent of the ability to walk.

In addition, SCI is not a stable condition, and so neuro-urological treatment strategies need to be flexible as they often need to be modified in almost all patients throughout life.

Points of Interest

Ideally, SCI patients should be managed in specialised SCI centres. The involvement of the neuro-urologist should not be confined to managing LUTD but should extend to addressing sexual dysfunction, fertility if relevant and bowel dysfunction.

In patients with complete SCI, sacral anterior root stimulation can be used to permit voiding but also requires sacral posterior root rhizotomy (also known as dorsal rhizotomy or sacral deafferentation) to suppress detrusor overactivity. Nowadays, sacral anterior root stimulation is rarely used as patients are reluctant to undergo concomitant dorsal rhizotomy which is a destructive, irreversible procedure resulting in the loss of reflex sexual function and reflex defecation. This is not ideal especially considering that the other minimally invasive options are available.

Of great interest is a recent study on the use of early bilateral sacral neuromodulation in patients with complete SCI during the spinal shock. Data suggest that this treatment could prevent the development of detrusor overactivity and urinary incontinence as well as improve sexual and bowel function. If the benefits of early sacral neuromodulation can be proven in randomised trials and if these findings are conveyed to other neurological disorders, then the management of neurogenic LUTD will be revolutionised. Adequately designed clinical studies will be required to confirm what looks to be a promising future in the field of neuro-urological care following SCI.

Autonomic dysreflexia is a sudden and exaggerated autonomic response to stimuli in patients with SCI or spinal dysfunction generally above level T6. Hypertension is a relatively common manifestation of autonomic dysreflexia and can have life-threatening results if not properly managed.

Multiple Sclerosis

Background

Multiple sclerosis (MS) is an acquired inflammatory disease in which the myelin sheath of nerve cells in the brain and spinal cord are damaged, leading to a diverse range of signs and symptoms. Symptoms can either occur in isolated attacks (relapsing MS) or steadily accumulate over time (progressive MS). Between attacks, symptoms may largely recover, but cumulative damage does steadily reduce patients' overall functional abilities. The cause of MS is unknown, but autoimmune mechanisms may be relevant. Genetic predisposition and environmental factors, e.g. infection, have been proposed. The disease usually begins between the ages of 20 and 50 and is twice as common in women as men. There is no current curative treatment, and disease modification to reduce progression is the current strategy. Life expectancy is reduced in comparison to an unaffected population.

Neurogenic LUTD has a profound effect on quality of life in patients with MS. Typically, it becomes apparent at a comparatively early stage in the progression of the illness, and it can be a presenting feature of MS. Ultimately, LUTD affects a

high proportion of MS patients, the occurrence being influenced by the type of MS, the duration of the illness, and the degree of disability. Storage LUTS are the most common urinary symptoms in MS, including increased daytime frequency, urgency, nocturia and urgency incontinence. Nonetheless, voiding dysfunction can be present at an early stage, and post-void residuals are common, whilst acute urinary retention can occur. Unfortunately, LUTD is often overlooked in MS, since urological input is not widely available in the care pathway for these patients. Consequently, diagnosis of preventable or correctable urological complications may be somewhat delayed. This is particularly the case in more advanced MS. The exact type of LUTD typically reflects the extent of the central nervous system affected by MS, and thus predictably can alter with any episode of disease relapse or progression, necessitating re-evaluation.

Alongside symptom management, potential complications affecting the upper urinary tract include renal calculi, hydronephrosis or vesico-uretero-renal reflux. Severe renal insufficiency is comparatively unusual in patients with MS. Nonetheless, some degree of renal insufficiency is a feature of more advanced cases of MS. An analysis of causes of death on death certificates in the United States of America showed a comparatively low prevalence of severe renal dysfunction. In fact, symptomatic urinary tract infection was listed as a contributing factor in 8.4 % of deaths, and this is one of the key management aspects for urological care in MS, with about two thirds of patients reporting at least one urinary tract infection annually. This may reflect the known high prevalence of asymptomatic bacteriuria in many neurological patients.

As a general principle in neuro-urology, video-urodynamics primarily aims to identify risk factors that may affect patient safety, with symptom management being very important but secondary. Urodynamic findings in MS can take many forms. Detrusor overactivity or stress urinary incontinence is well recognised during the storage phase, whilst detrusor underactivity or detrusor sphincter dyssynergia can affect voiding. The issues considered most concerning for subsequent problems of the upper urinary tract are impaired filling compliance, detrusor overactivity (especially in the presence of vesico-uretero-renal reflux) and clear-cut detrusor sphincter dyssynergia. Problematically, whilst video-urodynamics is a crucial part of evaluation, the exact risk associated with specific dysfunctions is not well defined. Rather disparate approaches are commonplace in MS assessment, either using video-urodynamics systematically and routinely as a surveillance test or pragmatically and reactively in the event of apparent risk of deterioration.

Points of Interest

Baseline function needs to be documented, and routine follow-up is required, with responsive support available in the event of persisting change in disease status. Patients should have urine checked regularly using dipstick urinalysis, and post-void residual should be screened. Frequency of renal function blood tests or upper urinary tract imaging should be individualised, largely based on disease severity and progression.

Urinary storage symptoms require management with fluid advice, behavioural adaptation, home adaptation and pharmacotherapy. Antimuscarinics are routinely used in MS. Nocturia can be managed with desmopressin if baseline serum sodium level is normal, and early checks of sodium levels are put in place on initiation of treatment. In many patients, storage function is improved by introducing intermittent self-catheterisation to counteract post-void residual. Intermittent self-catheterisation is generally well tolerated in MS, since manual dexterity and trunk control (balance) are usually sufficiently preserved, and urethral sensation is often somewhat reduced.

The use of intradetrusor onabotulinumtoxinA injections in neurogenic LUTD is largely based on high-level prospective clinical studies in MS, which formed the main study group alongside SCI patients. This is now the mainstream treatment of neurogenic LUTD in refractory bladder problems for MS patient able to undertake intermittent self-catheterisation or accept an indwelling urinary catheter.

Parkinson's Disease and Multiple System Atrophy (MSA)

Background

Parkinson's disease (PD) is a progressive acquired condition leading to movement disorder, caused by degeneration of dopaminergic neurons in the substantia nigra, along with a loss of dopamine-containing nerve terminals in the basal ganglia. Consequently, skeletal muscle control is affected, and additional consequences are seen for autonomic function, particularly affecting the gastrointestinal and urinary tracts. The basal ganglia generally maintain inhibitory influence promoting urine storage, so PD is commonly associated with detrusor overactivity. LUTD is highly prevalent in PD, giving rise to storage LUTS, voiding LUTS or both. The prevalence of LUTS appears to correlate with severity of the disease, but not so much with the duration. For most patients, the LUTD is evident after the motor disorder. LUTD substantially affects the quality of life in patients with PD. Bladder dysfunction generally correlates with the severity and stage of disability. Nocturia is highly prevalent. Voiding LUTS appears to be less prevalent, and post-void residual is generally not substantially elevated. Urodynamically, detrusor overactivity, bladder outlet obstruction or detrusor underactivity may be seen in PD. Failure of sphincter relaxation may reflect bradykinesia in the bladder outlet, rather than true detrusor sphincter dyssynergia.

Multiple system atrophy (MSA) is a rare, adult-onset progressive degenerative disease of the nervous system, with particular features of autonomic failure. The latter leads to impaired vascular control, LUTD and erectile dysfunction. A neurological picture similar to PD may be seen, but response to PD treatment is poor. Alternatively, cerebellar dysfunction may be the more prominent neurological pattern. MSA is the modern term incorporating the three conditions of striatonigral degeneration, sporadic olivo-ponto-cerebellar atrophy and Shy-Drager syndrome. Glial cytoplasmic inclusions are a diagnostic feature. A high proportion of patients with MSA develop urinary symptoms, either prior to or at the time of presentation with the motor disorder. A study of the urological symptoms in MSA patients found difficulty voiding in 79 %, nocturia in 74 %, sensation of urgency in 63 %, urgency incontinence in 63 %, diurnal urinary

frequency in 45 %, enuresis in 19 % and urinary retention in 8 %. Post-void residual appears to increase progressively with longer duration of MSA, and urodynamically, the initial dominance of detrusor overactivity progresses towards poor storage compliance and areflexia. Sphincter electromyography can be a useful part of diagnostic testing, which may distinguish MSA from PD.

Points of Interest

For known PD or MSA, initial assessment follows the lines of other neurological conditions causing LUTD. Clinicians should also be aware that urinary symptoms can be the presenting complaint in MSA and should consider screening for postural hypotension and erectile dysfunction in case of the possibility of undiagnosed MSA being present.

Antiparkinsonian medication may affect LUTD in PD, but beneficial effects are not reliable. Indeed, treatment adjustments that help motor symptoms may actually have a counterproductive symptomatic effect on LUTD. Centrally acting anticholinergics to treat the PD should not be confused with the peripherally acting antimuscarinics used to treat detrusor overactivity. Most neurologists are accepting of this latter indication, feeling that impact on the PD itself is generally marginal; however, it is essential to consider this aspect and a good practice to liaise with the patient's neurologist if considering such a prescription. Cognitive adverse events resulting from central nervous system influence of antimuscarinics used for LUTD can be important.

Deep brain stimulation is another treatment for the movement disorders of PD, and this can also influence the LUTD. Intradetrusor botulinum toxin A injections have been evaluated for treating intractable detrusor overactivity in patients with PD. This is likely to increase the chance of needing intermittent self-catheterisation, which is otherwise rather unusual in PD.

Recommendations for surgical intervention in PD are generally conservative, particularly in the context of stress urinary incontinence in women, or voiding LUTS in men, in view of the apparent risk of adverse outcomes. In particular, clear attribution of bladder outlet obstruction to benign prostate enlargement requires video-urodynamics, since very similar high-pressure slow-flow traces can reflect various causes of bladder outlet obstruction including neurogenic LUTD. Likewise, surgery should be employed very cautiously in MSA. For example, incontinence is very common after prostatectomy in these patients. In MSA, a tailored approach using conservative measures to treat storage and voiding dysfunction is the mainstay of treatment.

Cerebrovascular Accident

Background

Cerebrovascular accident (CVA) is a highly prevalent, acquired, nonprogressive neurological impairment caused by vascular occlusion or haemorrhage. The initial deficit may improve as a result of plasticity of the central nervous system, leading

to partial recovery of function using alternative neural pathways. At the time of maximal impairment following a CVA, 41 % of patients (46 % of women and 37 % of men) had urinary incontinence in one study. Urinary incontinence in the early stages of CVA recovery may be a prognostic indicator for poor survival and ultimate functional dependence. A high proportion remain incontinent at 6 months after the CVA, with effective treatment being important.

At 3 months, a range of LUTS can be reported, including nocturia, urgency incontinence and voiding dysfunction. Right cerebral hemisphere lesions have been linked to LUTD, but not all studies support a hemispheric predominance. Urinary incontinence in stroke patients may reflect loss of central inhibition, allowing emergence of detrusor overactivity. However, impaired bladder sensation (the conscious perception of subconscious sensory information) may also be a factor; this is more a feature of parietal lobe lesions. With acute brainstem stroke, voiding difficulty (28 %) or urinary retention (21 %) outweigh urinary incontinence (8 %). Urodynamically, detrusor overactivity is prevalent but detrusor sphincter dyssynergia is not expected (since CVA generally affects cortical function and brainstem function is usually, but not invariably, preserved).

Points of Interest

Basic diagnosis comprises history and examination, urinalysis, post-void residual assessment and a bladder diary. Immediately after the CVA, an indwelling urinary catheter may be needed to deal with initial LUTD pending recovery. The catheter should be removed at the earliest reasonable opportunity, but intermittent self-catheterisation may be needed if there is a large post-void residual. If incontinence is present, containment should be provided. Rehabilitation involves behavioural therapy, perhaps with antimuscarinics and pelvic floor muscle re-education. Botulinum toxin A injections may not be beneficial.

Intervertebral Disc and Failed Back Surgery

Background

Intervertebral disc prolapse is a prevalent condition that may give rise to neurological damage due to mechanical compression of the spinal cord or of the nerve fibres exiting the cord. In an early stage, stretching of the nerves may lead to irritation and detrusor overactivity, whereas when the disease progresses and becomes chronic, progressive atrophy of the fibres occurs with trophic changes and nerve demyelination resulting in an acontractile/hypocontractile detrusor. Aside from mechanical compression, disc prolapse may also impair nerve function by interfering with the blood flow leading to congestion and ischemia of the nerve roots.

Disc prolapse can occur at any level, but most frequently it occurs at the lumbar spine, followed by the cervical and thoracic spine. Depending on the level, the length and severity of compression, the clinical findings may differ. In general, prevalence of LUTS in patients with disc prolapses varies between 20 and 68 %. Cervical disc prolapse is most often characterised by detrusor overactivity with or without detrusor sphincter dyssynergia, which may lead to high detrusor pressures during storage phase jeopardising the upper urinary tract. Thoracic disc prolapse is less prevalent and leads to neurogenic LUTD in 25–35 % with storage LUTS being most common. The vast majority of disc prolapses occur at the lumbar or lumbosacral level, predominantly at L4/L5 and L5/S1. The spinal cord terminates at the midlevel of L1 forming the conus medullaris. Disc prolapses at the upper lumbar levels may therefore compress the terminal part of the spinal cord, whereas lower lumbar level disc prolapses may cause damage to the cauda equina. Sacral nerves are affected in 1–15 % of the patients with lumbar disc protrusion, and in around 25 %, an acontractile detrusor is found leading to impaired bladder emptying and urinary retention. However, detrusor overactivity also has been described in up to 25–50 % of patients with conus medullaris or cauda equina lesions and has been linked to early disc protrusion and irritation of the nerve roots. Depending on the underlying changes, patients may present with complaints suggestive of obstructive voiding and stress incontinence due to overflow or lack of resistance at the level of the external urethral sphincter, or they may present with complaints of urgency incontinence. Urodynamics reveal a prevalence of neurogenic LUTD between 25 and 75 % in these patients.

Points of Interest

Intervertebral disc prolapse usually includes somatic complaints such as paresthesia of the limbs, muscle weakness and back pain, which should raise suspicion for possible urological dysfunctions. However, LUTS may be the sole presenting symptom in some patients, making the diagnosis of spinal cord or cauda equina compression more difficult. Clinical neurological examination can be very informative in these patients. Disturbed or loss of touch sensation of the perineum or perianal area (saddle anaesthesia) and an altered bulbocavernosus reflex are often found and suggestive of nerve impairment. Furthermore, absence of perianal sensation may be considered a negative prognostic factor for recovery of bladder function after removal of the disc prolapse. If patients are still able to void spontaneously, uroflowmetry quite often shows a reduced maximum and mean flow rate, although a normal flow does not exclude presence of LUTD. Presence of an undulating flow is suggestive for the use of abdominal pressure during voiding.

Urodynamics form the cornerstone in the diagnostic workup, as they allow a detailed evaluation of both storage and voiding phase. Specific attention should be given to the presence or absence of detrusor overactivity and the perception of bladder filling. A reduction in bladder compliance has been reported in up to 30 % of the

patients. Furthermore, a reduction of the maximum urethral closure pressure can be indicative of pudendal nerve damage in patients with a conus medullaris or cauda equina lesion.

Cystoscopy is by some considered as informative as urodynamics in patients with disc prolapse and neurogenic LUTD. The combination of decreased sensation of urethral passage of the cystoscope, a changed perception of bladder fullness and absence of cystoscopic signs of obstruction in patients with impaired bladder emptying should raise suspicion for a possible lumbar or lumbosacral disc prolapse and subsequent neurogenic impairment.

Electromyography evaluates the pelvic floor activity and the integrity of the sacral reflexes. Furthermore, the use of concentric needle electromyography provides the possibility for separate analysis of the external urethral and external anal sphincter, which may be useful in cauda equina lesions to evaluate involvement of specific nerve roots.

Treatment of the herniated discs may improve bladder function, although the exact percentage of patients showing normalisation is unknown, due to the difficulty in evaluating the immediate and long-term results, as well as the lack of correlation between improvement of complaints and functional recovery as shown by the different test methods. Improvement of LUTD upon disc surgery has been reported in 20–64 % of the patients, but deterioration of bladder function postoperatively has also been described, ranging from 10 to 60 %. If recovery occurs, it may take years. Therefore, besides treatment of the disc prolapse, specific urological management and close follow-up are warranted. In general, neuro-urological strategies are in line with those of other neurological disorders mentioned above (see section "Clinical practice").

Further Reading

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Chapter 3
Overactive Bladder

Antonella Giannantoni, Silvia Proietti, Massimo Porena, Stephen Mock, Melissa Kaufman, W. Stuart Reynolds, Roger Dmochowski, Scott MacDiarmid, Hendrikje M.K. van Breda, and John Heesakkers

Introduction

Antonella Giannantoni, Silvia Proietti, and Massimo Porena

Overactive bladder is a complex of symptoms defined by International Continence Society as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTIs) or other obvious pathology."

Overactive bladder (dry or wet). In studies on prevalence of OAB conducted in both Europe and United States, many OAB patients complained of urgency without reporting urinary incontinence. This is the case of *OAB dry*, a condition usually more affecting men than women, in whom, conversely, there is a higher prevalence of *OAB wet.* The higher proportion of OAB wet in females could be explained by

A. Giannantoni, MD, PhD • M. Porena, MD
Department of Urology, University of Perugia, Perugia, Italy
e-mail: agianton@libero.it

S. Proietti, MD
Humanitas Clinical and Research Centre, Rozzano, MI, Italy

S. Mock, MD • M. Kaufman, MD, PhD • W.S. Reynolds, MD • R. Dmochowski, MD, MMHC, FACS
Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: stephen.mock@vanderbilt.edu; roger.dmochowski@vanderbilt.edu

S. MacDiarmid, MD, FRCSC (✉)
Department of Urology, Alliance Urology Specialists, University of North Carolina, Chapel Hill, NC, USA
e-mail: smacdiarmid@allianceurology.com

H.M.K. van Breda, MD • John Heesakkers, MD, PhD
Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands
e-mail: jetske.vanbreda@radboudumc.nl; John.heesakkers@radboudumc.nl

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the anatomic characteristics of bladder neck, urethral sphincter, and pelvic floor, which make women more subjected to lose urine. OAB dry and wet equally exert a negative impact on patients' quality of life (QoL).

Patient Presentation and Initial Assessment

To date, there is still insufficient evidence-based literature to address diagnosis of OAB, which remains a mere clinical diagnosis. Thus, it is important for clinicians to provide whether a diagnosis of OAB is appropriate and make the necessary differentiations. When daytime and nighttime urinary frequency and urinary urgency, with or without UUI, in the absence of infection or other pathologic conditions, are reported as bothersome and inconvenient by the patient, he/she may be diagnosed to have OAB.

History Taking and Physical Examination

A careful history and physical examination can be just useful to make a diagnosis of OAB (Fig. 3.1). Type of symptoms and of incontinence (UUI, stress urinary incontinence (SUI) or mixed UI incontinence) should be clearly assessed in the initial clinical evaluation. Furthermore, all predisposing or precipitant factors should be identified in order to require additional investigations and treatments. Current medications should be adequately controlled to ascertain that OAB symptoms are not related to medications. Clinician's questions should be addressed to investigate type, timing, duration,

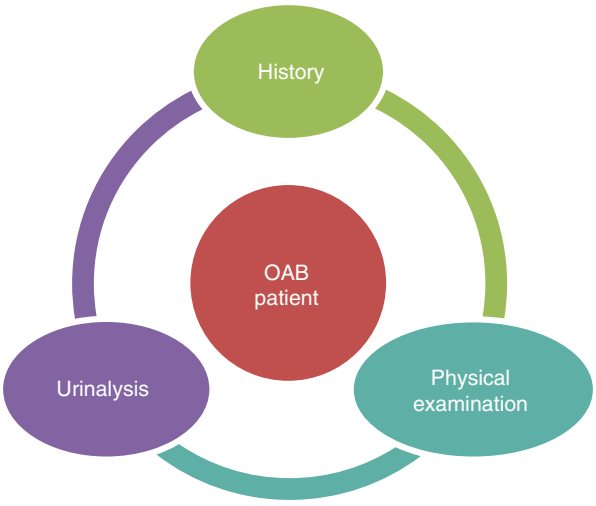

Fig. 3.1 Initial assessment of non-neurogenic patients with OAB: the minimum requirements for this diagnosis is history, physical examination, and urinalysis. American Urological Association (AUA) Guideline. Statement 1

and severity of urgency and urgency incontinence, by investigating on the behavior of both bladder filling and emptying, and the level of patient's bother should be assessed.

In *female patients*, physical examination including abdominal, pelvic, and perineal evaluation with digital examination of the vagina should be performed to assess voluntary *pelvic floor muscle* contraction, *estrogen status*, and presence of *urogenital prolapse (POP).* The *cough test* should be performed in order to objectively assess presence and type of incontinence. In *male patients*, a rectal/genitourinary evaluation with digital rectal examination should be performed, in order to assess the urethral and prostate status.

Risk factors in men for the development of UI and OAB include increasing age, prostatectomy, UTIs, and cognitive and functional impairment. Presence of neurologic diseases or other genitourinary conditions (i.e., benign prostatic enlargement, bladder tumor, bladder lithiasis, congenital pathologies) should be adequately considered due to the impact of these conditions on bladder function. When a neurologic disease has been identified as responsible for the presence of bladder-sphincter dysfunction with OAB, a specialized assessment and management are required.

Urinalyses and culture are also useful to confirm or exclude the diagnosis of OAB (Fig. 3.2). In the presence of isolated hematuria, without signs of infection, patients should perform an in-depth urologic evaluation.

The *assessment of residual urine* by measuring the postvoid urinary volume with bladder scan or catheterization is useful particularly when patients present with symptoms suggestive of voiding dysfunction, POP, or recurrent UTIs (Fig. 3.2).

According to Nice and EAU Guidelines on urinary incontinence, in the initial assessment of patients with OAB, the use of *micturition time charts*, *frequency volume charts*, *or voiding diaries* should be strongly encouraged. Micturition time charts are used to record only the times of micturitions for a minimum of 24 h; frequency volume charts are used to record urinary volumes and times of each micturition for a minimum of 24 h. "Voiding" or "bladder" diary is used to report more detailed information on daily frequency of micturition, fluid intake, episodes of

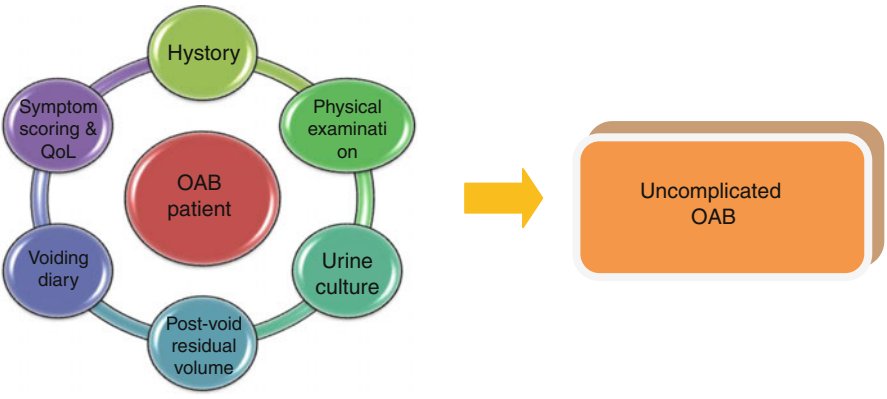

Fig. 3.2 Initial assessment of non-neurogenic patients with OAB: urine culture and/or postvoid residual assessment, bladder diaries, and/or symptom questionnaires are useful to make diagnosis. American Urological Association (AUA) Guideline. Statement 2

urgency and/or urgency incontinence, and pad usage. A minimum of 3 days voiding diary is usually required, and it should be completed during patients' usual activities, such as both working and leisure days (Fig. 3.2).

The use of *PAD test* in the routine clinical assessment of patients with UI is not recommended by the Nice, EAU, and AUA Guidelines. Nevertheless, there is at least a good evidence to show that repeat pad testing can detect change following treatment for UI.

Symptom Scoring and Quality of Life Assessment

Although there is no information about whether using questionnaires to assess urinary symptoms and QoL improves outcomes in patients with UI or OAB, *the use of validated symptom questionnaires is useful to quantify and characterize urinary symptoms and their impact on patient's QoL* (Fig. 3.2). Health-Related Quality Of Life questionnaires (HRQoLq) may be generic, as SF-36 or specific for a particular condition, as Incontinence Impact Questionnaire, the King's Health Questionnaire, OAB-q, to study OAB. Additionally, questionnaires can help in evaluating the response to treatment along follow-up and to better monitoring patients' condition along time. *Questionnaires should have been validated for the language in which they are being used.* Some of validated questionnaires mainly used for the assessment of OAB and urgency are showed in Table 3.1.

Urodynamic Testing

Multichannel cystometry, ambulatory urodynamics (UDS), or videourodynamics are diagnostic instruments including multiple tests to study lower urinary tract

Table 3.1 Some of validated questionnaires used for the assessment of OAB and urgency

Assessment of severity and impact of OAB	Abbreviations
Urinary Incontinence-Specific Quality of Life Instrument	I-QOL (ICIQ-Uqol)
Overactive bladder questionnaire	ICIQ-OABqol
King's Health Questionnaire	KHQ
OAB Satisfaction questionnaire	OAB-SAT
Overactive Bladder Symptom Score	OAB-SS
OAB-S = Overactive Bladder Satisfaction measure	OAB-S
Assessment of the Impact of Urgency	
Patient's Perception of Intensity of Urgency	PPIUS
Scale Urge Incontinence Impact Questionnaire	U-IIQ
10-Item Scale to Measure Urinary Urgency	UU Scale
Urge Urogenital Distress Inventory	U-UDI
Urgency Severity and Intensity Questionnaire: Quality of Life	USIQ-S

function during both bladder storage and emptying. While it is now recognized that UDS is not required to diagnose and manage OAB in non-neurogenic patients, information about the presence or absence of detrusor overactivity (DO) and the volume at which patients experiment OAB symptoms can be helpful in their management. In patients refractory to conservative treatment, UDS can help to identify DO, high pressure of uninhibited detrusor contractions, and a reduced compliance, which can all induce UUI and OAB. Importantly, it should be reminded that the diagnoses of UUI are not related to urodynamic presence of DO, and the presence of DO is neither sensitive nor specific for UUI. This is in agreement with the AUA Urodynamics Guidelines, which state that multichannel filling cystometry should be performed when it is important to determine whether "altered compliance, DO, or other urodynamic abnormalities are present or not in patients in whom invasive, potentially morbid, or irreversible treatments are considered." This is the case when OAB patients who are refractory to conventional anticholinergics need to be treated with surgical intervention, such as sacral neurostimulation or intradetrusor onabotulinumtoxinA injections. The AUA, OAB Guidelines and the EAU Guidelines on UI support these statements and underline that *UDS should not be used in the initial assessment of patients with uncomplicated OAB* (Fig. 3.3). Also the Nice Guidelines do not recommend the use of UDS before starting conservative management. Only after a detailed history and physical examination, UDS should be performed before surgery in women who present with OAB symptoms suspected for DO and voiding dysfunction, or who had previous surgery for stress incontinence or POP.

The use of videourodynamics or ambulatory urodynamics should be considered for OAB patients when the diagnosis remains unclear after standard UDS or for patients with OAB symptoms affected by neurogenic diseases.

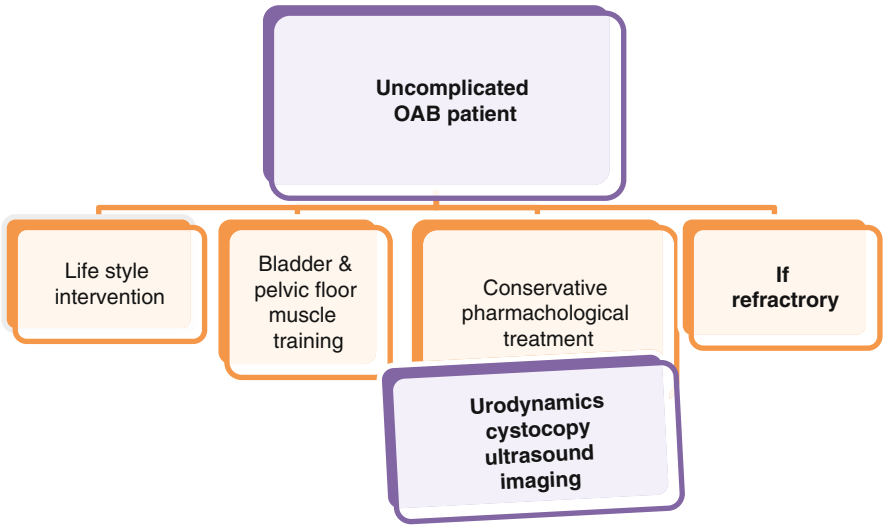

Fig. 3.3 Diagnostic investigations in patients with uncomplicated OAB

Other Investigations

For the routine assessment of patients with isolated OAB syndrome, the use of cystoscopy and imaging (MRI, CT, X-ray) is not required.

With regard to the use of ultrasound in the evaluation of OAB patients, it has been suggested that lower urinary tract ultrasound should be useful to study detrusor and bladder wall thickness, as bladder hypertrophy can be related to the severity of detrusor contractions in OAB patients. Indeed, ultrasound measurement of detrusor and bladder wall thickness may be influenced by several factors, as the ability of the operator, type of ultrasound probes and image resolution, and degree of bladder filling. Actually, there is no demonstration that studying these measures could improve the management of patients affected by OAB. Thus, *the use of ultrasound should be limited to the evaluation of postvoid residual urine volume.*

Differential Diagnosis

Differential diagnoses should be made between OAB syndrome and some conditions that can mimic the same symptoms as polydipsia, nocturnal polyuria, interstitial cystitis, and/or bladder pain syndrome. In the latter case, the presence of bladder and/or urethral pain can help to perform a correct diagnosis. Additionally, OAB symptoms could be referred in the presence of the following conditions: neurogenic diseases, depression, erectile dysfunction, dementia, clinically benign pelvic masses, associated fecal incontinence, symptoms of voiding difficulty due to BPE or POP, previous continence surgery, previous pelvic cancer surgery, and previous pelvic radiation therapy. These conditions require a further, specialized assessment and management.

Conservative Treatment

Stephen Mock, Melissa Kaufman, W. Stuart Reynolds, and Roger Dmochowski

All patients with OAB should be provided with education and an explanation of normal lower urinary tract structure and function and what is known about OAB. According to the AUA panel, “explaining what is normal can help the patient understand their condition and give a comparator for establishing mutually identified and realistic goals for treatment. Education empowers the patient to participate in their treatment, an essential factor when interventions rely on behavioral change.” Patients with OAB will likely require long-term or lifelong therapy to control their symptoms, and as a result, a treatment plan should weigh the burden of symptoms on a patients’ QoL, as well as factor that potential

benefit of a particular treatment against the treatment's risk. Treatment initiation presumes a perceived improvement can be generated. The patient has to be a willing and engaged participant who understands that OAB has a variable and chronic course, and acceptable symptom control may require multiple therapeutic trials before it is achieved. It may not be possible to eliminate all symptoms. It must be stressed that *no* treatment is an acceptable choice made by some patients and caregivers.

First-Line Therapy

Lifestyle and behavioral modification should be offered to all patients with OAB. Lifestyle changes include cessation of smoking, weight reduction, elimination of known dietary bladder irritants such as alcohol or caffeine, adequate fluid intake, and regular bowel habits. Nuotio et al. showed a correlation between smoking and urinary urgency in a large population-based survey. In further support, the EUA gave a grade A to smoking cessation advice in line with good medical practice in patients with UI, but the level of evidence that it improves UI symptoms was only based of expert opinion and not randomized data (Lucas 2012). Obesity has been shown to be an independent risk factor for the development of SUI and mixed UI in women, and evidence exists that nonsurgical weight loss intervention has the potential to improve UI in overweight women. Indeed, a weight loss of 8 % in obese women reduced overall incontinence episodes per week and UUI episodes by 47 and 42 % vs. 28 and 26 % in controls. Reduced fluid intake is a widely used, inexpensive and noninvasive intervention but can predispose to UTI, dehydration, stone formation, and constipation. The data available is conflicting on whether fluid modification changes symptoms and QoL, but a recent trial showed a 25 % reduction in fluid intake improved symptoms with OAB but not UI. Caffeine has an excitatory effect on detrusor muscles, and randomized controlled data demonstrates significant improvements in urgency-frequency and UUI in those who reduced caffeine to <100 mg/day. Alcohol has a diuretic effect by reducing the release of antidiuretic hormone. Newman et al. reported a nearly uniform positive association between straining at stool and constipation and lower urinary tract symptoms which the authors surmised to be due to progressive neuropathy in the pelvic floor secondary to repeated straining efforts.

Behavioral treatments are a group of risk-free therapies which improve individual symptoms by changing patient behavior or the patient's environment. They can be tailored individually and include bladder training, bladder control strategies, pelvic floor muscle training, and fluid management. This form of therapy relies on a patient with an intact nervous system to "relearn" to inhibit a detrusor contraction or a sensation of urgency. It generally consists of patient education, scheduling voiding with an aim to achieve an interval of 3–4 h between voids, and positive reinforcement that provides psychological support and encouragement. There is level 1 evidence in support of supervised bladder training but whose benefits are of

short duration unless the program is practiced repeatedly. In the MOTIVE trial (Male overactive Bladder Treatment in Veterans), where Burgio et al. demonstrated equivalence between behavioral and antimuscarinic therapy, behavioral treatment involved verbal instruction followed by guided practice using verbal feedback based on anal palpation to teach participants how to contract and relax pelvic floor muscles while keeping abdominal muscles relaxed, as well as delayed voiding, monitoring with bladder diaries, and urge suppression techniques to inhibit or suppress detrusor contractions and thus reduce urgency-frequency and incontinence (Burgio 2011). Similar findings from randomized trials have been published that have demonstrated equivalence or superiority to medications in reducing symptoms, while more limited literature exists that indicates behavioral and drug therapy simultaneously may improve outcomes.

Pelvic floor muscle training (PFMT) is used frequently in conjunction with bladder training. The purpose is to increase the strength and durability of contraction of the pelvic floor muscles, which may help inhibit bladder contractions in patients with OAB. Biofeedback therapy can be used to augment PFMT and involves the use of monitoring equipment to detect, measure, and amplify internal physiological responses to provide patients with feedback concerning those responses. It increases patient awareness of the pelvic floor muscles, using visual, tactile, or auditory stimuli and is used to help teach patients to exercise their musculature more effectively. The most common modalities include electromyography (EMG) and manometry that measures the activity of the anal or urinary sphincter, the pelvic floor musculature, as well as the detrusor muscle with the aim to restore bladder control by teaching patients to modulate the mechanism of continence. There is level 1 evidence supporting both PFMT and the addition of biofeedback for added benefit. Berghmans et al. conducted a meta-analysis study assessing the efficacy of biofeedback in UUI and concluded that patients were able to achieve improvement after biofeedback. They stated that the actions were easy to perform in cognitively intact patients but took personal effort and time to perform the exercises.

Second-Line Treatment

Antimuscarinic agents act via competitive inhibition at the postganglionic receptor sites and, as a result, reduce bladder contractility and particularly exert their effects on the filling phase of the bladder, reduce urgency, increase bladder capacity, and minimize the effects of the parasympathetic system. While effective in reducing symptoms, they are commonly associated with side effects (e.g., dry mouth, constipation, dry eyes, dyspepsia, urinary retention, impaired cognitive function) as a result of the affinity of the drugs to muscarinic receptors widely distributed in the body. Additionally, for those patients with narrow angle glaucoma, impaired gastric emptying, or a history of urinary retention, consultation with each respective

specialist should be sought prior to initiation of therapy. Clinicians must use caution in prescribing these agents in patients who are using other medications with anticholinergic properties. Agents available include darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium. Both the EUA and AUA performed an extensive review of the randomized trials evaluating these agents for OAB and found no compelling evidence for differential efficacy across medications. Thus, the choice of medication is largely determined by patient factors that include age, side-effect profile, and out-of-pocket costs. However, if extended-release formulations are available, they should be preferentially prescribed because of the lower rates of side effects (Grade A recommendation, EUA). For likewise reasons, transdermal preparations may be offered, if available (Grade B recommendation, EUA). In those individuals who experience inadequate symptom relief and/or unacceptable adverse events, with one antimuscarinic agent, then a dose modification or a different antimuscarinic medication may be tried.

Special attention should be given to the frail elderly, a group where data on the use of antimuscarinic is not as robust and side effects may be more severe. Elderly people have been underrepresented in randomized controlled trials (RCTs) of antimuscarinic agents, despite having a higher prevalence. There is level 2 evidence that oxybutynin IR may worsen cognitive function and as a result received a grade A recommendation against its usage in those at risk of cognitive impairment (Lucas 2012). However, the effectiveness and risk of adverse events, including cognitive dysfunction, of solifenacin, tolterodine, and darifenacin, do not differ with patient age (level 1b evidence (Lucas 2012)). Nocturia, a symptom with a multifactorial etiology, is an another especially concerning issue in the elderly as it has been linked to a risk of falls, fractures, and even death. The role of antimuscarinics for the management of nocturia in the context of OAB is limited. Pooled analysis and/or post hoc analyses have demonstrated significant reduction of nocturnal voids per night, but the effect size was low and the clinical significance doubtful. To our knowledge, only one RCT that compared tolterodine with placebo focused on nocturia as a primary endpoint. In this study, micturitions were classified as either OAB related or not depending on the degree of urgency prior to that micturition. Eight hundred and fifty patients were randomized, and while tolterodine did significantly reduce OAB specific symptoms, there was no difference between the two groups for nocturia for the non-OAB micturitions and when both non-OAB and OAB micturitions were considered together. This clearly demonstrates the complex nature of nocturia resulting from its multiple contributing etiologies.

Nearly all studies for OAB either require UUI for study inclusion or include a mix of patients with both OAB dry and wet. For this latter case, rarely is subgroup analysis performed and thus depriving the ability to compare efficacy of treatment between OAB dry and wet. While it is believed, based on expert interviews, that OAB is represented by a spectrum of severity, from mild OAB with no leakage (OAB dry) to severe OAB with frequent leakage (OAB wet), there is no evidence to substantiate this. Lacking this, it is unknown whether each represents a unique

clinical entity with differential treatment outcomes. This may largely be an academic exercise as urgency rather than incontinence has been cited as the most bothersome symptom and the one with the greatest impact on quality of life. Urgency data is available as an endpoint in most studies and is favorable (Table 3.2). Since OAB treatment is aimed at symptom relief, this may be more important than the dichotomy of OAB into wet or dry.

As seen, while anticholinergic agents are the mainstay of pharmacological treatment for OAB, results may be suboptimal or can have numerous side effects and contribute to poor patient compliance and high discontinuation rates. Mirabegron is a first-in-class medication whose mechanism of action is via β_3-adrenoceptor agonism and resultant detrusor relaxation and facilitation of urine storage. It gained Food and Drug Administration (FDA) approval in June 2012 and European Union approval in January 2013. Nitti et al. published the 12-week results of the phase 3 RCT of mirabegron vs. placebo. The study population was required to have an average of eight or more micturitions per 24 h and three or more urgency episodes with or without incontinence. Other OAB medications had to be stopped at screening. Patients were randomized to receive placebo, mirabegron 50 or 100 mg. Nearly 60 % had previously received antimuscarinic OAB medication. As a result of inclusion of both wet and dry OAB patients, the authors performed analysis on the composite study group (1270 patients) as well as just the OAB wet patients (933 patients). Both mirabegron treatment groups demonstrated significant greater reductions from baseline vs. placebo in mean number of incontinence episodes (−1.13, −1.47, −1.63), micturitions per 24 h (−1.05, −1.66, −1.75), mean level of urgency, mean number of grade 3 or 4 urgency episodes per 24 h, as well as greater increases in mean volume voided per micturition (7.0, 18.2, 18). Adverse events that included hypertension and cardiac arrhythmias were low and comparably to placebo, but small dose-dependent differences in a.m. and p.m. pulse rates were noted.

Third-Line Treatment

Please see chapter on chemical and electrical neuromodulation for OAB for more details.

Additional Treatments

Indwelling catheters are not recommended as a management strategy for OAB and, in our experience, can exacerbate symptoms. Additionally, indwelling catheterization has a high risk of catheter-associated UTIs, urethral erosion/destruction, and urolithiasis. Adjunctive measures such as pads, special undergarments, and condom catheters for men are valuable if symptoms prove refractory, especially in those

Table 3.2 Selected published series of randomized controlled trials of various anticholinergic agents

Author	Drug	Inclusion	Length of study	*n*	Results	Adverse events	Notes
Rudy et al. (2006)	Trospium 20 mg BID	Females and males, >18 years old, OAB >6 months; urinary frequency ≥10/day, +urgency, ≥7 UUI/week	12 weeks	658	Daily voids: −2.67 vs. −1.76, $p<0.0001$ Daily UUI episodes: −1.86 vs. −1.29, $p<0.0001$ Urgency score: −0.21 vs. −0.02, $p<0.001$ Volume voided per void/24 h: +35.59 vs. +9.44, $p<0.0001$	Dry mouth: 19.8 % vs. 5.2 % Constipation: 10.9 % vs. 5.8 % Discontinuation rate: 7.3 % vs. 4.6 %	Quaternary amine and ionized at physiological pH; low lipophilicity and reduced CNS penetrance
Dmochowski et al. (2008)	Trospium 60 mg extended release, daily	Females and males, >18 years old, OAB >6 months; urinary frequency ≥10/day, >1 severe urgency with void, mean >1 UUI/day	12 weeks	564	Daily voids: −2.5 vs. −1.8, $p<0.001$ Daily UUI episodes: −2.4 vs. −1.6, $p<0.001$ Urgency score: −0.28 vs. −0.13, $p<0.001$ Volume voided per void/24 h: +31.5 vs. +17.8, $p<0.01$	Dry mouth: 12.9 % vs. 4.6 % Constipation: 7.5 % vs. 1.8 % Discontinuation rate: 6.4 % vs. 2.8 %	
Van Kerrebroeck et al. (2001)	Tolterodine ER 4 mg daily, tolterodine IR 2 mg BID	Females and males, >18 years old, OAB >6 months; urinary frequency ≥8/day, ≥5 UUI/week	12 weeks	1529	Daily voids : ER −3.5 vs. −2.2, $p<0.001$; IR −3.3 vs. −2.2, $p=0.0002$ Weekly UUI episodes: ER −11.8 vs. −6.9, $p<0.0001$; IR −10.6 vs. −6.9, $p=0.001$ Volume voided per void/24 h: ER +34 vs. +14, $p<0.0001$; IR +29 vs. +14, $p<0.0001$	Dry mouth: ER 23 %, IR 30 %, placebo 8 % Constipation: ER 6 % IR 7 %, placebo 4 % Discontinuation rate: ER 5 % IR 5 %, placebo 6 %	Prodrug and requires cytochrome P450 activation; ER formulation 18 % more effective than IR in UUI episodes; ER 23 % less dry mouth than IR

(continued)

Table 3.2 (continued)

Author	Drug	Inclusion	Length of study	*n*	Results	Adverse events	Notes
Chapple et al. (2005)	Darifenacin 7.5 mg and 15 mg daily	Females and males, >18 years old, OAB >6 months; urinary frequency ≥8/day, 5–50 UI/week, mean of ≥1 urgency episode/24 h	12 weeks	1059	Mean voids/day: 7.5 mg −1.6 vs. −0.9, $p<0.001$; 15 mg: −1.9 vs. −1.0, $p<0.001$ Mean UI episodes/week: 7.5 mg −4.0 vs. −2.0, $p<0.001$; 15 mg −4.8 vs. −2.7, $p<0.001$ Mean urgency episodes/day: 7.5 mg −2.0 vs. −1.0, $p<0.001$; 15 mg −2.3 vs. −1.2, $p<0.001$ Average void volume: 7.5 mg +15 vs. +8, $p=0.007$; 15 mg +27 vs +6, $p<0.001$	Dry mouth: 7.5 mg 20.2 %, 15 mg 35.3 %, placebo 8.2 % Constipation: 7.5 mg 14.8 %, 15 mg 21.3 %, placebo 6.2 % Discontinuation rate: 7.5 mg 1.5 %, 15 mg 5.1 %, placebo 2.6 %	Selective muscarinic M3 receptor antagonist; randomized data available demonstrating no change in cognition or QTc intervals
Cardozo et al. (2005)	Solifenacin 5 mg and 10 mg daily	Females and males, >18 years old, OAB >3 months; urinary frequency ≥8/day, >3 urgency episodes and/or >3 UI during 3 day diary	12 weeks	907	Daily void: 5 mg −2.37 vs. −1.59, $p=0.002$, 10 mg −2.81 vs. −1.59, $p=0.0001$ Daily UI: 5 mg −1.63 vs −1.25, $p=0.002$; 10 mg −1.57 vs. 1.25, $p=0.016$ Urgency episodes: 5 mg −2.84 vs −1.98, $p=.003$; 10 mg −2.9 vs. −1.98, $p=0.002$ Mean voided volume: 5 mg +30.75 vs. +10.75, $p=0.0001$; 10 mg +36 vs. +10.67, $p=0.0001$	Dry mouth: 5 mg 7.7 %, 10 mg 23.1 %, placebo 2.3 % Constipation: 5 mg 3.7 %, 10 mg 9.1 %, placebo 2.0 %	

Abrams et al. (2005)	Solifenacin 5 and 10 mg daily	Females and males, >18 years old, OAB >3 months; urinary frequency ≥8/day, ≥1 urgency episodes /day	12 weeks	975	Daily voids: 5 mg −3.6 vs. −1.6, $p<0.001$; 10 mg −2.8 vs. −1.6, $p<0.001$ Urgency episodes/day: 5 mg −3.2 vs. −2.1, $p<0.001$; 10 mg −3.2 vs. −2.1, $p<0.001$ Mean voided volume 5 mg +25 vs +7, $p<0.001$; 10 mg +33.9 vs. +7, $p<0.001$	Dry mouth: 5 mg 10.8 %, 10 mg 24.4 %, placebo 3.6 % Constipation: 5 mg 4 %, 10 mg 12.2 %, placebo 1.3 % Discontinuation rate: 5 mg 2.8 %, 10 mg 7.8 %, placebo 6.2 %	Pooled analysis of 4 RCTs with subgroup analysis solely for OAB dry
Nitti et al. (2007)	Fesoterodine 4 mg and 8 mg daily	Females and males, >18 years old, OAB >6 months; urinary frequency ≥8/day and mean of >6 urgency episode or >3 UUI over 3 day diary	12 weeks	836	Daily voids: 4 mg −1.61 vs −1.08, $p<0.001$; 8 mg −2.09 vs. −1.08, $p<0.001$ Daily UUI: 4 mg −1.65 vs. −0.96, $p<0.001$; 8 mg −2.28 vs. 0.96, $p<0.001$ Daily urgency episodes: 4 mg −1.91 vs. −.079, $p<0.001$; 8 mg −2.3 vs. −0.79, $p<0.001$ Voided volume: 8 mg +33.6 vs. +8.38, $p<0.001$	Dry mouth: 4 mg 16 %, 8 mg 36 %, placebo 7 % Constipation: 4 mg 5 %, 8 mg 8 %, placebo 3 % Discontinuation rate: 4 mg 6 %, 8 mg 9 %, placebo 4 %	Prodrug with same active metabolite as tolterodine; dual excretion pathways

(continued)

Table 3.2 (continued)

Author	Drug	Inclusion	Length of study	*n*	Results	Adverse events	Notes
Versi et al. (2000)	Oxybutynin 5 mg/day IR vs ER, 5 mg dose increases q7 days to max of 20 mg/day	Females and males; >7 UUI/week; +prior response to oxybuytnin		226	IR group 76 % reduction in UUI ER 83 % reduction-no significant difference	Dose dependent significant difference in dry mouth between both groups	Has direct muscle relaxant effect as well
Dmochowski et al. (2003)	Oxybutynin transdermal patch 3.9 mg/day; tolterodine LA 4 mg/day	Females and males; +prior prestudy response; >4 UUI, >24 voids, <350 cc/void over 3 day diary	12 weeks	361	Daily UUI: patch −3 vs. placebo −2, $p=0.01$ Average void volume: patch +24 vs. placebo +5.5, $p=0.001$	Site erythema: patch 8.3 % vs placebo 1.7 % Pruritus: patch 14 % vs placebo 4.3 % Dry mouth: patch 4.1 %, tolterodine 7.3 %, placebo 1.7 % Constipation: patch 3.3 %, tolterodine 5.7 %	Avoidance of GI and hepatic first pass metabolism to DEO, which is responsible for anticholinergic side effects

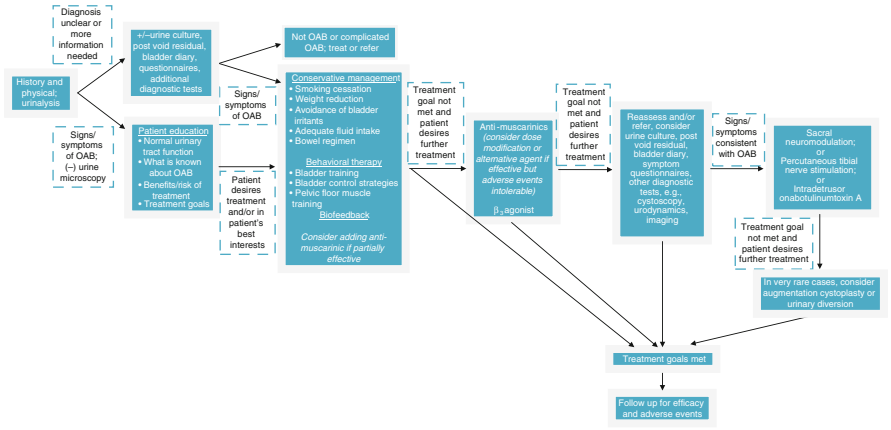

Fig. 3.4 Algorithm for diagnosis and treatment of idiopathic overactive bladder

where the risk of therapy outweighs the benefit. However, an indwelling catheter may be considered as a last resort in cases where UI contributes to progressive skin breakdown or decubiti. Intermittent catheterization may be an option when OAB symptoms are associated with incomplete emptying, a commonly seen phenomena in the elderly, but this approach requires patient willingness and/or caregiver support.

Very rarely is major abdominal surgery such as augmentation cystoplasty, detrusor myectomy to disrupt coordinated detrusor contraction, or urinary diversion needed for idiopathic OAB. It may be considered in cases of severe and refractory OAB, but the patient must know the substantial risk to these procedures, and the data to support it are poor (level 3 evidence, EUA (Lucas 2012)). Use of these options has decreased substantially due to its short- and long-term risks as well as the effectiveness of Botox and neuromodulation.

Figure 3.4 provides an algorithm for the diagnosis and treatment for idiopathic OAB.

Conclusion

OAB is a common symptom-driven clinical diagnosis that can have an adverse impact on a patient's QoL. After a full evaluation to exclude other possible pathologies, counseling and education on OAB should be discussed with the patient. The risk and benefits of the available treatment options should be given. Every OAB patient should be offered conservative and behavioral therapy as a first-line treatment as these are largely risk-free and tailorable to patients and their symptoms. If the response is inadequate, treatment should proceed in stepwise fashion from available pharmacotherapy to surgical intervention. While a lifelong problem, patients

now have the benefit of multiple lines of therapy to pursue and which continue to expand.

Tips and Tricks

1. Since OAB is a diagnosis based on symptoms, a thorough history and physical examination play a critical part in assessing a patient.
2. Once the diagnosis is made, the patient should be provided with education and an explanation of normal lower urinary tract structure and function and what is known about OAB as education empowers the patient to participate in their treatment, an essential factor when interventions rely on behavioral change.
3. A treatment plan should weigh the burden of symptoms on a patients' QoL, as well as factor that potential benefit of a particular treatment against the treatment's risk.
4. Treatment should proceed in stepwise fashion from conservative lifestyle and behavioral modification to pharmacological therapy to surgical intervention if OAB is symptomatic and refractory to current modes of therapy.

Botulinum Toxins

Antonella Giannantoni, Silvia Proietti, and Massimo Porena

Botulinum neurotoxins (BoNT) are protein complexes produced by *Clostridium botulinum*, an anaerobic gram-positive *Bacillus*. BoNT interferes with the release of acetylcholine (Ach) from presynaptic terminals, what clinically prevents muscle contractions and/or gland secretion. Since BoNT is used as a local injectable treatment, with fewer side effects as compared to systemic administered medications, and due to its ability to determine a robust muscle relaxation, it is used as treatment of choice in many neurologic diseases such as dystonia and limb spasticity and in other conditions, as glabellar lines, hyperhidrosis, and sialorrhea. Since the end of 1990, there has been an increasing use of onabotulinumtoxinA in the treatment of urinary incontinence due to neurogenic or idiopathic DO.

Botulinum Neurotoxin: Structure, Serotypes, and Subtypes

The neurotoxin is produced as a 150 kDa polypeptide and contains a heavy chain of 100 kDa (Hc) which is attached to a light chain molecule of 50 kDa (Lc) by a disulfide non-covalent bond. The heavy chain is divided into an amino domain (Hcn) and a carboxyl terminal domain (Hcc) (Fig. 3.5).

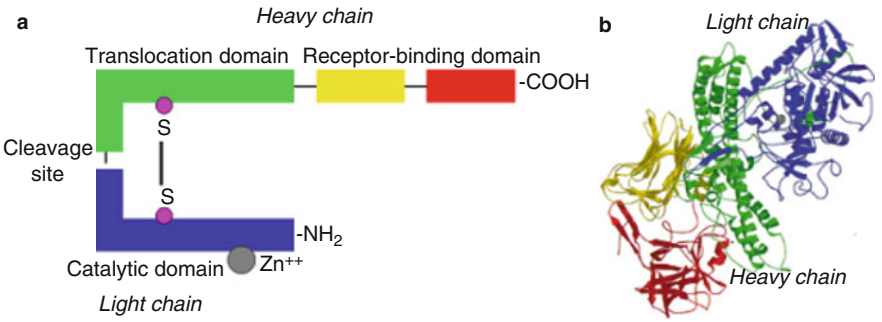

Fig. 3.5 OnabotulinumtoxinA molecular structure. OnabotulinumtoxinA molecular structure depicted in a schematic way (**a**) and threedimensional way (**b**)

Seven serologically different neurotoxins (designated as neurotoxin types A-G) are produced by four strains/species of *Clostridium botulinum*. Each of the A-G serotypes of BoNTs are divided in subtypes on the basis of differences in amino acid sequences and, consequently, of different immunological and biological properties. Five subtypes of BoNT/A have been described (A1–A5), all of which have a similar affinity for binding SNAP25 somewhat with less efficiency (i.e., BoNT/A3 and BoNT/A4).

Mechanisms of Action

Neuromuscular transmission starts with an action potential reaching the presynaptic endplate, which then transiently depolarizes the axon terminal and opens the calcium channels. The increase in intracellular calcium leads to the fusion of vesicle membranes containing Ach with the presynaptic endplate. The propagation of the action potential along the terminal axon of the motoneuron produces the release of ACh from the cytosol into synaptic clefts by the soluble N-ethylmaleimide-sensitive factor activating protein receptor complex (SNARE). Once in the synaptic cleft, ACh binds to postsynaptic membrane inducing a muscle fiber contraction. In the presence of BoNT, the carboxyl terminal of the heavy chain of the toxin binds to specific receptors from the presynaptic terminal. BoNT is endocytosed and then the N-domain of the heavy chain translocates the light chain into the cytoplasm. Once in the cytoplasm, the light chain cleaves SNAP25 of the SNARE complex protein, thus preventing Ach release (Fig. 3.6). This process can be subdivided into four steps: binding, internalization, membrane translocation, and proteolysis of specific SNARE proteins. More recently, it has been demonstrated that BoNTs are also able to act at the level of sensitive nerve fibers, by blocking the vesicular exocytosis of different substances, such as CGRP, SP, NGF, and ATP, which are involved in the afferent neurotransmission.

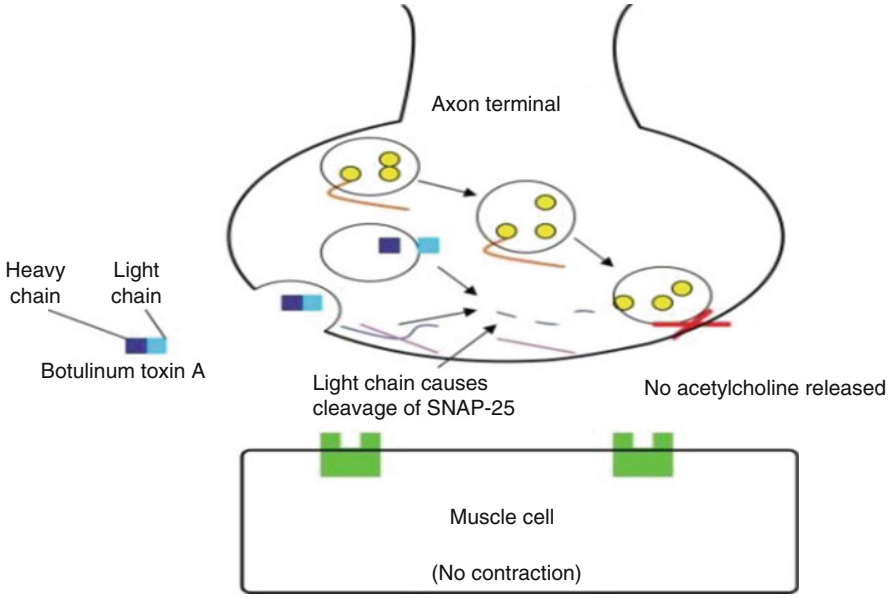

Fig. 3.6 OnabotulinumtoxinA mechanisms of action

Commercially Available Neurotoxins

Actually, there are only two serotypes available: BoNT/A (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) and a BoNT/B, patented by rimabotulinumtoxinB. Each brand has been approved by the US Food and Drug administration (FDA). Commercial preparations of BoNTs include the neurotoxin molecule, nontoxic hemagglutinin proteins, and non-hemagglutinin proteins, plus excipients. The associated proteins are thought to stabilize the neurotoxin. Protein complexes are not present in incobotulinumtoxinA, which is a formulation of botulinum toxin serotype A. Units of biological activity of different botulinum toxin A cannot be converted into units of any other botulinum toxin.

BoNTs and OAB

Although the use of botulinum toxin A (American and English brands) to treat neurogenic DO and idiopathic OAB was introduced about 15 years ago, only more recently, the use of onabot/A has been licensed for the treatment of neurogenic and idiopathic DO in US and most European countries, in patients who have been inadequately managed by $\geq$1 anticholinergic therapy. Onabot/A is not interchangeable with other botulinum toxin preparations.

Clinical Effects

In the treatment of idiopathic OAB, two large, double-blind placebo-controlled phase III trials demonstrated that onabot/A100U intravesically injected significantly reduced all symptoms of OAB, including episodes of incontinence, urgency, micturition, and nocturia compared with placebo. In these studies, improvements in OAB symptoms were also accompanied by clinically relevant improvements in patients' HRQoL. In patients with NDO, onabot/A has been observed to induce a reversible chemical denervation lasting for about 9 months. The efficacy of onabot/A has been demonstrated in patients with neurogenic diseases and urological disorders in phase III RCT randomized placebo-controlled trials. What is evident is that repeated injections seem to be possible without loss of efficacy. Histological studies have not found ultrastructural changes after injection. In the EAU Recommendations of minimally invasive treatment for NDO, botulinum toxin intradetrusorial injection is considered the most effective treatment to reduce NDO.

The efficacy of onabotulinumtoxinA can be attributed to its inhibitory effects at the level of both efferent and afferent nervous pathways controlling bladder function. In recent times, great importance has been attributed to the action of onabotulinumtoxinA into the bladder wall. It decreases the mucosal levels of the afferent receptors TRPV1 and P2X3, which are involved in sensory transmission and can reduce the levels of neurotransmitters involved in the mechanisms of urgency. Thus, the current notion is that onabotulinumtoxinA modulates the intrinsic reflexes thought to cause the OAB condition.

Side Effects The most important adverse events are UTI and an increase in postvoid residual volume, which may require the use of intermittent catheterization. The emergence of high PVR should be obviously avoided in patients who void spontaneously. Conversely, in patients with neurogenic disease unable to spontaneously empty the bladder and using CIC, the goal is properly to obtain detrusor areflexia with higher capacity. In this patient population, generalized muscular weakness can be an occasional adverse effect.

Doses In patients with idiopathic OAB with urinary incontinence, the established licensed dose of onabotulinumtoxinA is 100U diluted in 10 ml saline solution. In NDO, the established licensed dose of onabotulinumtoxinA is 200U diluted in 30 ml saline solution.

Recommendations of OnabotulinumtoxinA in the Treatment of NDO and IDO

In synthesis, EAU Guidelines state that onabot/A (100 U) intravesically injected can be offered to patients with urgency urinary incontinence refractory to antimuscarinic therapy. Patients have to be advised about the "risk of UTI and the possible

prolonged need to self-catheterize (ensure that they are willing and able to do so)." In addition, the EAU Guidelines outline some evidences related to the repeat use of onabot/A, the eventual need to perform CIC, the superiority of onabot/A in comparison with solifenacin per os, and other important information.

How to Perform OnabotulinumtoxinA Intradetrusorial Injection

- *In adult males and females with IDO and urgency urinary incontinence*: after a local anesthesia, or a mild general sedation, by using flexible or rigid cystoscope, 100U onabot/A diluted in 10 ml saline solution, intradetrusorial injections can be performed (20 injections into the bladder wall, with the exclusion of the trigone).
- *In adult males and females with NDO*: after a local anesthesia, or a mild general sedation, with flexible or rigid cystoscope, 200 U onabot/A diluted in 30 ml saline solution, intradetrusorial injections can be performed (30 injections into the bladder wall, with the exclusion of the trigone).
- In the procedure, the needle for the injection should be typically 22–27 gauge and 4 mm in length.
- While some information exist on repeat intradetrusorial injections of onabot/A in patients with NDO, very few data exist on long-term follow-up of intravesical onabot/A treatment in patients with IDO and OAB. Indeed in these few studies, onabot/A has been observed to induce a stable and significant amelioration of OAB symptoms, without serious side effects, and a long-lasting improvement of patients' QoL.

Points of Interest

- Overactive bladder (OAB) is a complex of symptoms defined by International Continence Society as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTIs) or other obvious pathology".
- The initial assessment of a patient with uncomplicated OAB symptoms should include a careful history and physical examination, urinalyses and culture, and the assessment of residual urine by measuring the postvoid urinary volume. The use of micturition time charts, frequency volume charts, or voiding diaries allow to confirm the clinical diagnosis. Validated symptom questionnaires are useful to quantify and characterize urinary symptoms and their impact on patient's QoL.
- The use of urodynamics is not recommended before starting conservative management. It should be performed before surgery in women who present

with OAB symptoms suspected for detrusor overactivity and voiding dysfunction, or who had previous surgery for stress incontinence or urogenital prolapse.
- First-line treatment consists of conservative measures (bladder training and anticholinergics). When OAB is refractory to these interventions, therapeutic options such as onabotulinumtoxinA intradetrusor injections, electrical stimulation, or surgical interventions can be applied.
- OnabotulinumtoxinA intravesically injected can be offered to patients with idiopathic urgency urinary incontinence and to patients with neurogenic detrusor overactivity refractory to antimuscarinic therapy. Patients have to be advised about the risk of urinary tract infections and the possible need to self-catheterize.

Percutaneous Tibial Nerve Stimulation: Neuromodulation for the Masses

Scott MacDiarmid

Overactive bladder (OAB) has a deleterious effect on nearly every aspect of daily life, greatly affecting the overall health and well-being of those who suffer from it. The mainstay of therapy for OAB is behavioral therapy and antimuscarinic agents and now a β-3 agonist. Percutaneous tibial nerve stimulation (PTNS) is a neuromodulation therapy that offers patients an attractive alternative when conservative measures fail.

In this section, I will discuss the significant clinical need supporting the liberal use of neuromodulation therapies in the treatment of OAB. I will review the literature regarding the efficacy and safety of PTNS as well as provide clinical tips to help make PTNS successful in your practice. Importantly, an algorithm for the treatment of OAB will also be presented. My personal mission is to inspire clinicians to strive for excellence in the management of OAB and to liberally offer neuromodulation therapies to their patients.

A New Disease in Town

Health providers worldwide are well aware that the primary treatment of OAB is behavioral modification and medication with the goal of relieving symptoms and balancing drug treatment efficacy with side effects and costs. Unfortunately, many patients do not reach their treatment goal with conservative therapy and suffer from a new disease that in day-to-day practice is seldom talked about by patients and healthcare providers. This disease is called “refractory OAB” and to which I have coined the term “ROAB.”

Who Has ROAB?

Simply stated – millions do! In fact, I believe that ROAB is more prevalent than OAB that is currently effectively managed by medical therapy. Let's face it; more than 50 % of OAB patients treated do not respond favorably to or do not reach their treatment goal with medication.

The American Urological Association (AUA) Guideline panel defines the refractory OAB patient as one who has failed appropriate behavioral therapy of sufficient length and a trial of at least one antimuscarinic medication administered for 6–12 weeks. Failure may include lack of efficacy and/or inability to tolerate adverse drug effects. The panel notes the importance of combining behavioral and medication and trying alternative antimuscarinics.

A more real-world definition of patients with ROAB include those who:

- Do not respond to medication in spite of trying multiple agents
- Cannot tolerate medication
- Cannot afford mediation
- Have a contraindication to taking medication
- Do not want to take medication

Patients with ROAB are those who keep coming back cycling through various agents and are still symptomatic. They are those who do not respond to their 2 weeks of samples and who simply give up thinking they cannot be helped and unfortunately surrender to their condition. In addition, think about the millions of men and women with OAB symptoms who are only partially satisfied with their antimuscarinic agent, alpha blocker, or β-3 agonist and who would jump at the chance of achieving better symptom relief by adding a noninvasive treatment to their current medical therapy.

We Have a Problem

Unfortunately, we have a significant clinical problem when it comes to the treatment of OAB, and that problem is that we are dramatically under treating ROAB.

The mainstay of OAB therapy consists of non-pharmacologic and pharmacologic approaches, either as monotherapy or in combination. Non-pharmacologic treatment includes dietary and fluid modifications, behavioral therapy, and pelvic floor muscle rehabilitation. The antimuscarinics darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride are recommended as second-line therapy. Mirabegron, a newly approved β-3 agent, is an alternative for both the treatment naive and for those who have failed antimuscarinics.

Although published improvements in urgency incontinence episodes with behavioral therapy range from 50 to 80 %, these were achieved in highly motivated patients treated by experts using strict behavioral protocols. Such improvement in daily practice may be unrealistic and many offices do not offer non-pharmacological treatments. Many patients benefit from antimuscarinics but the data and clinical

experience support a low adherence rate with them. Brostrom reported continuation rates with OAB agents of less than 50 % at 6 months, less than 25 % at 1 year, and less than 10 % at 2 years or longer.

The good news is that sacral nerve stimulation (InterStim®), percutaneous tibial nerve stimulation (Urgent®PC), and onabotulinumtoxinA (Botox®) are all FDA approved for treatment of refractory OAB. The bad news is that we are not liberally using them in our OAB population. For instance, there have been approximately 150,000 sacral nerve stimulators placed worldwide since 1997, with 25,000 implanted in the USA in 2012. In the same year, approximately 15,000 and 35,000 patients were treated with PTNS and onabotulinumtoxinA, respectively. Estimating 10,000 US Urologists and Urogynecologists, we are each treating on average 7 or 8 ROAB patients annually. Clearly we need to do better.

What Is Neuromodulation?

The International Neuromodulation Society defines therapeutic neuromodulation as "the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body." By altering neurotransmission processes and restoring neural balance, neuromodulation can have profound effects on pain relief, restoration of normal bowel and bladder control, tremor control, and many others.

Neuromodulation for the Masses

In spite of the effectiveness of sacral nerve stimulation, most urologists do not perform InterStim®, don't refer to those who do, and it is perceived by some as too invasive or expensive, especially in elderly patients and in those who are frail or have a number of medical comorbidities. OnabotulinumtoxinA injected directly into the detrusor muscle endoscopically is an excellent neuromodulation treatment, but its use in clinical practice is somewhat limited because of the risk of retention associated with the treatment.

Clearly we need new and less invasive therapies. Percutaneous tibial nerve stimulation (Urgent®PC) offers patients an in-office noninvasive treatment alternative and I believe it is neuromodulation for the masses: the masses of physicians who are not currently liberally using neuromodulation therapies and the masses of untreated ROAB patients including the frail and elderly.

What Is PTNS and How Does It Work?

PTNS is a minimally invasive neuromodulation system designed to deliver retrograde electrical stimulation to the sacral nerve plexus through percutaneous electrical stimulation of the posterior tibial nerve. The posterior tibial nerve contains

mixed sensory-motor nerve fibers that originate from L4 through S3 which modulate the innervation to the bladder, urinary sphincter, and pelvic floor. Although the specific mechanism of action of PTNS is unclear, it appears that stimulation of these nerves inhibits bladder activity by depolarizing somatic afferent fibers, which provides central inhibition of the preganglionic bladder motor neurons through a direct route in the sacral cord. It has been postulated that neuromodulation may also have a direct effect on the detrusor or a central effect on the micturition centers of the brain [7].

Using a battery-powered, handheld stimulator and a 34 gauge needle electrode, the tibial nerve is accessed and stimulated. Patients receive a 30-min weekly treatment in office for 12 weeks. Patients treated with PTNS may begin to see changes in their voiding parameters after 4–6 treatments. Following 12 weeks, treatment responders require additional therapy at individually defined treatment intervals for sustained relief of OAB symptoms.

Effectiveness of PTNS

The literature clearly supports the efficacy of Urgent®PC in the treatment of overactive bladder. The robustness of the PTNS data is supported by:

- Its consistency
- Its objective efficacy as measured by urodynamics
- Its comparison to medical therapy
- Its effectiveness compared to sham
- Its long-term effectiveness

What is noteworthy of the efficacy data is its consistency as measured by its effect on bladder diary variables. Govier et al. performed a well-designed, prospective, multicenter trial which assessed the efficacy and safety of PTNS for the treatment of refractory OAB. The primary endpoint was the change in mean daytime frequency from baseline to 12 weeks, typical for an OAB trial.

The treatment resulted in at least a 25 % reduction in daytime frequency in 55.2 % of patients, an overall 21 % reduction in nighttime voids, and a mean reduction of urge incontinence episodes of 35 %. Overall, 71 % of patients were classified as a treatment success based on acceptable criteria and were continued on long-term therapy.

In a prospective, 3-month, multicenter study, van Balken et al. evaluated the efficacy of PTNS for the treatment of OAB. Voiding diaries and general and disease-specific quality-of-life measures were utilized, and responders were defined as those patients who requested for long-term maintenance therapy after 12 weeks of treatment.

In all 33 OAB patients, the mean reduction in urinary frequency and nocturia was statistically significant and numerically similar to the results achieved with antimuscarinic agents in independent studies. In the patients defined as “responders,” the

mean reduction in daytime and nocturnal voids was impressive: −4.8 and −1.4 voids, respectively. Similarly, the statistically significant reduction in the number of leaking episodes and pad usage experienced in the 30 patients with urge incontinence at baseline was impactful (−4.8 and −2.5, respectively, for all patients; −6.2 and −3.3, respectively, for responders).

Klinger et al. evaluated the benefit of PTNS as measured by its effect on objective urodynamic parameters. The mean maximum cystometric capacity increased from 197 to 252 mL and the mean volume at first unstable bladder contraction from 95 to 133 mL. In responders, the mean increase in total bladder capacity increased from 175 to 266 mL. Similarly, Vandoninck et al. evaluated 46 PTNS patients with urodynamics and demonstrated an increase in cystometric capacity. Notably, the increases in bladder capacity achieved with PTNS are greater than the approximate 20–30 mL increase customarily observed with antimuscarinics, further supporting the efficacy of neuromodulation.

The Overactive Bladder Innovative Therapy (OrBIT) Trial was a randomized, multicenter, controlled study that compared the effectiveness of PTNS to extended-release tolterodine in 100 patients with OAB [8]. The global response assessment demonstrated that subject assessment of OAB symptoms compared to baseline was statistically significant in the PTNS arm with 79.5 % reporting cure or improvement compared to 54.8 % of subjects on tolterodine ($p<0.01$). After 12 weeks of therapy, objective measures improved similarly in both groups for reductions in urinary frequency, urge urinary incontinence episodes, urge severity, and nighttime voids, as well as for improvement in voided volume.

The Study of Urgent® PC vs. Sham Effectiveness in the Treatment of Overactive Bladder Symptoms (SUmiT) was a multicenter, double-blind, randomized, controlled trial comparing the efficacy of PTNS to sham through 12 weeks of therapy [9]. Two hundred twenty adults were randomized 1–12 weeks of treatment with weekly PTNS or sham therapy. The 13-week subject global response assessment for overall bladder symptoms demonstrated that PTNS subjects achieved statistically significant improvement in bladder symptoms with 54.5 % reporting moderately or markedly improved responses compared to 20.9 % of sham subjects from baseline ($p<0.001$). Voiding diary parameters after 12 weeks of therapy showed PTNS subjects had statistically significant improvements in frequency, nighttime voids, voids with moderate to severe urgency, and urinary urge incontinence episodes compared to sham. The level I evidence provided by this pivotal study demonstrated that PTNS is a safe and effective therapy in treating OAB symptoms. In a second sham study, Finazzi Agro demonstrated $a>50$ % reduction in urgency incontinence episodes in 71 % of the PTNS group vs. 0 % with placebo ($p<0.0001$).

In the second phase of the OrBIT Trial, the investigators assessed the sustained therapeutic efficacy of PTNS in OAB subjects over 1 year [10]. After 12 weeks, subjects randomized to weekly PTNS therapy with Urgent® PC were offered an additional 9 months of treatment with assessments at 6 and 12 months from baseline. Thirty-three PTNS responders continued therapy with 32 and 25 subjects completing 6 and 12 months of treatment, respectively. Subjects received a mean of 12.1 treatments over an average of 263 days and a mean of 21 days between treatments.

At 12 months, mean improvements from baseline included frequency 2.8 voids/day ($p<0.001$), urge incontinence 1.6 episodes/day ($p<0.001$), and nocturia 0.8 voids ($p<0.05$). The durability of response demonstrated supported that PTNS is effective as a viable, long-term OAB therapy.

Peters et al. followed 50 participants from the SUmiT Trial who met the primary effectiveness endpoint after 12 weekly PTNS. The patients were prescribed a fixed-schedule 14-week tapering protocol followed by a personal treatment plan aimed at sustaining OAB symptom improvement. Of this group, 29 patients completed the 36-month protocol and received a median of 1.1 treatments per month. At 3 years, 77 % maintained moderate or marked improvement in OAB symptoms. Compared to baseline, median voids per day decreased from 12.0 to 8.7, and urge incontinence episodes per day decreased from 3.3 to 0.3. All quality-of-life parameters remained markedly improved from baseline through 3 years.

Special Populations

The efficacy of PTNS has been demonstrated in patients with neurogenic bladder dysfunction. Nine of 14 patients (multiple sclerosis, Parkinson's, stroke, or spinal cord injury) showed a significant improvement of symptoms and of urodynamic parameters after PTNS. In Parkinson's patients, Kabay demonstrated statistically significant improvements in the volume at the first involuntary detrusor contraction and maximum cystometric capacity. Similar benefits in urodynamic parameters were observed in multiple sclerosis patients treated with PTNS.

Kim found that 90 % of patients with painful bladder syndrome showed an improvement >25 % in the VAS score for pain, with 60 % reaching improvement >50 %. Van Balken demonstrated efficacy in 42 % of pelvic pain patients. Kabay evaluated the efficacy of PTNS vs. sham in a large cohort of patients with category IIIB chronic nonbacterial prostatitis. A complete response on pain and symptoms was observed after PTNS in 40 and 66.6 % of patients, respectively, vs. no response from sham.

The benefit of PTNS in the treatment of fecal incontinence has also been demonstrated and is FDA approved for bowel complaints in Europe. Fecal incontinence episodes decreased from 19.6 ± 21.0 at baseline to 9.9 ± 15.5 ($p=0.082$) at 6 weeks and to 3.6 ± 4.8 ($p=0.029$) at 1 year. Findlay reported a 100 % response in 13 female patients with fecal incontinence, and Mentes concluded that PTNS could be effective in treating the same in those with partial spinal cord injury.

In a single-center unpublished retrospective analysis, we evaluated the effectiveness of PTNS in 286 primarily elderly patients with OAB (median age 78.5 years, range 19–96 years). In addition to demonstrating improvements in voiding parameters, 76.2 % desired to continue maintenance therapy after 12 weeks of therapy.

Hoebeke evaluated the effectiveness of PTNS in children with non-neurogenic voiding dysfunction. Seventeen of 28 patients (60 %) with urgency and 16 of 23 (69 %) with urgency incontinence significantly benefitted from therapy. Seventeen

percent of children became completely dry. De Gennaro found that PTNS is generally well accepted by children, with low scores measured by a visual analog pain score that further decreased during the therapy. The same author found that OAB children had symptom improvement in 80 % of cases and in 71 % with urinary retention. Durability of response with PTNS at 2 years has also been demonstrated.

Little data are available about prognostic factors for success or failure with PTNS. Studies on urodynamic changes by PTNS suggest that in cases of overactive bladder, without detrusor overactivity, patients are more prone to a successful treatment outcome. Clinical parameters for predicting SNS outcome were also tested in 132 patients treated with PTNS, but showed no significance.

A number of manuscripts have been published about the cost-effectiveness of neuromodulation therapies. In a comparative analysis, the initial and ongoing 2-year costs associated with PTNS and SNS were evaluated. During initial therapy, costs per patient were similar at $1773 for 12 weeks of PTNS treatment and $1857 for the SNS test. After 1 year, the costs were more than five times higher for SNS than PTNS ($13,746 vs. $2772) and more than three times higher at 2 years ($14,160 vs. $3850).

Clinical Relevance of PTNS Data

In addition to its robustness, the data supporting the efficacy of PTNS is clinically relevant for a number of reasons. In the majority of cases, the patients studied had failed prior medical and behavioral therapy. Not only does this potentially select for a more difficult-to-treat population, the patients evaluated are similar to the refractory patients we treat with PTNS in clinical practice. More importantly, I believe that most of the positive responders in the literature and in clinical practice may not have been offered onabotulinumtoxinA and sacral nerve stimulation or perhaps declined them due to their perceived invasiveness. If so, these PTNS responders would otherwise have been left untreated and living with their bothersome symptoms.

Maximizing Therapy with a Treatment Algorithm

In order to maximize efficacy and to help millions of OAB patients, we need to embrace and liberally offer all three neuromodulation therapies to them. In order to do so, I recommend the adoption of an OAB treatment algorithm in order to drive efficacy. Let me present to you mine (Fig. 3.7).

Most patients are initially treated with a combination of antimuscarinics and behavioral therapy. Nearly all patients are started on behavioral treatments including fluid modifications, bladder retraining, and pelvic floor rehabilitation. Many

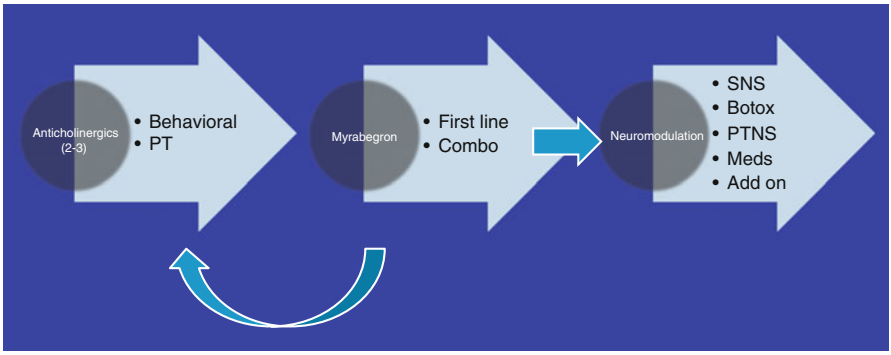

Fig. 3.7 Treatment algorithm for the treatment of overactive bladder

patients are offered to see our in-house physical therapy team who are experts in treating patients with voiding dysfunction.

When patients fail two (and perhaps three) antimuscarinics, they are offered mirabegron. We have had tremendous success treating ROAB with the β-3 agonist either as monotherapy or in combination with antimuscarinics. In milder patients, I tend to switch to mirabegron, and in the more severe partial responding population, I often add it to the antimuscarinic. The efficacy and tolerability of mirabegron has been such that I would not be surprised if it becomes first-line therapy for many urologists prior to starting antimuscarinics.

When medical and behavioral therapy does not reach the patient's treatment goal, I offer nearly all ROAB patients neuromodulation. Each of the three therapies has its inherent advantages and disadvantages, and in my opinion, it should be the patient's choice of which one best suits him, not mine. Utilizing a common sense approach, many elderly patients with multiple comorbidities are only offered PTNS.

Of course ROAB patients who have not exhausted all of the available antimuscarinics have the option of trying a third, fourth, or fifth medication, and in rare cases, this may be beneficial.

Patients declining neuromodulation and who have exhausted all pharmaceuticals unfortunately have reached the end of the treatment algorithm. Those who fail a neuromodulation therapy are usually reoffered the other two options, depending on patient factors. In addition, partial responders to neuromodulation may be restarted on an OAB agent that has helped minimally in the past to help augment their therapy.

The algorithm is simple and in my opinion helps maximize efficacy. The moment the pen or keypad orders an OAB agent, the patient is on a path to be offered neuromodulation unless they reach their treatment goal with conservative therapies. Patients are educated about the process with the help of an educational first-prescription treatment tool given to each and every one of them at the beginning of the treatment process. The booklet better educates them regarding their options and better equips them in making a more informed decision.

I find it equally rewarding to help patients with medication, behavioral therapy, neuromodulation, or with a combination of treatments. I strongly encourage my

colleagues to adopt such an algorithm and no longer accept the mediocre care many of our patients are currently receiving.

Practical Tips for Success
Let me give you five practical tips that may help you be successful in establishing PTNS into your practice:

1. The nurse or caregiver who performs PTNS should be passionate about helping patients with OAB. Do not underestimate the power of behavioral therapy, encouragement, and cheerleading when treating patients with voiding dysfunction.
2. Be efficient with your time and scheduling. Start with ½ day per week and increase the number of the time slots as your neuromodulation practice grows.
3. Treating more than one patient simultaneously may greatly increase efficiency.
4. Utilize the sales representative to make sure your staffs are experts in delivering the therapy.
5. And finally, be like the Adidas brand and *be all in*! Commit to driving excellence for your OAB patients and do lots of neuromodulation. Your patients will love you for it.

Conclusions

PTNS offers patients with refractory OAB or "ROAB" a minimally invasive, office-based procedure that is safe, effective, and is an important addition to our therapeutic armamentarium. Utilizing a treatment algorithm and adopting a mindset of treating patients beyond medication is integral in driving excellence and maximizing therapeutic outcomes for our OAB patients.

Sacral Neuromodulation

Hendrikje M.K. van Breda and John P.F.A. Heesakkers

Introduction

The International Continence Society (ICS) and the International Urogynecological Association (IUGA) have defined overactive bladder syndrome (OAB) as urinary urgency, usually accompanied by frequency and nocturia, with or without

urgency urinary incontinence in the absence of urinary tract infection or other obvious pathology. Symptoms of lower urinary tract dysfunction are often challenging to treat and have significant negative effect on the quality of life for many people; it lowers their self-esteem and health perception and are very expensive. An estimated 455 million people worldwide (10.7 %) experienced at least one OAB symptom in 2008, with the worldwide prevalence expected to increase to 500 million in 2013 and 546 million in 2018. In America, approximately 34 million inhabitants have OAB with associated costs exceeding $9 billion per year including direct care, health-related consequences, and lost productivity.

Conservative treatment, such as behavioral interventions and antimuscarinic drugs, does not always give sufficient improvement and/or is associated with considerable side effects such as dry mouth, blurred vision, constipation, erythema, fatigue, and urinary retention resulting in terminating the treatment in 70 % of the patients within 6 months. In the case of conservative treatment failure, sacral nerve stimulation (SNS) (InterStim®), percutaneous tibial nerve stimulation (PTNS) (Urgent®PC), and onabotulinumtoxinA (BTA) (Botox®) are all FDA approved for treatment of refractory OAB. The purpose of neuromodulation for the treatment of OAB is to target the innervation system that controls the pelvic floor organs and specifically the lower urinary tract. This chapter will discuss SNS treatment in clinical practice for OAB symptoms.

Historical Overview SNS Therapy

The history of electrical stimulation in the urology field started in 1864 when Budge observed detrusor contraction in animals when stimulating the sacral spinal cord. In 1954, Boyd suggested a technique for direct electrical stimulation of the bladder in humans. The first SNS implant in a urological patient was performed by Tanagho and Schmidt at the University of California in San Francisco in 1982. After that, in 1994, InterStim received the CE mark for treatment of chronic functional disorders of the pelvis, lower urinary tract, and intestinal tract in Europe. In 1997, InterStim received an FDA approval for treatment of urgency urinary incontinence in the USA which was expanded in 1999 for treatment of symptoms of urgency-frequency, and urinary retention. In 2002, the tined lead was introduced in SNS therapy to diminish the migration change of the lead.

Mode of Action

The precise mode of action of SNS is unknown. There are at least two presumed mechanisms of action: The first one claims that activation of efferent nerve fibers to the striated urethral sphincter reflexively causes detrusor relaxation. The second presumed

mechanism states that activation of afferent nerve fibers causes inhibition of the voiding reflex at a spinal and/or supraspinal level; pudendal nerve afferents seem to be particularly important for the inhibitory effect on the voiding reflex. In OAB, the inhibition by SNS may, in part, modulate the sensory outflow from the bladder through the ascending pathways to the pontine micturition center, thereby preventing involuntary contractions by modulating the micturition reflex circuit but allowing voluntary voiding to occur.

The assumption that there is not only an effect at the spinal level but that there is also a central effect is strengthened by studies that are performed in complete spinal cord patients versus incomplete spinal cord patients. Schurch performed a PNE test in three complete SCI patients; after stimulation with a lead in the S3 foramen, a good anal reflex was seen, but after 5 days of stimulating, no improvement was observed in detrusor hyperreflexia. Hohenfellner concluded in his study of chronic sacral neuromodulation that only the patients with nearly complete or complete spinal lesions seem unlikely to benefit from this treatment.

Procedure

The procedure can be preceded by a preliminary test phase referred to as a percutaneous nerve evaluation (PNE). This test uses a non-anchored test lead placed in the S3 foramen and connected to an external stimulator. The test extends between 4 and 14 days, after which the lead is removed. Success of this test phase is generally defined as improvement of at least one major voiding symptom by more than 50 %. The overall response rate for PNE is around 55 %. Lead migration is considered the main factor of false-negative results. A true-negative response to PNE of about 20 % can be explained because the pudendal nerve afferents seem to be particularly important for the inhibitory effect on the voiding reflex, and those afferents are confined to the S2 level only in 18 % of all subjects.

SNS is nowadays often preformed in a two-stage technique with a quadripolar lead with self-anchoring tines, first described by Spinelli et al. in 2003. This technique enables test stimulation to be performed using the permanent anchored lead that reduces the risk of migration. This lead is usually placed through the back skin in the S3 foramen at sacral level (Fig. 3.8) and tunneled subcutaneously, where it is connected to a temporary extension lead that exits the body and is connected to an external test stimulator (Fig. 3.9). This test period mostly extends to 1–2 weeks. If the voiding symptoms improve by more than 50 %, the subject might undergo surgery to implant the internal pulse generator (IPG) (Fig. 3.10).

Test Phase: PNE Versus First Stage Tined Lead

Leong et al. compared the patients' response rate to PNE versus 1st stage tined lead procedure. Eighty-two patients, comprising 69 OAB patients, were screened with

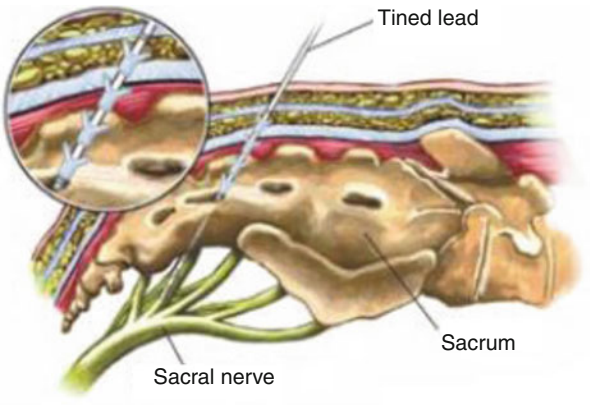

Fig. 3.8 Percutaneous insertion of the tined lead electrode through the sacral 3 (S3) foramen close the sacral nerve roots

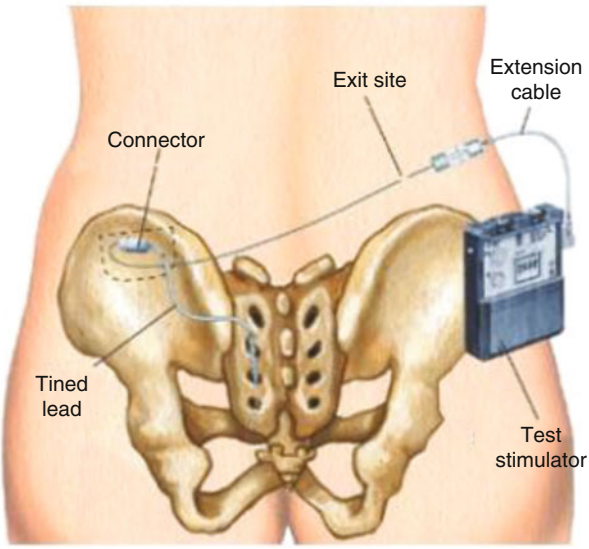

Fig. 3.9 Test situation of the first phase tined lead technique. The tined lead electrode has been inserted in the S3 foramen on the left side. It is connected to a test wire via an incision on the left lateral buttock side. The test wire is tunneled tot he right buttock side where it exits the skin and is connected to a external test stimulator

both PNE and with a 1st stage tined lead procedure. More than 50 % improvement in at least two relevant urinary symptoms was considered a positive response. The positive response rate on PNE was 47 %, while 1st stage tined lead showed a 69 % positive response rate. All patients with a positive 1st stage tined lead received SNS treatment. Failure rate after 2 years was 2.9 %. This study may suggest that 1st stage tined lead is a more sensitive screening rate method for SNS therapy.

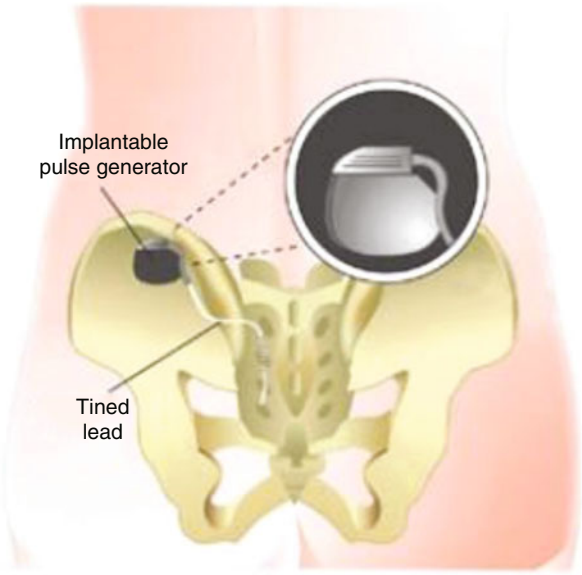

Fig. 3.10 The situation after the second phase tined lead technique. The tined lead electrode has been inserted in the S3 foramen on the left side. It is connected to the definite implanted pulse generator on the left lateral buttock side

Long-Term Effect

Long-term data about the success rates of SNS are scarce. Van Kerrebroeck et al. published a prospective multicenter trial evaluating the long-term safety and efficacy of SNS in patients with refractory urgency incontinence, urgency-frequency, and retention. A total of 17 centers worldwide enrolled 163 patients for test stimulation, of whom 152 patients received the implantation using InterStim. Voiding diaries were collected annually, and clinical success was defined as ≥50 % improvement from baseline in primary voiding diary variables. After 5 years, 105 patients completed the follow-up and of them 87 completed the voiding diary. Sixty-eight percent of patients with urgency incontinence, 56 % with urgency-frequency, and 71 % with retention had successful outcomes.

Groen et al. published the 5-year results of SNS in 60 women with refractory idiopathic urgency urinary incontinence. A non-tined lead procedure was used and success was defined as at least a 50 % decrease in the number of incontinence episodes or pads used daily. At 5 years, SNS was still used in 48 (80 %) patients of which 31 completed the voiding diaries. The success rate, patients with at least a 50 % decrease in the number of incontinence episodes or pads used daily, gradually decreased from 52 patients (87 %) at 1 month to 37 (62 %) at 5 years. Complete continence persisted in 15 % of patients.

As with all treatments, adverse events in SNS therapy are described, this mainly encompassed pain, infection, bowel dysfunction, and change in clinical effect often due to lead migration. Based on the summarized adverse event data,

many wound complications and some changes in efficiency can be managed conservatively without repeated surgery. Published rates of infection range from 0 to 11 % in various studies. Rates of surgical revision and explanations vary in literature.

There is a decline in therapy effect of SNS over the years. If patients are successfully treated with SNS, the battery will eventually empty and a surgical intervention to change the battery will be necessary. The typical battery life of InterStim I is 8–10 years, depending on the parameters used for stimulation. The expected lifespan of InterStim II lies around 3–5 years when used 24 h/day. There is also a percentage of patients treated with SNS who, after a few years, don't benefit from their therapy despite of adequate nerve stimulation. A suggested hypothesis for this phenomenon is habituation of the nerve system to prolonged stimulation of the sacral nerve.

If on-demand stimulation would be possible, it will lead to a longer battery life and it may decrease the risk of habituation of the nervous system. To answer this question, Oerlemans et al. completed a pilot intervention study for on-demand SNS in patients with urgency incontinence and urgency-frequency syndrome. Twenty-one patients participated of which 5 were randomized into a control group (continuous stimulation) and 16 into the on-demand group. The on-demand group was asked to switch the device off, and on again, when they felt recurrent symptoms. Of the study group, 10 patients reported no worsening of the symptoms by on-demand sacral nerve stimulation. The mean off-time was 12.4 h. The other six had worsening of their symptoms. Larger randomized studies with longer follow-up are needed, but this pilot study suggests that in the majority of patients, on-demand SNS treatment could be possible, implying less battery changes and therefore lower therapy costs. If on-demand stimulation reduces the decline in therapy effect over the years due to habituation of the nervous system, it could give better long-term results.

Costs

There are several publications about the cost-effectiveness of the treatment for OAB, in particular for PTNS and SNS. Various articles show different costs, since the medical care systems differ between countries. Leong et al. published that the cost of SNS as a treatment for OAB syndrome in the Netherlands is $15.743 over a 2-year time period. D'Ausilio et al. calculated the 10-year cost for SNS in Italy at €33.897. Staskin et al. compared the costs of PTNS to SNS for OAB syndrome in the USA. PTNS was the least costly with $7.565 for a three-year treatment, compared to SNS which costs $24.681 for the same treatment period. Martinson et al. also concluded that PTNS had substantially lower costs compared to SNS in the USA. Although it's difficult to compare between countries, the treatment costs for SNS seem to be higher compared to PTNS treatment.

Practical Advice

- If you want to apply SNS therapy, you need a passionate and motivated team. Especially in the first year, you and your team will see the patients frequently for the implantation and to apply the best program for their therapy. It can be time consuming, but good and precise settings can lead to a very satisfying therapy.
- Before the implantation, inform your patient about the expectations, the procedure, the long-term results, and the possible complications.
- With strict selection criteria, you will have a high success rate. But in less clear cases, who have tried other therapies, you can give them the benefit of the doubt by performing a test phase with a PNE or a tined lead and still keep strict implantation criteria. Offering the patients a test phase will help to treat or, when it does not work, to accept their problem.
- Take your time with implanting the lead to confirm the right position. If you perform it under local anesthesia, ask for the sensory response. If you implant under general anesthesia, make sure no muscle relaxant is used, because the motor response is the only response you can rely on.
- Yes it's expensive, but for patients the result can be priceless.

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Chapter 4
Bladder Pain Syndrome/Interstitial Cystitis: A Large but Heterogeneous Field in Functional Urology

David Castro-Diaz and Magnus Fall

Introduction and Definitions

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a distressing, chronic bladder disorder comprising symptoms of pain, pressure or discomfort perceived to be related to the bladder which is diagnosed primarily in women and of unknown aetiology, the diagnosis to be set after exclusion of many possible different confusable diseases. This debilitating condition was first identified in the nineteenth century, but it was not until 100 years later that an official definition, constructed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), became accepted. However, this definition has been debated because around 60 % of patients who were clinically diagnosed with interstitial cystitis (IC) were excluded when applying the NIDDK criteria. A further fundamental problem is that treatment requirements differ importantly between BPS/IC phenotypes. So far, the majority of available studies did not take important distinctions into account, limiting the utility of clinical research in BPS.

Due to increasing problems caused by international confusion as to definitions, there has been much activity during the last decade trying to harmonise terminology and the understanding of BPS/IC on the whole. The European Society for the Study of IC (ESSIC) has proposed a definition of "pelvic pain, pressure or discomfort perceived to be related to the urinary bladder". The American Urological Association (AUA) guidelines for BPS/IC management used "an unpleasant sensation (pain,

D. Castro-Diaz, MD, PhD (✉)
Department of Urology,
Universidad de La Laguna/Complejo Hospitalario Universitario de Canarias,
Santa Cruz de Tenerife, Spain
e-mail: dcastro@teide.net

M. Fall, MD, PhD
Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, Göteborg, Sweden
e-mail: magnus.fall@urology.gu.se

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pressure, discomfort) perceived to be related to the bladder". The European Association of Urology (EAU) guidelines on chronic pelvic pain stated that BPS/IC should be diagnosed on the basis of symptoms of pain associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time urinary frequency. The international Continence Society (ICS) defined painful bladder syndrome/interstitial cystitis 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. ICS reserves the diagnosis of IC to patients with "typical cystoscopic and histological features".

Epidemiology

Although BPS/IC mostly affects women, it can occur in people of any age, sex or race. Due to the controversies regarding both the definition and the diagnosis of BPS/IC, epidemiological studies have been in many aspects limited, based mainly on symptoms, and the symptoms have been interpreted and evaluated in various ways. Consequently, available studies are difficult to compare, and the reported prevalence ranges widely across different studies, definitions and populations. The Bladder Pain Syndrome Committee of the International Consultation on Incontinence has recently estimated the prevalence of BPS/IC to be 300/100,000 women and 30–60/100,000 men. BPS/IC seems to be more frequent in first-degree relatives of patients with interstitial cystitis.

Aetiology

The aetiology of BPS/IC is still unknown. Different possible aetiologies have been proposed although most of them without evidence good enough to be accepted as a general explanation.

Infection

No study has been able to demonstrate a relation between BPS/IC and urinary infection, neither Gram-negative or Gram-positive microorganism nor increase of urinary IgA and IgG. However, some reports have suggested a possible relation with urinary tract infection in a minority of patients. Other investigators have found absence of bacterial and viral DNA in bladder biopsies of patients with BPS/IC, while a possible role of nanobacteria has been suggested as a possible aetiology. In an intriguing recent congress report, it was stated that biofilm-forming *Corynebacterium* sp., identified in biopsy material but not in urine cultures, may be

associated with the occurrence of BPS/IC and especially the Hunner type of disease. In any case at present, although still unlikely, it is not possible to rule out a relation between infection and development of this disorder.

Mast Cell Activation

Mast cells are thought to play a role in the aetiology of BPS/IC. These are multifunctional immune cells that release a number of inflammatory mediators such as histamine, leukotrienes, serotonin and cytokines, which might be responsible for symptoms and findings in BPS/IC such as pain, frequency, oedema, fibrosis and angiogenesis in the lamina propria. Mast cells count has been observed to be tenfold higher in the bladder of patients with classic IC. In non-Hunner BPS/IC patients, the mast cell count is normal or slightly increased.

Neuronal Mechanisms

Neurogenic inflammation might be the result of abnormal release of neuropeptides by activation of sensory and sympathetic nerves. Such abnormal release is thought to promote mast cell activation and alteration of central nervous system processing of afferent stimuli as suggested in several reports. Furthermore, an increase of tyrosine hydroxylase immunoreactivity in bladder tissue of BPS/IC patients, compared with controls, has been reported as a sign of general increase of sympathetic flow raising the possibility of a neurogenic aetiology and/or pathogenesis.

Bladder Autoimmune Response

An autoimmune aetiology has been suggested since a number of autoantibodies have been found in patients with BPS/IC. Recently, it has been observed that the classic type of BPS/IC (type 3C) is characterised by a local adaptive response with elevated urinary antibody concentrations suggesting that quantification of urinary immunoglobulin levels might be used for a noninvasive diagnosis of the 3C type of BPS/IC.

Defective Bladder Epithelium

Although today it is well known that the bladder urothelium has a rich functional and metabolic activity, it is also a barrier to prevent low and high molecular weight solutes in the urine from leaking into the bladder interstitium. A dense layer of

glycosaminoglycans covering the cell layer composes this barrier and the intercellular junctions which can be compromised, allowing substances in urine to penetrate resulting in symptoms like in BPS/IC, the concept of lower urinary tract dysfunctional epithelium. Several studies have shown a defective glycosaminoglycan layer in patients with BPS/IC due to leaky epithelium allowing the transit of solutes to the interstitium. When this happens, submucosal nerves might be accessible to noxious agents in the urine that might explain symptoms in these patients as observed with scanning electron microscopy. Furthermore, it has been observed that Tamm-Horsfall protein is qualitatively different in patients with BPS/IC compared to controls, suggesting that an alteration of this protein may also be involved.

Antiproliferative Factor (APF)

Antiproliferative factor is a small glycoprotein made specifically by bladder cells in patients with BPS/IC that induces changes in expression of certain epithelial cell proteins and profoundly inhibits cell growth. APF has been identified in 86 % of patients with BPS, 12 % of patients with cystitis and 8 % of controls. The measurement of urine antiproliferative activity may be a useful noninvasive means for diagnosis of BPS/IC. APF has been shown to inhibit heparin-binding epidermal growth factor-like growth hormone factor (HB-EGF) release from the urothelium. It has been reported that this inhibition can be reversed by bladder hydrodistension.

Pathology

Although histological findings may be consistent with the diagnosis on BPS/IC, there is no histology pathognomonic for the entire spectrum of disorders. There is currently consensus that the role of histopathology in the diagnosis of BPS/IC is primarily to exclude other possible diagnosis. Several entities including carcinoma in situ of the bladder, eosinophilic cystitis, tuberculosis cystitis and some other diseases with specific histological findings must be ruled out. In patients with the Hunner type of IC (type 3C according to the ESSIC terminology), a number of characteristic findings are found though, like vacuolisation and urothelial detachment, perineural cell infiltrates, lymphocyte and plasma cell infiltrates and involvement of deeper layers of the bladder wall as well as a special mast cell response, including two distinct mast cell populations and a migratory capacity of cells. When trying to relate such findings to the entire BPS population, they will turn out to be unreliable due to the great variation of phenotypes among BPS/IC patients. A matter of concern is the report of variation of findings even among biopsies taken from the same patient over time. In this context, an issue of practical importance is noteworthy, that is, that the cooperation with a devoted pathologist with experience in

this particular field is a prerequisite for reliable reports. There have been lack of correlation between histological and cystoscopic findings when it comes to glomerulations, bleeding, mucosal tears and bladder capacity; completely normal biopsies may be found in patients with BPS who do not have Hunner lesions. Investigation with electron microscopy also failed to identify pathognomonic data. At this stage, characteristic and uniform findings have been identified in the classic type of IC only.

Diagnosis

As an analysis of data from the Interstitial Cystitis Database (ICDB) indicated that >60 % of BPS/IC cases may be missed when the NIDDK criteria are strictly applied, so the current diagnostic approach has rather been based on symptoms and exclusion of those painful conditions that resemble the disorder but have a different identifiable cause. Suspicion can be supported by cystoscopic and biopsy findings, including inflammation, Hunner lesions, glomerulations or general oedema. Nevertheless, in many non-Hunner patients, neither histological findings nor glomerulations or other lesions are found in severely symptomatic patients who may show a completely normal cystoscopy and/or biopsy. New means of assessment/diagnosis are needed.

Medical History

A detailed medical history is of paramount importance. A very thorough questioning on the localisation of pain, its possible relation to bladder filling and an explicit description of pain generators should be obtained. There should be special attention to previous pelvic surgery, urinary tract infections, other urological diseases or sexually transmitted diseases, any autoimmune disease, any other chronic pain condition or disease (like irritable bowel syndrome, vulvar pain syndrome, etc.), previous pelvic radiation treatment and chemotherapy.

Symptoms of BPS/IC

BPS/IC symptoms are urgency, frequency and/or pain quite often associated with dyspareunia. Some patients have only pain, while others have pain, urgency and frequency in various combinations. The overactive bladder syndrome (OAB) and BPS/IC share urgency as a common symptom. It should be noted that in OAB patients, urgency is linked to a fear of incontinence while in BPS/IC urgency is related to fear of pain.

Symptoms questionnaires have been found helpful in obtaining a complete picture of the patient's symptoms. The O'Leary-Sant Interstitial Cystitis Symptoms Index (ICSI) and Interstitial Cystitis Problem Index have demonstrated an excellent ability to discriminate characteristics from patients and controls. The Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) is another useful questionnaire that gives equal attention to pelvic pain, urinary urgency/frequency and symptoms associated with sexual intercourse. The PUF questionnaire correlates well with the results of the intravesical potassium sensitivity test, which is positive in some 80 % of patients with BPS/IC. An alternative questionnaire is the University of Wisconsin Interstitial cystitis scale (UW-IC scale).

A frequency/volume chart is extremely useful to determine voided volume, frequency and urgency episodes as recommended by the International Consultation on Incontinence.

Physical Examination

Physical examination should include an assessment of the pelvic floor in order to rule out pelvic floor dysfunction (PFD), which might be caused by BPS/IC. This is carried out through bimanual examination in women and rectal examination in men. The strength of the pelvic floor and the capability to contract and relax the sphincter should be taken into account, as PFD is not uncommon in highly symptomatic BPS/IC patients. In some women with BPS/IC, a bimanual examination might trigger pain at the bladder base or urethra, while digital rectal examination in men might be painful often leading to the diagnosis of chronic prostatitis.

In the more complex case, a very thorough clinical assessment has to be performed: a detailed history, scrutinising previous medical information including imaging examinations, neurologic examination especially of the lumbosacral plexus, when needed assisted by electrophysiologic examinations, testing of mechanosensitivity of various relevant areas and a detailed assessment of the musculoskeletal system. Thus, sometimes a very detailed examination is required before treatment can be contemplated.

Cystoscopy and Hydrodistention

Cystoscopy under anaesthesia is mandatory for the complete investigation of BPS/IC patients to identify lesions, with special attention to the presence or absence of Hunner lesions; adequate distention is required to identify such lesions with sufficient certainty. Plain cystoscopy is still a useful first step to examine the bladder and urethral mucosa and urethral calibre, to identify suspect lesions and to determine the degree of local tenderness of the bladder and/or urethra. Tenderness or increased external and internal genitalia sensations and/or tenderness of the various components of the pelvic floor (including trigger points) are also noted. A BPS/IC patient

can tolerate filling with only a limited volume in their unanaesthetised bladder, irrespective of the true bladder capacity during anaesthesia. Confusable diseases are excluded. Submucosal petechial bleedings, so-called glomerulations, seen after decompression of the previously distended bladder, have until recently been regarded as one of the endoscopic hallmarks of the disease. Current data is however casting severe doubt on the diagnostic usefulness of this finding.

The typical Hunner lesion is a circumscribed, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. It is not a true ulcer but rather a very vulnerable, inflamed area. On further bladder distension, this site ruptures (Fig. 4.1), with petechial haemorrhage from the lesion and the mucosal margins in a waterfall manner and with a central vulnus provoked by bladder wall stretch. The denomination Hunner ulcer is therefore incorrect, Hunner lesion to be the preferred term. A quite characteristic finding at the second filling of the bladder in a patient with this classic type of IC lesion is a varying degree of oedema, sometimes with peripheral extension. Diagnostic hydrodistention should be performed in a standard manner at a pressure of 80 cm H_2O above the level of the patient's bladder. Irrigating fluid is allowed to run into the bladder until it stops spontaneously at capacity, as observed when checking the dripping chamber of the fluid reservoir. This volume is then held for 2–3 min with any leakage around the cystoscope sheath controlled by urethral compression. The volume and the degree of bleeding into the bladder fluid are noted when evacuating the bladder. The bladder is refilled to approximately 20–50 % of capacity and again inspected for lesions and haemorrhages, which will not be conspicuous until the bladder is filled for a second time. The anaesthetic bladder capacity is a parameter of importance, since a reduced capacity together with other characteristics is a further indication of classic IC as being a destructive inflammation that can result in bladder contracture at end stage.

Over the years, controversy has developed as to the prevalence and even the actual existence of the Hunner lesion and some urologists maintain that they are rare, or do not exist, and the fact that they rarely detect them confirms this false impression. The distribution varies from 5 to 50 % of cases with BPS in various populations, centres and series. Detection is certainly a matter of attention and training though, and a rigorous routine increases detection. Supplementary techniques might be helpful to increase detection rate, like the narrow band imaging method.

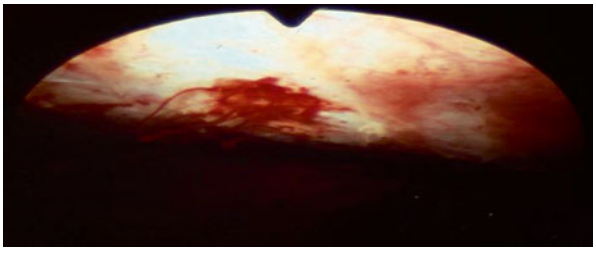

Fig. 4.1 Classic interstitial cystitis with Hunner lesion (bladder pain syndrome 3C), distension during anaesthesia provoking the lesion to split with petechial bleeding in a waterfall manner from the lesion site and the mucosal margins

It is important that these bladder lesions are identified as soon as possible since treatment options and responses differ considerably between the classic Hunner type of IC and other phenotypes.

Treatment

How to Select an Efficacious Treatment?

There are obvious dilemmas when trying to make a wise decision on therapy in BPS. A great variety of solutions have been tried, essentially on a trial-and-error basis. Many methods have been discarded; a few have stood the test of time. Correct classification and phenotyping of the heterogenic group of conditions that may result in pelvic pain is crucial for a good outcome of treatment, while in reality methods to reliably identify phenotypes are insufficient. The significance of this problem is very important but still not generally acknowledged. This is in contrast to a strive in urologic oncology to improve phenotyping and identify critical characteristics to optimize treatments. The fact is that, although the more inclusive attitude of later years has drawn a desirable attention to the entire spectrum of disorders resulting in bladder pain, the wish to include all of them into simple and handy entities has resulted in much scientific and clinical confusion. Ten years ago, a scientific association was founded, with one of its objectives to draw attention to the diagnostic and therapeutic problems in BPS/IC, denominated the European Society for the Study of Interstitial Cystitis (ESSIC), nowadays the International Association for the Study of Bladder Pain Syndrome. They suggested a standard on how to examine and classify patients with bladder pain, addressed the problem of so-called confusable diseases (Tables 4.1 and 4.2), stressed the importance of phenotyping and updated the terminology.

From a therapeutic standpoint, one entity stands out as especially important to identify. The so-called classic IC (Hunner disease, ESSIC type 3C) is a specific and well-defined entity and fulfils the requirements of the original denomination "interstitial cystitis": There are histological signs of a marked inflammation in the bladder submucosa and musculature (the bladder interstitium) together with typical cystoscopic features. Evidence is accumulating on unique and outstanding features of this entity, with great implications on treatment.

Conservative Treatment

In the pelvic area, abnormal activity in the pelvic floor musculature with possible involvement of joints, ligaments, fasciae and viscera may cause adverse interactions. Therapeutic approaches include *breath work, biofeedback techniques and soft tissue manipulations* to aid in muscle relaxation of the pelvic floor. Especially important seems the identification of trigger points, frequently found in, e.g. the pubococcygeus, piriformis, external oblique, rectus abdominis, hip adductors and

Table 4.1 Confusable diseases for bladder pain syndrome

Carcinoma and carcinoma *in situ*
Infection with
Common intestinal bacteria
Mycobacterium tuberculosis
Chlamydia trachomatis
Ureaplasma urealyticum
Mycoplasma hominis
Mycoplasma genitalium
Corynebacterium urealyticum
Candida species
Herpes simplex
Human papilloma virus
Radiation
Chemotherapy including immunotherapy with cyclophosphamide
Anti-inflammatory therapy with tiaprofenic acid
Bladder neck obstruction and neurogenic outlet obstruction
Bladder stone
Lower ureteric stone
Urethral diverticulum
Endometriosis
Vaginal candidiasis
Cervical, uterine and ovarian cancer
Incomplete bladder emptying (retention)
Overactive bladder
Prostate cancer
Benign prostatic obstruction
Chronic bacterial prostatitis
Chronic nonbacterial prostatitis
Pudendal nerve entrapment
Pelvic floor muscle related pain

van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53(1):60–7

Table 4.2 Cystoscopy with hydrodistension

	Not done	Normal	Glomerulations[a]	Hunner's lesion[b]
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

Adapted from van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53(1):60–7

[a]Cystoscopy: glomerulations grade 2–3

[b]With or without glomerulations

[c]Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

gluteus medius muscles. A number of soft tissue manipulative but also invasive techniques are available to release symptoms related to soft tissue pathology in BPS/IC, but presently, this is an underused asset in the treatment armamentarium of this disease complex.

A recent example is a report on myofascial treatments, a multicentre trial in the US, involving numerous prestigious authors. Eleven clinical centres were included in a randomised study of 10 scheduled treatments compared to global therapeutic massage. A total of 81 women were randomised to the two treatment groups. They had similar symptoms at baseline. Subjects had demonstrable pelvic floor tenderness on physical examination and no more than 3 years' symptom duration. The primary outcome was the proportion of responders who were improved in overall symptoms compared to baseline on a 7-point global response assessment scale. Secondary outcomes included ratings for pain, urgency and frequency, the O'Leary-Sant IC Symptom and Problem Index and reports of adverse events. The response rate was 59 % in the myofascial physical therapy group vs 26 % in the global therapeutic massage group, a difference found to be significant. Pain, urgency and frequency ratings, and O'Leary-Sant IC Symptom and Problem Index decreased in both groups during follow-up, not significantly different between the groups though. Pain was the most common adverse event, occurring at similar rates in both groups. No serious adverse events were reported.

Per Oral Drugs

Pentosan polysulphate sodium (PPS), a highly sulphated mucopolysaccharide, is the only oral therapy approved by the US Food and Drug Administration, recommended in the AUA guidelines. It also has a high degree of recommendation according to the EAU guidelines, level of evidence 1a; grade of recommendation A. PPS has efficacy in a subset of 50 % of patients, by time dropping to 30 % of those initially treated. As a rule, it will take up to 6 months before benefit is experienced. The usual dosage is 150–300 mg daily, divided in two or three doses. Treatment responses are rather duration dependent than dose dependent. The safety and efficacy of oral pentosan polysulphate sodium (PPS), hydroxyzine and the combination of the two were evaluated in a pilot randomised clinical trial. A nonsignificant trend was seen in the PPS treatment groups as compared to no PPS. The low global response rates for PPS (and hydroxyzine) suggested that neither provided benefit for the majority of patients with BPS/IC. However, a serious limitation of the study was low numbers of subjects for follow-up. With reference to phenotyping, it can be noted that in an early, open study, patients with the classic Hunner type of disease seemed to be better responders than non-Hunner patients.

Systemic cortisone has also a long tradition; anti-inflammatory treatment using cortisone has been used, although not as a standard option, in BPS/IC for

more than four decades. Efficacy has been demonstrated even more recently in the classic Hunner type of disease, but since the side effects of chronic steroid treatment can be very serious, it is difficult to justify systemic, long-term use. For this reason, the EAU guidelines do not recommend systemic cortisone in BPS/IC.

Amitriptyline, a tricyclic antidepressant, has a number of properties like blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and noradrenalin, and blockade of histamine H1 receptors. This drug is standard in chronic pain treatment and can be used alone or in combination with other treatments. It is used in doses starting at 10 mg daily that are slowly increased over several weeks to up to 50–75 mg daily as tolerated. It tends to diminish pain, increase bladder capacity, block the actions of histamine, act as a mild antimuscarinic, and aid sleep. It has a high degree of recommendation according to the EAU guidelines, level of evidence 1a, and grade of recommendation A.

Hydroxyzine The mast cells are regarded to have pivotal role in BPS/IC, and activation might induce neurogenic inflammation resulting in chronic bladder pain and voiding dysfunction. Hydroxyzine is a histamine H1 receptor blocker inhibiting neuronal activation of mast cells. Hydroxyzine hydrochloride (Atarax) has been on trial in doses of 25 mg increasing to 75 mg/day, if tolerated. Initial results were promising, but a prospective RCT of hydroxyzine/PPS compared to placebo failed to demonstrate statistically significant effects for the active drugs. It still has a high degree of recommendation according to the EAU guidelines, level of evidence 1a, and grade of recommendation A.

Various *immunosuppressants* have been on trial. The most recent and promising one is *cyclosporine A*. In a RCT, comparing 1.5 mg/kg cyclosporine to 3×100 mg PPS for 6 months, the former drug was superior. There were more adverse events like gingival pain, paraesthesia, muscle pain, etc. in the cyclosporine arm though. Careful follow-up on blood pressure and kidney function is mandatory. As would be suspected, Cyclosporine A had a high success rate for patients with Hunner lesions, also in those where more conservative options and endoscopic treatment had failed, while the success rate was low for patients without Hunner lesions. Adverse events were common and led to discontinuation of cyclosporine A for some patients. According to the EAU guidelines, the level of evidence is 1b and grade of recommendation B.

Intravesical Treatment

Intravesical treatment has been widely used (and overused). This kind of treatment refers to the direct introduction of medication into the bladder and is considered as second-line treatment for patients who have failed conservative and oral therapies. According to a Cochrane report, the overall evidence for treating BPS/IC using

intravesical preparations is limited. In that analysis, the quality of trial reports was found to be mixed. Randomised controlled trials were found to be needed with a study design to incorporate relevant and standardised outcomes.

The most commonly used regimens include:

DMSO

Dimethyl sulfoxide (DMSO), a standard treatment with the longest history in IC, has been used for decades. It is a by-product of the paper pulp industry, an organic solvent, and has various properties: analgesic, anti-inflammatory, collagenolytic and muscle relaxant properties. It is also a scavenger of the intracellular OH radical. It is administered weekly or biweekly, sometimes combined in intravesical cocktails with lidocaine, heparin and sodium bicarbonate. DMSO is the only intravesical therapy approved by the US Food and Drug Administration for BPS/IC, recommended in the AUA guidelines. DMSO has a high rating in the EAU guidelines, too, level of evidence 1b, grade of recommendation A. Although DMSO has been a standard treatment through so many years, details of mechanism of action are not yet resolved, but there is still an ongoing interest from basic scientists to explain the action of this compound. DMSO has been used in all presentations of BPS. In a study comparing the two main phenotypes of BPS/IC, side effects were similar in patients with classic compared to non-ulcer disease. For classic IC, there was a significant difference when comparing side effects experienced during the first three instillations and the three subsequent instillations, however. After DMSO instillations, a positive treatment effect lasting 16–72 months was reported.

GAG Replacement

In the abundance of theories regarding pathogenesis, one of the most popular ones is the “leaky urothelium”, i.e. that a defect in the bladder glucosamine glycan layer (GAG) allows noxious substances of the urine to penetrate and affect the sensory innervation. Replenishment of the GAG would then restore mucosal integrity and reduce or cure symptoms. Treatment can be administered orally or intravesically. A variety of mucopolysaccharide products (heparin, pentosan polysulphate sodium, chondroitin sulphate, hyaluronan) have been used intravesically with the objective to get a more direct and prompt effect, with less systemic side effects, however involving the significant disadvantage of repeated urethral catheterisation.

Heparin has been attributed to long-term symptomatic improvement in more than 50 % of patients, and the current American Urological Association (AUA) recommendations list this as one of three options for BPS/IC instillation therapy, namely, dimethyl sulfoxide, heparin and lidocaine. In contrast, the EAU guidelines give heparin treatment a level of evidence 3 and a grade of recommendation C due to limited data on effectiveness.

Pentosan polysulphate Placebo-controlled studies indicated long-term significant effect of this compound. Pentosan polysulphate has a high rating in the EAU guidelines with a level of evidence 1b and grade of recommendation A.

Hyaluronic acid Early studies were promising. Morales et al. (*J Urol*. 1996;156(1):45–8) used 40 mg of HA intravesically on a weekly basis for 4 weeks, then monthly. Response to therapy was evaluated by symptom score, voiding diaries and visual analogue scales.

An initial positive response was maintained until 5 months and then a moderate decrease in the effects on symptoms. There was no significant toxicity, so the response was found to be gratifying. The author's made the point that many therapies that were initially considered promising failed the test of controlled studies. Such studies have been scant and results have to be interpreted with this fact in mind. Hyaluronic acid has a moderate degree of recommendation according to the EAU guidelines, level of evidence 2b, and grade of recommendation B.

Chondroitin sulphate has been advocated for use in BPS/IC. In a Canadian meta-analysis on three studies, a total of 213 patients were included in the pooled analysis. The chance of being an ICSI responder was similarly 54 % higher in the chondroitin sulphate group compared to a vehicle group. The small decrease in total ICSI score and urinary frequency between the two groups was less impressive and not statistically significant. Chondroitin sulphate and hyaluronic acid share level of evidence 2b and grade of recommendation B in the EAU guidelines.

Lidocaine

Local anaesthesia Sporadic early reports on the use of intravesical lidocaine in BPS/IC indicate a potential role of such a regimen. Alkalisation of lidocaine before instillation is a means to improve pharmacokinetics, and in a placebo-controlled, multicentre study, actively treated patients had a significant, sustained symptom relief for up to 1 month. This modality has a high rating in the AUA as well as EAU guidelines (level 1b, grade of recommendation A). An important limitation is the need to use repeated urethral catheterisation, difficult to tolerate for many patients with BPS/IC. Other ways of administration is underway.

Vanilloids

Vanilloids disrupt sensory neurons, a conceptually attractive approach to control symptoms in BPS/IC. Capsaicin and resiniferatoxin (RTX) have been on trial, but a significant adverse event was pain on instillation, and although some preliminary reports were promising, this mode of treatment has not gained wide acceptance and is not recommended in the EAU guidelines. There might be room for vanilloids with improved drug formulas and modified treatment protocols.

Electrical Stimulation/Neuromodulation

Transcutaneous electrical nerve stimulation (TENS) The first trial of electrical stimulation in IC was presented in 1980: Fourteen women were treated either with long-term intravaginal or suprapubic transcutaneous nerve stimulation. Clinical and urodynamic evaluations were done after 6 months to 2 years. Improvement was not immediate but required a considerable period of continuous, daily use of electrical stimulation. The results were favourable although TENS was found to be more tolerable for long-term treatment in the target population. Since the methods were found to be effective and simple, cheap and non-destructive, electrical stimulation was recommended for all patients with chronic interstitial cystitis, and the favourable result of TENS was corroborated in a larger, open study. The response rate was much better in patients with the classic Hunner type of disease compared to non-Hunner subjects. The rationale behind the use of surface electrical nerve stimulation is to relieve pain by stimulation of myelinated afferents, thus activating segmental inhibitory circuits. In the last few years, tibial nerve stimulation has gained a wide acceptance, mainly for the treatment of overactive bladders. Quite recently, a systematic review was performed and four RCTs and six prospective observational cohort studies were identified. There is strong evidence for the efficacy of PTNS versus a sham treatment and a similar analysis for the treatment of CPP and BPS turned out favourably, too, although studies are scant on these indications. When treatment can be administered by the patient herself, surface stimulation techniques are cheap and with very few harmful effects.

Another off-label therapy is *sacral root stimulation*, often referred to as *neuromodulation* (mostly used for frequency and urgency syndromes), either by means of the sacral nerve approach but also pudendal nerve stimulation, and both with favourable preliminary results for patients with lower urinary tract dysfunction. This therapy has been suggested to be useful in the treatment of chronic pelvic pain, too. In an analysis of current literature, 12 relevant articles were identified. Of these articles, 10 mainly addressed the efficacy in patients with BPS/IC. Of the 10 articles, seven reported treatment outcome after implantation. The duration of follow-up ranged between 5 and 87 months. The mean reduction in pain scores was reported between 40 and 72 %. Two articles included patients with miscellaneous urogenital pain syndromes. The success rates after implantation ranged from 60 to 77 % with follow-up ranging between 19 and 36 months. So, at the present stage, there is not sufficient evidence to determine the role of sacral root stimulation in the treatment of chronic pelvic pain, and larger prospective trials with long-term evaluation are required to determine the ultimate efficacy of this treatment, statements in agreement with the moderate degree of recommendation according to the EAU guidelines, level of evidence 3 and grade of recommendation B. Alternative modalities like pudendal nerve positioning of the electrode are so far less explored in BPS/IC.

Botulinum Toxin

Botulinum toxin (BTX) injections, into the detrusor or the trigone, are used extensively in frequency, urgency and urge incontinence syndromes with varying aetiology. BTX has an anti-nociceptive effect; a decrease in daytime frequency, nocturia and pain and an increase in functional bladder volume have been demonstrated in BPS/IC. The results reported in the literature are conflicting though. Experimental observations suggest that BTX significantly attenuates bladder afferent nerve firing and inhibits ATP release from the urothelium, resulting in attenuation of the bladder afferent nerves involved in micturition and bladder sensation; BTX may exert its clinical effects on urinary urgency and other bladder symptoms through this effect on afferent nerves so an influence on symptoms in BPS might be quite plausible. A recent, interesting study aimed to determine whether intratrigonal Onabotulinum toxin A (OnabotA) injection produces a different symptomatic outcome and duration of effect in subjects with Hunner lesions vs non-Hunner BPS/IC patients and in addition to compare the urinary levels of neurotrophins in response to BTX. Ten Hunner and 14 non-Hunner BPS/IC patients were included in this study. OnabotA (100 U) was injected in 10 trigonal sites, each receiving 10 U in 1 mL of saline. Outcome measures included pain visual analogue scales (0–10), a 3-day voiding chart, O'Leary-Sant Score (OSS) and quality of life (QoL) from International Prostate Symptoms Score assessed before treatment, 1 month after injection and every 3 months afterwards. Treatment duration was determined as the time when patients requested repeated injections. The Hunner-type patients had a mean age of 40 ± 12 years vs 47 ± 13 years in the non-Hunner group (ns). Other parameters were identical in the two groups although patients with the Hunner type had a longer duration of symptoms (28.8 ± 11 vs 19.2 ± 8 months, $P = .018$). Both groups responded equally, with significant improvements in pain intensity, frequency, nocturia, OSS, QoL and urinary neurotrophins. The effect lasted for 9 ± 2.8 (Hunner) and 10.5 ± 2 (non-Hunner) months. So, in this cohort, Hunner lesion patients and non-Hunner patients had similar symptoms at baseline and comparable clinical response to intratrigonal OnabotA. The authors suggested that pain may not be directly and specifically related to the Hunner lesions (Pinto et al. *Urology*. 2014;83(5):1030–4), in contrast to reports that ablation of lesions leads to symptoms into remission. At this stage, BTX has a modest degree of recommendation: level of evidence 3 and grade of recommendation B, according to the EAU guidelines.

Cortisone Submucosally

Another modality is sub-lesional injection of cortisone, occasionally being reported to be efficacious in the Hunner type of BPS/IC. One study reported on thirty patients with Hunner lesions who underwent endoscopic submucosal injection of

triamcinolone; 21 of 30 patients (70 %) were very much improved. No perioperative complications were noted, and the submucosal injections of triamcinolone were well tolerated.

Surgery

Ablation of circumscript Hunner areas of chronic bladder inflammation is the mainstay current treatment of BPS type 3C. Transurethral resection techniques have been advocated since many years. TURB yielded quite favourable results, also long term, and implies complete resection of all lesions, including the peripheral oedema zone and the underlying superficial detrusor muscle, using a minimum of coagulation. Some 10 years ago, the long-term outcome in 103 patients with classic Hunner disease and their response to complete TURB of visible lesions were retrospectively evaluated. In that series, a satisfactory symptomatic effect in 9 of 10 patients with classic BPS/IC could be seen. TUR has been suggested to result in symptom improvement by the removal of intramural nerve endings engaged by the inflammatory process. Similar results have been reported following neodymium YAG laser treatment. Because of technical simplicity, fulguration of lesions is currently the most popular technique. Surgical destruction of lesions is applicable in the genuinely inflammatory Hunner type of disease (ESSIC type 3C) only. The excellent symptomatic effect in the majority of patients makes TURB or fulguration a first-line treatment, with few comparable alternatives. Since there are no RCTs (having been considered unethical when it comes to this kind of treatment), the degree of recommendation is still not high: level of evidence 3 and grade of recommendation B, according to the EAU guidelines.

Major surgery for bladder pain syndrome is contemplated in patients with severe symptoms who have failed standard attempts at treatment and when the disease course suggests that spontaneous remission is not to be expected. There are serious limitations to major surgery though. Patients with a small bladder capacity under anaesthesia are less likely to respond to conservative attempts at therapy but have been found to be the best candidates for bladder reconstruction. In fact, patients with end-stage Hunner's disease and severe bladder contracture have the most favourable results with major surgery. At this stage of the disease process, there is little pain but intolerable urinary frequency. On this indication, subtotal cystectomy and ileocystoplasty have yielded excellent results, while the results of major surgery, irrespective of method, are little encouraging in other presentations of BPS/IC. Favourable results in the Hunner type of disease have been reported repeatedly. Experiences differ from centre to centre though. One study reported on a long-term follow-up of ileal conduit operations in 20 patients, with or without cystectomy. Nineteen patients were alive at the time of the study and 15 returned the questionnaires. The quality of life in both the cystectomy and the non-cystectomy groups was comparable with that in the general population. Seven patients in the non-cystectomy group were free of specific BPS/IC symptoms. The remaining five

patients had minimal symptoms. There was no difference between the cystectomy group and the non-cystectomy group with regard to the proportion of patients who were symptom-free.

In non-Hunner BPS patients with debilitating symptoms not responding to more conservative treatment attempts, the decision is difficult, but if one conceptualises bladder pain syndrome as composed of two main components, one of pain and the other of frequency, it becomes somewhat easier for the patient and physician to rationalise the decision. Conduit urinary diversion can be relied upon to resolve the frequency symptoms, and if the patient would consider this alone sufficient, there is reason to seriously contemplate this option although pain may persist; diversion, or cystectomy with diversion, or even more extensive surgery, cannot guarantee a pain-free result, and it is critical for the patient to seriously take this fact into account before the decision to embark to this irreversible step. There are no RCTs; the level of evidence is 3 but the grade of recommendation is A, according to the EAU guidelines. They emphasise that great experience with BPS surgery is a determining factor for the result.

Complementary

Acupuncture In a debilitating condition with severe therapy resistance and very long duration, complementary and alternative therapies are bound to be tested as an addition to the regular therapeutic armamentarium. Such methods include dietary modification, bladder training, stress reduction and sex therapy. Dietary modification involves reduction of bladder irritants, fluid regulation and a bowel regimen. These lifestyle modifications are frequently used although therapeutic benefit has not been scientifically proved. In daily practice, however, multimodal, nonconventional management may add efficacy to the treatment of BPS/IC. Many patients report on beneficial effects of acupuncture. At this stage, limited scientific reports on traditional, electrical or laser posterior tibial nerve acupuncture stimulation have been negative; however, acupuncture is not recommended by the EAU guidelines.

Hyperbaric oxygen has been tested in small trials, with repeated sessions of inhalation of 100 % and found helpful in a small subgroup of BPS/IC patients. This treatment is limited by high costs, time-consuming care and restricted availability. One randomised study proposed the combination of hyperbaric oxygen and DMSO to prolong a symptomatic response.

The Multidisciplinary Approach

A systematic approach to the treatment of chronic pelvic pain, like the one taken in the EAU guidelines work should include all relevant aspects of the disease process. In some instances, referral to a multidisciplinary pain centre is the appropriate early

step in conjunction with ongoing treatment of BPS. The reason is that in chronic pain, it is believed that changes occur within the CNS throughout the whole neuraxis and that central changes may develop and explain some of the psychological changes that subsequently modifies pain mechanisms. Core muscles may become hyperalgesic with multiple trigger points or fibromyalgia. Other organs may also become sensitised like the bowel with irritable bowel symptoms. There have been many ideas to explain such associations, like neuronal sensitisation in spinal segments of common projection, or that the disease progresses from an organ-centred condition to a regional and finally a systemic pain syndrome. A maladaptive coping strategy such as a catastrophising personality is associated with greater pain, increased symptoms and poorer quality of life. Thus, many aspects and other components than bladder pain itself must be identified and deserve close attention. Involvement of various experts may be needed: pain specialists and the pain nurse, physiotherapists, psychologists and sometimes psychiatrists. When standard, organ-centred trials of treatment fail, early involvement of the multidisciplinary team is vital. If consultation is delayed, hypothetically there is a risk that CNS patterns of pain processing will be permanently changed, resulting in a chronic pain condition very difficult to treat.

Tips and Tricks/Dos and Don'ts

It has to be accepted that the systematic and complete assessment of a patient with CPP/BPS is demanding. Remember that a correct initial judgment may be decisive for the long-term outcome.

First step: Exclude confusable diseases (Table 4.1).

Second step: Never miss a Hunner lesion disease! To reveal all lesions, distension during anaesthesia is recommended. If present, local ablation of all lesions is the therapy of choice.

Third step: If organ-specific affections that could explain symptoms (like Hunner disease) can be excluded, a thorough and comprehensive whole body assessment is required (Quaghebeur, Wyndaele. *Scand J Urol*. 2015;49(2):81–9).

Fourth step: Use a systematic treatment algorithm, starting with less harmful therapies.

Fifth step: If no treatable localised condition is identified, an as early as possible referral to the multidisciplinary team should be made, to avoid that CNS pattern of pain processing will be permanently changed, resulting in a difficult to treat chronic pain condition.

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Chapter 5
Female Stress Urinary Incontinence

John Heesakkers, Frank Van der Aa, and Tufan Tarcan

Stress Urinary Incontinence In Women

John Heesakkers, Frank Van der Aa and Tufan Tarcan

Background

Stress urinary incontinence (SUI) is defined as the loss of urine in response to sudden increase in intra-abdominal pressure ('stress') in the absence of a detrusor contraction. It occurs primarily in women who have had vaginal deliveries. The prevalence of incontinence is about 13 %, and half of the women have complaints of SUI. The lifelong risk of women to undergo surgery for SUI or pelvic organ prolapse is about 10 %.

Stress urinary incontinence (SUI) is defined as the loss of urine in response to sudden increase in intra-abdominal pressure ('stress') in the absence of a detrusor contraction. It occurs primarily in women after vaginal delivery.

The diagnosis is based on patient history and physical examination. The severity can be assessed with pad testing. Urodynamic investigation has been the cornerstone for many years, but the importance is questioned lately. Well performed RCT's demonstrated that in clear cut cases the value of urodynamic investigation is lim-

J. Heesakkers, MD, PhD (✉)
Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands
e-mail: john.heesakkers@radboudumc.nl

F. Van der Aa, MD, PhD
Department of Urology, University Hospitals, Leuven, Leuven, Belgium
e-mail: frank.vanderaa@uzleuven.be

T. Tarcan, MD, PhD (✉)
Department of Urology, Marmara University School of Medicine, Istanbul, Turkey
e-mail: bilgi@tufantarcan.com

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ited. Therefore in most guidelines urodynamic investigation is only recommended in selected, non- clear cut cases.

Treatment options re conservative treatment with life style interventions, physical therapy and pelvic floor muscle therapy. The classical options for surgical intervention are bulking agents, bladderneck colposuspensions and pubovaginal slings. Since the end of the 20st century retropubic and transobturator tapes were introduced. Single incision slings have been developed since the beginning of this century.

Special attention should be paid to obese and elderly patients, patients with mixed incontinence and secondary procedures. Intraoperative, early and long term postoperative complications occur and should be dealt with carefully.

Clinical Practice

Diagnosis

After having a patient with the *complaint* of SUI, the *diagnosis* of SUI should be made. This consists of patient history, physical examination and additional tests like voiding diaries, pad testing and urodynamic investigation. The assessment should be based on existing guidelines.

Patient History

Patient history should focus on the confirmation of SUI, the onset and duration and the severity of incontinence. Since SUI is defined as the loss of urine in response to sudden increase in intra-abdominal pressure, one should focus on those individual circumstances that increase the intra-abdominal pressure. For one patient, this means playing volleyball, for the other, gardening or playing golf. The onset can also confirm the type of incontinence. If the complaints started directly after delivery, it is very likely that the incontinence type is SUI. The severity is indicative of the contribution of the ISD part to the SUI. A higher severity meaning severe urine loss during intra-abdominal pressure rise or also urinary loss under relatively mild circumstances implies a higher grade of ISD. This can help choosing the right therapy.

Other lower urinary tract symptoms and accompanying comorbidities should also be asked for.

Physical Examination

In this era of evidence-based medicine, it is fashionable to only perform those diagnostic and treatment activities that have proven value and are recommended by guideline committee. There is no evidence for the necessity of clinical examination, but the agreement is that clinical examination is essential. The physical examination should include the assessment of genital prolapse and oestrogen status of the vaginal mucosa.

Pelvic organ prolapsed should be assessed with an objective measure like the POPQ system. The examination of the vagina should focus on the amount of mobility of the bladder neck and urethra during a provoked Valsalva and cough manoeuvre. If the bladder neck and urethra is fixed, e.g. after a colposuspension or after pelvic radiotherapy, the choice of surgical procedure is more difficult and the outcome is lower than with a so-called hypermobile urethra. In patients with a hypermobile urethra, which is the majority of female patients with SUI, any kind of tape will have good results and patients' expectations can easier be met. It is also important to observe the loss of urine during coughing or Valsalva to confirm patient's *complaint* of SUI. This can be done in the supine position, but if no urine loss is observed in this position, it should be done in the standing position. If urinary loss is observed in with intra-abdominal pressure increase, then the *sign* of SUI is confirmed. The combination with urodynamic SUI gives the *condition* of SUI. Contraction, symmetry and coordination of the pelvic floor muscles are assessed by digital vaginal examination.

Assessing Urethral Hypermobility

Classically the amount of movement of the urethra during coughing or Valsalva is assessed by the Q-tip test. Here, a Q-tip swab is positioned in the urethra during physical examination in the supine position. The patient is asked to squeeze or cough, and the deviating angle from the resting position is determined. If the angle is more than 30°, urethral hypermobility is present. In clinical practice, the Q-tip test is not used frequently. Mostly eyeball diagnosis is used in the same way as doing the Q-tip test but without the swab. If one observes a freely rotating descent of the urethra around the symphysis pubis, the conclusion can be drawn that urethral (hyper)mobility is present and that a tension-free application of a midurethral tape can be done successfully. If at the same time with coughing or Valsalva urine loss is observed, the *sign* SUI is established. Of course, one has to be sure that the bladder is not empty during the provocative procedure.

Voiding Diaries

It is possible to reliably quantify the amount of urinary loss by noting down events of the voiding cycle. The best way to do this is to use the so-called voiding diaries. During optimally 3 days, patients note down how much they drink every time and when. They note how much they void per void and also when. They have to mark the time they go to bed and when they wake up. What is very important is that the moment is noted when urine loss occurs and how much this is. This should be noted with scores like 1= drop, 2 = dash and 3 = complete void. The occurrence of urge and/or urgency can also be noted. With these data, it is possible for the experienced caregiver to distinguish SUI from OAB wet. Drops of urine loss during the day and not at night and without urgency occurring at the same moment most likely SUI. If the number of voids is normal, meaning less than eight times per day, and the functional capacity is normal, this strengthens the likelihood of SUI.

Diaries can also be used to monitor treatment response and are widely used in clinical trials as a semi-objective measure of treatment outcome.

Pad Testing

Quantification of the amount of urine loss allows objectivation of the incontinence. From the available options like the Stamey grading, the standardised 1-h pad test and the 24-h pad test, the last one is the most reliable. The standardised 1-h pad test has limited validity and a high false-negative rate. Moreover, it often does not reflect the situation in which the patient experiences urine loss. The 24-h pad test is sensitive and has a low false-negative rate. It is not needed to extend the testing period, and it is representative for patient's daily situation. The only requirement is to have a scale that can measure grams.

Urodynamic Investigation

Urodynamic investigation (UDI) is one of the cornerstones for diagnosing SUI. The urodynamic principles have been described by the International Continence Society in 'The Good Urodynamic Practice Guidelines'. This means that SUI can be demonstrated and other abnormalities like detrusor overactivity and incomplete bladder emptying diagnosed. UDI is therefore used to demonstrate SUI and to predict postoperative problems like OAB or post-void residual. For a long time, urodynamics have been used to distinguish intrinsic sphincter deficiency (ISD) from urethral hypermobility. This can be done by urethral pressure measurement (UPP) or by abdominal leak point pressures. The indicators for ISD with UPP are a low maximal urethral closing pressure (MUCP). The cut-off value is put at 20 cmH_2O. If the MUCP is below 20 cmH_2O, ISD exists, above 20 cmH_2O, this is not clear. Urethral hypermobility is diagnosed with pressure transmission ratios (PTR). If the PTR is lower than approximately 80 %, urethral hypermobility can be present.

Abdominal leak point pressure (ALPP) determines the lowest intravesical pressure at which urine loss occurs as observed by the urodynamicist or by the flowmeter. If the ALPP is low (<40 cmH_2O), this indicates ISD. If it is high (>80 cmH_2O), no ISD should be present. UPP and ALPP have been used to make therapy choices in older times. If urethral hypermobility and no ISD was present, a colposuspension was the choice. If a lot of ISD was present, a pubovaginal sling was the treatment of choice. As well UPP and ALPP do not correlate well with clinical practice, and their role in diagnosing ISD or choosing the type of surgery is limited.

Since the introduction of the polypropylene midurethral slings, things have changed. The assessment of urethral hypermobility by physical examination is the most important diagnostic tool to choose therapy or to predict the outcome of tape surgery. If substantial urethral hypermobility is present, any tape (retropubic tape,

transobturator tape or single incision slings) has a good outcome with respect to the cure of SUI. If urethral hypermobility is not or hardly present, it is more difficult to cure SUI with a tape. Since the retropubic tapes give more support to the urethra and are easier to comply in a compressive manner, they give better results and they are the tapes of choice. This is especially so in redo surgery where the movement of the urethra is mostly limited.

Recently, the role of urodynamics has been questioned and this debate is still ongoing. It appears that in women with primary SUI complaints, with urethral hypermobility and without complicating factors, a urodynamic examination might not be mandatory. Certainly urodynamics are not needed when only conservative therapy is being considered. When surgery is being planned, use urodynamics if the findings might change the choice of invasive options. There is only limited evidence that performing urodynamics can predict the outcome of the treatment. Urethral pressure measurements such as MUCP and ALPP have not been shown to be able to grade the severity of the incontinence nor to be able to predict the outcome of treatment.

Conservative Treatment of SUI

Although SUI can be worsened by underlying diseases such as diabetes, COPD, neurological disorders, cardiac failure, etc., there is little evidence that correcting these underlying conditions will improve the incontinence significantly.

Medication reviews should be taken in all patients with urinary incontinence since medication. Alpha-blockers, drugs acting on the CNS, might have an impact on the urinary continence. Diuretics do not seem to have a significant impact on incontinence, while systemic oestrogens will increase the risk of developing incontinence or can worsen pre-existing incontinence.

Lifestyle Interventions

Despite the fact that there is an association between constipation and urinary incontinence, there is limited evidence that treatment of constipation will improve SUI.

In the elderly, however, multimodal behavioural therapy including the treatment of constipation showed to improve the urinary continence.

Often lifestyle interventions are promoted to improve continence: weight reduction, smoking cessation, increased level of physical activity and avoiding caffeine-containing drinks, etc.

Many patients will restrict their fluid intake in an attempt to reduce the amount of urine loss. Patients should be advised that the 24-h diuresis should be between 1500 and 3000 cc and that reduction of fluid intake has not been shown to improve the incontinence significantly. A micturition diary is an indispensable tool in the

diagnosis and the management of fluid intake problems, and patients should be taught to manage their fluid intake and diuresis using this tool.

Caffeinated drinks and fizzy drinks are often blamed for aggravating incontinence, but there seems to be little evidence that reduction of caffeine-containing drinks will reduce urinary incontinence. However, reducing caffeine might improve symptoms of urgency and frequency.

Obesity certainly is a risk factor for UI. The prevalence SUI increases proportionately with rising body mass index. A significant proportion of patients who undergo surgery for incontinence are overweight or obese.

Weight reduction of 5 % or more will improve UI. Even bariatric surgery in obese women can significantly improve or cure incontinence. Therefore, obese patients should always be stimulated to lose weight first, before undergoing surgical treatment for SUI.

Smoking by itself is a health hazard and every health professional should stimulate smokers to quit. In relation to continence, the role of smoking is less clear. The cessation of smoking has no clear effect on UI except maybe for those with severe incontinence.

Behavioural Therapy and Bladder Training

While behavioural therapy prompted voiding and bladder training might have a role in the treatment of urgency/frequency and urgency incontinence, their role in the treatment of SUI is limited. Only in the elderly – mostly institutionalised and frail – these forms of continence management can be useful.

Pelvic Floor Muscle Therapies

The pelvic floor musculature weakens with increasing age. At the same time, the proprioception of the pelvic floor deteriorates. This process is negatively influenced by vaginal deliveries, pelvic trauma and menopause. The weakened muscles can however be retrained to a certain level. This will improve the position and support of the urethra and will increase the closure pressure.

Patients are taught to identify their pelvic muscles, usually by vaginal examination by a specialised physiotherapist or trained nurse. Once they learn which muscles to contract, the strength of these muscles is enhanced by several types of muscle exercises. There is a large variability in techniques, methods of delivery, etc. of these exercises. In some cases, just some paper instructions are given to women; in others, women are following individual or group sessions with trained professionals. Typically all these exercises have to be repeated several times a day for several weeks.

The exercise regimes can be enhanced by the use of electrical stimulation, biofeedback, etc.

The effect of PFMT in women with SUI does not seem to decrease with increased age: in trials with older women with SUI, it appeared that both primary and secondary outcome measures were comparable to those in trials focused on younger women.

The literature about pelvic floor muscle therapy (PFMT) is difficult to interpret because of poor design of the trails, the use of different techniques that are often not well described and the use of a variety of outcome measures.

However, systematic reviews and meta-analysis were able to show that PFMT is effective for curing and improving UI.

A Cochrane review comparing different approaches to delivery of PFMT concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions. Nor was there a significant difference between techniques.

Long-term adherence to PFMT is low and 50 % will end up having surgery anyway.

Women with SUI or mixed incontinence should be offered supervised intensive PFMT for at least 3 months. The PFMT program should be as intensive as possible. Biofeedback can be helpful to motivate the patient. Electrical stimulation (skin, vaginal or anal) alone is not helpful and should be combined with a multimodal exercise program.

Magnetic extracorporeal stimulation has not been proven to improve or cure SUI.

Medical Treatment

For SUI only duloxetine is being considered at this moment. Several studies have shown a positive effect of duloxetine 2×40 mg/day on the leakage of urine and on the quality of life. Duloxetine however does not cure SUI, and patients must be willing to take this drug for a long period. Usually the drug is used for patients on waiting lists or for those who want to delay surgery.

Duloxetine has significant gastrointestinal and CNS side effects. There is a high incidence of nausea, vomiting, dry mouth, constipation, insomnia, somnolence, fatigue and dizziness. These lead to a high rate of treatment discontinuation: even in trial conditions, up to 40 % of the patients withdrew, while in long-term studies, up to 90 % stopped the drug.

Evidence-Based EAU Guidelines on Incontinence 2014

Surgery for SUI should as much be based on evidence as possible. This means that the results of the described techniques have been published in order to appreciate its value. This does not mean that the described operations are prefect but

that the surgeon is able to consult the patients about expected successes and risks of the procedure and that the patient can make a choice based on facts. These facts about the surgical procedures as regarded by the EAU in 2014 are listed hereunder.

Uncomplicated SUI Surgery in Women

Evidence summary	LE
Anterior colporrhaphy has lower rates of cure for UI especially in the longer term.	1a
Open colposuspension and autologous fascial sling are similarly effective for cure of SUI in women.	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de novo urgency.	1a
Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.	1a
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and postoperative UTI.	1b

Evidence summary	LE
Compared to colposuspension, the retropubic insertion of a midurethral synthetic sling gives equivalent patient-reported cure of SUI and superior clinician-reported cure of SUI at 12 months.	1a
Compared to colposuspension, the transobturator insertion of a midurethral synthetic sling gives equivalent patient-reported and clinician-reported cure of SUI at 12 months.	2
Insertion of a midurethral synthetic sling by the transobturator route gives equivalent patient-reported and clinician-reported cure rates at 12 months compared to retropubic insertion.	1a
The skin-to-vagina direction of retropubic insertion of midurethral sling is less effective than a vagina-to-skin direction.	1a
Midurethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
The retropubic route of insertion is associated with a higher intraoperative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of chronic perineal pain at 12 months than the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of postoperative voiding dysfunction.	1b

Evidence summary	LE
Single-incision midurethral slings are effective in curing SUI in women in the short term.	1b
Operation times for insertion of single-incision midurethral slings are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with standard midurethral slings.	1b

Evidence summary	LE
Single-incision slings are less effective than other midurethral slings at medium-term follow-up*.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with standard midurethral slings.	1b

Evidence summary	LE
Adjustable midurethral synthetic sling device may be effective for cure or improvement of SUI in women	3
There is no evidence that adjustable slings are superior to standard midurethral slings.	4

Evidence summary	LE
Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.	2a
Repeat injections to achieve therapeutic effect are very common.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	2a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
Periurethral route of injection may be associated with a higher risk of urinary retention compared to transurethral route.	2b

Recommendations for surgery for uncomplicated stress urinary incontinence in women	GR
Offer the midurethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.	A
Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if midurethral sling cannot be considered.	A
Warn women who are being offered a retropubic insertion synthetic sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.	A
Warn women who are being offered transobturator insertion of midurethral sling about the higher risk of pain and dyspareunia in the longer term.	A
Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	A
Do a cystoscopy as part of retropubic insertion of a midurethral sling, or if difficulty is encountered during transobturator sling insertion, or if there is a significant cystocoele.	C
Women being offered a single-incision sling device for which an evidence base exists, should be warned that short-term efficacy is inferior to standard midurethral slings and that long-term efficacy remains uncertain.	C
Only offer single-incision sling devices, for which there is no level 1 evidence base, as part of a structured research programme.	A
Only offer adjustable midurethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.	C
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.	A

Complicated SUI Surgery in Women

Evidence summary	LE
The risk of treatment failure from surgery for SUI is higher in women who have had prior surgery for incontinence or prolapse.	1b
Open colposuspension and autologous fascial sling appear to be as effective for first-time repeat surgery as for primary surgery.	1b
The midurethral sling is less effective as a second-line procedure than for primary surgery.	2

Recommendations for surgery for complicated stress urinary incontinence in women	GR
The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient.	C
Women should be warned that the outcome of second-line surgical procedures is likely to be inferior to first-line treatment, both in terms of reduced benefit and increased risk of harm.	C
Offer implantation of AUS or ACT as an option for women with complicated stress urinary incontinence if they are available and appropriate monitoring of outcome is in place.	C
Warn women receiving AUS or ACT that there is a high risk of mechanical failure or a need for explantation.	C

Surgical Treatment

Bulking Agents

The application of bulking agents has been performed for many years as the treatment for SUI and especially ISD. Various materials have been used like autologous fat, silicone particles, collagen or polyacrylamide hydrogel. The working mechanism is thought to be coaptation of the urethra. Since bulking agents are mostly applied in cases of ISD, they should enforce the urethra in order to compensate for the intrinsic sphincteric defect. The concept is not to keep the urethra in the proper position during intra-abdominal pressure increase like tapes, but to reinforce the sphincter itself by injecting material somewhere in the sphincteric complex.

Indications

Bulking agents are applied in cases where no urethral mobility is present, e.g. after an earlier procedure for SUI. Since bulk can be applied locally, it is also frequently applied in those patients that can't stand extensive operations. Other indications are minor to mild SUI and poor bladder emptying and those who can't stand polypropylene tapes.

Technique

It is not known what the best position and the best way to apply bulk is. Bulk can be injected transurethrally, paraurethrally, at the bladder neck and midurethrally. Injection of bulk can be done under cystoscopic vision or blindly with standardised application device. If the bulk is injected blindly, it is possible to standardise the procedure and to combine results from various surgeons. The cystoscopic procedure allows better visual control and is preferred by many experienced surgeons. Normally, the bulk is injected at three to four locations opposite each other in order to be capable to coapt the urethral lumen.

Points of Interest
There are some important factors that have to be taken into account when injecting bulk:

- When the injection is done under local anaesthesia, enough time should be allowed between applying the local anaesthesia and the injection of bulk.
- The anatomy of innervation of the anterior vaginal wall and the urethra should be known in order to inject regionally effectively and not to close to the urethra in order to avoid extra oedema because of the local anaesthesia.
- The bulk should be injected very slowly in order to inject the bulk between the tissue layers of the urethra without rupturing them.
- Backflow of the material should be avoided by not withdrawing the needle too quickly.
- After having finished the procedure, the bladder should preferably not be emptied or emptied with a small calibre catheter to avoid the bulking agent to be forced into the external layers of the urethra.

Bladder Neck Colposuspension

Background

Bladder neck colposuspension was first described by Burch in 1961. After having firstly described the attachment of the paravaginal fascia to the arcus tendineus, he later improved his technique by attaching the paravaginal fascia to Cooper's ligament, which allowed for more firm fixation points and less chance of infection as compared to the Marshall-Marchetti-Krantz (MMK) procedure, which is another type of retropubic colposuspension. The goal of these procedures is to suspend and stabilise the urethra so that the bladder neck and proximal urethra are replaced intra-abdominally. This anatomic placement allows normal pressure transmission during periods of increased intra-abdominal pressure restoring continence. Although its durability has been proven, the open repair is less commonly performed due to the

advent of less invasive procedures. Laparoscopic surgeons have also demonstrated that the repair can be performed via a laparoscopic approach, decreasing morbidity, while still providing a satisfactory outcome.

Technique

A catheter is inserted into the bladder. The incision is either a Pfannenstiel or lower midline abdominal incision to access the Retzius space. After incision of the rectus fascia, the rectus muscles are separated in the midline. Downward pressure behind and lateral to the symphysis pubis gives access to the lateral walls of the pelvis and to the endopelvic fascia. The peritoneal reflection is swept of the bladder. After dissection of the retropubic space, the bladder neck, the anterior vaginal wall and urethra are exposed.

The bladder neck is identified with palpation of the balloon of the catheter. The pubocervical fascia may be identified by sweeping away the overlying fat. To identify the anterior vaginal wall and distinguish this from the urethra, a gloved and protected finger can be inserted intravaginally in the vagina to tent the vagina laterally.

The bladder should be displaced medially and cranially away from the site of suture placement using a small swab. Haemostasis at this point of the procedure may be necessary. It is important to identify the white-coloured pubocervical fascia. This is the place where the suspending sutures must be placed.

Two to four sutures are placed on each side of the bladder neck through the pubocervical fascia. It is important to take good bites of overlying fascia and anterior vaginal wall. If nonabsorbable sutures are used, it is important not to incorporate the vaginal mucosa. If (slow) absorbable sutures are used, this is less critical. Double bites of tissue to lessen the risk of the suture pulling through can be applied.

The most distal suture is placed just distally or at the level of the bladder neck and approximately 2 cm laterally. The sutures are placed in the pubocervical fascia and anterior vaginal wall proximal to the bladder neck about 1 cm apart. The sutures are placed into the Cooper's ligament at the same level. Care must be taken to leave a suture bridge and do not apply excessive tension. Sometimes the most distal sutures need to be placed in the periosteum and in the fibrous insertion of the rectus muscle instead of in Cooper's ligament. Elevation of the anterior vaginal wall with a gloved and protected finger in the vagina helps with tying the sutures without tension. The goal is to approximate the anterior vaginal wall to the lateral wall of the pelvis. Tension may lead to pulling through of the sutures.

Points of Interest

- Avoid entry into the peritoneal cavity.
- Identify the white-coloured pubocervical fascia to place the suspending sutures properly.
- When using nonabsorbable sutures, care must be taken not to perforate the vaginal mucosa.
- Leave a suture bridge and do not apply excessive tension in order to overcorrect the descended bladder neck.
- Cystoscopy can be performed to rule out injury to the bladder.

Pubovaginal Slings

Background

Many types of pubovaginal slings have been described more than 100 years ago. Only after numerous improvements and reintroduction by McGuire in 1978, the pubovaginal sling became more popular. Traditionally the sling has been used only when other incontinence procedures, like especially the Burch colposuspension, have failed.

Indication

The most common indications for a pubovaginal sling are intrinsic sphincter deficiency with or without urethral hypermobility and a prior failed incontinence procedure. Also certain patients with SUI due to urethral hypermobility may be better served with a sling procedure, because of the long-term success and durability of the pubovaginal sling.

Technique

It is beneficial to teach the patient clean intermittent catheterisation before surgery because incomplete emptying is common for a short while postoperatively. One dose of intravenous antibiotics can be given preoperatively. General or regional anaesthesia can both be used.

The procedure is performed in the low lithotomy position. The legs should only be moderately flexed at the hips to allow simultaneous exposure to the vagina and the lower abdomen. A Foley catheter is placed and the balloon inflated to allow palpation of the bladder neck and urethra. A vaginal speculum is placed ad good view on the anterior vaginal wall should be possible. A pfannenstiel incision is made. The rectus fascia is cleared, and a fascial area is selected that looks strong and is scar free. A fascial sling of about 10 cm length and 2 cm width is obtained by incising parallel to the fibres. This can be done lengthwise or widthwise. It is possible to make a so-called sling-on-a-string in this way. If you want to leave one end fixed to the body, you should leave the part of the sling close to the pubic bone intact and cut the other end of the sling in order to use that part to wrap it around the urethra. The sutures on the sling may be placed before or after transection. Make a choice for the type and size of suture based on personal preference. The suture should be strong and durable like 1-0 or 2-0 vicryl absorbable suture. The sutures are placed perpendicular to the direction of the fibres at 1.0 cm from the ends incorporating all of the fibres in the bites.

The vaginal part starts by placing an Allis clamp midway between the bladder neck and the urethral meatus. Hydrodisection by injecting saline over the urethra can be used to facilitate the dissection. A midline incision of 3 cm is made over the proximal urethra. The vaginal dissection is performed in the proper plane,

superficial to the white-coloured periurethral fascia. The dissection is continued to the lateral area. Afterwards the retropubic space is entered at bladder neck level, inferiorly to the ischium. The endopelvic fascia is perforated with curved Metzenbaum scissors. Blunt finger dissection should not be used in order not to cause bladder damage.

Through the abdominal incision a lateral defect is created at the level where the rectus muscle inserts onto the symphysis. With gentle dissection, easy access is obtained to the retropubic space. This can be done by finger dissection or with scissors over the posterior pubic bone. This can be helpful after prior procedures. After completion no tissue should be palpable between fingers inserted from above and from the vaginal incision. Make sure that the bladder is not between the pubic bone and the dissection plane. A similar procedure is performed on the opposite side.

After having developed the plane left and right, two clamps can be passed on both sides. Cystoscopy can be performed to look for urethral or bladder damage. The sling sutures are pulled into the abdominal incision and the sling is placed under the proximal urethra. It is critical that a good portion of the sling extend into the retropubic space to allow good fixation. Some absorbable sutures are placed through the edge of the sling and superficially through the periurethral fascia to secure its place. The sling sutures are passed through the rectus fascia. The vagina is closed. The sling sutures are pulled up and tied over the rectus. A clamp can be used to hold tension on the untied sutures until the appropriate tension is obtained. The appropriate tension is when one or two fingers can easily slide under the suture knot. In the situation where the patient does not void and permanent urinary retention is desired, increased tension can be applied. The skin is closed and a vaginal pack can be placed.

Points of Interest

- Teach patients how to perform clean intermittent catheterisation before surgery.
- Avoid extensive retropubic dissection when developing a plane for the sling.
- Take care not to incorporate the bladder or urethra into the retropubic dissection route for sling placement.
- Perform urethrocystoscopy after dissecting the retropubic plane to rule out bladder injury.
- Allow one to two fingers to be put between rectus fascia and the sling sutures to avoid a too tight sling placement.

Retropubic Tapes

Some developments have paved the way to the introduction of the revolutionary retropubic tension-free vaginal tape (TVT) in 1996. The first was that it was recognised to restore the function of the urethral closing mechanism instead of correcting

anatomy. The second was the importance of the midurethra in the continence mechanism. This was supported by the discovery of the pubourethral ligaments, the awareness that the maximum urethral closing pressure is located at the midurethral level and that in continent women the urethra closes in the middle part. Therefore, the new concept of the integral theory by Petros and Ulmsten stated that SUI was caused by a lacking midurethral closing mechanism. This could be caused by failure of the pubourethral ligaments, lacking support of the anterior vaginal wall to the midurethra or by defective functioning of the pubococcygeal muscles that support the adjacent part of the urethra. Since connective tissue is regarded very important in the integral theory, surgical treatments are aiming at restoring these connective tissue structures (ligaments).

Success rates of retropubic slings in prospective studies show 80 % and higher success rates after 12 months.

Retropubic tape is the technique with the most longstanding experience of all midurethral tape procedures. Follow-up data up to 17 years have been published, showing that the technique has a long time performance.

Technique

The TVT procedure is a tape procedure that uses a polypropylene mesh with a pore size of 75–150 micrometres that allows ingrowth of connective tissue cells and cells of the immune system. This prevents colonisation of the tape with bacteria. The tape size is 11 mm by 40 cm. It is covered with a plastic sheath that allows easy passage retropubically and protects the tape for potential contamination with bacteria.

Most surgeons will give prophylactic antibiotics at the beginning of the procedure.

The tape originally was inserted under local anaesthesia that was injected in the operating region. Nowadays most procedures are done under regional anaesthesia, but it can be performed under general anaesthesia as well. The advantage of local anaesthesia is that it is possible to test the effect of the TVT during the procedure with Valsalva manoeuvres of the patient in order to position it with the appropriate tension.

The patient is positioned in the lithotomy position with hip flexion. After inserting a catheter, an incision is made at the anterior vaginal wall of approximately 2 cm length starting 0.5–1 cm from the urethral meatus. After having made the midline incision, the space between the anterior vaginal wall and the pubocervical fascia is prepared bluntly with Metzenbaum scissors. It is very important to be in the right plane. This makes dissection easy. If the preparation of the space is too deep, the urethral sphincter complex is unnecessarily damaged; if the plane is too superficial, healing problems and subsequently erosion may occur. The paraurethral space is prepared up to the inferior rim of the pubic bone. Afterwards two suprapubic skin incisions are made. The incisions are approximately 1 cm long, starting 3 cm from the midline and 2.5–3 cm cranially of the pubic bone. Then the tape is mounted to the placement needle.

The original technique is to apply the tape tension free. This means that urethral hypermobility is blocked during intra-abdominal pressure increase. The second effect is that at the place of the tape, kinking of the urethra occurs that enhances the closing effect. However, after gaining experience with the tape, experienced surgeons make in some patients the choice to put some tension on the tape especially when there is suspicion of ISD. This can be based on urodynamic testing with ALPP or UPP. Another indication for a non-tension-free tape is SUI without urethral mobility, e.g. after a previous colposuspension. If necessary, the bladder can be filled with 300 ml of saline and Valsalva manoeuvres performed to check for residual SUI.

Points of Interest

- Empty the bladder at the start of the procedure.
- After having made the midline incision, get into the right plane between vaginal mucosa and the pubocervical fascia.
- Divert directly from the midline, and dissect parallel to the vaginal mucosa.
- Put your finger between urethra and needle in order to avoid urethral damage.
- Do cystoscopy after having passed the needle with a 30 or 70° optical.
- Adjust the tape tension free or tension it with a partially filled bladder (300 ml) and Valsalva of the patient
- Keep the tape on the proper width and positioned at the midurethral level.

Transobturator Tapes

The new era of stress incontinence surgery started with the introduction of TVT. This new classic implied the retropubic technique to give support to the midurethra and to prevent dislocation of the midurethra during intra-abdominal pressure rise. The midurethral tape is U-shaped and runs retropubically. The most frequent occurring complication is bladder perforation when the needles with the connected tapes pass the pubic bone dorsally. Since the bladder is in the vicinity, it is easily possible to perforate it. Therefore, urethrocystoscopy is recommended during the procedure. In order to avoid bladder perforation and urethrocystoscopy during the procedure, the transobturator approach was introduced by Delorme in 2001. With this technique, the tape runs from one obturator foramen along the anterior vaginal wall via the midurethra to the opposite obturator foramen in a V-shaped fashion. There are two ways of introducing the tapes.

Inside-Out Technique

The patient is placed in the lithotomy position with thighs in flexion. A catheter is inserted into the bladder. The anterior vaginal wall is incised at a length of 1–2 cm and starting 1 cm proximally to the urethral meatus. Now the dissection path is developed

towards the upper part of the ischiopubic ramus on with a 45° angle to the urethral sagittal plane. It is important to start in the good layer between the vaginal mucosa and the pubocervical fascia for developing a proper dissection plane. Once the upper part of the ischiopubic ramus is reached, the obturator membrane can be perforated with the tip of the scissors. A needle introducer, with the open side of its gutter facing the surgeon, is pushed along the developed dissection canal up to the obturator membrane. The distal end of the tube that is mounted on the spiral needle is slipped along the gutter of the introducer in order to pass through the obturator foramen. Then, the needle introducer is removed. Now the tube with the needle has passed through the obturator foramen and has appeared at the previously determined skin exit point. The tube is removed from the supporting needle, which is removed and the tube and the tape is pulled through the whole tract. The same technique is applied at the other side.

Next, the ends of the tape are cut; the tape is aligned tension free under the middle of the urethra. The plastic sheaths are removed and the tape ends are cut in the subcutaneous layer and the incisions are closed. The technique was first described by De Leval in 2003.

Outside-In Technique

This is the classic technique that was used as a first transobturator route. It implies the tape is going from outside to inside. The same plane is developed from the incision on the anterior vaginal wall under the urethral meatus. The insertion points in the thighs are determined, and the spiral-shaped needle is inserted through the skin. The correct insertion points are easily found when palpating the origin of the adductor muscles on the pubic bone. The incisions are made 1 cm under this origin and medial from the bone, which is directly at the upper inner corner of the obturator foramen.

Points of Interest

- After having made the midline incision, get into the right plane between vaginal mucosa and the pubocervical fascia.
- Divert directly from the midline, and dissect parallel to the vaginal mucosa.
- Consider doing cystoscopy after having passed the needle with a 30 or 70° optical.
- Pay special attention to the vaginal fornix at both sides for mucosal perforation.
- Keep the tape on the proper width and at the midurethral level.

Single Incision Slings

The idea behind single incision slings is to avoid the drawbacks of the transobturator route as well as the retropubic route. The theoretical advantage of the SIS is the avoidance of the retropubic space and obturator fossa and the lack of necessary

thigh or suprapubic incisions. The effect of the tape for SUI is that it fixes the midurethra. This restores the hammock effect which restores proper sphincter functioning. It also induces kinking of the urethra on the spot of the tape which increases bladder outlet resistance and restores continence. Fixation of the two ends of the tape is in the pubocervical fascia. It creates a U-shaped look in cases of the retropubic approach and a V-shaped in case of the transobturator approach. The fixation of the tape ending in the pubocervical fascia also means that parts of the tape beyond that point are redundant. This means for retropubic tapes that those ends running lateral to the bladder neck and through the rectus abdominus muscle and the rest of the abdominal wall are redundant. If those ends would not be there, bladder perforation could be avoided. In cases of transobturator tapes, nerve and vascular injury in the obturator foramen and groin pain can be avoided. This should theoretically result in an easier procedure with shorter operating times and less postoperative pain.

Technique

The technique can vary according to the specific device that is being used. One technique has been described by Kennelly et al. A 1.5–2 cm single incision in the midline over the anterior vaginal wall, followed by subsequent periurethral dissection. The sling mounted to the needle is advanced behind the ischiopubic ramus in a dissection area towards the obturator space on both sides. The needle is removed after fixation of the sling with some kind of anchoring device into the obturator internus muscle after penetration of the obturator internus fascia. At this moment, the sling is fixed on one side. The tensioning of the sling now depends on the fixation of the opposite anchoring system at the contralateral transobturator foramen. This implies that the surgeon needs to decide with how much tension the sling is fixed before release of the needle. Adjustment after insertion of the tape and release of the needle is not easy, although some other devices allow for determining the tension before definite fixation of the sling. The clinical success therefore determines the dexterity and experience of the surgeon and the robust anchoring mechanism to the obturator complex with a strong post-insertion pull-out force.

Points of Interest

- Determine beforehand the fixation strength of the tape.
- Make sure that anchoring of the tapes at both sides is robust.
- Perform urethrocystoscopy when in doubt.
  - Pay special attention to the vaginal fornix at both sides for mucosal perforation.
  - Use a tape that has proven its efficacy and safety.

Tips and Tricks/Dos and Don'ts

Obese

Obesity and overweight are often seen as risk factors for developing stress incontinence and vaginal prolapse as well as for undergoing surgery. Indeed a relationship between BMI and continence has been demonstrated in several studies, where in morbidly obese women the prevalence of incontinence ranged between 66 and 71 % compared to 4–50 % in the nonobese population.

It has been shown that lifestyle adaptations that lead to weight loss as well as bariatric surgery in the obese leads to significant improvements or even cure of incontinence.

Concerning the outcome of surgical interventions for SUI in obese women, the literature is less clear. Most studies are retrospective and of poor quality. Some studies claim to have similar results in normal and obese women, while others showed less favourable objective cure rates in obese women. In one prospective long-term study on TVT, obesity was an independent risk factor for recurrence with a hazard ratio of 17!

Practically, surgeons planning incontinence surgery in the obese should counsel the patient thoroughly about the anaesthesiological and surgical risks related to obesity. Although there is no clear evidence or guidance on this subject, an appropriate approach should be chosen since a retropubic approach might be too risky in obese women. A transobturator approach might be more feasible. Surgeons should be aware that some kits only provide standard needles that might be too short in some women.

Good postoperative care with early mobilisation is mandatory.

Mixed Incontinence

Careful history taking is of utmost importance in the preoperative workout of urinary incontinence. In 20–36 % of cases, a concomitant history of urgency with or without urgency incontinence will be present. When this is the case, it is important to determine the predominant complaint of the patient. A micturition diary is an essential part of this workout. Whenever in doubt, a urodynamic study should be performed. All these investigations aim to determine the chief complaint of the patient.

In all cases, conservative treatment remains the first-line treatment. In patient with mixed incontinence, pelvic floor exercises with bladder training can significantly improve both symptoms.

When predominant SUI is present, surgical treatment of stress incontinence should be offered. It is hard to predict in individual cases how the pre-existing urgency will evolve after the treatment of SUI. As a rule of thumb, it will be improved to even absent in 1/3th of patients, unchanged in 1/3th and worsened in 1/3th. As some patients will develop preventive frequency (to avoid SUI when the bladder gets filled), this symptom will improve after sling surgery.

When predominant urgency incontinence is present, one should not directly offer surgery for SUI. It is likely that the patient will not be satisfied after the surgery. At first, classical approaches to treat urgency and urgency incontinence should be offered, such as antimuscarinics/botulinum toxin or sacral neuromodulation. Only when the urgency complaints are substantially improved, one should offer sling surgery to patients with persistent SUI. Again, it is hard to predict in individual cases how the pre-existing urgency will evolve after the treatment of SUI. Similar is stated above; as a rule of thumb, it will improve to even disappear in 1/3th of patients, remain unchanged in 1/3th and worsen in 1/3th.

Second Operation

As described before, most incontinence procedures have very high success rates. Nevertheless, due to the very high numbers of incontinence procedure performed all over the world, the relative low failure rates do constitute a large number of patients that will have persistent or recurrent SUI. In the literature, there is conflicting evidence whether repeat surgery for SUI results in inferior outcomes as compared to primary surgery.

Recurrent incontinence is in general defined by the presence of urinary incontinence that is preceded by a period of total continence of at least 6 weeks after the first surgery. Persistent incontinence is usually defined by urinary incontinence that has never disappeared after the treatment.

When a patient has persistent or recurrent urinary incontinence, a new thorough workout has to be performed. We refer to the diagnostics section of this manuscript for details regarding preoperative workout. In the setting of recurrent or persisting incontinence, it is of utmost importance to clearly distinguish between (de novo) urgency urinary incontinence and persistent or recurrent SUI. Of course, mixed incontinence is also possible. Whenever mixed incontinence is present, the predominant complaint will be treated first as in the setting of primary mixed urinary incontinence (see previous section).

In the setting of urgency urinary incontinence after previous surgery for SUI, treatment modalities are similar to the treatment modalities of urgency urinary incontinence in primary setting. One major difference is that the treating physician has to address the possibility of obstructive voiding after the first sling surgery. Evaluating obstruction after previous sling surgery is not easy. A history of straining, Valsalva voiding, micturition in several times, post-void residual urine and frank urinary retention that emerged after surgery for SUI are suggestive for obstructive voiding. Several authors have tried to define urodynamic parameters to determine the presence of obstructive voiding in females. Until now, there exists no generally accepted and validated nomogram for female voiding function. Most of the nomograms are developed using pressure flow analysis with or without free flow. Others use radiographic imaging to define obstruction. In clinical practice, it is important to realise that these proposed nomograms have their strengths and weaknesses. They are an important aid in medical diagnosis when they are

interpreted in the light of the complaints and the history of the specific patient. They are however not an exact scientific tool to objectively determine the presence or absence of voiding obstruction.

Whenever clinical and/or urodynamic findings are suggestive of obstructive voiding after anti-incontinence surgery, desobstructive surgery has to be considered. In the case of previous sling surgery, this surgery can vary between simple sling transection over partial sling excision to complete excision of the sling. In the case of previous colposuspension, a complete urethrolysis will have to be performed. This procedure has a high success rate with absence of obstructive voiding in more than 80 %. The absence however of obstructive voiding is not always a synonym for satisfied patients. A proportion of these patients will still suffer overactive bladder complaints or SUI mandating further treatment.

In the case of persistent or recurrent SUI, the usefulness of repeat surgery has to be estimated. Again, there exists no accurate, scientific or objective tool to guide our decisions. A good clinical examination followed by urodynamic study is the mainstay of these patients' work out. During clinical examination, one of the key elements is to evaluate urethral mobility. In the presence of urethral mobility, repeat sling surgery has proven its efficacy in several nonrandomised studies.

In all these studies, repeat sling surgery was technically easy, associated with low blood loss and with short surgery times and hospital stays. Complication rates were higher as compared to primary surgery, but acceptable. Most complications were mild and easy to treat.

On urodynamics, the presence or absence of 'intrinsic sphincter deficiency' (ISD) can be judged. In literature, a Valsalva leak point pressure of 60 cmH_2O or less and a mean urethral closing pressure of 20 cmH_2O or less are considered to determine ISD. The prevalence of ISD in literature varies between 10 and 100 % of reported series. It is clear that the real prevalence is not known and that this wide variety reflects a selection bias.

In the presence of ISD or a fixed urethra, subsequent surgery for SUI will obviously be much more difficult. Sling surgery will, by definition, consist of a non-physiological obstructive sling with high postoperative rates of voiding dysfunction. There is some evidence in literature that cure rates for retropubic slings are higher than cure rates for transobturator slings. Some case series where adjustable sling systems were used also show high cure rates. Most of these studies are small case series with variable definitions of cure and satisfaction. One has to be cautious to interpret these results. When the use of synthetic sling material is undesirable, also pubovaginal slings have shown high success rates. As in the synthetic slings, these slings will be obstructive in nature and the patient has to be warned for the possibility of postoperative retention and subsequent need for intermittent catheterization.

In selected cases, also the use of in artificial urinary sphincter (AMS 800) should be considered. The use of the device in females is less known and less widespread as compared to its use in males. Nevertheless, some large series have been published with good results. A high revision rate is an inevitable consequence of the use of the device. The surgery is more invasive as compared to the different sling solutions. Previous anti-incontinence surgery and higher age are independent predictors of failure. This surgery should only be performed in tertiary centres.

In summary, a second operation can offer a solution for recurrent or persistent incontinence in selected cases. The indication for a second operation should always be made with great caution and most energy should be put in the preoperative diagnosis of the problem. With the right diagnosis, a second operation will improve patients' quality of life and satisfaction.

Elderly

There are limited specific data on SUI treatment in the elderly.

Concerning conservative therapy, it has been shown that elderly patients benefit as well as younger women.

There are no direct comparative trials on surgical treatment in older versus younger women, but subgroup data have been published.

Elderly women benefit from surgical treatment of SUI, and age by itself is not a contraindication for surgery. It has been shown that cure rates decrease with age. Elderly women are also prone to have persisting incontinence and have a higher risk for de novo urgency. There are no data showing that one or another type of surgery or sling would have better results in elderly patients.

Complications of Female Stress Incontinence Surgery

Introduction and General Recommendations

This section will focus on the prevention and management of the complications related to tension-free midurethral synthetic slings (MUSS) based on the classification of the *5th International Consultation on Incontinence* (Table 5.1). It is noteworthy that most of the recommendations in this section are derived from level four studies or 'majority evidence' from level 2/3 studies or Delphi processed expert opinion with the recommendation grade of C according to Oxford system.

The basic principles of the management of MUSS complications are summarised as follows:

Table 5.1 Classification of complications of MUSS surgery [6]

Intraoperative complications	Immediate postoperative complications	Chronic problems
Vessel injury Bladder injury Urethral injury Visceral injury	Infection Urinary retention and emptying difficulty Groin pain	De novo urgency Sling erosion/extrusion

1. Thorough preoperative clinical evaluation, correct indication of surgery, informing the patient about all possible complications regarding surgery, utilising proper surgical technique and material are basic needs to minimise the complications.
2. Increased surgical experience is associated with decreased complication rate; however, complications do occur even in very experienced hands. A high index of suspicion is needed for every surgeon to diagnose the complication timely and treat it properly.
3. Type 1 synthetic mesh with larger pore size should be chosen since it facilitates vascular and tissue ingrowth and optimises mesh incorporation compared to other types of synthetic meshes.
4. Any postoperative complaint dictates a thorough physical examination, urinary analysis, assessment of the urinary tract and its function since no symptom is specific for any particular pathology.
5. Regular follow-up after surgery with physical examination and basic clinical assessment is necessary since MUSS-related complications may occur even years after.
6. There are no reliable urodynamic criteria to diagnose postoperative obstruction and to predict the outcome of urethral release surgery in women with de novo voiding dysfunction. The temporal relationship between symptoms and the surgical procedure is the primary criterion in selecting patients for urethrolysis or tape release.

Dealing with Intraoperative Complications

Vessel Injury

Minor to Moderate Haemorrhage

Haemorrhage during surgery should be managed first by local compression to decrease blood loss and prevent postoperative haematoma. Local compression can be continued postoperatively by intravaginal tamponade with surgical sponges. Intraoperative blood loss more than 100 mL may occur twice as frequently in the retropubic (RP) compared to transobturator (TO) route. Due to the route of needle passage, haematoma and intraoperative haemorrhage rarely occur in TO MUSS procedures. Inserting redon drains in patients with increasing bleeding during RP MUSS may reduce the risk of retropubic haematoma that is a risk factor for infection, voiding difficulty and mesh problems.

Major Haemorrhage Due to Major Vessel Injury

Seven deaths were reported in the database of the US FDA from 1998 to 2005 due to major vessel injury during trocar passage in RP procedures, whereas major vascular injury has not been reported in TO procedures. During surgery, haemodynamic instability, growing hematoma or excessive bleeding at the operative site may

indicate major vessel injury that necessitates urgent primary vascular repair to prevent mortality. Prompt intervention can save the life of the patient as it was reported in a case of external iliac artery injury during an RP MUSS. The low risk for large vessel injury reported in TO procedures – given the anatomy of TO trocar passage – does not mean that it is impossible, considering the few centimetres distance of the trocar from obturator vessels.

Injury to the Bladder and Urethra

Injury to the lower urinary tract may occur at the level of the urethra and bladder during dissection or more commonly during trocar passage. RP procedures are more commonly associated with this complication compared to TO route where top-to-bottom or bottom-to-top passage does not affect the bladder perforation rates. Violation of the urinary tract can be managed successfully without causing significant morbidity unless it is not recognised intraoperatively. Missing an injury to the urinary tract may cause fistula, stone formation, haematuria, infection and even progressive cellulitis in the postoperative period and will necessitate additional surgical intervention(s). If severe progressing cellulitis occurs in a patient despite broad-spectrum antibiotic coverage unrecognised bladder perforation and nonbacterial causes of infection should be ruled out.

Traditionally, cystourethroscopy with a 70° optic lens is advised to rule out any violation to the urinary tract in all RP MUSS procedures. The decision to perform cystourethroscopy in TO procedures is usually made by the surgeon according to his experience and preference where any suspicion mandates cystourethroscopy. A simple method to predict urinary tract damage may be the intraoperative irrigation of the bladder with saline through the Foley catheter after insertion of the trocars to reveal blood in the bladder or extravasation from the urinary tract. It should be also kept in mind that bladder perforation can occasionally be missed during cystourethroscopy where perforation may be determined by suprapubic incisional fluid leakage after removing the trocars.

In the presence of a urethral injury, the urethra should be repaired appropriately without placing any suburethral synthetic sling since this would lead to urethral erosion. Utilising a Martius flap and continuing the surgery with autologous fascial graft depends on the decision of the surgeon and prior consent of the patient. When there is a bladder perforation by the trocar, the trocar should be gently pulled out and then correctly reinserted without the need for any repair of the bladder. After completing MUSS placement, the bladder should be drained 2 days by a urethral catheter. Some authors even discharge patients with bladder violation the same day of MUSS surgery without catheter drainage.

Visceral Injury

Bowel injury is an extremely rare complication of MUSS surgery exclusively seen after RP procedures especially in patients with previous history of pelvic operations. It may manifest postoperatively with persistent low abdominal pain resistant

to analgesics, fever and sepsis in late cases. Immediate laparoscopy or laparotomy should be performed whenever bowel injury is suspected. Subsequent repair of bowel peroration site is indicated to solve the problem.

Dealing with Immediate Postoperative Complications

Infections

Infections after MUSS include a spectrum from uncomplicated urinary tract infections reaching necrotising fasciitis and pelvic or thigh abscess formation. The presence of positive urine culture, vaginal discharge, pelvic discomfort or unexplained fever mandates a careful clinical assessment to rule out increased post-voiding residual urine (PVR)/obstruction, mesh erosion or extrusion and pelvic infections. Infected pelvic hematoma, diabetes and morbid obesity are risk factors for necrotising infections. Infection-related complications after TO route have included thigh abscess requiring drainage and an infected obturator hematoma also requiring exploration and drainage.

Urinary Retention and Emptying Difficulty

Voiding problems after MUSS's may vary in terms of the type and the severity in a range between urinary frequency and urinary retention (Fig. 5.1). The pathophysiology of de novo voiding problems is not well understood, but it is linked to the mesh-related urethral obstruction or irritation. Other causes such as bladder perforation, pelvic haematoma, urethral erosion or vaginal extrusion of the mesh should always be considered in the differential diagnosis.

Urinary retention stands at the edge of the voiding symptom spectrum after MUSS as the most annoying one both for the patient and the surgeon (Fig. 5.1). However, its treatment is more straightforward than the other voiding problems since it is obviously caused by urethral obstruction. Urinary retention may be defined as catheter dependency for at least 28 days where there is no consensus about the cutoff level of PVR that necessitates catheterisation. It is not only the PVR volume but also the discomfort of the patient that necessitates catheterisation.

Urinary retention may be first recognised when the patient fails to empty her bladder at the first voiding trial after surgery. Women are more likely to empty their bladders effectively if they are evaluated with a backfill-assisted voiding trial compared to spontaneous natural bladder filling and emptying. Therefore, the bladder should not be overfilled for the initial voiding trials after surgery. Emptying difficulty is common in the early postoperative period but may be transient and associated with the immediate voiding conditions such as increased fluid load and bladder overdistention. Among patients who fail the initial voiding trial, about 1/3 successfully can void on subsequent trials. Therefore, multiple voiding trials are advised

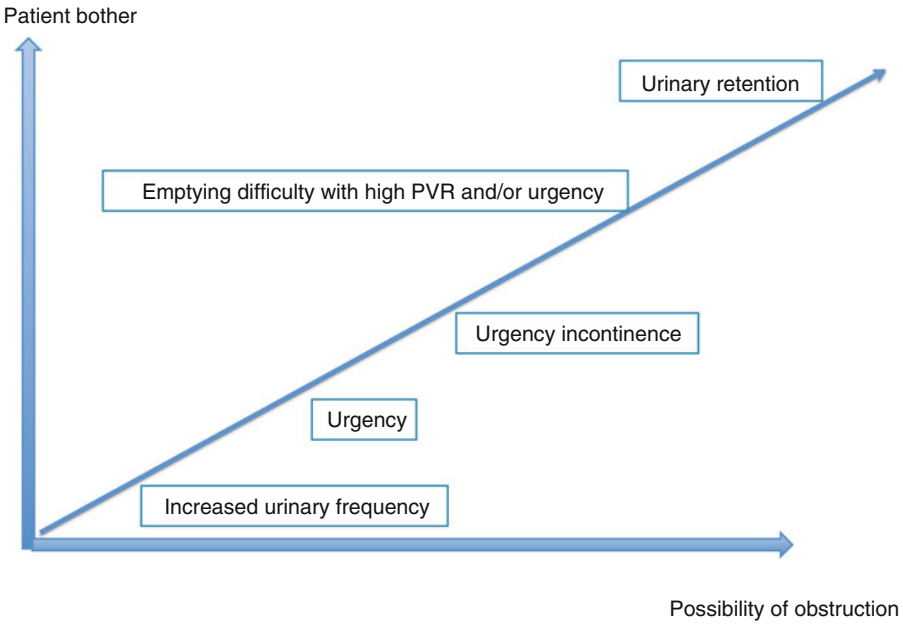

Fig. 5.1 Spectrum of de novo voiding symptoms after MUSS

before making any decision. Interestingly, 16 % of patients who pass the initial voiding trial may fail on the second necessitating at least two successful voiding trials before discharge.

The conventional approach to urinary retention includes indwelling catheterisation up to 1 week (3–7 days) and retesting the patient after catheter removal (Fig. 5.2). Some authors prefer tape release in the early postoperative period that is possible up to 10 days. Retention lasting longer than 1 week may be managed by an early tape cut or clean intermittent catheterisation up to 1 month. There is no benefit in waiting more than 4 weeks since symptoms persisting beyond that time rarely resolve spontaneously. Waiting period of at least 14 days but optimally 4 weeks prior to tape cut is usually recommended to allow suburethral fibrosis to prevent recurrent incontinence.

Groin Pain and Other Neurological Symptoms

Neurologic adverse effects such as numbness and/or weakness in the legs or pelvic area and dyspareunia are more common after TO compared to RP procedures. Transient groin pain occurs in about 2.3–15.9 % of patients after TO MUSS and generally responds to nonsteroidal anti-inflammatories. The aetiology of the pain is likely to be due to either subclinical hematoma or a transient neuropathic phenomenon. In patients who present with neurological symptoms, dyspareunia or pain, the

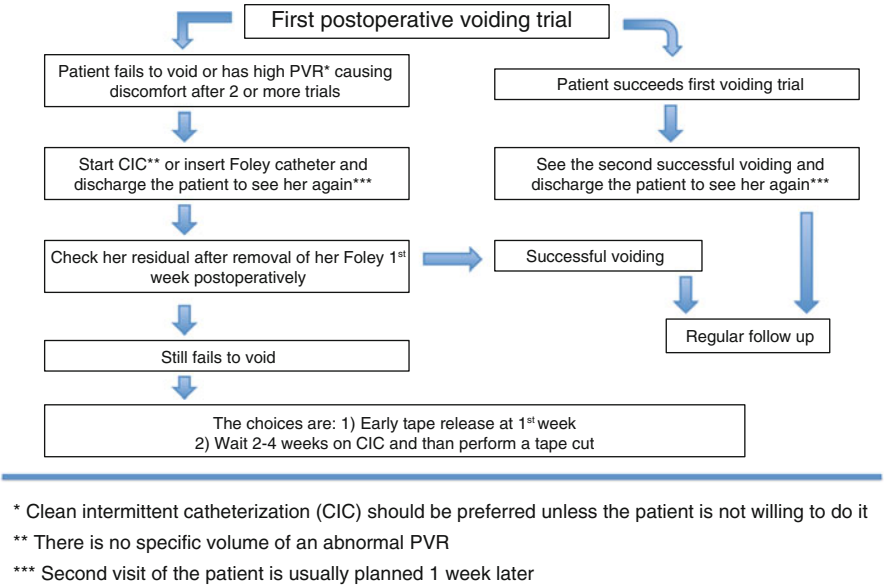

Fig. 5.2 A suggested algorithm for the management of urinary retention after MUSS

physician should try to locate the origin of the pain. Persistent leg pain should raise the suspicion of urethral erosion or vaginal extrusion.

Dealing with Chronic Problems

De Novo Urgency

Storage symptoms that were not present preoperatively but appear after surgery should be considered as mesh or surgery related. However, these symptoms may sometimes have a gradual onset and may not be temporarily related to the previous MUSS surgery. Furthermore, mild symptoms may be underdiagnosed and under-reported. Cystoscopy is mandatory in patients with haematuria, bladder pain or recurrent cystitis especially when bladder perforation or urethral mesh erosion is suspected (Fig. 5.3). Urethrocystoscopy may further reveal urethral kinking.

Urodynamic evaluation may include noninvasive tests such as PVR measurement and uroflowmetry and invasive tests such as cystometry and pressure flow studies. Diagnosis of obstruction in women lacks well-defined urodynamic criteria since women empty their bladder by relaxing the pelvic floor without a strong detrusor contraction. Furthermore, there are no predicting factors including urodynamics to show which patients would benefit from urethrolysis. Comparison of the pre- and

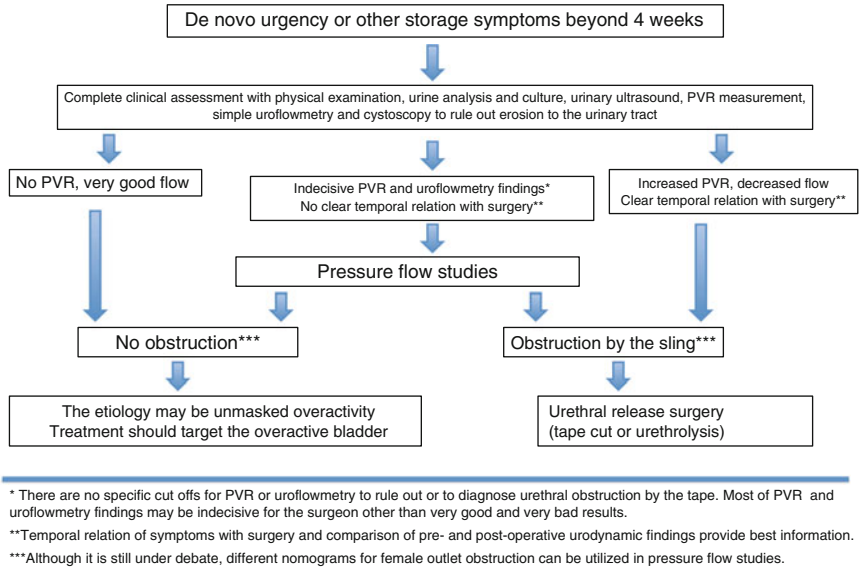

Fig. 5.3 A suggested algorithm for the management of de novo urgency after MUSS

postoperative uroflowmetric studies may help better in the diagnosis of mesh-related obstruction than a single postoperative pressure flow study (Fig. 5.3). The temporal relationship correlating symptoms with an antecedent surgical procedure should be the primary criterion in selecting patients for urethral release. Midline transvaginal tape cut without urethrolysis is the most often performed surgical treatment, and this treatment provides resolution of symptoms with maintenance of continence in the majority of patients. A part of the sling should be excised for pathological confirmation. Antimuscarinic treatment may be utilised after urethral obstruction by the mesh is ruled out or managed.

Sling Erosion/Extrusion

Vaginal Extrusion

Wound infection, impaired wound healing, improper vaginal dissection plane and vaginal atrophy may be causative factors. Presenting symptoms may include vaginal discharge, palpable rough surface in the vagina, sexual discomfort (usually partner related) and lower urinary tract symptoms including haematuria. The management options are not standardised and include local oestrogens, partial and complete tape excision and reapproximation of the vaginal mucosa over the exposed tape. Initial observation of small vaginal erosions with topical oestrogen creams is recommended. Excision should be reserved for conservative treatment failures or

for larger defects. Partial mesh excision with reapproximation of the vaginal mucosa will not cause incontinence in the majority of patients.

Urethral Erosion

Surgeon-related factors play the most important role in the aetiology of urethral erosion such as entering wrong plane during dissection beneath the urethra, compromising thickness of suburethral tissue or even causing an unrecognised urethral perforation and finally applying excess sling tension on the urethra. Urethral erosion may present itself with storage or emptying lower urinary tract symptoms or urinary tract infection or haematuria. Observing the tape within the urethral lumen during cystoscopy makes the diagnosis. Conservative observational treatment is not an option, and endoscopic tape transection or transvaginal excision of the tape with closure of the urethrotomy is needed. A Martius fat pad graft may be used in case of extensive urethrotomies. A sling preferentially autologous can be placed at the time of surgery or in a delayed stage to treat possible SUI.

Intravesical Erosion

This complication almost exclusively occurs secondary to an unrecognised bladder perforation during trocar placement. Therefore, intravesical tape erosion rate is lower for TO procedures compared to RP route. Patients may present with storage symptoms, haematuria, recurrent urinary tract infections and pelvic pain. Observational treatment is not an option. The sling material inside the bladder must be removed either endoscopically or by open surgery. Only patients with complete tape removal develop recurrent stress incontinence. Reduced pore size is associated with higher erosion rates and type 1 synthetic slings with larger pore size are favourable since they facilitate vascular and tissue ingrowth optimising mesh incorporation.

Tips and Tricks

1. Perform a thorough history and good clinical examination including evaluation of urethral mobility.
2. Women with SUI or mixed incontinence should be offered supervised intensive PFMT for at least 3 months.
3. Different surgical procedures have different target groups; use tapes when urethral (hyper)mobility is present, and consider other techniques or obstructive tapes in the absence of urethral mobility.
4. Use new devices only in trial setting or when they have proven long-term efficacy and safety.
5. Complications of anti-incontinence surgery are best treated in centres of expertise to pool experience.

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Chapter 6
Male Stress Incontinence

Frank van der Aa, Jean-Nicolas Cornu, Fawzy Farag, and Julian Shah

Background

All health professionals are familiar with the problem of stress urinary incontinence in females. Female anatomy predisposes to incontinence of urine due to sphincter weakness and in particular in association with childbirth. Health professionals however are less likely to be aware of the problem of stress incontinence in males, which does not usually occur as a primary condition. Since a male is not subjected to childbirth, the pelvic floor does not become weak unless it is affected by specific medical conditions. Thus stress urinary incontinence is much less common in males and less likely to present. Men have a tendency to draw less attention to the problem of urinary incontinence. Although a cause of much distress, incontinence in males tends to often remain a hidden condition. Incontinence is a common condition worldwide and leads to much suffering and in addition significant cost to society.

F. van der Aa, MD, PhD
University Hospitals Leuven, Leuven, Belgium
e-mail: frank.vanderaa@uzleuven.be

J.-N. Cornu, MD, PhD, FEBU
Tenon Hospital, Hôpitaux Universitaires Paris-EST, Assistance publique Hôpitaux de Paris, Université Pierre et Marie Curie Paris 6, Paris, France
e-mail: jeannicolas.cornu@gmail.com

F. Farag, MD, PhD (✉)
Department of Urology, Sohag University Hospital, Sohag, Egypt

Radboud University Medical Center, Nijmegen, The Netherlands

J. Shah, FRCS
Institute of Urology and University College London Hospitals, London, UK
e-mail: j.shah@ucl.ac.uk

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Incontinence is a distressing condition, and thus an understanding of the causes of male incontinence, its investigation and treatment is essential to those involved in treating male patients. Resolving incontinence brings major benefits in improvement of quality of life.

Male stress incontinence has to be distinguished from other types of urinary incontinence, and the condition alone may be associated with other conditions affecting bladder storage and emptying, which need to be excluded or treated if they coexist.

Male Continence Anatomy

Male continence depends upon an intact and functioning neural system. The bladder needs to be able to store urine to a normal volume (circa 500 ml) and with low filling pressure (less than 15cmH20). With these provisos, the male continence mechanisms are an intact and functioning bladder neck mechanism (bladder neck, internal sphincter) and an intact external striated sphincter mechanism (rhabdosphincter). Any changes in any of these structures either from disease or surgery can affect continence. Surgery has had a major effect on the continence mechanisms in men and has lead to an increase in the incidence of male stress incontinence.

Causes of Male Urinary Incontinence

Transurethral prostatectomy and the alternatives are associated with a relatively low incidence of post-operative incontinence. The incidence has reduced significantly over the years and is probably due to advancing technology allowing excellent views of the surgery by camera techniques and more effective supervision of training.

Male stress urinary incontinence has become more common in recent years because of the increase in the use of surgical treatment for prostate cancer by radical prostatectomy. Whether a radical prostatectomy is performed by the open surgical route or by laparoscopic or robotic means, incontinence will occur in a proportion of men due to sphincter weakness. It is not surprising that men become incontinent of urine after a radical prostatectomy. The bladder neck mechanism is lost and the sphincter may be weakened by resection of part of that sphincter. There is also a loss of support to the urethra by division of the puboprostatic ligaments and incision into the endopelvic fascia. Fortunately most men are continent after a radical prostatectomy or regain continence over a period of months. However, there will be men who will have persistent stress incontinence, which will require treatment.

There are few primary conditions that can give rise to male stress incontinence. The principal one being lower motor neurone spina bifida patients, who will have a poor or acontractile bladders and sphincter weakness incontinence. Sphincter weakness incontinence can occur in patients after a spinal cord injury. A lower motor neuron lesion will be associated with pelvic floor denervation. Patients tend to have poorly contractile or acontractile bladders and thus tend to strain to void if not using intermittent catheterisation. They may also have sphincter weakness incontinence or develop stress incontinence with time due to additional pelvic floor weakness.

One potential cause of stress incontinence but hopefully rarely seen follows a pelvic fracture injury where a urethral rupture has led to a stricture treated by a urethroplasty. The sphincter may be weakened by such surgery, and in later life, should bladder neck or prostatic surgery take place, there is a significant risk of incontinence occurring.

Clinical Practice

Clinical Assessment

Symptoms of stress incontinence are those associated with any event that increases intra-abdominal pressure beyond the resistance within the bladder outlet/sphincter mechanism. Thus coughing, sneezing, laughing and movement will give rise to incontinence of urine. In a catastrophically wet patient, continuous incontinence may be present. This can and does occur after a radical prostatectomy or TURP.

Male patients with stress urinary incontinence tend to be continent at night provided the bladder pressure is stable. However, once movement occurs to the upright position, incontinence may develop. Classically, in this group of men, stress incontinence occurs when moving from the sitting to the standing position. Certain activities also make a man wetter, such as playing golf or tennis.

During history taking, it is important to gain information about the patient's bladder function. This is an assessment of urinary frequency, nocturia, urgency and urge incontinence symptoms, which are likely to be due to an overactive bladder or poorly compliant bladder.

Voiding symptoms should be discussed – hesitancy, the state of the stream, terminal and post-micturition dribbling. Straining usually represents a stricture or poor bladder contractility as does a feeling of incomplete emptying.

The degree of urinary leakage with stress incontinence should be assessed. The number of pads used and how wet they tend to be should be assessed. A pad weighing exercise should take place in all men with stress incontinence as it will indicate the degree of incontinence, may affect the choice of surgery and can be used for an assessment of post-treatment success. Some patients will be wearing a conveen sheath, which allows a more accurate knowledge of urinary loss.

Diagnostics

The first part of investigation of course is to take a careful history, then perform a clinical examination. What is most useful is to see what sort of pad the patient is wearing and whether it is wet and if leakage occurs with coughing or sneezing. The genitalia should be assessed and look for excoriation from urine wetness. A rectal examination can be helpful in patients with generalised pelvic floor weakness caused by neurological dysfunction, but it is not usually necessary in patients who have had a radical or transurethral prostatectomy.

A frequency volume voided chart is important in assessing fluid intake as reducing fluid intake may reduce incontinence episodes. Volumes voided will give an indication as to whether the bladder is able to store urine, and this particularly can help at night if a patient can hold urine during the night as it is useful for the later management of that patient.

Voiding function should be known and this can be simply assessed with a free flow rate based upon a volume voided more than 150mls and a post-micturition residual assessment. It is essential to know that the bladder is emptying satisfactorily particularly if any surgical intervention is to be considered.

Urodynamic Investigations

Should we use urodynamic investigations in the incontinent male patient? The assessment of bladder function in a patient with stress incontinence by urodynamic studies can be controversial. However, urodynamic studies are very useful in understanding storage and emptying bladder function. If combined with x-ray screening (video urodynamic studies), much useful information can be gained. Filling cystometry will demonstrate whether or not the bladder has overactivity, and this can be useful in providing the start of treatment of a patient with mixed symptoms. Voiding function is assessed by a pressure flow study, and if obstruction is present, this will need to be dealt with before treating stress incontinence. The benefit of video screening of the bladder and outlet during urodynamic testing gives a view of the bladder shape, presence of the competence or incontinence of the bladder neck and whether or not stress leakage is taking place. The site of obstruction during voiding cystometry will be screened. The presence of reflux and assessment of bladder emptying is also seen with video urodynamic studies. It is the author's view that videourodynamic studies have an essential place in the management of the patient with urinary stress incontinence.

Decision to Treat

Any male patient suffering with stress urinary incontinence will be distressed by the symptoms. Most patients are not particularly accepting of urinary leakage. Often there is a concern about urine smell. There is the ongoing problem of wearing pads.

These are expensive to purchase and not always available on prescription. The penis may become sore due to persistent urinary leakage. Most patients are therefore very keen to become dry.

Containing the Incontinence

Containing the urinary loss may be acceptable to some patients. A single pad for a minimally wet patient may be sufficient to contain the leak and be acceptable.

For the patient with a greater degree of incontinence, a conveen sheath applied to the penis and a leg drainage bag may be comfortable. For elderly patients, this may be a suitable choice. This may also be suitable for the patient with neurological dysfunction such as a spinal cord injury. The old-fashioned penile clamp is often overlooked and can be beneficial to some patients who would like to be out and about without wearing a pad. Wearing a penile clamp for a short period of time whilst out and about may be acceptable as a short-to-medium-term solution. It is not a solution to the problem but can be a helpful method of containment.

Conservative Options

Conservative options for post-prostatectomy incontinence can be palliative (focused on comfort of the patient, with no aim at curing incontinence itself) or active. The former includes penile clamps, penile sheaths and protections, and the latter includes pelvic floor muscle training and duloxetine.

Palliative Options

Penile clamps have been used for years for post-prostatectomy incontinence management. A clinical trial has compared three types of clamps (Cunnigham device, U-shaped clamp and C3 clamp), in a randomised, open-label study. The devices evaluated have shown high efficacy but variable tolerance among patients. The use of penile clamp is not recommended by currently available clinical guidelines.

Methods for containment of urine have been extensively reviewed in the literature. In men with post-prostatectomy incontinence, condom catheters are seen as a valuable solution. About protections, there are no reliable data to state whether a type of protection is better than another. Different pads have their advantages and disadvantages; they are chosen depending on the patients' preferences, degree of incontinence and activity.

Lifestyle habits have not proven to substantially modify symptoms. However, abnormal fluid intake or bad habits have to be modified, according to good medical practice.

Therapeutic Options

Behavioural therapy such as pelvic floor muscle training has been evaluated in the field of post-prostatectomy incontinence. It is recommended by the current EAU Guidelines and the ICS document for management of post-prostatectomy incontinence with a level of evidence grade 2. Many different types of pelvic floor muscle training programmes have been described, according to the types of exercises, training and degree of supervision, timing (preoperative, immediate post-operative or delayed), use of biofeedback and associated stimulations. According to a review by the Cochrane collaboration, there is no influence of physiotherapy on the continence rates after one year. However, pelvic floor muscle training can be recommended to fasten continence recovery in a post-operative setting. Early rehabilitation seems the best choice for patients who want to get continence back within a minimal time frame. Supervised training is probably better than alone exercises, but biofeedback has no clear impact on the results. It is thus not routinely recommended when pelvic floor muscle training is prescribed.

Duloxetine has been proposed as a medical treatment of post-prostatectomy incontinence. The rationale for the introduction of this treatment is based on the results obtained in women for stress urinary incontinence management. This drug is a serotonin-noradrenalin reuptake inhibitor, acting on the Onuf's nucleus by blocking the reuptake of noradrenalin and serotonin, thus raising the activity of pudendal motor neurons, leading to increase of striated urethral sphincter tonus and detrusor relaxation. Duloxetine has proven its efficacy in cases series and in one randomised controlled trial at the dose of 80 mg. The drug has been shown to be superior to placebo at an 80 mg/day regimen. However, the use of duloxetine for male post-prostatectomy management is not recommended by current clinical guidelines, because of the paucity of the studies published. It is sometimes used off-label. Moreover, this treatment can lead to numerous side effects, like fatigue, sweat, insomnia, loss of libido, constipation, nausea, diarrhoea, dry mouth, anorexia or psychiatric issues.

Surgical Treatment

Bulking Agents

In some men with mild to moderate SUI, urethral bulking agents are a less effective treatment, with early failure rate of a 50 % and gradual loss of effect with time (LoE: 3; GoR: C). Bulking agents have been used over many years to treat post-prostatectomy incontinence. Collagen was the first material used for treating stress incontinence but had very poor outcomes. There have been a number of other injectable agents used for treating stress incontinence in men. The popular current ones available are Macroplastique and Coaptite. The success rate however with these treatments is relatively poor with only approximately 34 % of men benefiting in the

long term. The only benefit of injectable treatment is that it is a minimally invasive treatment without any incisional surgery, and if this technique works, it can be beneficial and satisfying for the patient. It is important however to warn the patient that the results may not last for long and the incontinence condition can be worsened in a small percentage.

Male Slings

What Do the Guidelines Say?

According to recommendations and available guidelines, the standard surgical management for male stress urinary incontinence is the implantation of an artificial urinary sphincter. Current clinical guidelines mention the use of male slings as an alternative to the implantation of an artificial urinary sphincter, especially in men with mild to moderate symptoms. Overall, all guidelines are in accordance that the level of evidence supporting the use of male slings is rather low, mainly based on cohort studies (generating grade C – level of evidence three recommendations). The current clinical guidelines distinguish the fixed compressive male slings (like InVance™), transobturator repositioning male slings (like AdVance™) and adjustable male slings, like Argus™.

InVance™ is considered as a historical device in some countries where it has been removed from the market. Based on available data, this sling has been shown to lead to heterogeneous cure rates, with a high risk of post-operative infection, erosion and removal of the device. At least 20 different case series have been published about InVance™ according to reviews of the literature, up to midterm follow-up. Infection has been reported being as high as 15 % of cases, and other complications included recurrence of incontinence, acute urinary retention and perineal pain.

Transobturator repositioning AdVance™ male sling has been introduced in 2007, and there has been multiple prospective studies showing the efficacy of this device. After AdVance™ implantation, 50 % of patients are being dry, 25 % are improved and 25 % fail. However, the complication rate has been proven to be very low, with a very limited rate of erosion and infection. The usual complications are rather transient urinary retention (around 10 %) and perineal pain (less than 10 %).

The Argus™ male sling is considered by the current guidelines as an ‘adjustable’ male sling. The guidelines point out the paucity of the data supporting the use of Argus™ system, with published data on a few hundreds of patients and limited follow-up. Based on the available data from the literature, there is grade 3 evidence that Argus™ system can cure SUI (subjective cure rate of around 57 %, but very heterogeneous according to available studies), but the rate of complications (especially sling explantation) is considered as high. External comparison of available cohort studies seems to show that there is no additional benefit with the Argus male sling compared to other types of slings. Recently, a small direct comparative trial between Argus™ and AdVance™ sling has shown no significant difference in efficacy outcomes between after midterm follow-up.

Overall, male slings are reasonable options for management of mild to moderate stress urinary incontinence and are a possible alternative to urinary sphincter implantation. Almost all evidence is level 3, and there is no clear data showing the superiority of a sling over another.

Clinical Practice and Results

Male sling implantation is considered in clinical practice as an alternative to the artificial urinary sphincter in men, particularly for post-prostatectomy incontinence management. Before considering this option, a specialised evaluation is required and includes:

- Complete medical history: date and type of prostatic surgery, alternatives causes of urinary incontinence such as neurological diseases, additional treatments (pelvic radiation therapy), cancer status (PSA level).
- Evaluation of the symptoms: a 24 h pad test is welcome preoperatively to check the severity of incontinence (estimation of pad use is also widely used). An objective evaluation by validated questionnaires is useful.
- Endoscopy of the urinary tract: this is often required to check the integrity of the urethra and the vesico-urethral anastomosis. It also permits to rule out a urethral disease (such as stenosis). Some authors have also proposed that endoscopy of the urinary tract make a 'repositioning test' possible, in order to check for residual sphincter function.
- Urodynamic study: this is often required to rule out bladder dysfunction and detrusor abnormalities and identify the intrinsic sphincter deficiency. For some authors, the interest of urodynamics has to be discussed, but a uroflowmetry and post-void residual estimation seem required.
- Urine culture is also mandatory before surgery, as well as the preparation for anaesthesia.

This rigorous and comprehensive preoperative workup sets the basis for a rigorous evaluation, based on patient characteristics. Indeed, some predictive factors influencing outcomes after male sling implantation have been proposed in the literature (mostly reliable for AdVance™ sling). The factors associated with a higher success rate are absence of pelvic floor irradiation, mild to moderate symptoms (leakage of less than 300 g/24 h), absence of history of urethral stricture and good residual sphincter function (checked by the repositioning test). It is however important to state that these factors are not fully consensual and are mostly based on single centre experience.

The AdVance™ male sling has been studied in multiple prospective cohort studies. Mean success rate (no pad use) at medium-term follow-up (around 3 years) is about 60 %. Usually, an additional proportion of patients is improved, and 20–25 % failed. Major complications are exceptional; minor complications occur in 5–15 % of cases and include transient urinary retention, haematoma, perineal pain, urinary tract infection, neurapraxia and superficial wound infection. In the vast majority of cases, these minor complications resolved spontaneously (Table 6.1).

The Argus™ male sling has been evaluated through a limited number of cohort studies. Efficacy has been stated variable in the literature, between 17 and 79 % of patient being cured. The rate of complications has been shown to be quite high with a lot of cases of explantation. Other complications included transient retention, bladder or urethral injury, OAB, haematomas, perineal pain, wound infections and urinary tract infections (Table 6.2).

The InVance™ male sling has shown to have limited efficacy for cure of post-prostatectomy incontinence (with cure rate of around 40–50 %), with a high rate of complications. Explantation rate as well as reintervention has shown to be as high as 30 % (Table 6.3).

Background

Male sling implantation is considered as a case of stress urinary incontinence following prostate surgery (mainly radical prostatectomy and, in a few cases, after surgery for benign prostatic obstruction). The underlying pathophysiology of stress urinary incontinence after radical prostatectomy is not perfectly clear, but deficiency of the external urinary sphincter (rhabdosphincter), associated with anatomical changes (reduction of the length of membranous urethral and loss of periprostatic support), and abnormalities of innervation (consecutive to injury of the neurovascular bundles) have been pointed out as the most important causes. Incontinence following benign prostatic surgery is more often linked to a direct injury of the urethral sphincter.

The concept of male sling has been developed in the 1970s by Berry, then by Kaufman and Schaefer, as a compressive device. The principle of the surgery was to provide a resistance to bladder outflow, enough to reduce the symptoms of incontinence, but not too much, to avoid urinary retention. This compressive approach has been the only one considered in the past century. The InVance™ male sling is the very last evolution of this concept.

During the last ten years, numerous innovations have been proposed to improve the concept of male slings. The two major inputs were the noncompressive, repositioning concept of the retrourethral transobturator male sling (AdVance™) and the introduction of adjustable device, where the compression is adjustable with time (Argus™).

Several slings can be used. Variations include sling material (synthetic (e.g. polypropylene) or autologous biological material), shape of the sling (length, width), way of anchoring (slings mainly act by self-anchoring in pelvic tissue or are anchored to the bone) and routes in the body for slings placement (retropubic or transobturator). Many brands and types of slings exist, and you urologist will choose the best one according to your case, his habits and sling availability on the market. The principle of male sling implantation is to produce some degree resistance (especially for purely compressive slings), by urethral compression, to the urine output, in order to reduce urinary leakage during efforts but preserving an open urethra to avoid complete obstruction. Some device of different types exist (retrourethral, adjustable, bone anchored) and have never been compared to each other in terms of efficacy.

Table 6.1 Data from the literature related to efficacy and complication following the implantation of AdVance™ male sling

Authors	*N*	F-up (months)	Definition of success	Success	Improved	Failed	Major complications	Minor complications
Gozzi (2008)	67	3	No pad	52 %	38 %	10 %	None	Transient AUR (16.4 %)
Davies (2010)	13	6	0 or 1 pad	85 %	–	15 %	None	Transient AUR (15 %)
								De novo OAB (7 %)
Gill (2010)	33	8.2 ± 17.9	No pad	51 %	20 %	29 %	None	Transient AUR (9 %)
								Rash (3 %)
Cornel (2009)	33	12	No pad and pad test <2 g	9 %	46 %	37 %	1 infection	Transient AUR (3 %)
Rehder (2010)	118	12	No pad	74 %	17 %	9 %	None	Transient perineal pain (19.5 %), transient AUR (5 %)
								Groin pain (2 %)
Cornu (2011)	136	21 ± 6 (12–36)	No pad	62 %	16 %	22 %	None	Transient voiding difficulties (14 %)
								Haematoma (1 %)
								Transient perineal pain (12 %)
Bauer (2011)	126	27 (20–37)	No pad or security pad	52 %	24 %	25 %	2 explantations	Transient AUR (15 %)
								Transient perineal pain (1 %)
Rehder Eur Urol (2012)*	156	39 (37–4)	No pad or security pad	53 %	23 %	23 %	1 explantation	Transient perineal pain (50 %)
								Transient AUR (9.6 %)
								Dysuria (4.5 %)
								Haematoma (3.2 %)
								UTI (<1 %)
								OAB (<1 %)
								Superficial wound infection (<1 %)
Suskind (2012)	36	19 (1–40)	No pad	38 %	42 %	20 %	NA	NA

Mueller ISRN Urol (2012)	32	9 (3–14)	No pad	56 %	22 %	22 %	1 explantation	Transient AUR (15.6 %)
Li J Urol (2012)	56	24 (17–28)	No pad	39 %	23 %	38 %	None	Rash (3 %)
								Transient AUR (11 %)
Berger (2012)	26	12	No pad	62 %	27 %	11 %	None	Transient AUR (35 %)
								Transient perineal pain (19 %)
Kowalik (2015)	30	39 (36–44)	No pad or security pad	60 %	13 %	27 %	None	Transient AUR (30 %)
								Wound infection (3 %)
								Neurapraxia (3 %)
								Chronic pain (6 %)
Collado Serra (2013)	61	26 (12–53)	No pad use	80 %	0	20 %	None	Transient AUR (15 %)
								Haematoma (4 %)
								Neurapraxia (10 %)
								OAB (10 %)

Table 6.2 Data from the literature related to efficacy and complication following the implantation of Argus™ male sling

Reference	*N*	Median follow-up (months)	Definition of success	Cured	Improved	Failed	Revisions	Major complications	Minor complications
Bochove-Overgaauw	100	27 [14–57]	No pad use or security pad	38 %	30 %	32 %	32 %	Urethral stenosis (12 %) Explantation (11 %)	Transient retention (16 %) Bladder injury (6 %) Transient pain (11 %) OAB (1 %) Haematoma (1 %) Wound infection (6 %) UTIs 2 %
Romano	48	45 [36–54]	No pad use	66 %	13 %	21 %	>11 %	Explantations (19 %)	Perineal pain (4 %) Transient retention (15 %) Urethral perforation (6 %) Transient dysuria (21 %)
Hubner	101	28	20-min pad test of 0–1 g	79 %	ND	ND	39 %	Explantation (16 %)	Transient perineal pain (15 %)
Dalpiaz	29	35 [29–45]	Satisfaction	17 %	11 %	72 %	10 %	Explantation (35 %) Persistent perineal pain (27 %) Erosion (3 %)	Transient retention (35 %) Perineal pain (28 %) OAB (14 %)

Table 6.3 Data from the literature related to efficacy and complication following the implantation of InVance™ male sling

Author	Year	*N* patients	Follow-up	Cured (%)	Improved (%)	Failed (%)	Reintervention (*N*)	Infection/Erosion (*N*)	Explantation (*N*)
Fassi-Fehri	2007	50	6 (1–22)	50	26	24	1	3	3
Madjar	2001	16	12.2 (4–20)	85	15	0	0	0	0
Comiter	2002	21	12 (5–21)	76	14	10	0	0	0
Ullrich	2004	22	25 (6–42)	60	32	8	0	0	0
Comiter	2005	48	48 (24–60)	65	20	15	2	1	1
Gallagher	2007	31	15 (9–21)	38	37	25	0	2	4
Fischer	2007	62	15 (3–37)	34	24	42	9	5	5
Mouracade	2008	29	4.1 (1–8.5)	37	42	20	0	3	5
Guimarães	2009	62	28 (ND)	65	23	12	1	2	2
Giberti	2009	40	35.2 (2–62)	55	12.5	32.5	1	6	5
Athanasopoulos	2010	43	24.2 (4–38)	30	40	30	14	5	5
Carmel	2010	45	36 (2–64)	36	40	24	0	1	1
Claudon	2011	69	13.7 (8–45.6)	61	34.8	4.2	0	6	6
Crites	2011	41	46 (1.5–112)	31.7	NA	68.3	NA	NA	NA
Castle	2005	42	18 (6–26)	16	24	60	NA	3	NA

Technique

All three devices have specific characteristics that make the surgical steps different for each device. However, for all cases, the preparation of the patient is quite similar, as well as the patient positioning in the operating room. Before the intervention, a urine culture has to be negative or treated by antibiotics if positive. Antiseptic wash of the perineum is done in the operating room, whilst shaving is preferably done before. Anaesthesia can be general or regional, depending on the choice of the patient and the anaesthesiologist. A urinary catheter is put in place at the beginning of the intervention. The main surgical approach is perineal for the three slings.

AdVance™ Male Sling

The AdVance™ male sling has been introduced in 2007 as an innovative therapy. The sling is manufactured by the company American Medical Systems (Minnetonka, Minnesota, USA). The sling is made of precut polypropylene monofilament. In 2010, a new version of the sling, called AdVanceXP™, has been introduced with minor modification of the length/shape of the sling and the ancillary. The results with this new version seem to be comparable to those obtained with the first generation.

Principles

The concept of the retrourethral transobturator male sling has been described in 2007 by Rehder and Gozzi. The sling is put behind the urethra, in contact with the urethral bulb and goes out via transobturator route (Fig. 6.1). It is then fixed to the posterior urethra and when the sling is pulled for tensioning, the urethra is attracted posteriorly and towards the bladder neck (Fig. 6.2). Urodynamic and MRI investigations have postulated that this action results in relocating the proximal urethra and increases functional urethral length. As specified here under, this underlines the need for a significant dissection of the proximal urethra during the surgical approach.

Surgical Technique

The patient is placed on dorsal lithotomy position. The surgical approach is perineal, median, and should be of 5–6 cm. The first layer (subcutaneous) is dissected with electrocautery, and the bulbospongiosus muscle is opened medially, to expose the urethral bulb. The dissection should be continued enough, posteriorly, until the urethra begins to turn towards the pelvis, so that the corpus spongiosum is free from the central tendon of the perineum. The bulb is thus well exposed; pulling the lowest part of the wound with a retractor is a good means to check that this step is adequately completed. After having made two small incisions at the proximal part of the groin, left ancillary is passed towards the transobturator fossa through the skin and the obturator membrane. A rotation of the hand is necessary to make the end of the needle

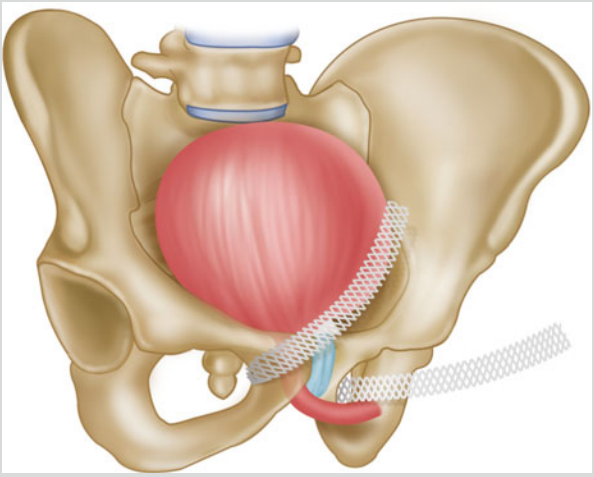


Fig. 6.1 Anatomic position of the retrourethral AdVance male sling (transobturator route)

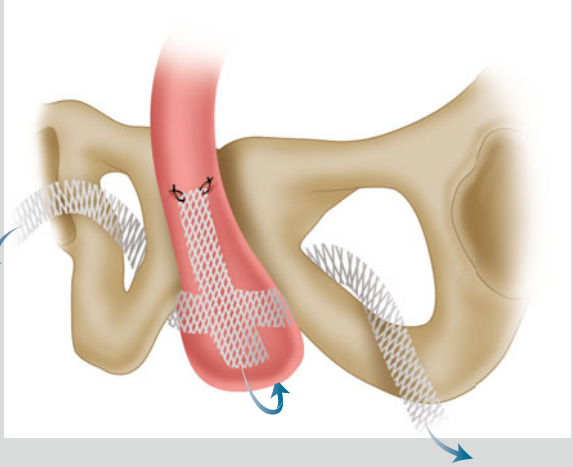


Fig. 6.2 Infero-lateral view of the AdVance male sling; the two arms of the sling are pulled through obturator foramen, and the sling is fixed to the bulbar urethra, leading to relocation of the bladder neck

come out just between the urethra and the origin of the corpus cavernosum (putting a finger laterally in the wound to guide the needle is of great help). The mesh is then attached to the needle by the connector and the sling is pulled out gently. The procedure is repeated on the other side. The central part of the sling is then fixed to the urethra by resorbable sutures. The tension of the sling is then made progressively and carefully, with the surgeon seeing the

urethral bulb going away towards the bladder neck. The wound is then simply closed by layers, including the bulbospongiosus muscle, using resorbable sutures.

Some authors complete the procedure by tunnelling the sling under the skin on each side to prevent slippage post-operatively, but it is not mandatory. Similarly, a urethrocystoscopy immediately after sling placement is fully optional and usually not practiced outside the learning curve.

Post-operative Care

After surgery, the catheter is usually left in place for 24 h, and the patient is discharged at day 1 if bladder emptying is correct without significant post-void residual volume. Oral medications are usually prescribed for post-operative pain management. In the short term, the main secondary effect can include voiding difficulties, wound infection and perineal pain. Other complications are exceptional. Due to the importance of 'repositioning' of the urethra, specific advice is given to the patient in order to avoid intense abdominal efforts and possible sling slippage. Those include rest (incl. work interruption if needed), avoidance of lifting heavy charges and treatment of constipation if any.

Argus™ Male Sling

The Argus™ male sling has been introduced in 2006. The sling is manufactured by Promedon SA (Cordoba, Argentina).

Principles

The concept of the Argus™ sling is presented as an adjustable sling, able to cure post-prostatectomy incontinence by a compressive mechanism. The system is adjustable to permit relief of excessive obstruction of the urethra, as well as re-tensioning in case of lack of efficacy or recurrence of symptoms. Two types of the device are available on the market: Argus™ adjustable male sling system (designed for retropubic approach) and ArgusT™ adjustable male sling system (designed for the transobturator approach that is useful in obese patients)

The system is presented as a single-use kit, containing a rectangular piece of elastomer (the 'pad'), two polydimethylsiloxane elastomer fixation arms (made of multiple conal subunits), two adjustment rings (two sizes), two ring positioners and a ruler. The needles are designed for transobturator approach or retropubic approach. The central pad is compressive, placed behind the urethra. The adjustment rings are placed either on the abdominal wall or the transobturator membrane (Figs. 6.3 and 6.4). The tension has to be smooth enough to minimise the risk of ischaemia or direct injury to the ureter, but strong enough to make a passive coaptation of the urethral walls.

Adjustability is possible intraoperatively and post-operatively.

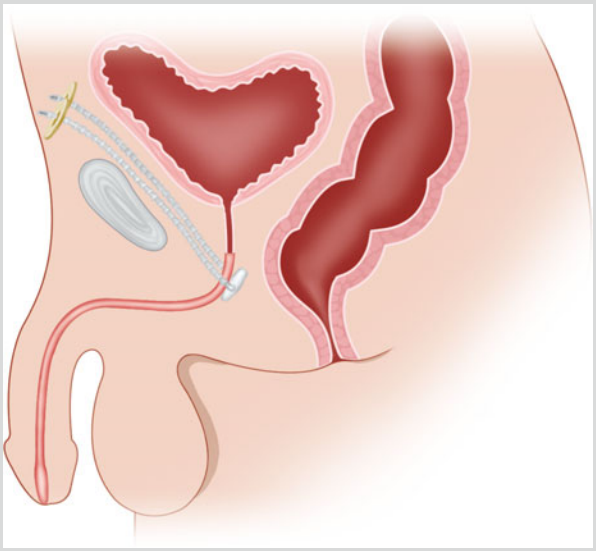


Fig. 6.3 Sagittal view of the Argus male sling system whilst in place. Compression is made posteriorly

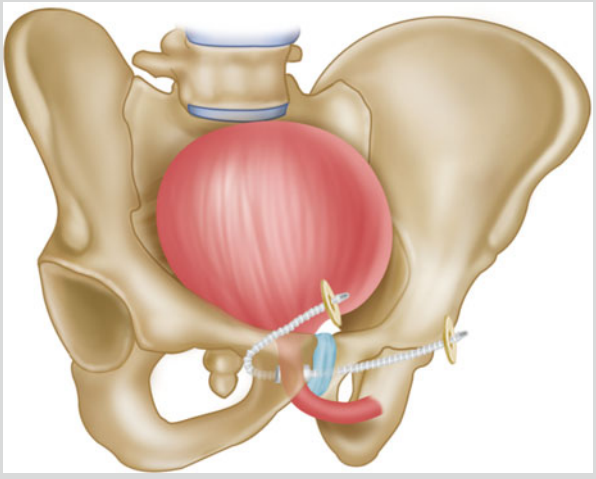


Fig. 6.4 Anterolateral view of the Argus male sling in place

Surgical Technique

The patient is placed on dorsal lithotomy position, under spinal of general anaesthesia. A catheter is usually inserted at the beginning of the procedure, after usual skin preparation. The surgical approach is perineal, median, and should be of 5–7 cm. The first layer (subcutaneous) is dissected with electrocautery, and the bulbospongiosus muscle is kept intact. The space

between the urethral bulb and the ischiopubic ramus, laterally to the root of the corpus cavernosum is dissected. The space towards the edge of the pubis is then dissected.

For retropubic approach (Fig. 6.3), two incisions are made on the abdominal wall and 2 cm over the upper edge of the pubis, until the fascia of rectus abdominis muscle. The 'retropubic' needle is then inserted in the place between the urethral bulb and the corpus cavernosum and passed just behind the posterior part of the pubis to go out by the incisions, repeated on both sides. A cystoscopy is often done at this stage to rule out a bladder perforation. Fixation arms are then connected to the needle and passed on both sides. Adjustment rings are then placed in each abdominal wound. The perineal wound is then simply closed by layers, using resorbable sutures.

In case of transobturator approach, the two lateral incisions are made in the inguinal region a few centimetres below the insertion of the adductor magnus muscle, until the external obturator muscle fascia. Helicoidal needles are inserted on both sides according to an out-in movement, towards the finger placed in the triangular space between the urethral bulb and the corpus cavernosum. The arms are then passed and the rings are placed in contact with the fascia of the external obturator muscle. Some authors recommend to place the arms in the prepubic area through a subcutaneous tunnel, upwards and parallel to the inguinal fold towards the midline, and not below the inguinal fold.

Adjustments are made by moving the rings on the cones that are all along the arms. It can be done during the intervention or afterwards, by simply reopening the lateral/suprapubic wounds under local anaesthesia.

Post-operative Care

After surgery, the catheter is usually left in place for 24 h, and the patient is discharged at day 1 if bladder emptying is correct without significant post-void residual volume (checking the correctness of bladder emptying is mandatory). Oral medications are usually prescribed for post-operative pain management. In the short term, the main secondary effects are perineal pain, retention and dysuria, local inflammation and wound infection. Other less frequent complications are infection, necrosis or erosion of the urethra, sometimes requiring removal of the sling. Patients are usually advised not to practice intense exercise during 6 weeks and abstain from sexual intercourse during 4–6 weeks.

InVance™ Male Sling

The InVance™ male sling has been introduced in the early 2000s. The sling is manufactured by the company American Medical Systems (Minnetonka, Minnesota, USA). Its clinical use has progressively decreased after the introduction of the AdVance™ male sling concept, and there are some countries/institutions where the bone-anchored male sling is not more marketed.

Principles

The InVance™ male sling system is a compressive device for the urethra, using a mesh sling anchored with small bone screws fixed on the pubic ramus. The system is presented as a single-use kit, containing a single-use inserter, battery powered, driving the screws at low speed in the bone. Titanium bone screws are delivered with pre-attached polypropylene sutures to fix the device accurately. The sling is a silicone-coated polyester mesh. Compression is achieved by providing a local support to the urethra that is kept anterior to the mesh (Fig. 6.5).

Surgical Technique

Three screws are placed on each side of the descending ramus to act as six fixation points for the InVance sling. Each of the screws has sutures attached. The sutures are passed through the sling pores and tied tightly. The patient is placed on dorsal lithotomy position, under spinal or general anaesthesia. A catheter is usually inserted at the beginning of the procedure, after usual skin preparation. The surgical approach is perineal, median, and should be of 3–4 cm. The first layer (subcutaneous) is dissected with electrocautery, and the bulbospongiosus muscle is kept intact. Dissection is continued laterally to expose the pubic bone (pubic rami). The screws (with their sutures) are positioned on each side, on the pubic ramus, the first one being placed close to the pubic symphysis. Screws are separated from each other by a one-centimetre interval. The mesh is the placed and sutured to the screws after having tested the good tension (either by cough test if patient is awake or by evaluating the retrograde leak point pressure). The perineal wound is then simply closed by layers, using resorbable sutures.

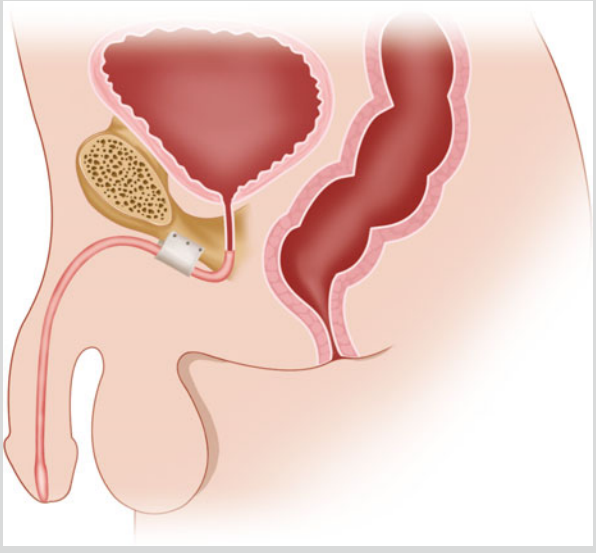


Fig. 6.5 Sagittal view of the InVance, bone-anchored male sling

Post-operative Care

After surgery, the catheter is usually left in place for 24 h, and the patient is discharged at day 1 if bladder emptying is correct without significant post-void residual volume (checking the correctness of bladder emptying is mandatory). Oral medications are usually prescribed for post-operative pain management. In the short term, the main complications are perineal pain, retention and dysuria, local inflammation and wound infection. Other less frequent complications are infection, necrosis or erosion of the urethra and osteitis, sometimes requiring removal of the sling. Patients are usually advised not to practice intense exercise during 6 weeks.

Points of Interest

- Male sling are a reasonable option for mild to moderate post-prostatectomy incontinence. However, there are no valuable comparative study available, including compared to artificial urinary sphincter. This field is moving with studies underway.
- AdVance male sling is regarded as the most widely used sling with the most important clinical experience, but numerous new slings are ready to be marketed.
- Preoperative evaluation before a male sling is also being reconsidered nowadays with new prognostic factors evolving. MRI data are of great interest and may have a future role for patient selection.

AMS 800

Brief History

The artificial urinary sphincter (AUS) has been used in clinical practice since 1972. In the first one and a half decades, several technical improvements of the device have been made, such as the introduction of kink resistant tubing. In 1987 the device reached its current design with the development of quick snap connectors and the narrow back cuff. Over the last 27 years, no major technical changes have been made on the AMS 800. In recent years, the addition of antibiotic coating on pump and cuff and also the introduction of 3.5 cm cuff were the most important novelties.

It is estimated that to date more than 150,000 patients worldwide have been implanted with an artificial urinary sphincter type AMS 800.

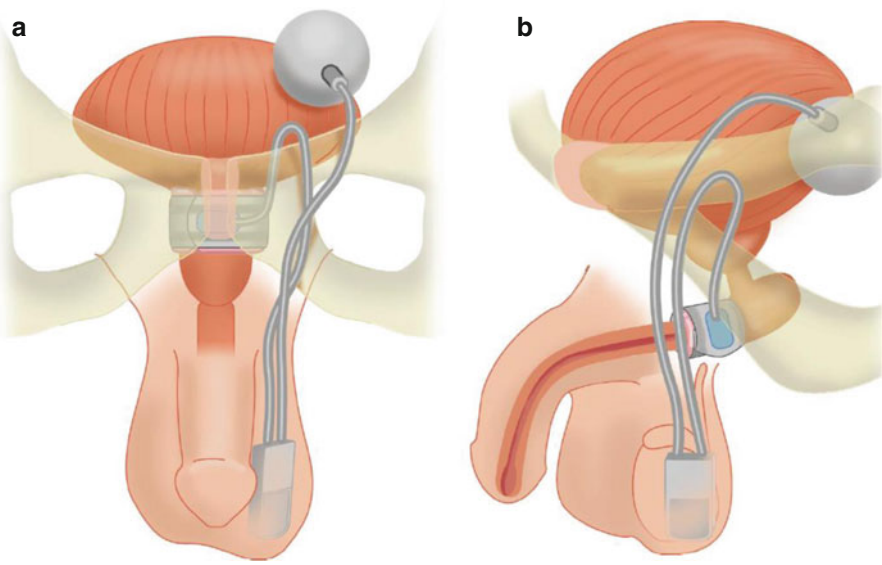
As such the AMS 800 is by far the most implanted device to treat urinary incontinence. Also the length of clinical follow-up is unseen in other devices.

Working Mechanism

The AMS 800 is a complete hydraulic system.

After implantation of the separate parts (cuff, pressure balloon and control pump), the system is filled with an iso-osmotic fluid and connected using quick snap connectors.

At rest, the cuff is inflated and closes the urethra by gentle external pressure (in accordance with the type of pressure balloon used, generally 61–70 cm H_2O). When the person needs to void, he stabilises the pump with one hand at a level of the tubing and pushes 1–3 times at the distal part of the pump. One can feel the fluid movement in the system during this manoeuvre. Fluid is now transferred from the cuff to the balloon by means of a one-way valve inside the pump. After this manoeuvre, the cuff is opened and the patient is able to void. The fluid inside the system will automatically return to the cuff in the following seconds to minutes because of the pressure balloon. The patient doesn't need to close the device Klijn (1999).



The Ideal Candidate

The AMS 800 is mainly implanted in patients with post-prostatectomy incontinence.

The device should only be offered to and implanted in persons with adequate dexterity and mental capacity to use the device. The need for future endoscopy should be limited to a minimum, because of the risk of urethral damage and subsequent cuff erosion. Therefore untreated urethral strictures or bladder neck contractures are relative contraindications. They should be diagnosed and treated prior to implant. Untreated detrusor overactivity will also have a negative impact on the efficacy of the device. Ideally it should also be diagnosed and treated prior to implant. Low bladder compliance of the bladder is a contraindication. In order to diagnose detrusor overactivity and low compliance, urodynamic study is a crucial step in the preoperative workout.

It is to be expected that several patient factors will influence the efficacy of the artificial urinary sphincter. Prior irradiation, current smoking, diabetes mellitus, prior treatment of urethral strictures or bladder neck contractures and all other conditions that influence tissue oxygenation, vascularisation, fibrosis and wound healing can theoretically increase erosion and urethral atrophy rates. These factors are at most relative contraindications, since many large cohort series have proven the safety and efficacy of AMS 800 implants in patients with these characteristics. As in every candidate for an artificial urinary sphincter, these patients should be adequately counselled about the high revision rates but acceptable success rates after implantation of an AMS 800 device.

Work-Out Prior to Implant

A detailed history is mandatory to confirm the presence of invalidating stress urinary incontinence. This is preferentially completed by a micturition diary with recording of the amount of urine loss (e.g. pad weight). A clinical examination to look for chronic skin conditions, scars and other abnormalities should also be performed.

A cystoscopy prior to implant of an AUS is mandatory to confirm the absence of bladder neck contracture or urethral strictures and to evaluate a normal bladder aspect. Coincident treatment of strictures with an implant has been described in literature but increases the risk of complications. Also future treatment of these problems with an AMS 800 in situ increases the risk of complications and should be avoided as much as possible.

Urodynamic study is usually performed to determine the cystometric bladder capacity and to confirm the absence of detrusor overactivity and compliance loss. The latter two might mandate other therapy before embarking on AMS 800 implant. A low cystometric bladder capacity can predict frequency and urgency complaints after implant. As such, urodynamic study is a good tool to counsel your patient and to set the right expectations.

In the days before the implantation, a urine culture can be checked to exclude the presence of bacteriuria. If present, directed antibiotic prophylaxis is advisable. If a patient is using an indwelling catheter or a condom catheter, these should be removed 1 week prior to implant to reduce the risk of bacteriuria.

Implant Technique

The patient is placed in lithotomy position. The perineum is shaved immediately before surgery. Prophylactic antibiotics are administered (e.g. 2 g cefazoline). The operating field is disinfected with alcoholic solution and draped. A transurethral 16 French catheter is placed. A perineal incision is made over the bulbar urethra. After incision of the subcutaneous fat, the bulbocavernosus muscle is split in the midline and the bulbar urethra is dissected laterally from the muscle and dorsally from the corpora cavernosa. The urethra is sharply dissected circumferentially until the measuring device can be tunnelled underneath. The ideal location is the proximal bulbar urethra where the corpora diverge. The catheter is removed before measuring the cuff size. In normal circumstances, a 3.5 to 5 cm cuff will be measured.

A right inguinal incision is made, and after dissection, the oblique fascia is incised. The Retzius space is entered by perforating the transversal fascia, and using blunt dissection, a small space for the balloon is made in the Retzius space. Using a clamp or Hegar dilators, a subdartos scrotal pouch is made from the inguinal incision just above the oblique fascia.

The different components of the devices (cuff size as measured, 61–70 cm H_2O balloon and control pump) are prepared and placed in the dissected areas. The cuff tubing is tunnelled to the inguinal incision. All tubes are flushed and connected with the quick connectors.

The operating fields are rinsed with aqueous solution (+/− antibiotics) during the procedure. Care is made to place the device directly from the preparation table, directly into the patients without placing it on wet drapes, patient skin or penis. The different wounds are closed in layers. It is very important to deactivate the device after implant.

The device will only be activated after several weeks, to allow for healing of local tissues. Early activation will increase erosion rates.

Learning Curve

The vast majority of patients receiving an AMS 800 implant are operated by surgeons early in their learning curve. Sandhu and colleagues showed that the learning curve for AMS 800 implant is steep. A patient operated by a surgeon that has performed <5 previous AMS 800 implants has got 24 % chance of needing reoperation vs. 18 % for a surgeon with an experience of <100 implants and 13 % for a surgeon with an experience of <200 implants. Possible explanations for this persisting learning curve are the need for adequate measuring and filling of the device and correct placement of the bulbar cuff.

Alternative Techniques

Over the years, alternative techniques have been proposed for several indications. Hereunder, we briefly report the most important alternatives.

Transverse Scrotal Incision

A transverse scrotal incision has been advocated, at first in the setting of revision surgery and later as an alternative to the classical perineal approach as described above. The so-called penoscrotal approach is proclaimed to be faster and easier as compared to the classical perineal approach. It also allows for bulbocavernosus muscle-sparing surgery. It is an ideal approach in the case of a combined implant with an inflatable penile prosthesis.

Whether the cuff position after a penoscrotal approach is comparable to the position after a perineal approach is under debate. Sceptics of the technique believe that the cuff is rather located in a distal bulbar position. It has also been reported that dry rates of this alternative approach are inferior to the classical perineal approach. Advocates of the technique claim that adequate dissection of the bulbar urethra is possible to place the cuff in a comparable position.

Transcorporal Implant

In cases where the urethra is very thin or when an increased risk of cuff erosion exists (such as patients who had a previous erosion or urethroplasty), a transcorporal technique can be chosen. Instead of dissecting the urethra from the corpora, risking urethral injury and/or a thin barrier, the tunica albuginea of the corpora is incised bilaterally 3–5 mm lateral to the urethra and through blunt dissection, both corporotomies are connected. As such a 'patch' of corpora cavernosa is left on the bulbar urethra at the dorsal side. This technique has proven its efficacy and its safety in the above-mentioned high-risk population, although long-term follow-up are lacking and the experience is limited to relatively small numbers of patients.

Ectopic Balloon Placement

Especially in the scarred retroperitoneum, it can be interesting to avoid perforating the transversalis fascia. By blunt dissection, a space is created above the transversalis fascia. The reservoir is positioned at the lateral aspect of the penis and medial of the spermatic cord. This technique has been described in 2005 and has been found quicker and easier than the classical positioning in the Retzius space. Avoiding the perforation of the transversalis fascia decreases the risk of perforating blood vessels and underlying organs. It is important to close the opening in the neighbourhood of the inguinal ring with an absorbable suture to prevent migration of the balloon on Valsalva.

Double Cuff

The use of a double cuff has been popularised 20 years ago in order to diminish the number of patients that had persistent urinary leakage after single cuff implant. Where initial reports were very optimistic and presented improved outcome in

terms of dry rates, longer follow-up has learned that double cuff placement might not be superior to single cuff implants and is also associated with a higher risk of complications. As always, there exists no well-designed prospective trial, and this data is drawn from cohort studies, limiting the power of the evidence. The existing evidence does not support the use of double or tandem cuff in a routine setting.

High- and/or Low-Pressure Balloon

There is no published data that specifically addresses the results and complications of the different pressure reservoirs that are on the market (51–60 cm H_2O, 61–70 cm H_2O and 71–80 H_2O). It is generally accepted that low-pressure balloons (51–60 cm H_2O) result in lower dry rates. The use of high-pressure balloons (71–80 cm H_2O) on the other hands will increase erosion rates. Therefore, it should be noted that the standard of care consists of using a 61–70 cm H_2O balloon. As a matter of fact, there is no reason to use another pressure balloon.

Early Complications

Surgical Perforation of Urethra

During dissection of the urethra, inadvertent perforation of the urethra can occur. When the perforation is clear, cuff implant should be abandoned. Undiagnosed urethral perforation will result in early cuff erosion or infection. Whenever in doubt, a control of urethral integrity should be performed. One way to do this is to inject a coloured (e.g. isobetadine) aqueous solution in the urethra and check for abnormal leakage in the operating field.

Bladder Perforation

During perforation of the fascia transversalis and creation of the space for the pressure reservoir, the bladder can be accidentally perforated. Undiagnosed bladder perforation will again result in early infection of the prosthesis and will require early removal. When bladder perforation is diagnosed during surgery, the procedure can continue, but the reservoir needs to be relocated to the intraperitoneal space of to the above-mentioned ectopic location. Whenever in doubt of bladder perforation, a control of bladder integrity should also be performed, for example, by injection of a coloured aqueous solution in the urethra and check for abnormal leakage in the operating field.

Infection

Early infection in general is clinically apparent by the classical dolor, tumor, rubor and calor and can also be accompanied by fever. These sign will mandate prompt removal of the prosthesis. There have been reports of ‘salvage procedures’ where a

new device is implanted in the same time after thorough rinsing the operating field with antibiotic or antiseptic solutions. The majority of implanters will however advice explant followed by a reimplant at a later stage (in terms of months). Most important underlying causes of early infection are probably perioperative inoculation of bacteria or unrecognised perforation of bladder or urethra. It is off course mandatory to perform implants under appropriate antibiotic prophylaxis. We know that a course of 24 h antibiotics diminishes infection rates in orthopaedic surgery. It is thus wise to continue antibiotics for 24 h. It is unclear whether longer antibiotics are useful. Nevertheless, many implanters will currently prescribe a longer course of antibiotics. Also irrigation of the operation field with aqueous solution (+/− antibiotics), shaving immediately prior to implantation and placing the prosthesis directly from the preparation table directly into the patients without placing it on wet drapes, patient skin or penis are believed to diminish infection rates, again not supported by strong evidence.

Early infection rates are not often reported separately from late infections or from erosions. The rate of infection and erosion in contemporary series with a follow-up of at least 12 months is believed to be around 8.5 % with a wide variability in reported series.

Late Complications

Urethral Atrophy

When recurrent stress urinary incontinence occurs during follow-up of patients with an implanted AMS 800 device, urethral atrophy is suspected. Due to the chronic compression of the urethral cuff, tissue hypoxia occurs, which in turn results in tissue atrophy. This is also an explanation why radiation, which can result in obliterative endarteritis, is believed to favour urethral atrophy. This has however not been proven in current literature. Current atrophy rates are reported to be around 8 %. In a prospective study, urethral atrophy occurred at a median of almost 30 months after implantation. Other series have reported atrophy to occur from 3 up to 23 months after implantation.

Erosion/Infection

Erosion and infection of implants usually occur within 24 months after implant surgery. As stated above, early infections probably arise from perioperative inoculation of bacteria or unrecognised perforation of bladder or urethra. Infection and erosion have been reported to occur even after more than 7 years after implantation. Patients can have years of satisfactory results of the device and nevertheless present with late erosion. Low-grade infection or repetitive injury of the prosthesis material in the tissue might be causative factors. As mentioned above (in the early infections section), the rate of infection and erosion in contemporary series with a follow-up of at least 12 months is believed to be around 8.5 % with a wide variability in reported series.

Mechanical Failure

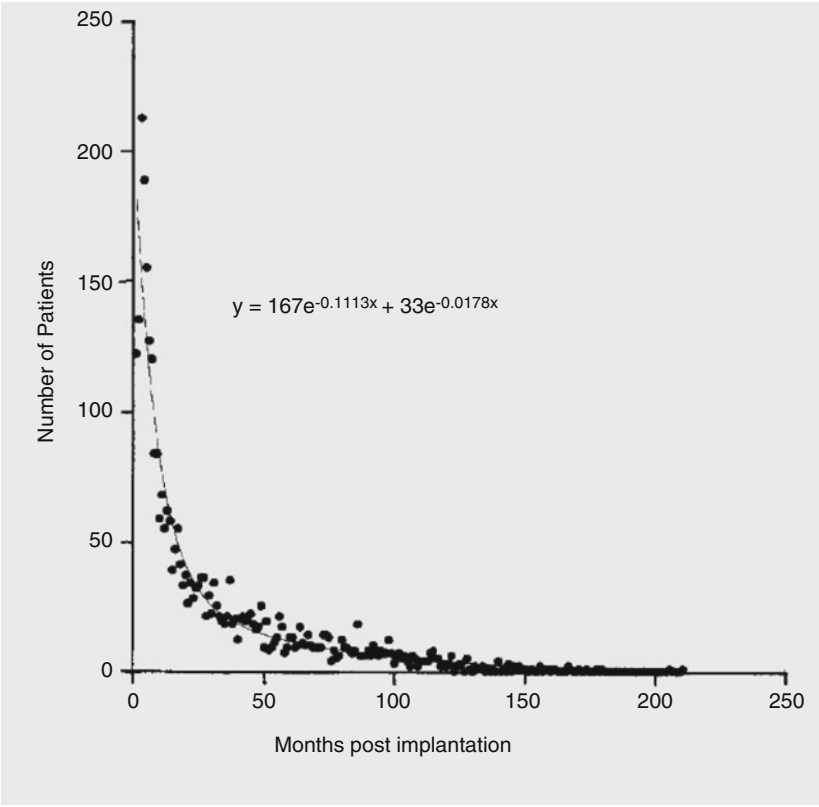
Mechanical failure can occur within each of the different components of an artificial urinary sphincter (balloon, control pump or cuff), in the tubing or in one of the connections. It is well known that implanted artificial urinary sphincters can remain functional for very long periods, way over 10 years. The actuarial 5-year survival rates of these devices have however not been well described. In literature, rates of mechanical failure vary between 2.0 and 13.8 % with a mean of 6.2 % after a follow-up of at least 2 years. It is clear that the rate of mechanical failure is dependent of the follow-up period.

AUS implant in severe non-neurogenic male stress incontinence[a]	Risk (no comparator)	*N* of participants (*n* of studies)	Quality of evidence (grade)
Infection/erosion	8.36 % (range 3.3–27.8 %)	754 (13)	Low
Mechanical failure	6.4 % (range 2.0–13.8 %)	754 (8)	Low
Urethral atrophy	11.6 % (range 1.9–39.7 %)	601 (8)	Low
N patients with reinterventions	28.0 % (range 14.8–44.8 %)	719 (12)	Low
N reinterventions	79 interventions in 52 patients that needed revision (mean of 1.5 reinterventions/patient)	52 (5)	Low
N patients social continent (≤1 pad/24 h)	82.4 % (range 60.9–100 %)	425 (8)	Low
N patients completely dry (0 pads/24 h)	48.4 % (range 4.3–85.7 %)	409 (8)	Low
Quality of life	VAS scoring impact of incontinence preoperative 5.0 vs. post-operative 1.4	40 (1)	Low

[a]Mean follow-up was not extractable from the different subgroup datasets, but all included studies have a follow-up from >24 months

Revision Rates

The overall reintervention rate for patients undergoing artificial urinary sphincter implants is an important comparator to other techniques and offers important information to counsel a patient prior to proceeding with implantation. In a recent pooled analysis of published data, the mean reintervention rate for all causes after AMS 800 implantation was 26 %. It has been shown that 50 % of reinterventions occur in the first 8 months and that 90 % of reinterventions occur in the first 3 years after implantation of the artificial urinary sphincter. Patient satisfaction seems to be mainly linked to the presence of a functioning device, rather than the necessity to re-intervene. The majority of patients (up to 98 %) will have a functioning device at more than 2 years follow-up, independent of the need for revision.



Efficacy

The efficacy of the AMS 800 device can be measured in terms of continence rates and in terms of quality of life.

When continence is defined as being dry (no pad use), the dry rates vary from 4.3 to 85.7 %. The high variability shows that more standardisation is necessary in the evaluation of the efficacy of the AMS 800 device. Improvement of incontinence is seen in the vast majority of patients, up to 100 % in certain series. A recent small prospective study suggest that about half of all patients implanted with an AMS 800 device will be dry and that 90 % of patients will report a markedly improved continence. Failure seems to be linked to infection and subsequent removal of the device and to reduce to bladder compliance on preoperative urodynamic study.

Quality of life is not well studied in this patient population. All studies that the use-specific quality of life measures have shown a very significant impact of the AMS 800 device on the quality of life. As said before, the number of reinterventions does not seem to have an important impact on the final quality of life, as long as patients have a functional AMS 800 device after revision.

Risk Factors for Failure

Although one would expect that risk factors for failure of AMS 800 are well known and described, because of the long-standing service of this device, these relations are not always well established. Risk factors such as diabetes and irradiation do not necessarily have a negative impact on patient's outcome. Several cohort series have reported similar outcome for irradiated patients vs. nonirradiated patients. In some of these series, however, this was at cost of a higher revision rate in the irradiated patient group. Previous erosion of a sphincter, previously treated urethral stricture disease or bladder neck contractures have been associated with higher failure rates in several series. On the other hand, some small series have also shown good results in these difficult patient cohorts.

In conclusion, whenever a patient suffers severe incontinence, he should be offered the possibility of an artificial urinary sphincter implant, even in the presence of risk factors. Adequate counselling and explanation of the risk for revisions is obviously a mandatory step prior to implant.

Summary

The AMS 800 device has been used in its current form for more than 25 years. Therefore, it is by far the most well-known surgical technique to treat severe incontinence. After implantation of an AMS 800, the vast majority of patients will have improved continence and quality of life. Not all patients will be completely dry however. A non-negligible proportion of the patients will require revisions, but this will result in improved continence and quality of life again. Only a small proportion of patients will be left incontinent without further possibilities for prosthesis surgery.

Tips and Tricks

1. Discuss the high success rate and also the high revision rate of this surgery with your patient prior to implant.
2. Pay attention to the dexterity and cognitive function of your patient.
3. If you perform only a few implants a year, consider referring your patient to a high-volume centre.
4. Plan the surgery in advance, but be prepared to change technique when encountering difficulties (e.g. ectopic balloon placement, transcorporeal cuff placement,…).
5. An infected/eroded AMS 800 should be explanted without significant delay. Antibiotics will not cure the patient but will result in delay and possible increased damage of the urethra. This might diminish the chances for a second implant.

Stress Urinary Incontinence in Neurogenic and Irradiated Patients

Irradiated Patients

Radiation therapy is increasingly offered to patients after radical prostatectomy in the course of treatment of their prostatic carcinoma. Radiotherapy prior to implantation of AUS or male slings in men with SUI is assumed to cause morbid changes to the irradiated bladder and urethral tissue. This morbid effect may finally lead to worsening of the continence status in these patients. Radiation endarteritis obliterans of small blood vessels leads ischaemic changes in the irradiated tissue. Cellular radiotoxicity causes fibrotic changes to the detrusor muscle, disturbs its function and decreases its compliance. Radiation hemorrhagic cystitis may necessitate multiple endoscopic interferences that is quite a problem after insertion of AUS. Similar changes are assumed to take place in the bulbar urethra – even though it is not involved in the radiation field – due to compromised vascularity.

Studies that have addressed the effect of radiation therapy – prior to implantation of AUS or male slings – on the surgical outcome in this particular patient population are not that many. Manunta et al. (2000) reported higher complication and reoperation rate in the irradiated group of patients. Sathianathen et al. (2014) reported a higher incidence of coexisting urethral stricture in the irradiated patients. Walsh et al. (2002) found that revision due to urethral atrophy, erosion and infection occurred more frequent in the irradiated patients and that complete resolution of incontinence was significantly higher in the unirradiated group.

In a group of 37 male patients with post-prostatectomy incontinence who received AdVance male sling, Torrey et al. (2013) reported statistically significant higher frequency of pad usage in the subgroup of patients who underwent external beam irradiation (3.5 pads vs. 0 pads, $p=0.007$). Three of the seven irradiated patients experienced worsening of their incontinence status compared to 1 of 30 patients without irradiation. About 63 % of unirradiated patients became pad free, whilst none of the seven irradiated patients achieved complete dryness.

Neurogenic SUI

Management of neurogenic stress urinary incontinence (NSUI) is one of the challenging topics in daily urological practice. A substantial number of school aged patients with bifid spine and patients with infrasacral spinal cord injuries (SCI) have weak urinary sphincteric mechanism and, therefore, suffer from SUI. Looking at the literature, although so many studies have investigated various approaches to treat patients with NSUI – such as artificial urinary sphincter (AUS) and suburethral slings – there is no single, blinded, randomised trial to standardise an optimal surgical approach dealing with such specific patient population.

Neurological assessment and further investigations reveal an underactive sphincteric mechanism; this should be accompanied by assessment of the functionality of the detrusor muscle whether it is normal, overactive or underactive. This is of utmost importance to assess the gravity of the condition and to plan the future treatment. The neurological assessment of the patient should include testing of the integrity of sensations in the urogenital area and the assessment of anal sphincter tone and the ability to voluntarily contract the anal sphincter and pelvic floor muscles. This gives indirect information about the functionality of the external urinary sphincter. Part of the clinical assessment of a male patient with NSUI is to complete a bladder diary, generic (SF-36) and I-QOL to assess the amount of incontinence and its impact on patient's quality of life. Urinalysis helps reveal any urinary tract infection. Imaging and renal function test can detect any deterioration of the upper urinary tract, especially after surgeries that aim to increase the urinary bladder outlet resistance as they might result in development of DO or decrease in bladder compliance in some cases.

Filling cystometry and videourodynamics have a particular role in patients with NSUI, both preoperatively and during follow-up of patients after surgery. They help the urologist to document the presence of incontinence, sphincteric underactivity and any coexisting DO and/or low bladder compliance and the impact of these co-findings on the upper urinary tract. Urethral pressure measurement is used at some functional urology centres around the world; however, according to the EAU Guidelines, it has a very limited role in neuro-urological disorders.

The EAU Guidelines for the treatment of NSUI highlight some priorities, particularly protection of the upper urinary tract, improvement of urinary continence status, restoration of lower urinary tract function and improvement of patient's quality of life. Management of a male patient with NSUI is challenging; in many cases, the NSUI is accompanied by DO and/or low bladder compliance that may be part of the pathogenesis of the underlying neurological deficit or may develop later after surgery. Therefore, a thorough clinical assessment and further specific investigations are mandatory, with close follow-up of the patients after surgery to ascertain achievement of the above-mentioned urological priorities. Moreover, some additional surgical procedures are mandatory to guard against deterioration of the upper urinary tract function by increasing the capacity of the bladder, e.g. bladder augmentation.

Drug treatment in NSUI is not recommended and should not be prescribed (LE: 4, GR: A). Whenever possible, suprapubic catheters and indwelling transurethral catheters should be avoided (LE: 3, GR: A). Urethral lengthening and bladder neck procedures such as Young-Dees-Leadbetter approach can help regain continence in patients with NSUI due to sphincteric incompetence. However, these procedures are invasive and quite challenging with success rate of about 50 % in primary procedures. Less invasive procedures are available and should be tried out in the first place. These procedures are urethral bulking agents, suburethral slings and artificial urinary sphincters (AUS). The use of AUS is recommended by the EAU Guidelines for the treatment of men with NSUI (LE: 3, GR: A).

However, none of the studies, on which the above-mentioned recommendation is based, was a randomised, controlled trial. Only one systematic review was found in the literature that comprehensively described the surgical outcomes and quality of

reporting of 30 studies that applied less invasive surgical procedures to correct NSUI. All studies were either cohort prospective or retrospective of level 3 evidence with overall quality of reporting 43–81 %. The analysis included 849 patients, of whom 525 were males, median age of 21 years (range 3–80). The majority of cases were incontinent because of spina bifida (69 %) or SCI (22 %). About 47 % of patients used intermittent catheterisation to empty their bladders. A total of 322 male patients (60 % of males) received AUS, 108 males (21 %) received suburethral slings, 82 males (16 %) received urethral bulking agents and 13 males (3 %) received Pro-ACT implant.

A follow-up of the patients for 48 months (range 12–62) revealed an overall successful treatment in 64 % of patients, 16 % improved whilst 20 % of patients experienced no change in their continence status after surgery. The overall success rate in this systematic analysis showed no correlation with the type of neurological deficit or the associating bladder augmentation procedures in the course of treatment of the patients.

Surgical complications were reported in 20 % of male patients. About 25 % of the patient underwent one or more reoperation, whilst 5 % of patients received an additional urethral procedure – other than the original one – to achieve continence.

Further analysis of the surgical outcomes of this systematic review revealed that the studies where AUS was applied reported the highest rate of success (77 %) and the lowest rate of failure (10 %), followed by suburethral slings which had a success rate of 58 % and failure rate of 22 % and urethral bulking agents (27 % success and 50 % failure).

However, AUS studies reported the highest complication rates (32 %) and the highest rate of reoperation (51 %), whilst slings had 14 % complication rates and 7 % reoperation rates. Finally, the bulking agents had only 4 % complication rates and 12 % reoperation rates.

Points of Interest

- Filling cystometry and videourodynamics have a particular role in the assessment of male patients with NSUI.
- AUS shows higher success rate in achieving continence in male patients with NSUI compared to slings and urethral bulking agents.
- AUS implantation is technically feasible in patients with previous radiotherapy.

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Chapter 7
Pelvic Organ Prolapse

Elisabetta Costantini, Franca Natale, Antonio Carbone, Antonio Luigi Pastore, and Giovanni Palleschi

Pelvic Organ Prolapse Quantification

Elisabetta Costantini

Pelvic organ prolapse (POP) is one of the most common problems faced by every gynecologist. Understandably, terminology is very important when describing vaginal or uterine descent, for two reasons. First, the physician's notes must represent the clinical problem and be able to communicate it to another colleague exactly as it has been seen. The second reason is quality assurance in research, where exact terminology is needed to accurately describe changes in pelvic organ prolapse and to allow comparisons between institutions and studies.

Urogenital prolapse has traditionally been classified according to the degree of anatomical descent, the site of the defect and the presumably involved pelvic viscera. The large number of different grading systems that have been used reflects the difficulty in designing an objective, reproducible system for grading prolapse. Intra- and interobserver variability is often of importance and may lead to confusion. This makes difficult comparing successive examinations over time in the same woman or between different women.

E. Costantini, MD (✉)
Urology and Andrology Clinic, Department of Surgical and Biomedical Science, University of Perugia, Perugia, Italy
e-mail: elisabetta.costantini@unipg.it

F. Natale, MD
Department of Urogynecology, San Carlo-IDI Hospital, Rome, Italy
e-mail: francanatale@libero.it

A. Carbone, MD • A.L. Pastore, MD • G. Palleschi, MD
Department of Sciences and Medico-Surgical Biotechnologies, Sapienza, University of Rome, Rome, Italy

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The Baden–Walker halfway system is one of the most used for POP classification. It consists of a simple 0–4 grading scale which classifies prolapse according to the defect site (urethra, bladder, cervix, or cuff, pouch of Douglas, rectum, and perineum) and descent above or below the vaginal introitus. For its simplicity, the Baden–Walker system has maintained considerable popularity among gynecologists in their daily clinical practice.

In 1996 Bump et al. published a new classification: the POP-Q system that has been widely accepted and has become the de facto standard in clinical medicine and research.

It has been adopted by major organizations including the International Continence Society (ICS), the Society of Gynecologic Surgeons, the American Urogynecologic Society, and the National Institute of Health (NIH) as an accepted method of describing pelvic support and comparing exams over time or before and after interventions. The POP-Q has been shown to have reproducibility in several centers when the exam is conducted in a standardized fashion. The clinical description of pelvic floor anatomy is determined during the physical examination of the external genitalia and vaginal canal. It is critical that the examiner sees and describes the maximum protrusion noted by the individual during her daily activities and during physical examination in gynecological position (better on 45° angle) at maximum effort or Valsalva maneuver. The system relies on specific measurements of six defined points in the midline of the vaginal wall: Aa, Ba, C, D, Ap, Bp, and three other landmarks: GH (genital hiatus), TVL (total vaginal length), and PB (perineal body). Each of the six points is measured in centimeters above or proximal to the hymen (negative number) or in centimeters below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0). The hymen was selected as the reference point rather the introitus because it is more precisely identified. Each reference point is measured and recorded.

Measurements may be recorded as a simple line of numbers (e.g., −3, −3, −7, −9, −3, −3, 9, 2, 2 for points Aa, Ba, C, D, Bp, Ap, TVL, GH, PB, respectively). Note that the last three numbers have no + or – sign attached to them because they denote lengths, not positions relative to the hymen. Alternatively, a three-by-three "tic-tac-toe" grid can be used to concisely organize the measurements (Fig. 7.1).

Points and Landmarks for POP-Q System Examination Table 7.1 illustrates the reference points: three reference points are anteriorly (Aa, Ba, and C) and three posteriorly (Ap, Bp, and D). Points Aa and Ap are 3 cm proximal to or above the hymenal ring anteriorly and posteriorly, respectively. Points Ba and Bp are defined as the lowest points of the prolapse between Aa anteriorly or Ap posteriorly and the vaginal apex. Anteriorly, the apex is point C (cervix), and posteriorly is point D (pouch of Douglas). In women after hysterectomy, point C is the vaginal cuff and point D is omitted. Three other measurements are taken: the total vaginal length (TVL) at rest, the genital hiatus (GH) from the middle of the urethral meatus to the posterior hymenal ring, and the perineal body (PB) from the posterior aspect of the genital hiatus to the mid-anal opening. Normal position of the reference points is

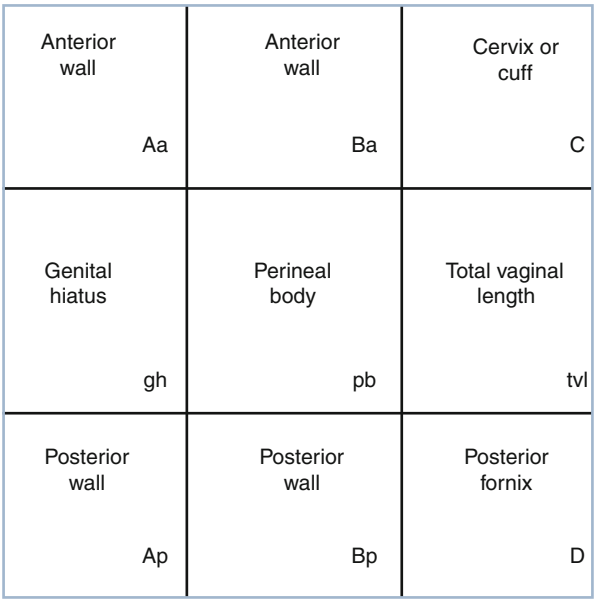


Fig. 7.1 Three by three grid for recording quantitative description of pelvic organ support

Table 7.1 Description of the points and their range of values

Points	Description	Range of values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	−3 cm to + 3 cm
Ba	Most distal position of the remaining upper anterior vaginal wall	−3 cm to + tvl
C	Most distal edge of cervix or vaginal cuff scar	−10 cm to + 10 cm
D	Posterior fornix (N/A if post hysterectomy)	
Ap	Posterior vaginal wall 3 cm proximal to the hymen	−3 cm to + 3 cm
Bp	Most distal position of the remaining upper posterior vaginal wall	−3 cm to + tvl

Additional measurements:
Genital hiatus (gh) measured from middle of external urethral meatus to posterior midline hymen
Perineal body (pb) measured from posterior margin of gh to middle of anal opening
Total vaginal length (tvl) depth of vagina when point D or C is reduced to normal position

illustrated in Fig. 7.2. Once the measurements are taken, the patients are assigned to a corresponding stage (Fig. 7.3).

The POP-Q system has been criticized for being cumbersome and difficult to learn, although some instructional videotapes are available through the websites and facilitate the learning process. Some tips and tricks can be used to improve the system measurements. Different kinds of devices facilitate the examiner in making the measurements. Figures 7.4 and 7.5 show a home-made system in which a uterine dilatator is used to measure the point Aa (Fig. 7.4) and the point PB (Fig. 7.5). An

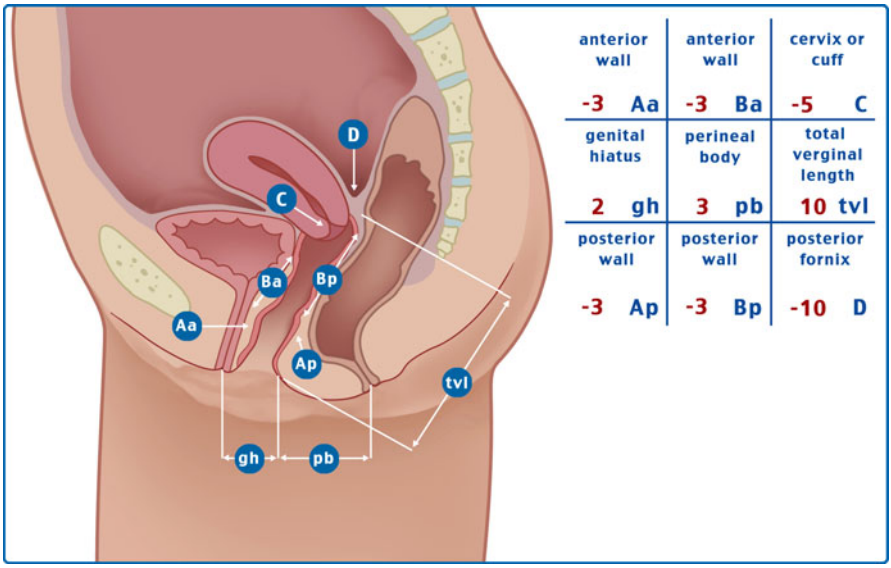


Fig. 7.2 Normal position of the reference points

Pelvic organ prolapse quantification system (POP-Q)	
Stage	Description
0	No prolapse, anterior and posterior points are all –3 cm, and C or D is between -TVL and -(TVL-2) cm
1	The criteria for stage 0 are not met, and the most distal prolapse is more than 1 cm above the level of the hymen (less than –1 cm)
2	The most distal prolapse if between 1 cm above and 1 cm below the hymen (at least one point is –1, 0, or +1)
3	The most distal prolapse is more than 1 cm below the hymen but no further than 2 cm less than TVL
4	Represents complete procidentia or vault eversion; the most distal prolapse protrudes to at least (TVL-2) cm

Fig. 7.3 POP-Q staging

alternative useful method in the clinical practice mark centimeters on the examiner's finger and using it as a ruler (Fig. 7.6).

It has been shown that the routine use of the POP-Q system decreases significantly the amount of time needed to collect the desired data. Experienced examiners averaged 2.05 min per examination while new examiners averaged 3.73 min. There is also a high correlation between the POP-Q findings in left lateral and lithotomy position.

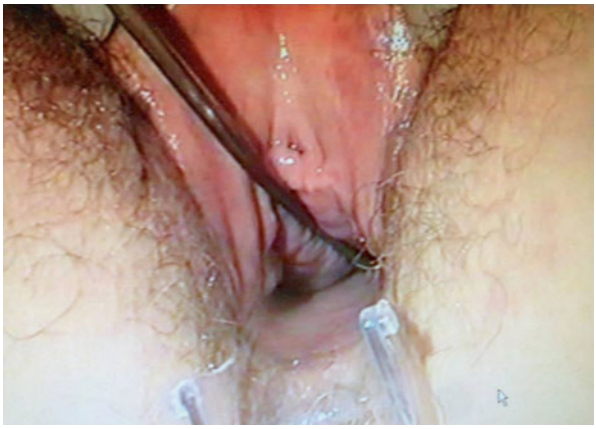


Fig. 7.4 Uterine dilatator is used to measure the point Aa

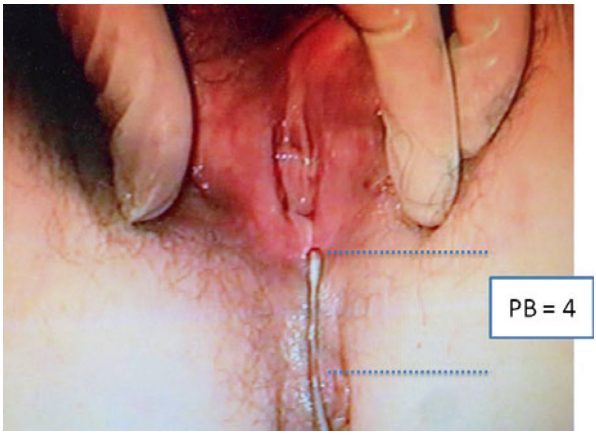


Fig. 7.5 Uterine dilatator is used to measure the point PB

Figures 7.7, 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, and 7.14 illustrate some examples of the different stages of prolapsed anterior and posterior compartments, vault and uterus prolapse.

The POP-Q system does not include findings that some investigators believe to be essential for complete patient description, such as vaginal caliber, status of paravaginal sulci, pelvic muscle strength, or the presence of symptoms, although all of these information should be collected during POP evaluation.

Pelvic organ prolapse quantification (POP-Q) system is an objective, site-specific system for describing, quantifying, and staging pelvic support in women. It provides a standardized tool for documenting, comparing, and communicating clinical findings with proven interobserver and intraobserver reliability. It has been used for longitudinal follow-up of a population of women with prolapse and extensively for outcome reporting after prolapse repairs.

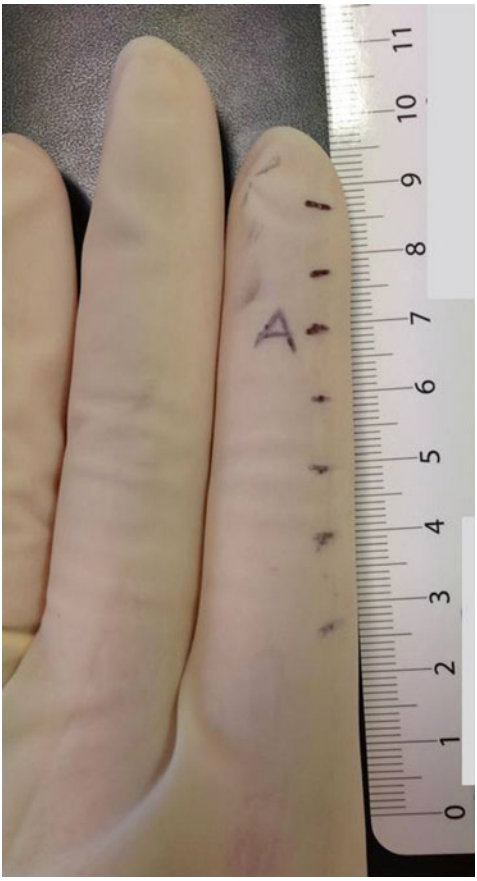


Fig. 7.6 Finger with centimetric scale marked

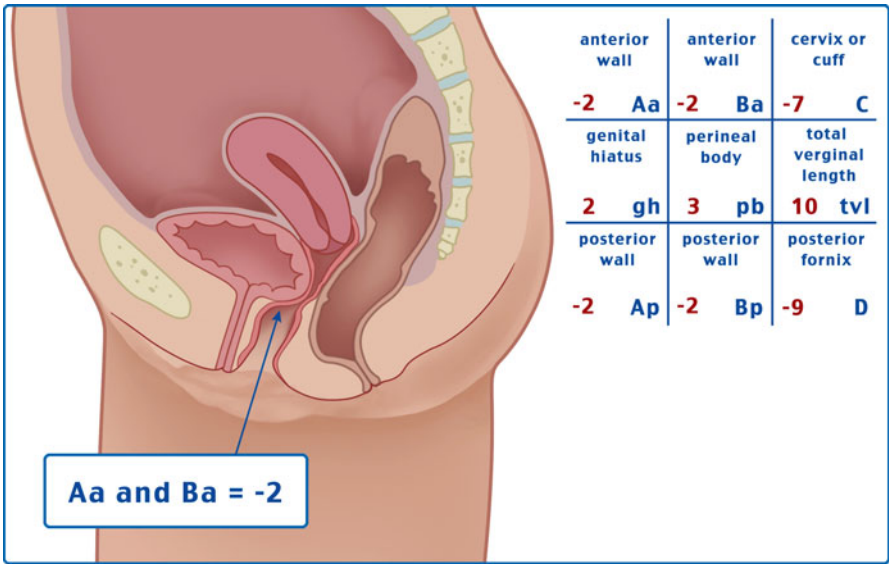


Fig. 7.7 Anterior prolapse stage 1 (with uterus)

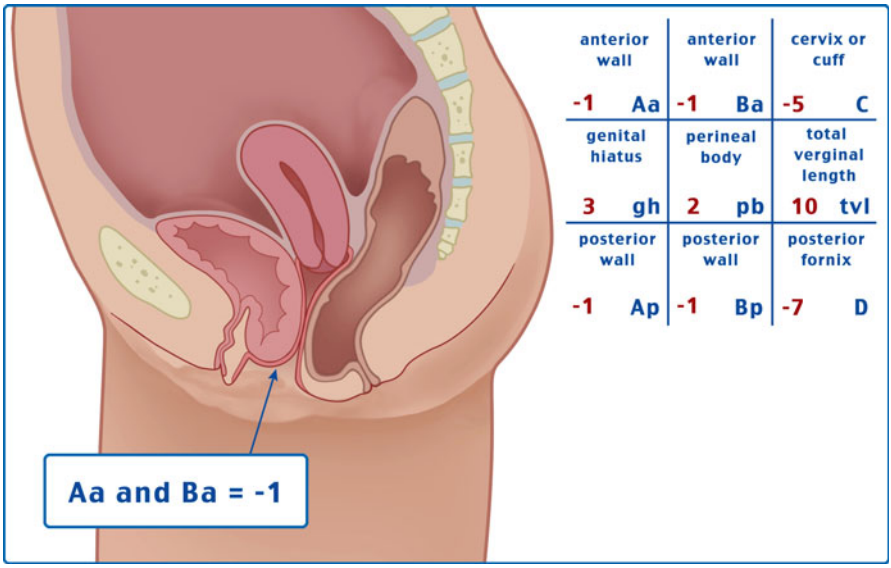


Fig. 7.8 Anterior prolapse stage 2 (with uterus)

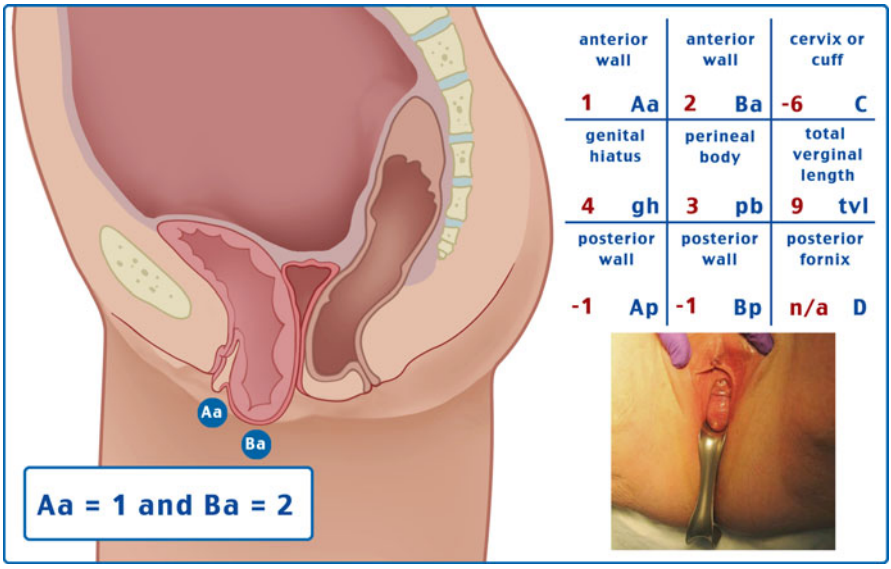


Fig. 7.9 Anterior prolapse stage 3 (without uterus)

Recently a POP-Q simplified system has been developed, based on POP-Q with similar ordinal staging but with only four points measured instead of nine (Aa, Ba, C, D). Evaluation of the interobserver reproductibility and intersystems reliability (in comparison with the standard POP-Q system) showed good correlation.

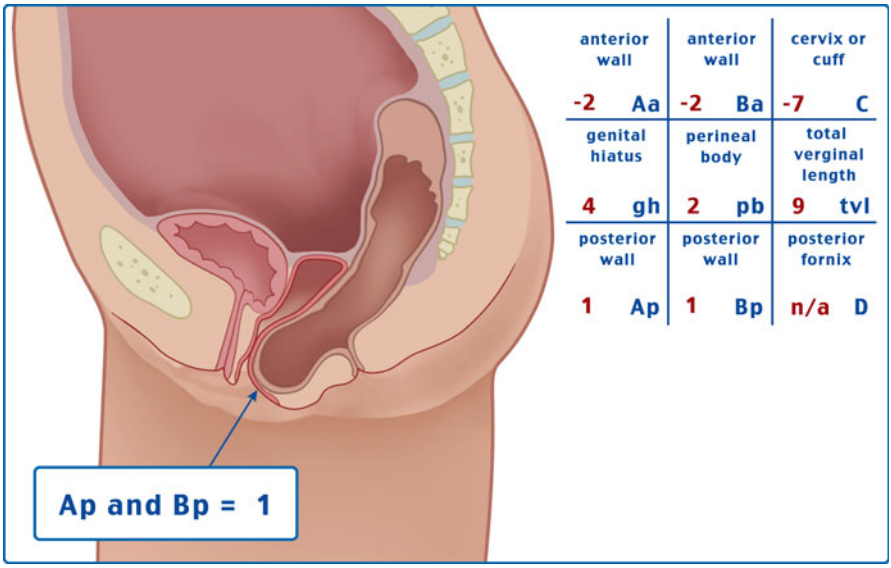


Fig. 7.10 Posterior prolapse stage 2 (without uterus)

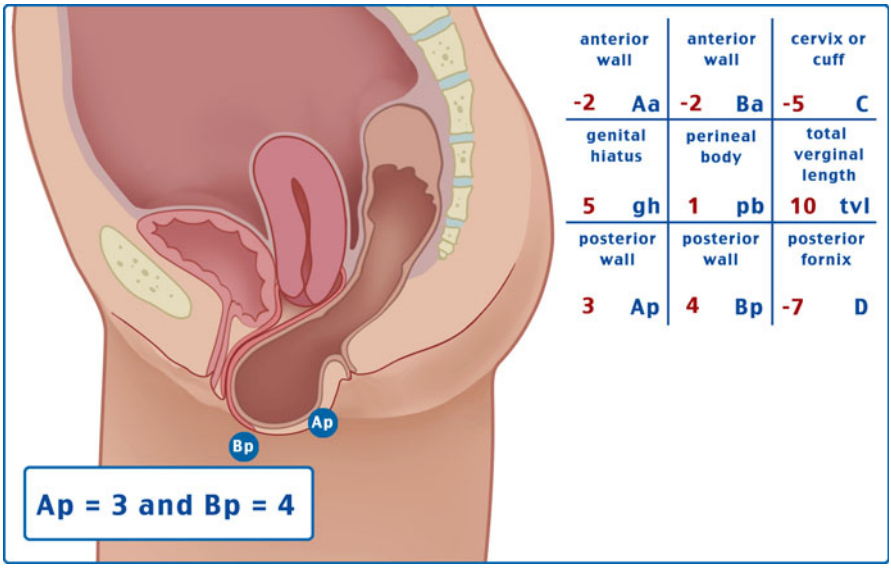


Fig. 7.11 Posterior prolapse stage 3 (with uterus)

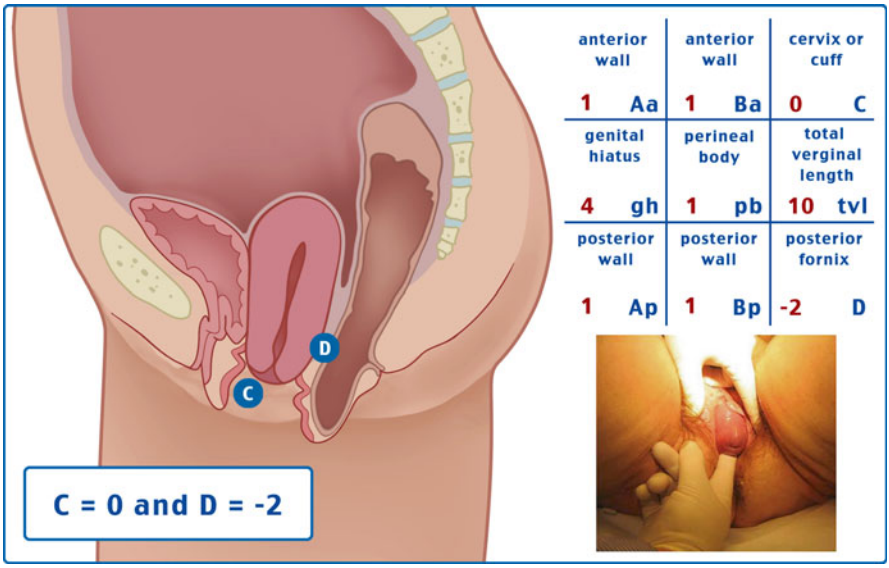


Fig. 7.12 Uterine prolapse stage 2

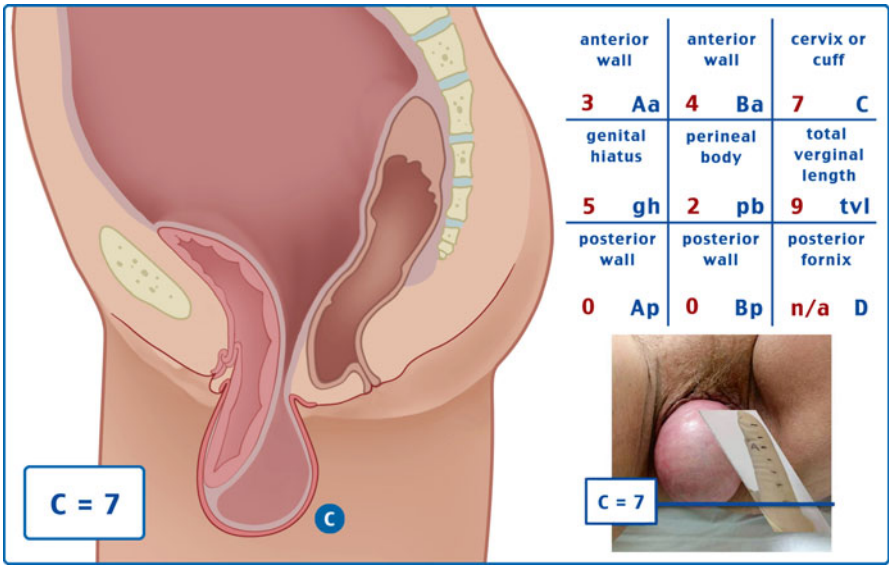


Fig. 7.13 Vaginal vault prolapse stage 4

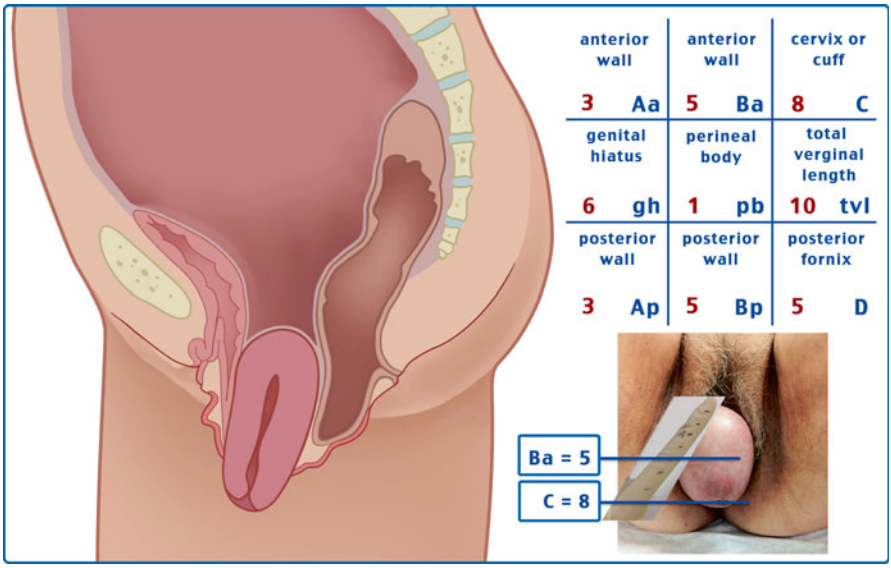


Fig. 7.14 Uterine prolapse stage 4

Pessaries

Elisabetta Costantini

Pelvic organ prolapse (POP) is common and is seen in up to 50 % of parous women in a clinic setting. In the general population, an estimated 30 % of women will have signs of prolapse although the majority are asymptomatic. The etiology of pelvic organ prolapse is complex and multifactorial. Risk factors include pregnancy, childbirth, congenital or acquired connective tissue abnormalities, denervation or weakness of the pelvic floor, aging, menopause, and factors associated with chronically raised intra-abdominal pressure such as obesity, cough, and heavy lifting. Women with prolapse may have a variety of pelvic floor symptoms. Only some of the symptoms are directly related to the prolapse, including pelvic heaviness, a dragging sensation in the vagina, a bulge, lump or protrusion coming down from the vagina, and backache. Symptoms of bladder, bowel, or sexual dysfunction are frequently present. Symptoms may negatively affect body image, quality of life, and a woman's ability to perform everyday activities. Prolapse treatment may be dependent on a number of factors including the severity of prolapse, the bothersomeness of the associated symptoms, the woman's general health, and the woman's treatment preference. Options available for treatment are conservative (pelvic floor muscle training), mechanical support (such as vaginal pessaries), estrogens, and surgery. Before the nineteenth century, the primary POP treatment was the vaginal pessary and Fig. 7.15 shows some of spiral-, oval-, and doughnut-shaped pessaries

Fig. 7.15 Pessaries in the nineteenth century from Stromayr C: Die Handschrift des Schnitt-und Augenarztes Caspar Stromayr. Berlin, 1925

used for prolapse during the eighteenth century. Despite numerous technological breakthroughs in the medical field over recent decades, pessaries have remained essentially unchanged throughout the twentieth century. The use of pessaries has become commonplace over many years without full evaluation of their efficacy in comparison to other modes of treatment such as surgery, estrogens, or pelvic floor muscle training. Eighty-seven to 98 % of clinicians report using pessaries in their clinical practice and 77 % of gynecologist report using pessaries as the first-line treatment for prolapse.

In 2013 the Cochrane review demonstrated a lack of consensus on the use of different types of the device, the indications, and the pattern of replacement and follow-up care. However *pessaries are commonly used when conservative treatment, like physiotherapy, and surgery have either failed or are not suitable*. They present a good option for patients who have not completed childbearing, do not desire surgery, or are poor surgical candidates.

The pessary is inserted into the vagina in order to physically support the vaginal walls, holding the prolapsed organs inside the vagina, supporting the pelvic structures and relieving pressure on the bladder and bowel. In this way it should be able to prevent the prolapse becoming worse and in some cases it is used to avert or delay the need for surgery.

Pessaries are now generally made of an inert plastic or silicone material to prevent odors and absorption of vaginal secretions. Silicone pessaries can be autoclaved and latex allergy is not a contraindication. There are currently many shapes and sizes of pessaries available to suit individual needs, all with their own advantages and disadvantages.

The clinicians choose the type of pessary based on severity of prolapse, presence or absence of the uterus, sexual activity, and concomitant stress urinary incontinence. A cystocele is best treated with a ring with support (filled-in center), uterine prolapse with a ring without support (hollow), and stress incontinence with a ring with a knob. Two main groups of pessaries are available: ***support pessaries*** and ***space-filling pessaries*** (Fig. 7.16). Generally the first-line pessary for clinicians is

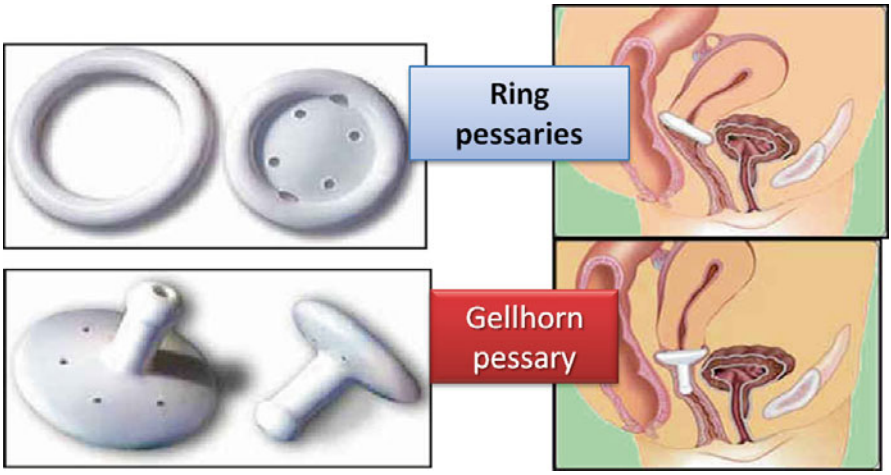


Fig. 7.16 Different pessaries and how they fit

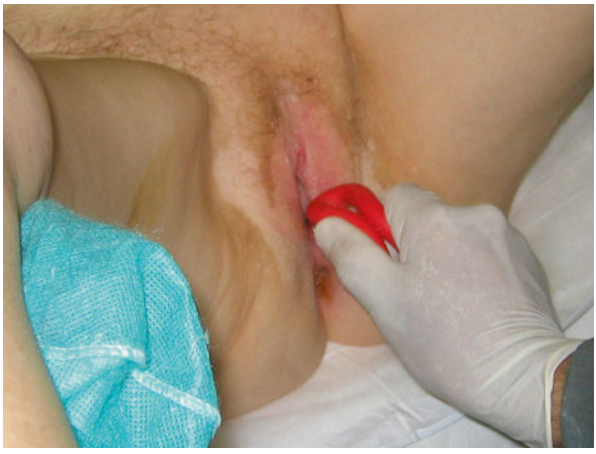


Fig. 7.17 Insertion of a ring pessary

the *ring pessary*, due to ease of insertion and removal. The ring is easy to insert by folding the ring in half and placing a small amount of lubricant on the tip of the pessary to aid in insertion (Fig. 7.17). It is then placed into the vagina where it unfolds once above the pubic symphysis. For removal, the pessary is gently pulled and folded in half. A string can be attached to the ring to aid in insertion and removal. Patients can easily be taught to do this by themselves.

Another kind of pessary is the *Gellhorn*, generally used for more advanced-stage prolapse or in a patient who is no longer sexually active. It is a space-occupying pessary; its removal and insertion is more difficult and therefore cannot be done by the patient. This pessary has a concave portion attached to a stem that faces into the vagina (Fig. 7.16). To insert the Gellhorn, the pessary is folded in half with the use

of lubricant on the leading edge to ease insertion. Once the pessary is behind the pubic symphysis, it will expand and rest against the leading edge of prolapse creating suction. To remove the Gellhorn, the knob is grasped, generally with the help of a ring forceps, while the concave end of the pessary is rotated to release the suction and the pessary is pulled downward, folded, and removed. Another space-filling pessary is the *cube pessary*. It is made of flexible silicone and is an option in cases of stage III and IV prolapse. The pessary has a string on one end for ease of removal. To insert, the cube pessary is compressed and inserted into the vagina. The cube applies suction to the leading edge of prolapse and often vaginal secretions are trapped in the crevices of the pessary, leading to malodorous discharge; it is usually the pessary of last resort. This pessary should be removed on a nightly basis when possible.

For ***pessary placement*** the patient should empty her bladder before pessary fitting. To begin fitting, the clinician can estimate the width of the mid-vagina and use this information to select the appropriate size pessary. The patient should be fitted with the largest size pessary that fits comfortably. The patient is examined in supine and standing position with and without Valsalva. The examiner should be able to comfortably fit a finger on either side of the pessary. If atrophy is present, estrogen should also be prescribed, generally in cream, ring, or tablet form. The patient is then instructed to ambulate, sit on the toilet, and strain to further assess comfort and appropriate pessary fitting. Once the correct pessary type and size are chosen and successfully fitted in place, the patient should attempt to remove and reinsert the pessary on her own. This is commonly possible with the ring type. It is always reassuring if the patient can void with the pessary in place before she leaves the office. Patients should be warned that urine leakage may increase with prolapse reduction. Pessaries can be removed daily, weekly, or monthly, at patients' discretion, for washing with regular soap and water. Ring pessaries can be removed or left in place for intercourse. If patients are unable to care for the devices on their own, they will require health-care providers to remove, wash, and reinsert them every 3–6 months. To prevent infections and odors, an acidifier (usually supplied with the pessary) or estrogen must be applied vaginally 2 or 3 times a week. Oral or transdermal estrogen and an estradiol-17 ring (placed behind the pessary) are also options. All patients wearing pessaries should be examined by health-care professionals every 3–6 months to check for vaginal erosions or ulcers. If lesions are found, pessaries should be removed until the lesions have healed, and affected areas should be treated with topical estrogen.

There are very few ***contraindications*** to pessary use, which allows clinicians to offer pessaries to almost all patients presenting with prolapse and incontinence. Pessaries should not be placed in patients with evidence of an active pelvic infection or severe ulceration or allergy to silicone or those patients who are noncompliant and unlikely to comply with follow up. Risks of wearing a pessary include vaginal infection, erosions, discharge, odor, pain, bleeding, failure to reduce the prolapse, and expulsion. Serious complications from pessaries are rare; however, vesicovaginal fistula, rectovaginal fistula, erosion, and subsequent impaction have all been reported.

In conclusion the use of pessary is one possible option for conservative POP treatment. It is cheap and complications are reported to be rare; however the efficacy of pessary use in the management of prolapse still requires to be clearly established. In the 2013 Cochrane review, one randomized controlled trial compared ring and Gellhorn pessaries and the results showed that both pessaries were effective for approximately 60 % of women who completed the study with no significant differences identified between the two types of pessary. So far there is little evidence and no consensus on the indications, choice of device, or follow-up for pessaries. Although serious side effects are infrequent, insertion and removal of most pessary types still pose a challenge for many patients. Pessary design should continue to improve, making its use a more attractive option.

Anterior Repair

Elisabetta Costantini, Franca Natale

Background

Anterior compartment support depends on the connection of the vagina and periurethral tissues to the muscles and fascia of the pelvic wall via the arcus tendineus fascia pelvis. On both sides of the pelvis, the arcus tendineus fascia pelvis is a band of connective tissue attached at one end to the lower sixth of the pubic bone, 1 cm lateral to the midline, and at the other end to the ischium, just above the spine (Fig. 7.18).

Anterior vaginal prolapse can result from defects in different areas of pelvic support including:

1. Defects of the vaginal wall in the midline that result in “distension cystocele”
2. Loss of the lateral attachment of the anterior vaginal wall to the pelvic side wall, referred to as a “’displacement cystocele”
3. Loss of bladder neck support (urethrocele)
4. Separation of the cardinal–uterosacral ligament complex from the vaginal apex (superior defect)

The goal of surgery is to repair these defects to recreate a strong anatomical support of the anterior vaginal wall.

Clinical Practice

Surgical correction of anterior vaginal prolapse should be proposed in case of symptomatic ≥2 stage cystocele.

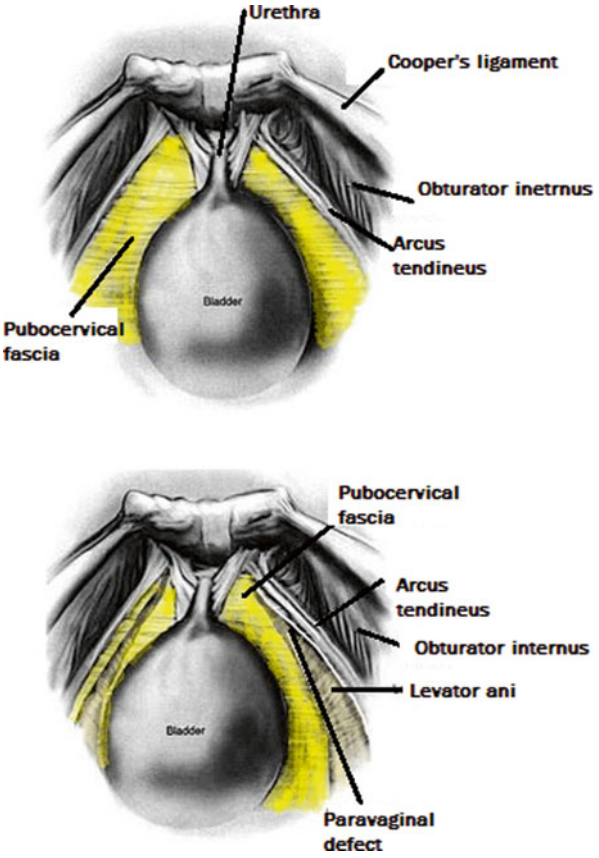


Fig. 7.18 Scheme of anterior compartment support

Patients could complain of symptoms directly related to the prolapse: vaginal bulging and heaviness in the suprapubic area and/or pelvis; vaginal bleeding, discharge, or infection related to ulceration of the prolapse; need of digitally replace the prolapse to assist voiding; and low backache. Often patients refer also symptoms of bladder dysfunction and in particular storage symptoms (increased daytime frequency, urgency, nocturia), voiding symptoms (hesitancy, slow stream, feeling of incomplete emptying), urinary incontinence (stress, urgency or mixed incontinence), and sexual difficulty.

Diagnostic Evaluation

After a detailed history of bladder, bowel, and sexual function, a *pelvic examination* should be performed with patient in lithotomy position. A detailed assessment of the support of all segments of the vagina should be made using the pelvic organ prolapse quantification (POP-Q) system and an assessment for central, lateral, and

superior anterior vaginal support. If physical findings do not correspond to symptoms or if the maximum extent of the prolapse cannot confirmed, the patient should be examined in standing position.

Urodynamics is useful to assess symptoms of urinary incontinence and voiding dysfunction that are common in women with advanced vaginal prolapse. Additionally, because significant anterior vaginal prolapse often results in kinking of the urethra that may mask underlying stress incontinence, a preoperative urodynamics with vaginal packing or pessary is recommended, to evaluate the lower urinary tract in these patients.

Magnetic Resonance Imaging (MRI) can be useful to further define the nature of the prolapse and evaluate for potential enterocele, rectocele, or uterine prolapse.

Preoperative *cystoscopy* is useful in the evaluation of the prolapse in patients with lower urinary tract symptoms such as urinary urgency, hematuria, and obstructed voiding to rule out concurrent bladder pathology.

Surgical Technique

Anterior vaginal prolapse resulting from a central defect is traditionally corrected with anterior colporrhaphy. *Anterior colporrhaphy* was popularized by Howard Kelly in 1911 and still remains the most common technique for transvaginal correction of the anterior vaginal prolapse. Recently to improve the outcomes and avoid the recurrences, the anterior colporrhaphy with use of graft has been proposed. On July 13, 2011, the FDA issued a statement that serious complications are not rare with the use of surgical mesh in transvaginal repair of pelvic organ prolapse. For this reason and on the basis of the Cochrane review conclusions that the transvaginal repair of pelvic organ prolapse with mesh does not improve symptoms or quality of life more than non-mesh repair, the use of mesh during transvaginal surgery is recommended only in the context of RCTs.

Although many variations of anterior repair technique have been described in the last century, the basic approach is still similar to that originally described by Kelly.

A longitudinal mucosal incision is made near the apex of the vagina (Figs. 7.19 and 7.20) and, through this, the vesicovaginal space entered with the tip of a pair of Metzenbaum scissors. Dissection is then performed bluntly by opening and closing the scissors just beneath the vaginal mucosa. The mucosa is incised and the dissection continues along the length of the vaginal wall to within 1 cm of the urethral meatus. Sharp and blunt dissection are used to mobilize connective tissue (vesicovaginal fascia), bladder, and urethra away from the overlying epithelium, just beneath the mucosa. Thompson speculated that the success of the procedure depends on the integrity of the fascial layer left attached to the bladder. Later dissection into the space beneath the inferior pubic ramus is necessary bilaterally (Fig. 7.21). Kelly plication is then performed: a tissue bite is taken laterally in the

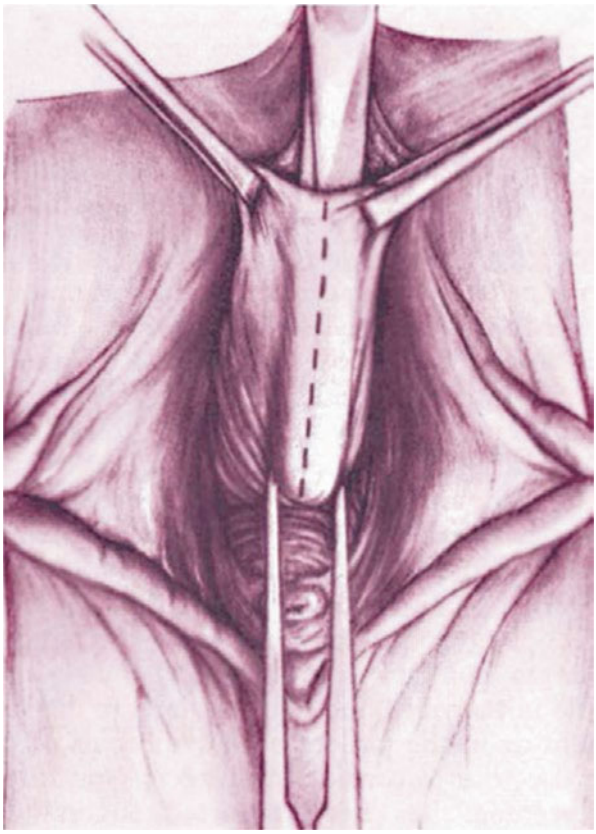


Fig. 7.19 Anterior midline incision

periurethral tissue just under the symphysis pubis, with the suture crossing under the bladder neck, before a similar bite is taken on the other side. Then, three to five delayed absorbable sutures are placed to reduce the cystocele (Figs. 7.22, 7.23, and 7.24). Care must be taken to avoid deep tissue bites, as such bites may result in ureteral kinking. Then excess vaginal mucosa is trimmed bilaterally (Fig. 7.23) and the anterior vaginal wall is closed with interrupted vertical mattress sutures that include the underlying connective tissue. A vaginal pack can be placed for 24 h to minimize the chance of postoperative hematoma formation. Cystoscopy should then be performed to ensure bladder and ureteral integrity.

When anterior vaginal prolapse results from a lateral detachment of the anterior vaginal wall at the pelvic side wall, the goal of surgery is to reattach the lateral vaginal sulcus to its normal lateral attachment. The lateral vaginal attaches to the levator ani (LA) muscle along a line from the anterior pubic rami to the ischial spine known as the "white line" or arcus tendineus fascia pelvis (ATFP) (Fig. 7.18).

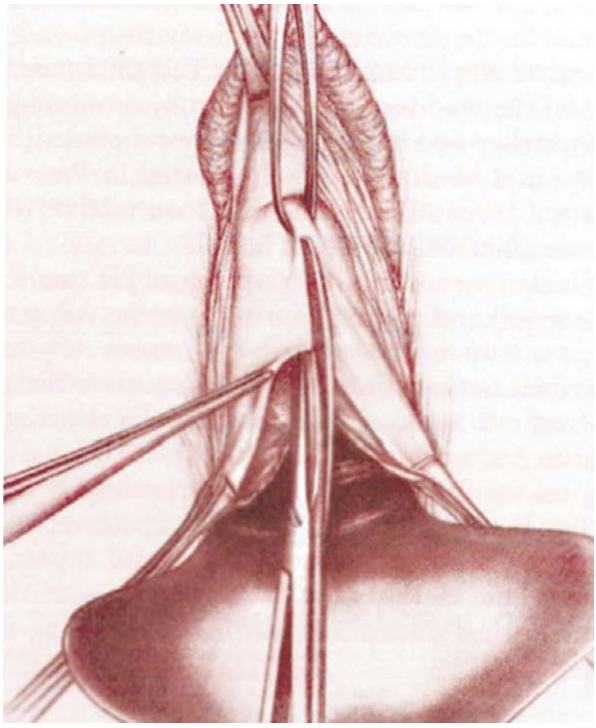


Fig. 7.20 The vaginal mucosa is incised to enter the vesicovaginal space

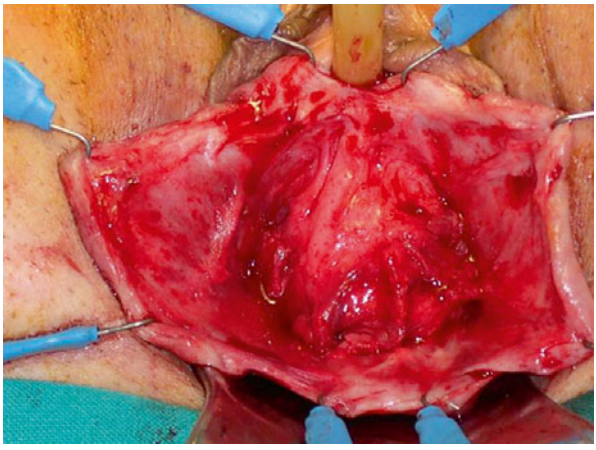


Fig. 7.21 Surgical view: the bladder is isolated and dissected from the vaginal wall mucosa

The paravaginal defect can be repaired retropubically or vaginally. The transvaginal approach (*vaginal paravaginal repair*) can be more challenging than the retropubic approach but has the advantage of avoiding an abdominal incision and facilitating a concurrent central defect. In case of transvaginal approach, the vaginal epithelium

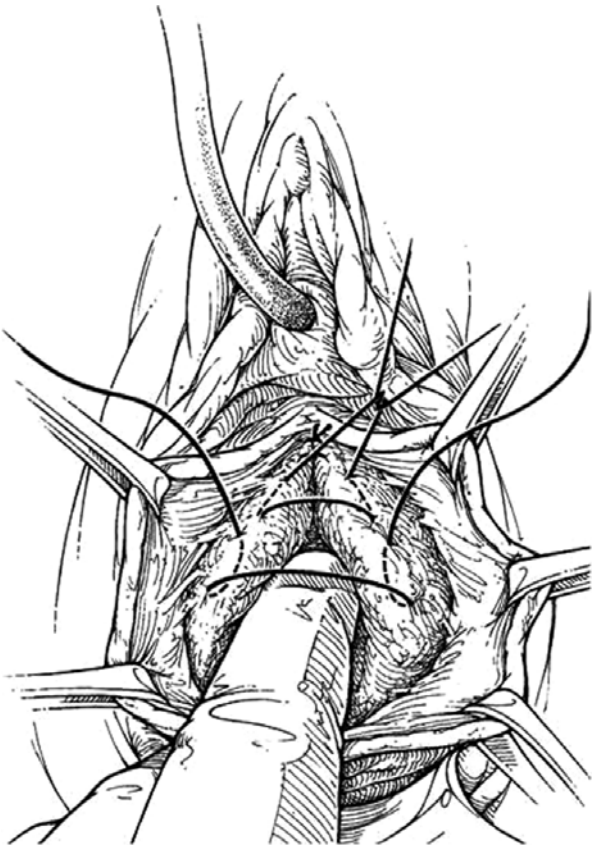


Fig. 7.22 Delayed absorbable sutures are placed on the lateral edges of the fascia to reduce the cystocele

is sharply dissected from the underlying vaginal muscularis and the dissection is continued laterally to the ATFP. Four to six interrupted nonabsorbable sutures are placed through the ATFP and the aponeurosis of the LA muscle at 1 cm intervals. Each stitch is then placed through the lateral edge of the pubocervical fascia and then tightened.

Complications

- *Accidental cystotomy*, particularly in women with previous vaginal surgery. In this case, the defect is closed in two layer using delayed absorbable sutures, and the bladder is drained for 5–7 days to allow for adequate healing.
- *Ureteric injury*, particularly during placement of the Kelly plication sutures. To avoid this complication, the distance between the sutures and the ureteric orifices must be greater than 0.9 mm.

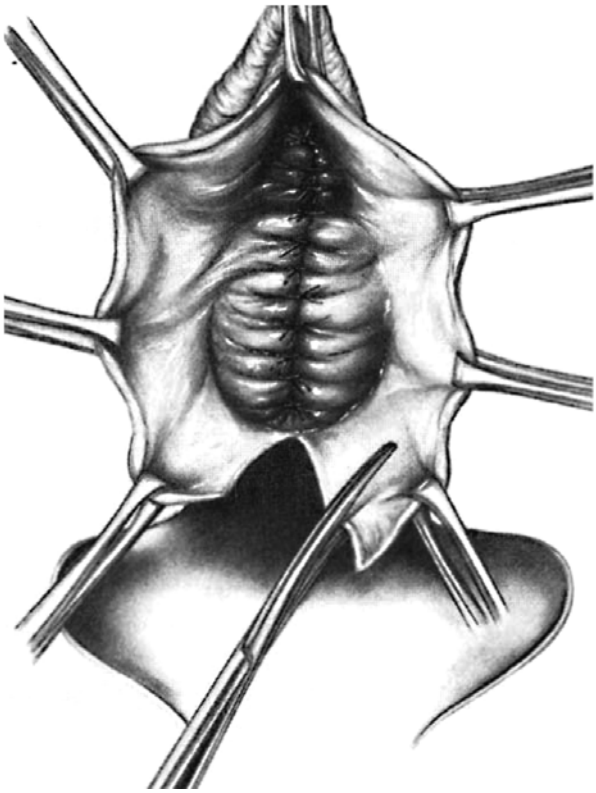


Fig. 7.23 Colporrhaphy is completed and the excess vaginal mucosa is trimmed of bilaterally

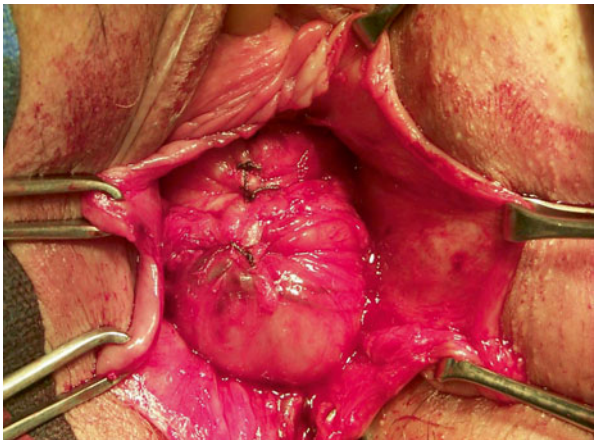


Fig. 7.24 Surgical view of Anterior repair sutures

- *Voiding symptoms* (greater than 3 months), which occurs more often in women with some degree of preoperative voiding dysfunction as suggested by preoperative urodynamic parameters (elevated post-void residual >100 ml, decreased peak voiding flow rate <15 ml/s, and low voiding detrusor pressure

>15 cmH_2O). Long-term voiding difficulty is best managed with clean intermittent self-catheterization.
- *Detrusor overactivity*, which could be due to the surgical dissection around the urethra and bladder neck that damages the parasympathetic and sympathetic nerves leading to denervation of the urethra and detrusor muscle.
- *De novo stress incontinence*, which was attributed to a hypercorrection of the cystocele with a loss in the normal posterior urethrovesical angle between the bladder base and the bladder neck. Currently it is believed that de novo stress incontinence could be due to the denervation of the urethral sphincter or to a condition of latent stress incontinence that is unmasked when urethral kinking is surgically corrected.
- Decreased mobility and capacity of the vagina with subsequent *dyspareunia* and *sexual dysfunctions* (avoid to remove the vaginal walls in excess).

Regarding vaginal paravaginal repair, significant complications have been reported such as ureteric obstruction, retropubic hematoma, vaginal abscesses, and abnormal bleeding.

What Do the Guidelines Say

Outcomes of the traditional surgery for the correction of the anterior vaginal prolapse are largely limited to retrospective reviews and case series. Moreover, reporting of outcomes has been extremely subjective and, before the advent of POP-Q system, pre- and postoperative staging have been quite variable between surgeons.

Considering these limitations, the success rates of anterior colporrhaphy ranged from 80 to 100 % in retrospective series, while the success rates of the vaginal paravaginal repair for cystoceles vary from 67 to 100 % in case series. Studies that differentiated lateral from central recurrences have revealed that central recurrence (22–25 %) is more common than a lateral recurrence (2–8 %).

Comparing anterior colporrhaphy alone to anterior repair with graft or mesh reinforcement, it was demonstrated that absorbable polyglactin mesh (Vicryl) might reduce objective prolapse recurrence and this is true also using absorbable porcine dermis or polypropylene mesh. However improved outcomes including patient satisfaction, quality of life, and reduced operations for recurrences have not yet been demonstrated. Furthermore, anterior polypropylene mesh alone demonstrated an improved subjective outcome as compared to native tissue anterior repair, but there was no difference between the groups in the rate of dyspareunia. The operating time, blood loss, rate of apical or posterior compartment prolapse, and de novo stress urinary incontinence were greater in the polypropylene mesh group, which was associated with an 11.4 % rate of mesh erosion and 6.8 % requiring surgical reintervention.

Sacrospinous Fixation

Franca Natale, Elisabetta Costantini

Background

Post-hysterectomy vault prolapse and uterovaginal prolapse are challenging problems for the pelvic reconstructive surgeon. The main cause of these apical prolapses is the weakness of the uterosacral/cardinal ligament complex, and the restoration of this support is the "cornerstone" of the reconstructive surgery. Various approaches are available to achieve this: vaginal and open, or laparoscopic techniques. The vaginal approach includes: the iliococcygeus fascia fixation, the uterosacral ligament suspension, the Mayo/McCall culdoplasty, and the sacrospinous fixation (SSF).

Clinical Practice

The SSF gained popularity in the second half of the twentieth century, and its most common indication is the resuspension of a symptomatic, post-hysterectomy prolapsed vaginal apex.

Sacrospinous fixation is also indicated when women desire to preserve fertility or the uterus. SSF may also be used to decrease the operative time and morbidity in elderly women who have no evidence of uterine pathologies.

Diagnostic Evaluation

After a detailed history, a *pelvic examination* should be performed with the patient in the lithotomy position using the pelvic organ prolapse quantification (POP-Q) system. In cases of post-hysterectomy vaginal vault prolapse, a *simultaneous rectal and vaginal examination* may aid in detecting the presence of an enterocele and in differentiating an enterocele from a high rectocele. Many radiologic modalities have been used in the diagnosis, including defecography, fluoroscopy, dynamic cystodefecography, and MRI. In cases of severe uterovaginal prolapse of the anterior and apical vaginal wall, the upper urinary tract must be evaluated because severe prolapse can cause angulation of the ureters resulting in ureteral obstruction.

Surgical Technique

Several modifications of the SSF have been described. The original technique described by Nichols involves suspension of the vaginal vault to the sacrospinous ligament (SSL) (Fig. 7.25) through the posterior compartment (Table 7.2). A modification was introduced by Winkler et al., suspending the vault to the SSL through the anterior compartment, with the aim to reduce the postoperative narrowing and lateral deviation of the upper vaginal wall. In 1993 Kovac and Cruikshank proposed the sacrospinous hysteropexy, in which the uterus was suspended bilaterally to the SSLs.

SSF is typically performed unilaterally on the right side (Fig. 7.26), which offers the anatomical advantage of absence of the sigmoid colon on this side. In cases of severe genital prolapse, bilateral suspension may be considered. In this latter case the surgeon must ensure that there is adequate vaginal space, so that the bilateral suspension does not cause stricture in the rectum.

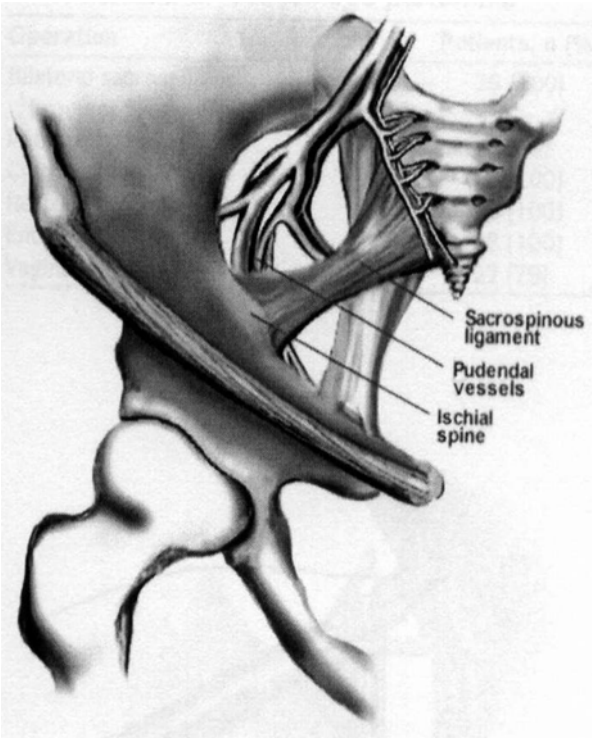


Fig. 7.25 The sacrospinous ligament and its relation with pudendal vessels and nerves and ischial spine

Table 7.2 The technique step-by-step

Identification of the pararectal space
Visualization of the sacrospinous ligament
Avoid injury of pudendal vessel and nerve (behind the ligament and the ischial spine)
Sutures >2 cm medial to the spine
Nonabsorbable sutures

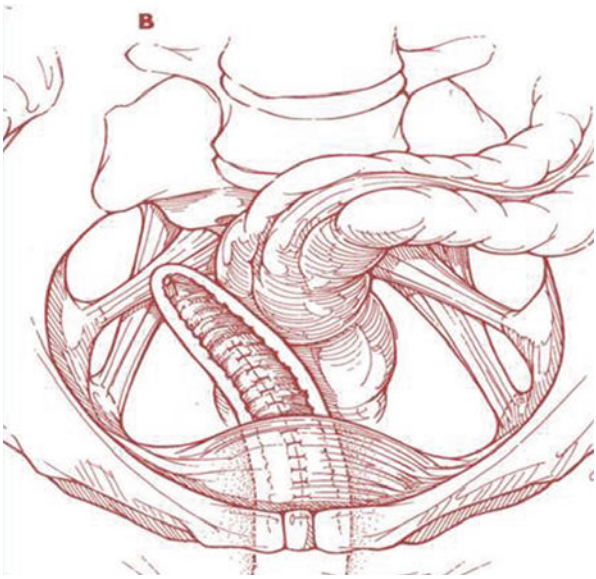


Fig. 7.26 Schematic view of monolateral sacrospinous ligament fixation

The posterior approach involves a posterior vaginal incision and a posterior colporrhaphy dissection, with subsequent perforation of the rectal pillar near the ischial spine. With blunt dissection of the pararectal space medial to the ligament, the coccygeus muscle and the sacrospinous ligament are exposed (Fig. 7.27). *The anterior approach* involves an anterior vaginal wall incision and a dissection of the ipsilateral paravesical and paravaginal area from the level of the bladder neck to the ischial spine along the arcus tendineus fasciae pelvis (Fig. 7.28). This dissection opens a large space for the vaginal apex and avoids the narrowing often caused by the posterior approach. Then the ligament is exposed with posterolateral dissection within the retroperitoneal place using two Breisky-Navratil retractors (one placed medially to sweep the rectum medially off the ligament and the other laterally) and a Haney retractor posteriorly, just in front of the coccygeus muscle at the 7 o'clock position. Various devices (Fig. 7.29) have been used to place sutures into the sacrospinous ligament, including the Deschamps ligature carrier, Miya hook, and Capio in-line "push and catch" suturing devices. The lateral suspension suture is placed through the ligament 1–2 cm medially to the ischial spine to avoid injury to the pudendal vessels. Fixation of the vaginal apex is most commonly performed with permanent

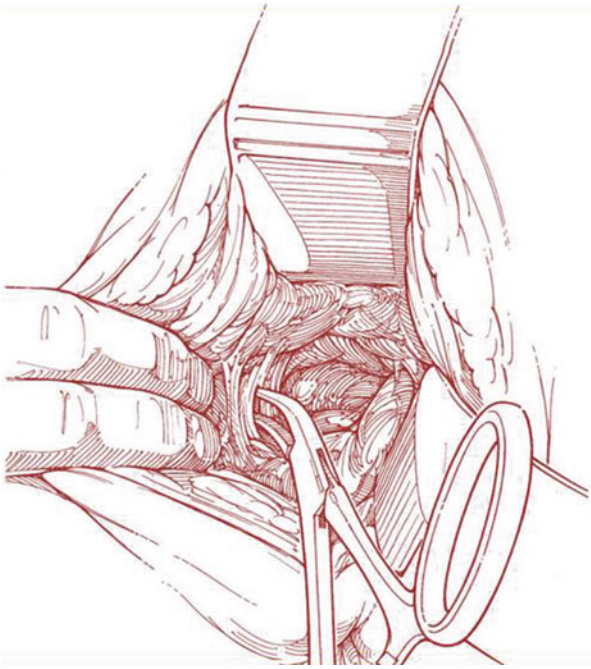


Fig. 7.27 Exposure of sacrospinous ligament

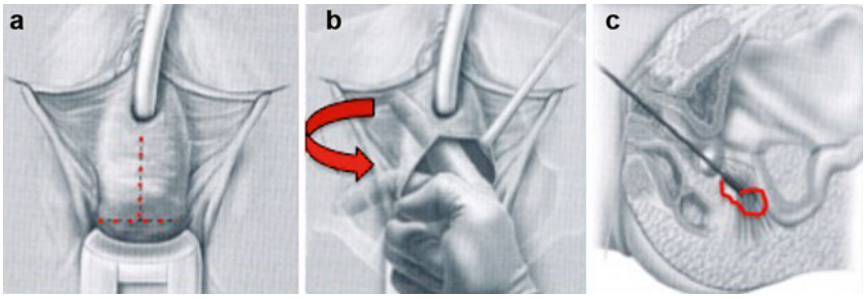


Fig. 7.28 Sacrospinous ligament fixation – anterior access: (**a**) anterior vaginal wall incision, (**b**) dissection of paravesical and paravaginal area, (**c**) placement of suture into the sacrospinous ligament

monofilament sutures (Fig. 7.30), but some surgeons prefer absorbable sutures to reduce the risk of suture erosion and granuloma formation. The relative advantages of permanent versus absorbable sutures have not been evaluated.

In cases of uterine hysteropexy, the dissection and suture placement are similar to those of vault suspension. The difference is that, after suture placement in the sacrospinous ligament, the end of the suture is brought through the uterosacral ligament and then through the vaginal epithelium.

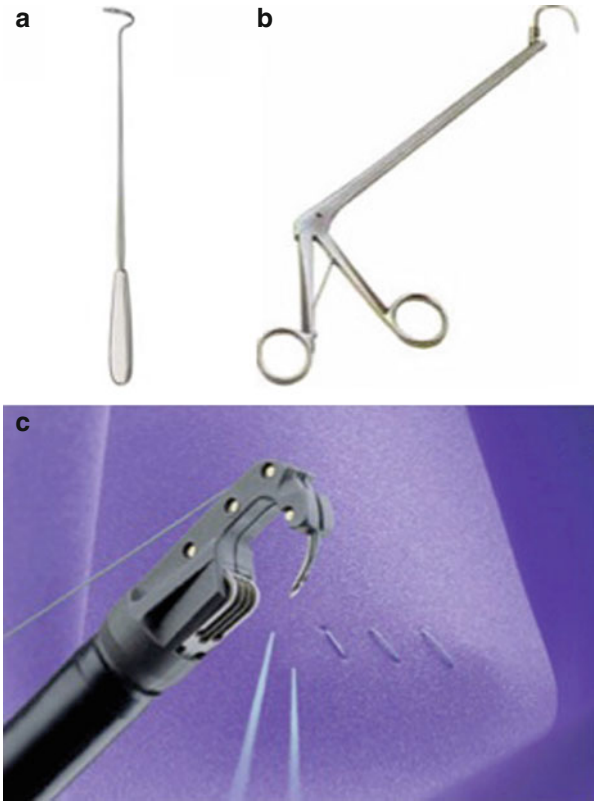


Fig. 7.29 Devices used to place sutures into the sacrospinous ligament – (**a**) Deschamps ligature carrier, (**b**) Miya hook, (**c**) Capio™ suturing device

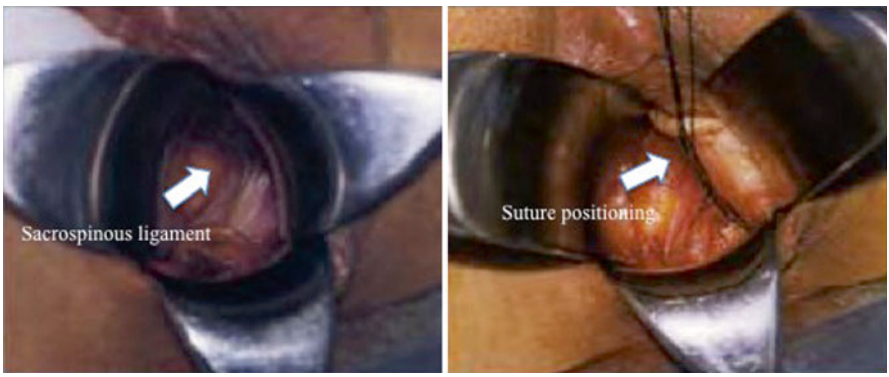


Fig. 7.30 Sacrospinous ligament fixation: intraoperative images

Complications

Local *neurologic complications* may include pudendal, sacral, or sciatic neuropathy. A direct injury to major nerves is rare. In this case a re-operation is mandatory to remove the sutures. More frequently pudendal nerve entrapment occurs and

results in pain localized in the buttock or perineum. The pain may improve after replacement of lateral fixation sutures more medially. Moreover, gluteal pain or paresthesias occurs after SSF, possibly due to peripheral nerve trauma. Usually these symptoms are transient and self-limited; sometimes they persist for weeks or months postoperatively.

Serious *vascular injury* is a rare complication, but it can be life-threatening. It usually results from injury of small vessels along the medial aspect of the rectum. Less commonly, the medial retractor can disrupt deeper vessels in the presacral area. For most cases, sutures or surgical clips to the involved vessels can be placed under direct vision after exposure with simple retraction. If the vessels cannot be visualized, the use of prolonged pressure packing may become necessary. Rarely a selective arterial embolization is necessary.

More rare complications of SSF include: infections, suture abscesses, bowel injury, and bladder lacerations.

Point of Interest

The anatomical cure rate of the apical vaginal segment after SSF ranges from 89 to 90 %, but the anterior vaginal segment represents a site particularly vulnerable to recurrence. *Recurrent cystoceles* have been reported in 7.6–92 % of patients after SSF, depending on the other concomitant procedures performed. It has been proposed that posterior deflection of the vaginal wall after SSF leads to increased exposure of the anterior compartment to intraperitoneal forces. It has also been suggested that underestimation of the severity of anterior prolapse on preoperative examination may play a role. A preoperative identification of all areas of prolapse and a subsequent modification of the pelvic reconstruction technique according to intraoperative findings are important key elements to reduce this kind of complication.

Sexual dysfunction has been reported after SSF. The retroversion of the vaginal apex and deviation after unilateral SSF appear to have no adverse effects on coital function, but the postoperative vaginal narrowing is likely correlated with this kind of dysfunction. Some papers underlined that vaginal narrowing after SSF was more likely the result of repair of other concurrent vaginal defects (mainly anterior colporrhaphy), rather than of SSF itself.

What Do the Guidelines Say

Abdominal Sacral Colpopexy Versus Vaginal Sacrospinous Colpopexy

SSF showed a higher rate of recurrent vault prolapse, more dyspareunia, shorter operating time and recovery time, and lower cost. Data on the subjective success rate, patient satisfaction, and impact of the surgery on quality of life were too few for reliable conclusions.

Comparing Different Vaginal Approaches: One Type of Upper Vaginal Prolapse (Uterine and Vaginal Vault) Repair Versus Another

The last Cochrane review on POP surgery (2013) concluded that all vaginal approaches to correct upper vaginal prolapse, i.e., uterosacral ligament suspension, McCall culdoplasty, iliococcygeus fixation, and colpocleisis, are relatively safe and effective interventions (level 3 evidence, grade C), but there is no evidence that one technique is better than another.

Vaginal Sacrospinous Uterine Suspension Versus Vaginal Hysterectomy

Women undergoing sacrospinous hysteropexy had a median hospital stay that was 1 day shorter than that in the hysterectomy group, and the mean number of days to return to work was 23 days less compared to the hysterectomy group. No differences were reported in domain scores for quality of life and urogenital symptoms between the two procedures. There were more adverse symptoms in the SSF group, mostly due to buttock pain. No differences were found between the two groups in terms of apical, anterior, and posterior prolapse recurrences.

Total Vaginal Polypropylene Mesh (TVM) Versus Sacrospinous Colpopexy

The SSF group had a higher objective recurrence rate. No differences were identified between the groups in terms of de novo SUI, bladder overactivity, dyspareunia, and pelvic pain or in functional outcomes measured with the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), the Urinary Impact Questionnaire (UIQ), the Colo-Recto-Anal Impact Questionnaire (CRAIQ), or the Pelvic Organ Prolapse Impact Questionnaire (POPIQ).

Meshes

Franca Natale, Elisabetta Costantini

Background

Despite modifications and evolutions of the technique, traditional surgery for pelvic organ prolapse (POP) has a failure or recurrence rate of 30–50 % and a prevalence of reoperation of 29–40 % within 3 years.

The highest rates of reoperation occur for apical defects (33 %), combined anterior and apical defects (15 %), or posterior and apical defects (12 %).

In an effort to improve outcomes in POP repair, especially of the anterior compartment, multiple biological and synthetic graft materials have been introduced.

Prosthetic materials have at least four main purposes in pelvic reconstructive surgery:

- Substitution, where lacking supportive tissue is replaced by mesh
- Reinforcement, where inadequate tissue is augmented to improve its performance
- Generation, which involves the induction of new supportive tissue
- Consolidation, where mesh is used to complement surgery

On the basis of these premises, the rationale for the use of mesh is:

- To replace the damaged visceral fascia
- To restore cohesion between visceral and parietal fascia to rebuild the hammock connected to the arcus tendineus fascia pelvis
- To stabilize the bladder hammock

Unfortunately, because of secondary complications associated with the use of mesh, all the guidelines and reviews recommend their use under strict control. In particular the evidence is not sufficient to support the use of permanent meshes or grafts at the time of vaginal apical or anterior compartment repair surgery except in the context of randomized controlled trials.

Type of Meshes

The ideal graft/mesh should be:

- Clinically and physically inert
- Noncarcinogenic
- Mechanically strong
- Without allergic or inflammatory reaction
- Sterile
- Not physically modified by body tissue
- Readily available
- Inexpensive
- With minimal risk of infection and rejection

The optimal implant, once healed, would restore normal anatomy and function to the vagina and the surrounding pelvic organs and be more durable or equally durable to autologous tissue. It would be biocompatible, and, if biodegradable, it should persist long enough for incorporation of the surrounding native tissue. It should resist to mechanical stress and shrinkage, be pliable and easily manipulated during surgery, and not result, once implanted, in adhesion formation at the visceral surfaces.

Currently, there are no biologic or synthetic implants that meet all the above criteria.

Surgical mesh materials can be divided into three general categories:

- Synthetic
- Biologic
- Composite (i.e., a combination of any of the previous two categories)

Synthetic Meshes

Synthetic mesh can be absorbable or nonabsorbable. Once absorbable synthetics are implanted, macrophage activation leads to mesh absorption and subsequent recycling of by-products into new collagen fibers. The commercially available absorbable synthetic mesh implants are polyglycolic acid and polyglactin 910. Although both products are considered absorbable, their properties are distinct. Polyglactin 910 starts to hydrolyze during the third week after implantation and loses the majority of its mechanical value after 30 days, whereas polyglycolic acid requires 90 days for absorption.

The main characteristics of nonabsorbable synthetic meshes are pore size, fiber type, and stiffness, and on the basis of pore size and fiber type, they have been classified in four types (Fig. 7.31):

- *Type I meshes* (Prolene®, Marlex®) contain large pores (>75 μm) that allow the admission of macrophages to prevent infection and in-growth of fibroblasts, blood vessels (angiogenesis), and collagen, to form fibrous connections to the surrounding tissue.

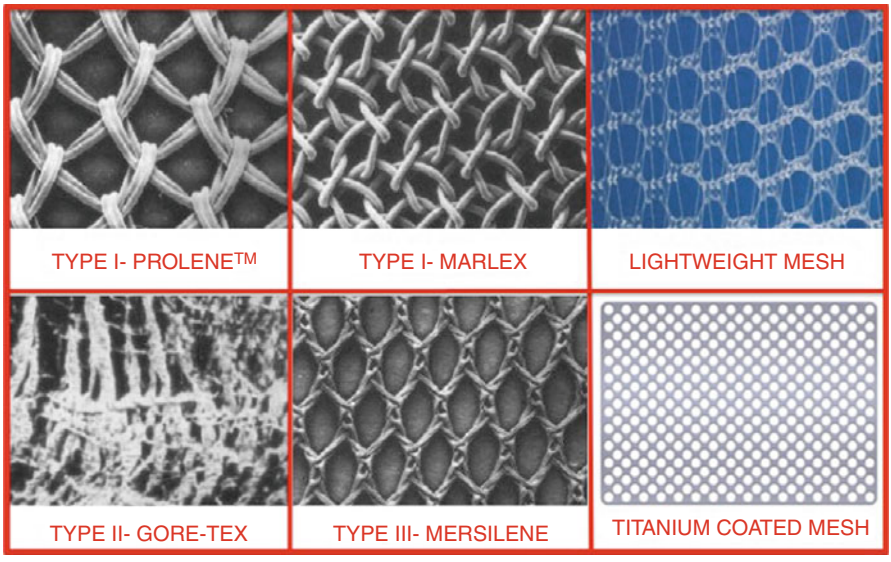


Fig. 7.31 Different synthetic meshes used in urogynecology

- *Type II meshes* (Gore-Tex®) have a pore size <10 μm in at least one of the three dimensions (microporous).
- *Type III meshes* (Mersilene®) are macroporous but have microporous components that often include braided and/or multifilament materials.
- *Type IV meshes* have submicronic pore size.

Flexibility is an important property that appears to be related to pore size: the greater the pore size and the more the mesh flexibility, the lower the erosion rate. Currently the type I meshes are considered the best choice in urogynecology.

Recently other kinds of meshes have been introduced: the *titanium-coated mesh, the ultralightweight mesh and the polyvinylidene fluoride (PVDF)* monofilament mesh (Fig. 7.31). Some studies found that coating the mesh with titanium causes less severe inflammatory reactions than non-coated polypropylene. Ti-mesh® is a titanium-coated low-weight mesh and combines the advantages of light material with a superior biocompatibility due to the titanium coating, at least in terms of chronic inflammatory reactions.

Another mesh today available is the *lightweight mesh*, to add more favorable biocompatible characteristics without losing any critical tensile strength mesh. The main characteristics of lightweight meshes are:

- Reduced overall "mesh load," high hydrophilic
- Low memory and easily intraoperative handling while maintaining durability
- Generally not palpated during postoperative examinations

Different types are available in different shapes including Artisyn® Y-Shaped Mesh, Alyte® Y-Mesh Graft, and Restorelle™ Y.

The Y-meshes, particularly useful in colposacropexy, have a vaginal section with anterior and posterior flaps and a sacral section. The anterior and posterior flaps are used for anterior and posterior vaginal attachment, and the sacral flap for attachment to the sacral promontory (Fig. 7.32). Finally the polyvinylidene fluoride (PVDF) (DynaMesh®) mesh, widely used in abdominal hernia repair, has been recently introduced in the POP surgical treatment. It is highly biocompatible, it seems to be

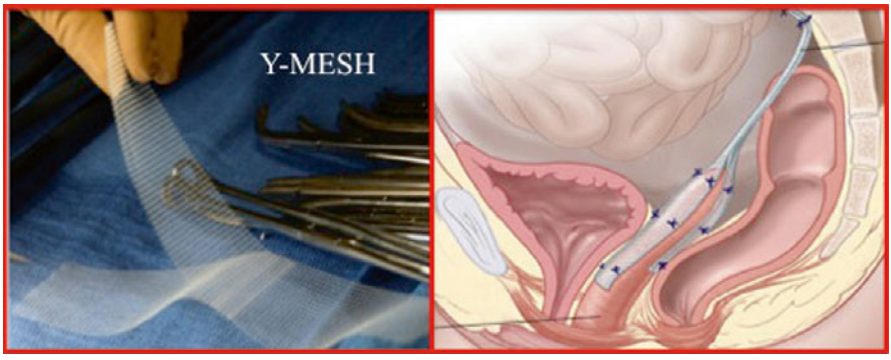


Fig. 7.32 Y-mesh used in colposacropexy. The anterior and posterior flaps are used for anterior and posterior vaginal attachment and the sacral flap for attachment to the sacral promontory

more resistant to hydrolysis and degradation in comparison to polyester and polypropylene. It also shows a reduced inflammatory and fibrotic reaction compared to polypropylene.

Up to now it is not clear whether the features of these new meshes would translate into any direct clinical benefit. Such questions can only be answered through clinical research.

Biologic Grafts

The most commonly used biologic materials available for POP repair include:

- Autograft (rectus fascia)
- Allograft (cadaveric fascia)
- Xenograft

Xenografts may be either nonabsorbable (i.e., Pelvicol®) or absorbable (small intestine submucosa [SIS]) (Fig. 7.33). Pelvicol® is derived from porcine dermis: a patented process removes all fats and cellular materials through a series of organic and enzymatic extraction that leaves the material without any DNA. Then the matrix is stabilized using a cross-linking agent to maintain strength and provide permanence. Gamma sterilization of the tissue ensures sterility. It has been demonstrated that perforating the porcine dermis improves the graft take and decreases wound infections by allowing for increased tissue in-growth and revascularization of the vaginal epithelium overlying the graft. Tensile strength and suture pullout strength were maintained in the perforated graft.

SIS is harvested from porcine jejunum and is composed of mucosa, muscularis mucosa, and submucosa. Processing leaves the extracellular collagen matrix intact, thus allowing the presence of collagen, growth factors, glycosaminoglycans, proteoglycans, and glycoproteins to promote host cells proliferation through SIS layers. Theoretically, the SIS scaffold should be entirely remodeled and replaced by the host's connective tissue in 90 days.

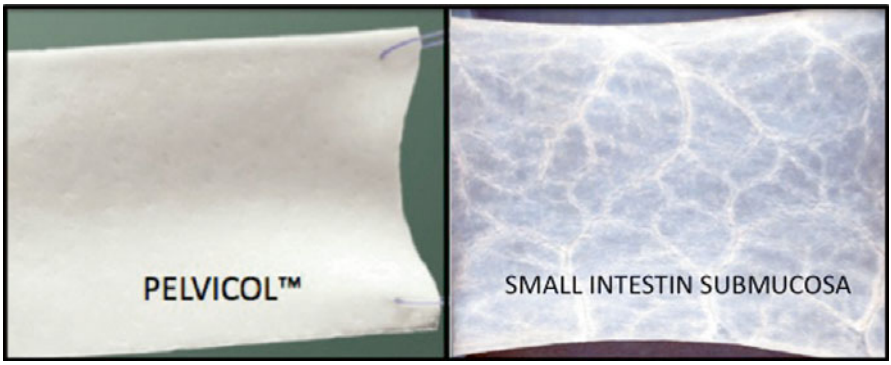


Fig. 7.33 Biological grafts

Surgical Techniques Using Meshes

Historically the first mesh used in POP repair refers to abdominal colposacropexy, the gold standard for the surgical correction of vaginal vault prolapse, a technique which demonstrated a long-term durability and precise anatomical restoration. The goal of this procedure is to elevate the vaginal apex to the sacral promontory using a mesh bridge: the resultant vaginal axis is the most physiologic of all reconstructive procedures, and the vaginal length is maintained.

Colposacropexy can be also performed by laparoscopic- or robotic-assisted procedure with the aim to improve visualization of anatomy of the peritoneal cavity because of laparoscopic and robotic magnification; decrease postoperative pain; shorten hospitalization, resulting in potential cost reduction; and allow more rapid return to work.

In the last two decades, the meshes started to be used also in the vaginal approach to correct cystocele (anterior repair) and rectocele (posterior repair) and also the top of the vagina to correct uterine prolapse or vaginal apical prolapse (apical repair).

Vaginal Anterior Repair

Hand-Tailored Mesh

In the 1990s, urogynecologists began using surgical mesh for transvaginal POP repair and, to do so, surgeons cut the mesh to the desired shape, placing it through a corresponding incision. A variety of permanent *polypropylene mesh overlays* have been evaluated in case series for the management of anterior wall prolapse with an anatomical success rate ranging from 76 to 100 % (Fig. 7.34a).

With the aim to reduce the complications associated with the synthetic meshes, *biologic materials* (cadaveric fascia lata, porcine dermis, porcine small intestine submucosa, bovine pericardium collagen) have been used (Fig. 7.34b). The reported success rate widely ranges from 52 %, using porcine dermis, to 100 % using cadaveric fascia lata.

Trans-obturator Kits

Over the next years, surgical meshes for transvaginal POP repair became incorporated into "kits" that included tools to aid in the delivery and insertion of the mesh. The surgical mesh kits continue to evolve, adding new insertion tools, tissue fixation anchors, and surgical techniques, using absorbable and biologic materials. The *trans-obturator kits* consist of four helical needles and a polypropylene mesh with four arms, two for each side. After the dissection of the bladder laterally toward the ischiopubic ramus, the superior needle is inserted lateral to the level of the clitoris,

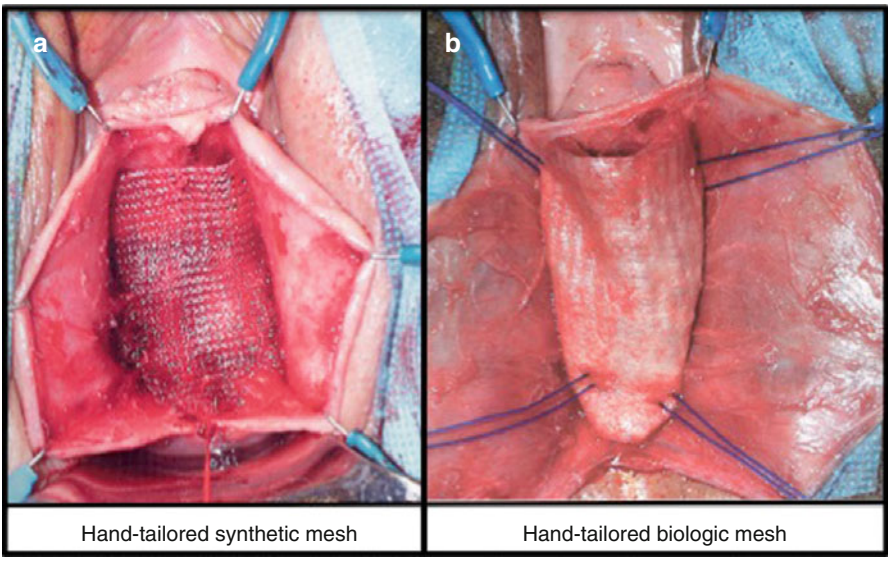


Fig. 7.34 Tailored synthetic (**a**) and biological grafts (**b**)

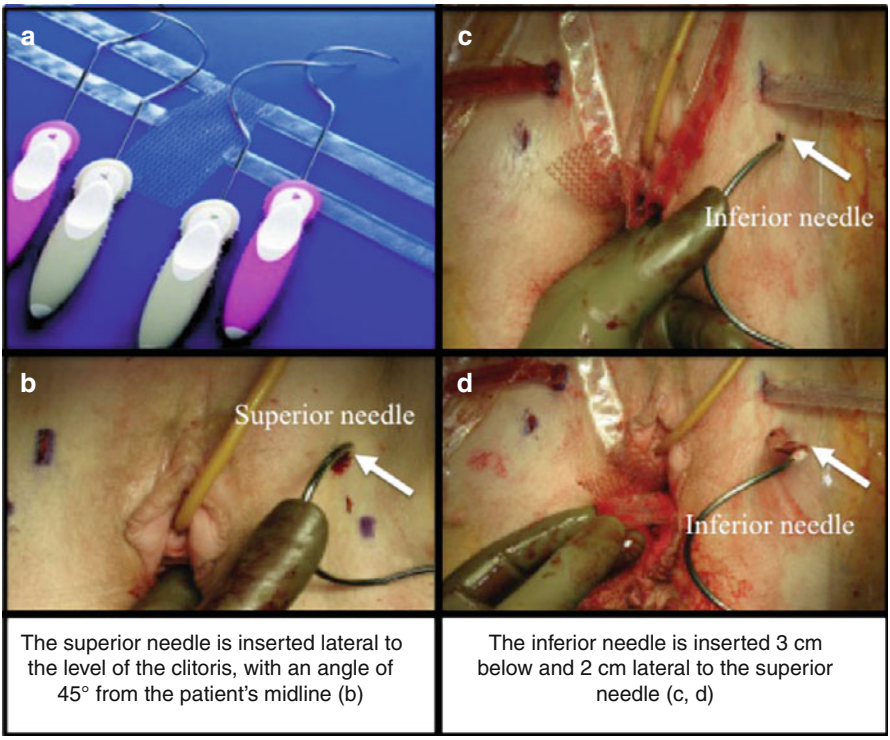


Fig. 7.35 Trans-obturator kits for anterior vaginal POP repair: (**a**) the elicoidal needles and the polypropylene mesh; (**b**) position and insertion of the superior needle; (**c**, **d**) insertion of the inferior needle

with an angle of 45° from the patient's midline (Fig. 7.35a, b). Then the inferior needle is inserted 3 cm below and 2 cm lateral to the superior needle (Fig. 7.35c, d). The tip of the needle should be pointed directly at the ischial spine. The procedure is repeated on the contralateral side. The endoscopy is then performed to ensure the integrity of bladder and urethra. The mesh should now site underneath the cystocele in a tension-free manner, the tail is attached at the vault and under urethra, and the redundant tail is trimmed off. The vaginal incision is closed, the plastic sheaths are removed, and the mesh arms are cut at skin incisions.

Single-Incision Kits

Recently new single-incision kits were introduced in the market. The devices allow a minimally invasive approach to treat anterior and apical defects. The mesh is inserted through a small vaginal incision and secured in their position using self-fixating tips attached to the mesh (Fig. 7.36); they are inserted into the sacrospinous ligament (SSL) and the obturator internus muscle without trocars to secure the correct positioning of the mesh until natural tissue ingrowth occurs.

Currently, there are not long-term data to recommend the use of these kits.

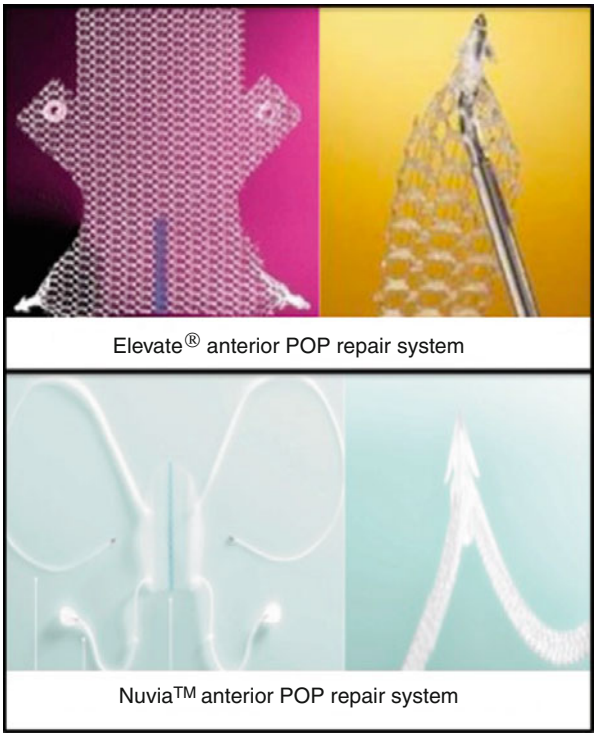


Fig. 7.36 Single-incision kits

Vaginal Posterior Repair

As traditional posterior repair is associated with high success rates (76–90 %), the need for mesh augmentation in the posterior compartment is questioned, and the use of the prosthetic surgery is limited. Furthermore physicians have been hesitant to place mesh in the posterior compartment, secondary to its proximity to the rectum and potential infection issues with foreign body placement. Moreover the mesh avoids the expansion during evacuation or coitus, leading to difficult defecation and dyspareunia, the most frequent complications of this kind of surgery.

Vaginal Posterior and Apical Repair

For the simultaneous repair of an apical and posterior defect, it is possible to use kits consisting of two curved needles and a central polypropylene mesh (Fig. 7.37). The needle is inserted 3 cm lateral and posterior to the anal orifice, crossing the ischio-rectal fossa underneath the iliococcygeus muscle. At 2 cm posterior and 3 cm medial to the ischial spine, the trocar pierces the sacrospinous ligament and passes through the pararectal space emerging in the vaginal incision. In this way, the vaginal apex is suspended at the level of the ischial spine, replicating a more normal vaginal axis. Locking connectors on the ends of the arms of the mesh attach to each needle tip and are used to hold the mesh secure to the needle during passage of the mesh through the body. Once snapped onto the needle tip, the connectors cannot be removed.

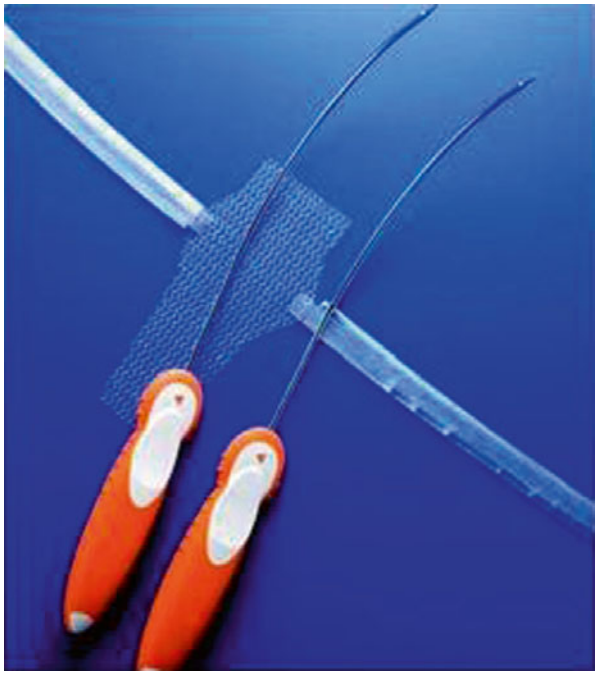


Fig. 7.37 Anterior and apical support system (Apogee system, AMS)

The most important complication associated with this kind of surgery and generally in the sacrospinous ligament suspensions is the vessel injury, and the inferior gluteal artery is the most susceptible vessel. To avoid complications, it is important to insert the needle into the sacrospinous ligament 3 cm medial and 2 cm lower than the level of the ischial spine to avoid the pudendal and inferior gluteal bundles.

Complications

The most common complication of transvaginal POP repair with mesh is vaginal *mesh erosion* – also called *exposure*, *extrusion*, or *protrusion* – which occurs in approximately 10 % of cases but reported in higher percentages in some series. More than half of the women who experienced erosion from nonabsorbable synthetic mesh required surgical excision in the operating room and some women required two or three additional surgeries. Another new complication, increasingly reported in the literature, is *mesh contraction* – which causes vaginal shortening, tightening, and pain.

New-onset stress urinary incontinence has been reported to occur more frequently after mesh-augmented anterior repair than after traditional anterior repair without mesh. Other reported complications are *pain* (including dyspareunia), *infection, urinary problems, bleeding, organ perforation, recurrent prolapse, neuromuscular problems, vaginal scarring or shrinkage, and emotional problems*. Many of these complications need additional intervention, including medical or surgical treatment and hospitalization, and some sequelae (e.g., pain) may continue despite mesh removal.

Research continues to look for reducing these complications through less invasive surgical techniques, expertise, and new type of mesh.

The FDA Warning

In order to better understand the use of surgical mesh for POP and SUI, the Food and Drug Administration (FDA) in 2011 conducted a systematic review of the published scientific literature from 1996 to 2011 to evaluate its safety and effectiveness. The literature review revealed that:

- Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
- Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomical benefit compared to traditional POP repair without mesh, this anatomical benefit may not result in better symptomatic results.

Basing on these data, FDA recommends that health-care providers should:

- Obtain specialized training for each mesh placement technique and be aware of the risks of surgical mesh.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder, and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall in POP repair using surgical mesh.
- Provide patients with a copy of the patient labeling from the surgical mesh manufacturer if available.

In addition, the FDA also recommends that health-care providers should choose mesh surgery only after weighing the risks and benefits of surgery with mesh versus all surgical and nonsurgical alternatives.

What the Guidelines Say

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organization (WHO). In the last 10 years ICUD has held consultations on several urological pathologies, including urinary incontinence and POP. This branch of the consultations is known as the International Consultation on Incontinence (ICI).

ICUD issues guidelines and subsequent recommendations are based on the published evidence and graded as follows:

- Grade A: highly recommended
- Grade B: recommended
- Grade C: optional
- Grade D: not recommended

ICI 2013

On the basis of the latest ICI evaluation, we summarize the most important conclusions reached:

- Absorbable mesh augmentation of native tissue repair improves the anatomical outcome as compared to native tissue repair alone with no increased complication rate (Grade B).
- Biological grafts in meta-analysis have improved anatomical outcomes with no change in subjective outcomes as compared to native tissue repairs (Grade B).

- Consistent data supports a superior anatomical outcome for polypropylene mesh as compared to biological graft (Pelvicol) in the anterior compartment. Mesh exposure rate was significantly higher in the polypropylene mesh group (Grade A).
- Consistent evidences demonstrate improved anatomical and subjective outcomes for polypropylene mesh as compared to anterior colporrhaphy (Grade A). These outcomes did not translate into improved functional outcomes using validated questionnaires or a lower reoperation rate for prolapse. The mesh group was also associated with longer operating time, greater blood loss, and a not significant tendency toward higher cystotomy, de novo dyspareunia, and de novo stress urinary incontinence rate as compared to anterior colporrhaphy without mesh. Apical or posterior compartment prolapse was significantly more common following anterior repair using polypropylene mesh and mesh extrusion rate was 10.4 % with 6.3 % undergoing surgical correction (Grade B).
- To date no study has shown any benefit to mesh overlay or augmentation of a suture repair for posterior vaginal wall prolapse (Grade B).

All these data were confirmed by the last Cochrane review on POP surgery (2013) which showed that the use of absorbable polyglactin mesh overlay, absorbable porcine dermis, or polypropylene mesh at the time of anterior vaginal wall repair reduces the risk of recurrent cystocele on examination; however improved outcomes including patient satisfaction, quality of life, and reduced operations for recurrences have not yet been demonstrated. Furthermore, anterior polypropylene mesh alone demonstrated an improved subjective outcome as compared to native tissue anterior repair without any difference between the groups in the rate of dyspareunia. The operating time, blood loss, rate of apical or posterior compartment prolapse, and de novo stress urinary incontinence were greater in the polypropylene mesh group, which was associated with an 11.4 % mesh erosion rate and 6.8 % requiring surgical reintervention.

Sacrocolpopexy

Elisabetta Costantini

Pelvic organ prolapse (POP) is estimated to affect nearly half of all females over 50 years of age and has a negative impact on the patient's quality of life. Women have an 11 % lifetime risk of undergoing pelvic reconstructive surgery for POP or urinary incontinence and the costs of POP surgery, as recorded in the North American population, might be in excess of $1 billion dollars. The etiology of POP is complex and multifactorial. Treatment depends on factors such as the severity or grade of POP, symptoms, the patient's general condition and expectations, and the surgeon's experience. Diverse surgical approaches are available for POP repair, the goals of which are to restore normal pelvic anatomy, restore or maintain normal urinary, bowel and sexual function, reduce the impact of symptoms, and improve quality of life.

Sacrocolpopexy (SP) is a procedure used to treat apical pelvic organ prolapse (POP) including uterine prolapse and posthysterectomy vaginal vault prolapse. Vaginal vault prolapse is an increasing problem in the United States, accounting for more than 30,000 surgical procedures in 1999. The risk of post-hysterectomy vaginal vault prolapse is estimated to be 1 % at 3 years and 5 % at 17 years. Although defects in the supporting structures of pelvic organs have been thought to be the cause of pelvic organ prolapse, the increase in surgical procedures over one decade suggests that other factors exist, including problems with surgical technique or improvements in POP diagnosis. Vaginal vault prolapse remains a challenging condition for pelvic surgeons. Clinical presentation varies and is associated with other compartment defects (cystocele, rectocele, or enterocele) in nearly 75 % of affected patients. Successful therapy for vaginal vault prolapse depends on a comprehensive evaluation including an assessment of all potential sites, specific vaginal support defects, and an assessment of urinary, fecal, and sexual function. These factors must be considered when selecting therapy for each patient. In addition, associated comorbidities will greatly influence the route of treatment. Thus, *effective management of POP hinges on an individualized, comprehensive evaluation of the pelvic floor tailored to fit each patient*.

Restoration of apical support can be carried out through vaginal or abdominal approaches. The transvaginal approach avoids the morbidity of an abdominal incision and affords access to and fixation of other concomitant vaginal defects. Transvaginal techniques require fixation of the apex to a number of pelvic supporting structures (sacrospinous ligament, iliococcygeus fascia, uterosacral ligaments). Some of these structures may be weakened or they can often be difficult to identify, particularly in the posthysterectomy patient. Depending on the method of apical support, the vaginal apex may also be anatomically displaced. Most commonly, the vagina is displaced posteriorly after a sacrospinous ligament fixation placing the anterior compartment at risk for recurrent cystocele. With some of the vaginal approaches, one must be concerned about reducing vaginal length. Reduction in vaginal length is a significant concern for younger, sexually active women. Despite the potential limitations, transvaginal sacrospinous fixation has been shown to preserve vaginal length and achieve an up to a 79 % success rate for correction of vault prolapse. The benefits of transabdominal approaches include consistent, reliable restoration of anatomy. The *abdominal sacral colpopexy* offers consistent fixation of the vaginal apex, by using a synthetic mesh and attaching it to the sacrum (Fig. 7.38). Thus, there is less dependence on weakened points of attachment. In addition, there is little anterior or posterior displacement of the vaginal axis. The major benefits of this approach, therefore, include a more reliable fixation of the vaginal apex with minimal changes to the vaginal anatomy. In addition, the transabdominal approach allows for concomitant enterocele repair via culdoplasty, concomitant cystocele, and rectocele repair and finally in some cases urinary incontinence can be treated, with the option of additional concomitant anti-incontinence surgical techniques, although the last point remains controversial.

Nowadays SP is considered the gold standard treatment and the most durable technique for repairing vaginal vault prolapse (Fig. 7.39). The technique, described by Huguier and Scalin in 1958 and subsequently by Lane in 1962, has a success rate

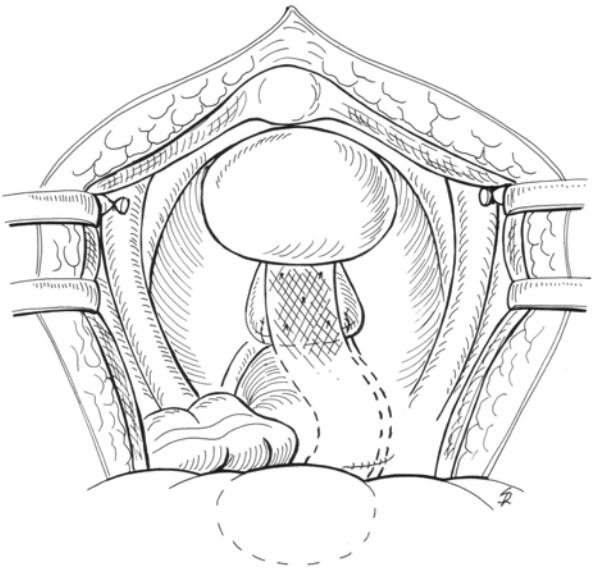


Fig. 7.38 Schematic SP draw: two meshes fix the vaginal apex to the sacrum

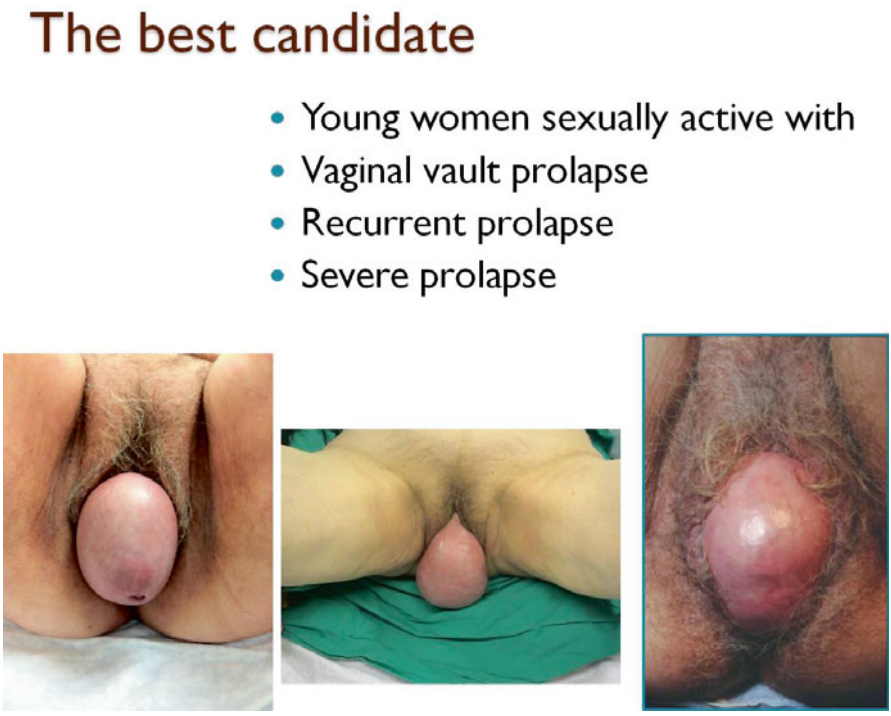


Fig. 7.39 Indications of SP

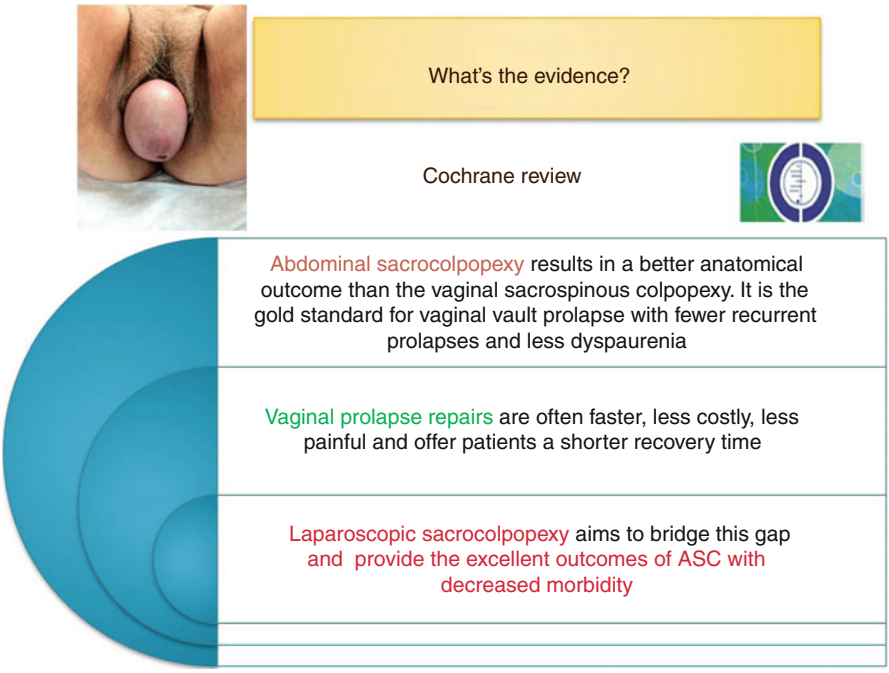


Fig. 7.40 Results from Cochrane review

of more than 95 % at 3 years and 84 % at 5 years. The Cochrane review in 2013 confirmed SP has superior outcomes to a variety of vaginal procedures including sacrospinous colpopexy, uterosacral colpopexy, and transvaginal mesh. 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 (Fig. 7.40). Although predominantly used in posthysterectomy vaginal vault prolapse, *SP can be performed with a uterus in situ either with or without concomitant hysterectomy*. Hysterectomy at the time of sacrocolpopexy for management of uterine prolapse, although it allows the same excellent result in terms of functional and anatomical outcomes, may be associated with increased rates of mesh exposure. In recognition of this increased risk, some surgeons have advocated supracervical hysterectomy as an alternative to total hysterectomy before SP. Powered uterine morcellation is required when subtotal hysterectomy is performed at laparoscopic- or robotic-assisted minimally invasive sacrocolpopexy and has become controversial following a recent US Food and Drug Administration safety communication. While subtotal hysterectomy appears to reduce the risk of mesh exposure, further evaluation is required in the light of unanticipated uterine pathology. In case of severe uterine prolapse, another option is the uterus preservation, which recently has gained popularity.

The feasibility of *uterus-sparing POP procedures* has been investigated since the late 1990s. There are three major controversies associated with uterus

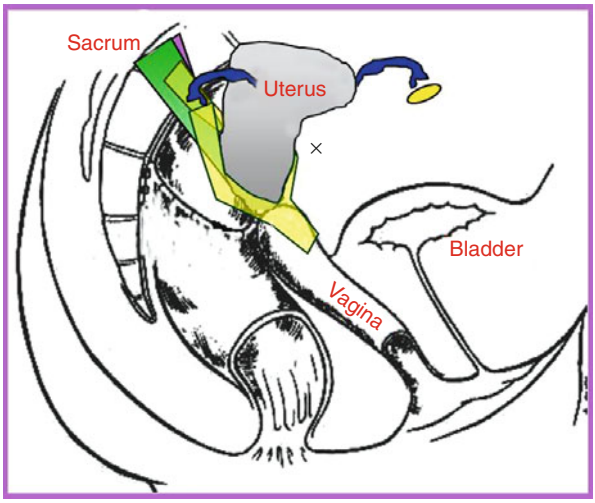


Fig. 7.41 Hysterocolposacropexy

preservation surgery for POP. First, many surgeons believe hysterectomy prevents prolapse recurrence, because the presence of the uterus might subject pelvic reconstruction to undue stress and this is particular true when a mesh is not used. On the other hand, hysterectomy-associated pelvic floor dissection might increase the risk of pelvic neuropathy and disrupt natural support structures. The second argument is that uterus preservation can expose the patient to potential pathologies (such as cancer) in what might be considered an almost useless organ. The risk of potential malignancy is estimated to be different in women with or without symptoms of abnormal vaginal bleeding: 1.09 % versus 0.22 %, respectively. The third controversial point concerns the complications that are associated with hysterectomy apart these considerations, the decision to remove a healthy organ, such as the uterus in POP repair, must take the patient's preferences, needs, and values into consideration. Moreover, other major factors have come into play such as the profound changes in women's lifestyles, beliefs, and perspectives, particularly with regard to sexual function and pregnancy. In the last two decades, several studies have described successfull anatomical and functional outcomes after uterus preserving POP repair including the abdominal and the laparoscopic approach, i.e., the *hysterocolposacropexy* (HSP) (Fig. 7.41). These studies confirm that uterus-sparing surgery is feasible in women who want to preserve integral vaginal function and satisfaction with their body image. The advantages of uterus preservation include the maintenance of pelvic anatomy integrity, reduction of intraoperative blood loss, shortened operating times and hospital stays, and reduced rate of mesh erosion. Finally, uterus preservation appears to contribute positively to the patient's self-esteem, body image, confidence, and sexuality. Consensus is growing that the uterus can be preserved at the time of pelvic reconstructive surgery in appropriately selected women who desire it. Although the decision will be determined by the

patient's preference and the surgeon's skills and experience, it is imperative that women fully understand the risks of incurring uterine and cervical pathology over time and the need for continued routine surveillance measures.

Both SP and HSP can be performed laparoscopically or robotically assisted. The *laparoscopic sacrocolpopexy* was initially popularized in an attempt to improve pelvic visualization, operative morbidity, and postoperative functional results. The laparoscopic approach provides the excellent outcomes of the abdominal SP with the decreased morbidity of the vaginal approaches. Following the Food and Drug Administration (FDA) transvaginal mesh alerts in 2008 and 2011, there has been a significant increase in uptake of minimally invasive sacral colpopexy performed in the USA. Furthermore the robot-assisted laparoscopic sacral colpopexy was then introduced to shorten the learning curve associated with traditional laparoscopic SP. Currently the preferred route of entry to performing SP is the laparoscopic approach which has been demonstrated to have reduced blood loss, postoperative pain, and recovery time as compared to the open approach and reduced operating time, postoperative pain, and cost as compared to the robotic approach.

Surgical Technique

While the data supporting SP is robust, has been described for over 50 years and nearly 20 years have passed since Dr Benson's landmark randomized surgical trial, there are still many uncertainties relating to the preferred technical aspects of the procedure. In particular there have been many modifications of the technique in recent years, with a variety of materials (expanded polytetrafluoroethylene, cadaveric fascia, light meshes) and attachments to the sacrum (bone screws, tackles) being advocated. One major modification has been the method of attaching the graft to the vaginal wall, from a simple apical attachment as described by Lane to grafts that extend down to the ventral and dorsal aspects of the vagina. Additional procedures such as paravaginal repair of the anterior vaginal wall or concomitant posterior colporrhaphy have been advocated to increase the durability of abdominal SP, but the success of these modifications and additional procedures has not been definitely studied.

Sacrocolpopexy Technique

The procedure has been performed for many years with several modifications and includes different procedures with different outcomes. The technique most widely used is that described by Timmons with mesh attached to the anterior and posterior aspects of the vault/apex with "extension" to correct prolapse in all three vaginal compartments.

The Procedure Step by Step

Step 1 – The peritoneal cavity is entered through a lower midline incision or a Pfannestiel incision. Large and small bowel is mobilized as needed to expose the pelvis and posterior peritoneum.

Step 2 – After identifying the vaginal vault, the peritoneum over the vaginal cuff is incised and dissected away from the vaginal apex. The anterior and posterior vaginal walls are dissected. Some surgeons attach the mesh directly on the vaginal vault without extension on the vaginal walls (Fig. 7.42). This makes the procedure easier and with less complications but the long-term results could be worse due to the higher probability of anterior and posterior compartment recurrences. Furthermore the large contact between mesh and vaginal walls avoids inadequate traction making the risk of mesh erosion lower, reduces the risk of recurrent anterior central defect, and partially corrects urethral hypermobility. So to obtain the best results, dissect the rectum-vaginal septum as far as the levator ani muscle and create a cleavage plane between the anterior vaginal wall and the bladder extending as far as the bladder trigone (the identification of the catheter balloon is the key point) (Fig. 7.43a–c).

Step 3 – Fix the mesh/meshes on the vaginal walls. Graft material selection: a variety of different graft materials were have been employed at the surgeon's discretion. Monofilament polypropylene mesh seems to be the best because the reported vaginal erosion rate seems to be lower than that of other synthetic grafts. What is demonstrated is that absorbable meshes do not work. *The design of graft material* is variable on the basis of surgeon preference: two rectangular meshes and one single mesh fixed on the anterior vaginal wall and then on the posterior vaginal wall or Y-shaped graft (Fig. 7.44). The Y-mesh is the most used in laparoscopic approach. *Suture on the vagina*: both permanent and absorbable sutures have been reported. As stitch erosions are reported, some surgeons prefer reabsorbable sutures. Another argument in favor of reabsorbale sutures is that when

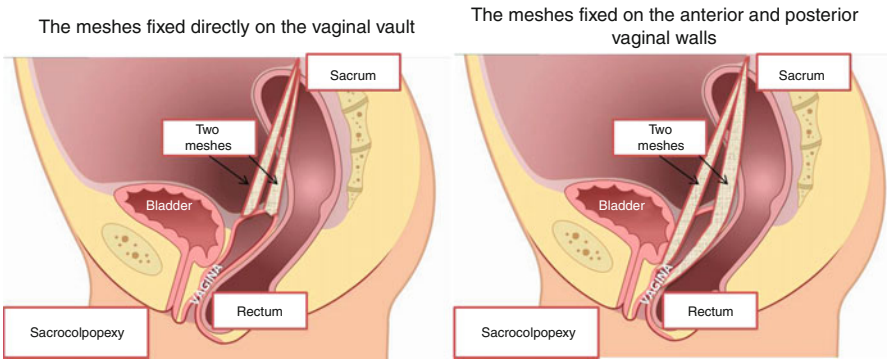


Fig. 7.42 Different attachments of the meshes to the vaginal vault

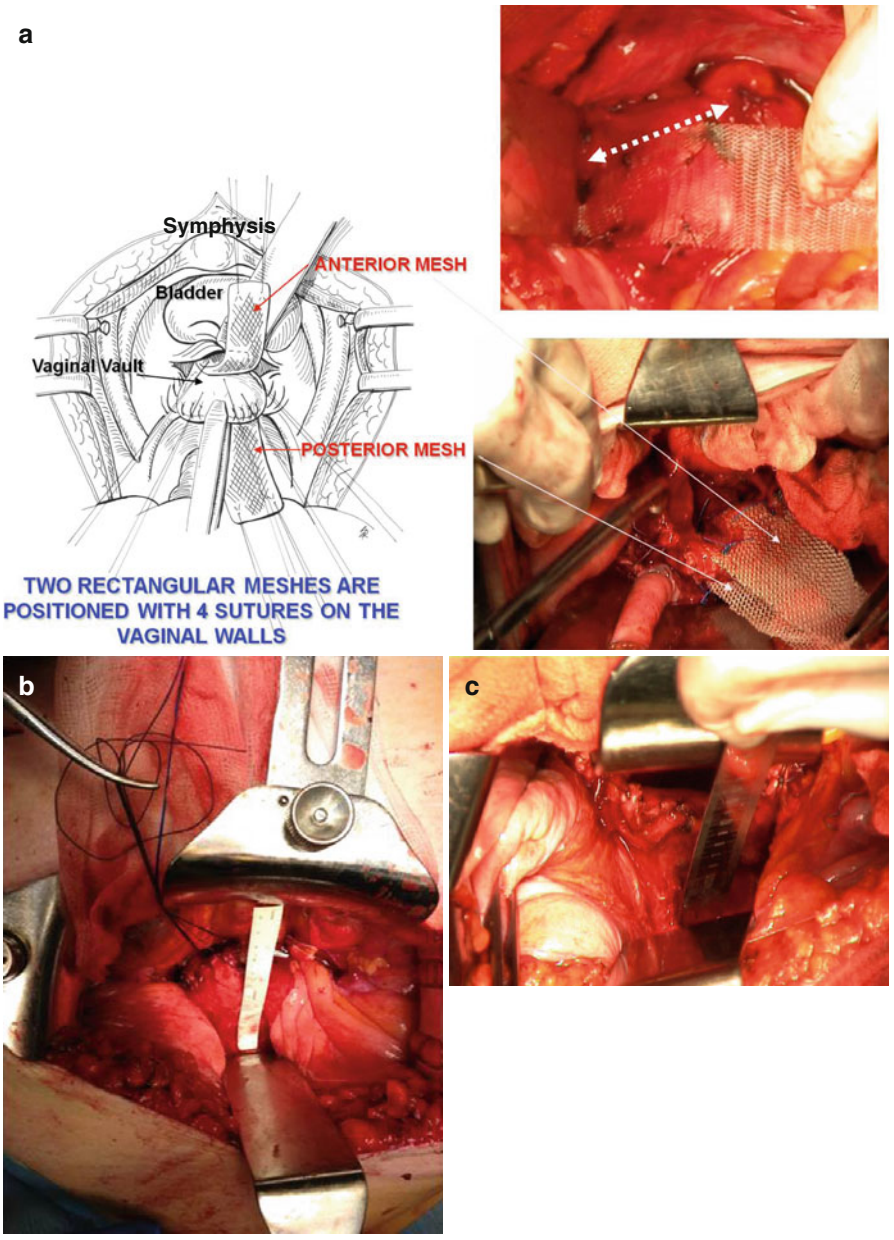


Fig. 7.43 (**a**) Two meshes are fixed on the anterior vaginal wall after an extended preparation of the anterior space between the vagina and the bladder, *double side arrow* indicates the anterior and posterior meshes; (**b**) the anterior vaginal wall preparation reaches the bladder neck level; (**c**) the posterior vaginal wall is prepared reaching the levator muscle plane

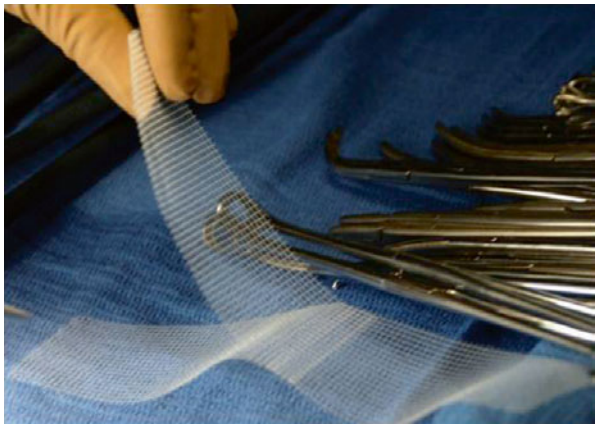


Fig. 7.44 The Y-mesh commonly used in laparoscopic SP

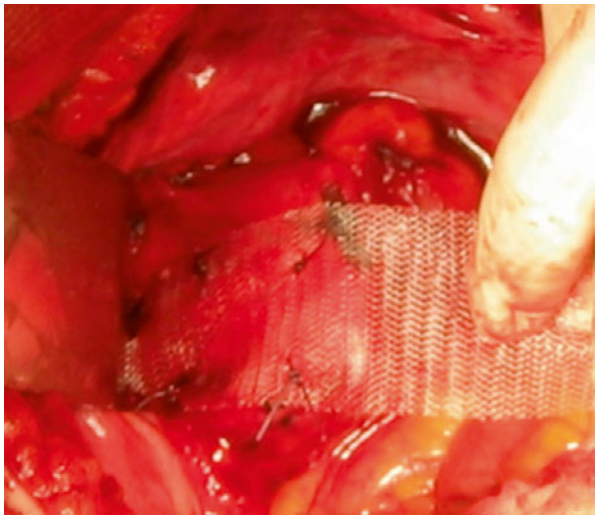


Fig. 7.45 Four sutures fix the mesh on the anterior vaginal wall without folds and well stretched

the mesh is adherent to the vaginal walls, it easily will be incorporated in a short time with no need of permanent sutures. No evidence-based consensus has been reached on the *number of sutures* necessary to secure the mesh to the vagina. They range from 2 to 3 on the anterior vagina to 6–10 in the posterior vagina (Fig. 7.45). In some reports the meshes are fixed with two longitudinal continue sutures. Whatever the number of sutures is, the recommendation is to avoid folding and wrinkling and the mesh must be well stretched to avoid postoperative dyspareunia and mesh exposure. Controversial point is also the fixation of the posterior mesh. Some surgeons prefer fixing the mesh on the levator ani muscle to avoid mesh erosion and to correct rectocele but this benefit is counteracted a relevant high risk of dyschezia and pelvic pain syndrome. The fixation of the posterior mesh to the levator ani muscle is commonly reported in the laparoscopic series.

Step 4 – The posterior peritoneum over the sacral promontory is incised and the *sacral promontory exposed*. This is commonly the first step in the laparoscopic approach. The anatomical landmarks must be recognized (vessels, ureter) to avoid complications (Fig. 7.46) and the general recommendation is to secure the meshes at or just below the level of the sacral promontory (Fig. 7.47). One or two nonabsorbable stitches can be inserted remembering to include the periosteum or

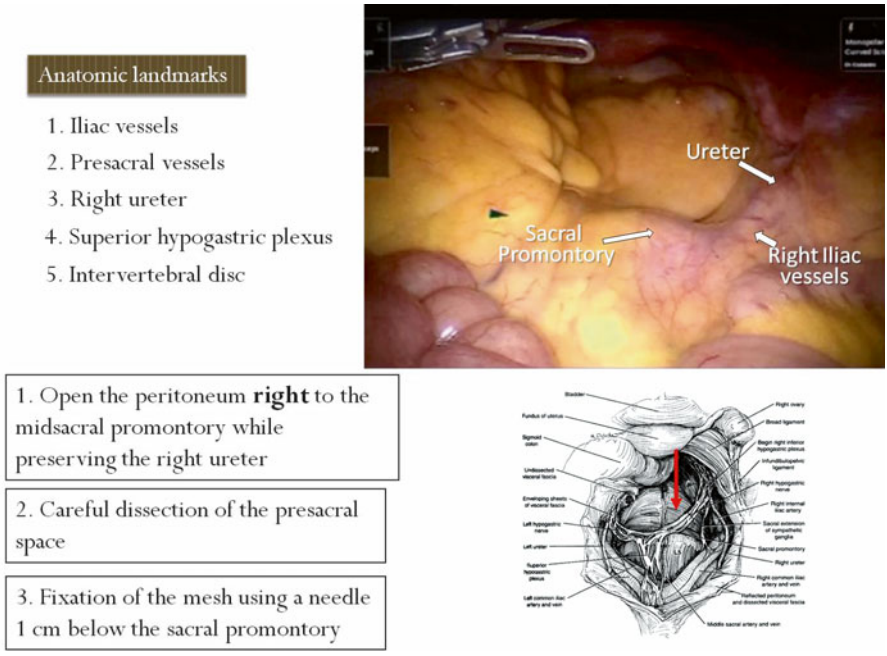


Fig. 7.46 How to prepare the sacrum; *red arrow* indicates the sacrum

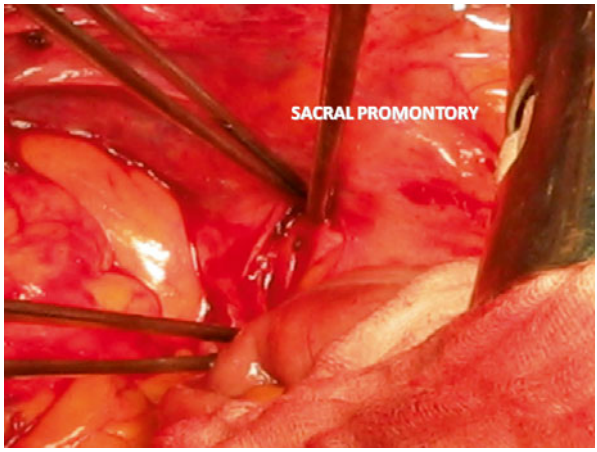


Fig. 7.47 Intraoperative image of the sacral promontory

the anterior longitudinal ligament in the stitches so as to ensure a firm hold. Recently titanium tackers have been introduced on the market, some complications were reported, but there is no evidence they cannot be used.

Step 5 – A tunnel under the peritoneum is created to pass the meshes through to the sacral promontory (Fig. 7.48a, b). Alternatively the peritoneum can be completely opened from the sacrum to the vaginal vault (commonly performed in the laparoscopic approach). The meshes are then anchored to the sacrum avoiding excessive tension and the redundant mesh is trimmed off. How to determine the right tension is a debatable point; expertise is fundamental.

Step 6 – Peritoneal closure over mesh. The majority of the surgeons prefer to close the peritoneum but the decision is left to the surgeon's discretion. Controversial data on postoperative bowel complications are reported; however closure of the peritoneum at the completion of SP seems to be a good approach to avoid adhesions and subsequent long-term complications. Table 7.3 illustrates the most important surgical tip and tricks.

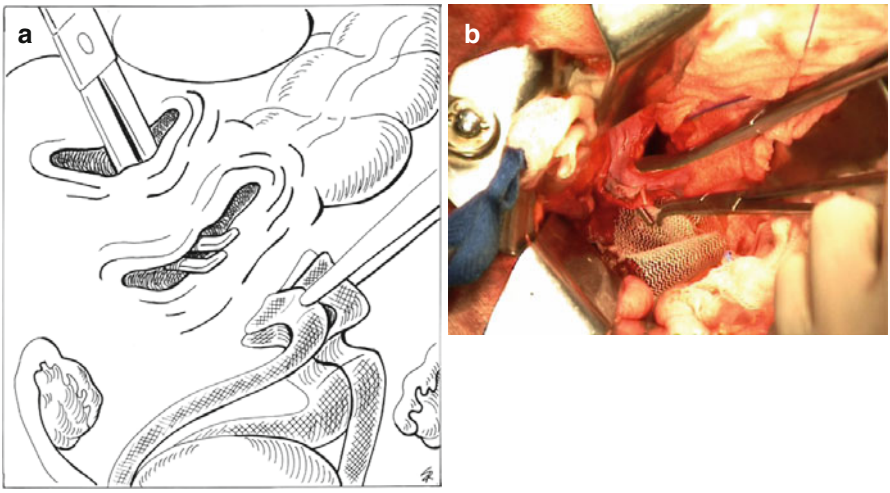


Fig. 7.48 (**a**) Schematic subperitoneal tunnel; (**b**) intraoperative image

Table 7.3 Tips and tricks

Extended preparation of the vaginal walls
Prefer polypropylene meshes
Use reabsorbable suture on the vagina
Avoid folding and wrinkling; the mesh must be well stretched
Fix the mesh on the posterior vaginal wall and not on the levator ani muscle
Prepare carefully the sacral promontory. All the anatomical landmarks should be recognized (vessels, ureter)
Use nonabsorbable suture to fix the meshes on the sacrum
Avoid excessive tension on the meshes
Close the retroperitoneum over the mesh

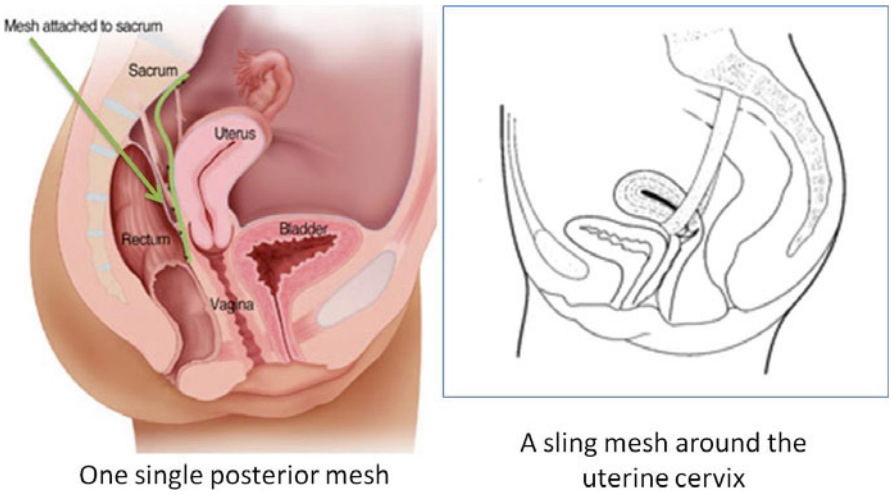


Fig. 7.49 Different meshes to fix the uterus to the sacrum

Hysterocolpopexy Technique

The procedure is similar to SP but several modifications are reported regarding the number, the shape, and the fixation of the meshes on the uterus. In step 2 the visceral peritoneum is incised over uterine isthmus. In some reports, a single posterior mesh is fixed on the uterine cervix; in others a sling mesh is positioned around the cervix (Fig. 7.49), or two meshes can be used: a mesh fixed on the anterior vaginal wall passed through the right broad ligament and a second mesh fixed on the posterior vaginal wall or on the levator ani muscle. Figures 7.50 and 7.51 illustrate the technique with the use of two meshes: the anterior Y-shaped mesh whose arms are passed through the broad ligament bilaterally and a posterior rectangular mesh in the rectovaginal space. The other steps are similar to SP technique.

Laparoscopic/Robotic Approach

Basically the technique of performing an open or LSC is identical. Figure 7.52 illustrates the trocar position. The first surgical step is sacral promontory preparation and opening the peritoneum from the sacrum to the vaginal cuff or the uterus. To make the procedure easier, a single Y-mesh is preferred to the use of two meshes (Fig. 7.44). Technical devices to fix the meshes to the sacrum and to the vagina are still evolving in order to avoid the need of sutures, which generally make the procedure longer although no consensus has been reached on the grade of recommendation. Longer follow-up is necessary to reach a conclusion.

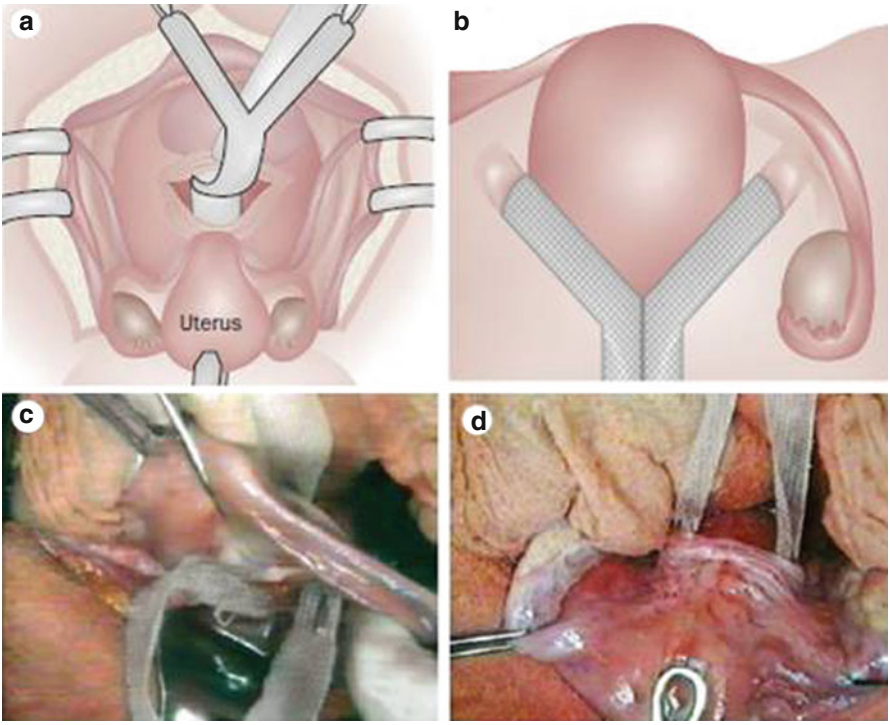


Fig. 7.50 HSP with anterior mesh Y-shaped. (**a**) schematic showing the Y-shaped mesh fixed to the anterior vaginal wall (**b**) the arms are then passed through the broad ligaments bilaterally (**c**) surgical image showing the passage of one arm of the Y-mesh through the broad ligament on the right (**d**) both arms are passed

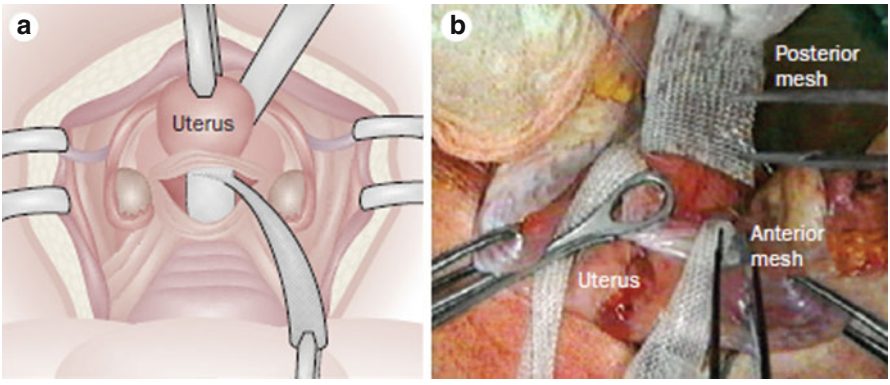
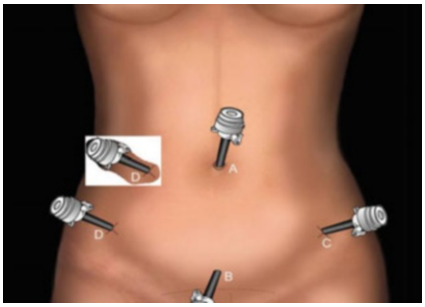


Fig. 7.51 HSP and posterior rectangular mesh. (**a**) schematic view of the rectangular mesh fixed to the posterior vaginal wall (**b**) surgical image showing arrangement of anterior and posterior meshes



Trocar's position

- A: 10 mm, infra-umbilical (view)
- B: 5 mm, halfway between the umbilicus and the pubic symphysis
- C: 5 mm, in the left iliac fossa, 2 to 3 cm medical to the anterior-superior iliac spine
- D: 5-10 mm, in the right iliac fossa, 2 to 3 cm medical to the anterior-superior iliac spine
- Additional D (10 mm) between trocar A and D for bowel retraction

Fig. 7.52 Laparoscopic trocar position

Table 7.4 Complications

Overall complications
UTIs
Wound infections
Abscesses
Hemorrhage
Dyspareunia
Urethral obstruction
Voiding and/or storage symptoms
Bladder–intestinal–ureteral–pelvic nerve injuries
Sacrocolpopexy (abdominal, laparoscopic-assisted) complications
Ventral hernia
Bowel occlusion, bowel lesions
Bladder lesions, ureteral obstruction or lesions
Vascular injury (sacral promontory!)
Problems at the trocar site
Mesh exposure, erosion in other organs

Complications

Complications of the technique are illustrated in Table 7.4. Mesh erosion, reported in 3–9 % of the cases, typically occurs in the first 2 years after surgery, generally located at the level of the vaginal cuff or on the posterior vaginal wall, and the percentage is higher when contemporary hysterectomy is performed at the time of SP. For this reason supracervical hysterectomy is preferred by some surgeons but no consensus has been reached on this topic so far.

The Manchester Fothergill Procedure

Elisabetta Costantini, Antonio Carbone

Background

The Manchester Fothergill procedure was first proposed in 1888 by Archibald Donald of Manchester, England, and William Fothergill. It was initially described for the treatment of cervical elongation. It was an alternative to vaginal hysterectomy for the management of uterovaginal prolapse in patients with uterine cervical elongation and intact uterosacral-cardinal ligaments. While not commonly performed today, the Manchester procedure and the uterosacral ligament suspension represent the evolution of uterine-sparing techniques.

Clinical Practice

The advantages of the Manchester operation are that the surgeon does not enter the peritoneal cavity, the operating time is reduced, and the operation is not associated with a prolonged or morbid recovery. For all of these reasons, it is ideal for the elderly patient with no other uterine disease. The operation is designed to correct uterine descent associated with cystocele and rectocele where the preservation of the uterus is desirable. So the indications are: (1) preservation of reproductive function and (2) symptomatic vaginal prolapse associated with elongation of the uterine cervix.

Surgical Technique

The procedure consists of transvaginal cervical amputation, colporrhaphy, and fixation of the cervical stump to the cardinal ligaments.

With the patient in gynecological position, the first step of the procedure consists of putting a downward traction on the uterine cervix exposing the junction of the vagina and cervix where a 360° circumcision incision is made (Fig. 7.53). A preliminary uterine dilatation and curettage is generally performed. In this way the surgeon has confirmed the elongation of cervix and the dilatation of the cervical canal facilitates the passage of the sutures through the cervical canal during covering of the amputated cervix by vaginal flaps. It also ensures adequate uterine drainage

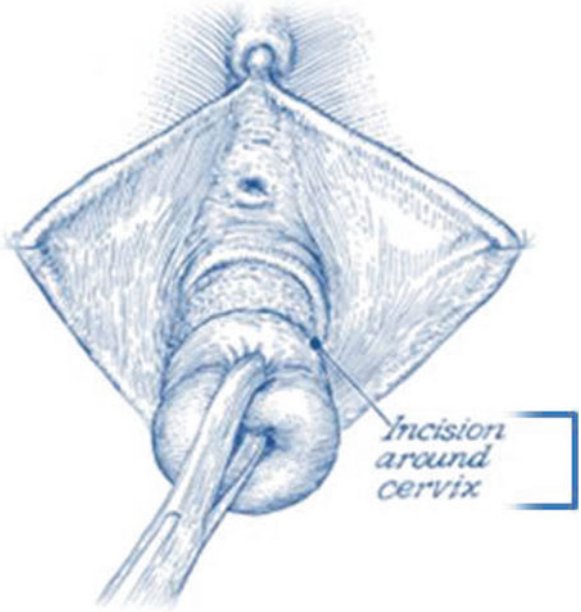


Fig. 7.53 Uterine cervix is exposed and a circular circumcision incision is made

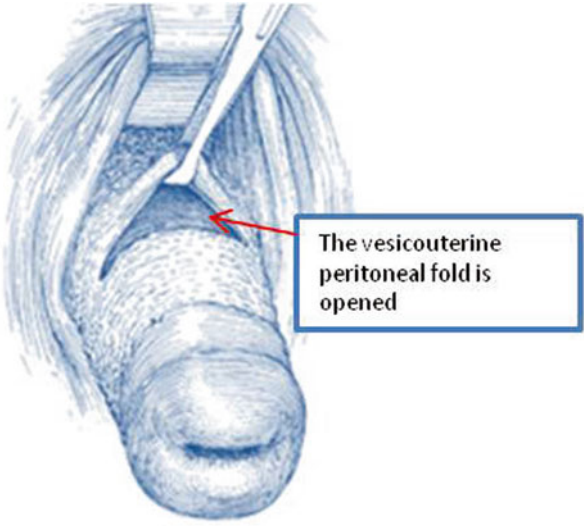


Fig. 7.54 The vesicouterine peritoneal fold is exposed and incised

and prevents cervical stenosis during healing of the external os. The bladder is then sharply and bluntly dissected off the lower uterine segment up to the vesicouterine fold. A right-angle retractor is placed under the bladder to expose the vesicouterine peritoneal fold which is then opened (Fig. 7.54). A retractor is placed in the anterior cul-de-sac, allowing elevation of the bladder and ureter. The cervix is rotated ante-

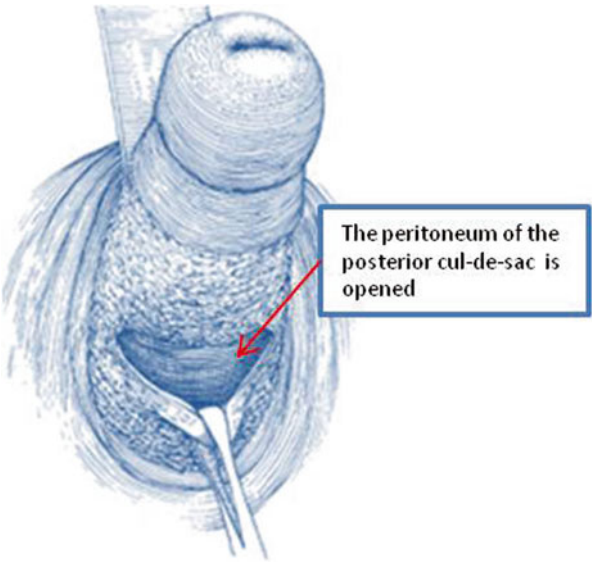


Fig. 7.55 The peritoneum of the posterior cul-de-sac is picked up and opened

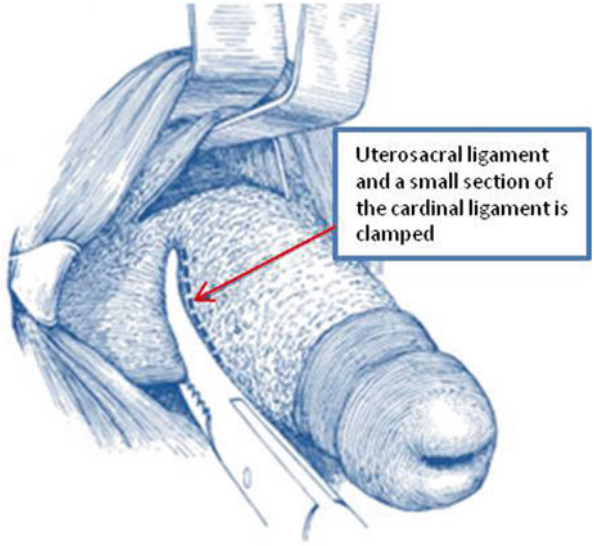


Fig. 7.56 The uterosacral and cardinal ligaments are clamped, incised and tied with a suture

riorly, and the posterior cul-de-sac is exposed. The peritoneum of the posterior cul-de-sac is picked up and opened (Fig. 7.55). The cervix is retracted to the contralateral side, exposing the uterosacral and cardinal ligaments which are clamped, incised, and tied with a suture, bilaterally (Fig. 7.56). Depending on the length of the cervix, several bites may be required to remove a long cervix. With two retractors which elevate the bladder and the ureters anteriorly and depress the rectum posteriorly, traction is made on the cervix. The amputation is made with a scalpel at the lower

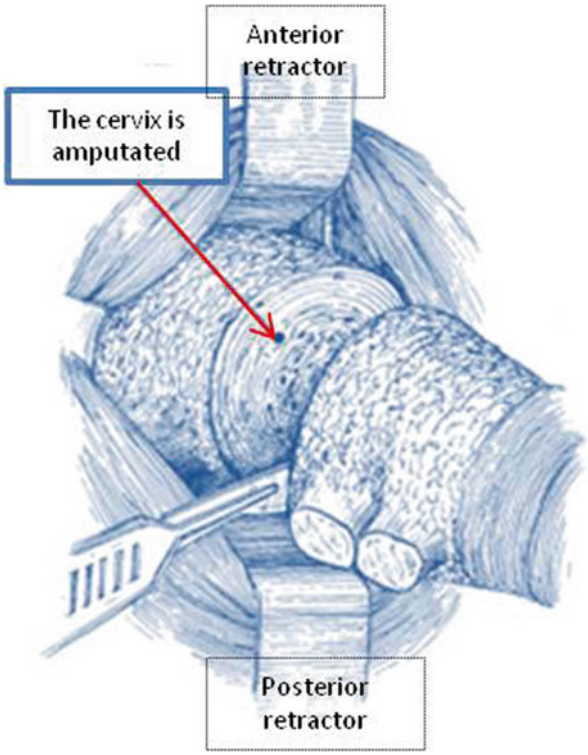


Fig. 7.57 The cervix amputation is made with a scalpel at the lower uterine segment

uterine segment (Fig. 7.57). Where future reproduction is required, low amputation is to be done. The right cardinal and uterosacral ligaments are brought across the anterior surface of the cervix and sutured to the lower uterine segment with absorbable sutures (Fig. 7.58). The left cardinal and uterosacral ligaments are sutured overlapping those from the right side creating a firm barrier which holds the lower uterine segment posteriorly, bringing the fundus anteriorly (Fig. 7.59). In most cases of second- and third-degree uterine descensus, there will be significant cystourethrocele. Therefore, a standard anterior repair is performed. Posterior colpoperineorrhaphy is performed in selected cases. Finally the vaginal mucosa is closed with interrupted absorbable suture so that it covers the lower uterine segment leaving the uterine canal opened for drainage of mucus (Fig. 7.60). A Foley catheter is placed in the bladder and left in place for 4–5 days when an anterior repair and Kelly plication have been performed.

Results

Cure rates between 94 and 95.7 % have been reported, and it has been noted to be lower operative time and blood loss as compared to patients undergoing vaginal hysterectomy with anterior and posterior colporrhaphy. Several concerns regarding

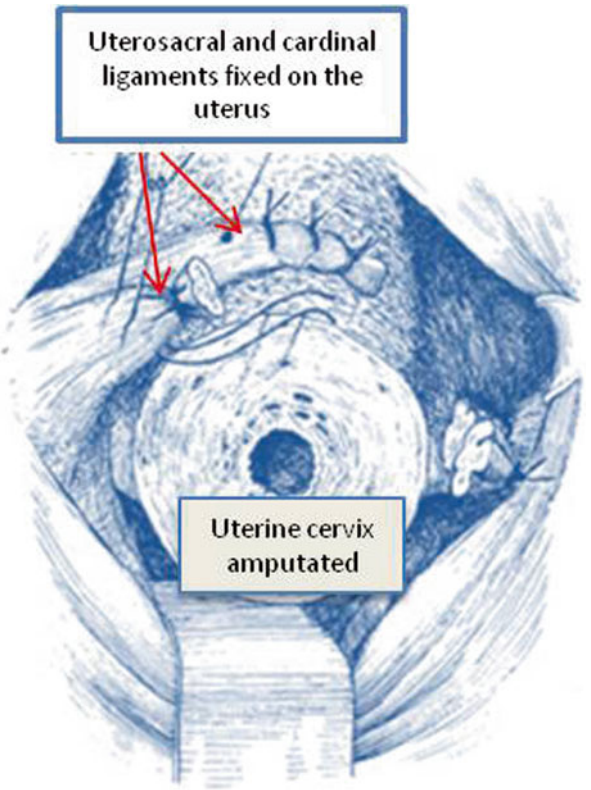


Fig. 7.58 The right cardinal and uterosacral ligaments are brought across the anterior surface of the cervix and sutured to the lower uterine segment

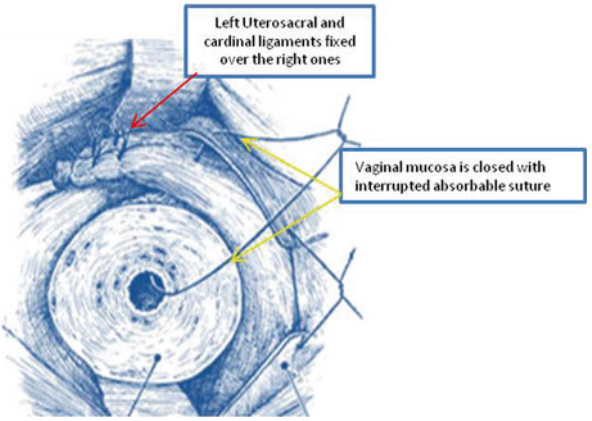


Fig. 7.59 The left cardinal and uterosacral ligaments are sutured overlapping those from the right side

the Manchester procedure include a reoperation rate of 21 %, including reoperation for prolapse, as well as uterine and cervical disease. Recently a 50 % recurrence rate of the anterior compartment has been reported. Furthermore, because the Manchester procedure requires cervical amputation, it has been associated with infertility, miscarriage, and preterm delivery. For these reasons its role is still controversial; it is used in selected cases and generally by gynecologist.

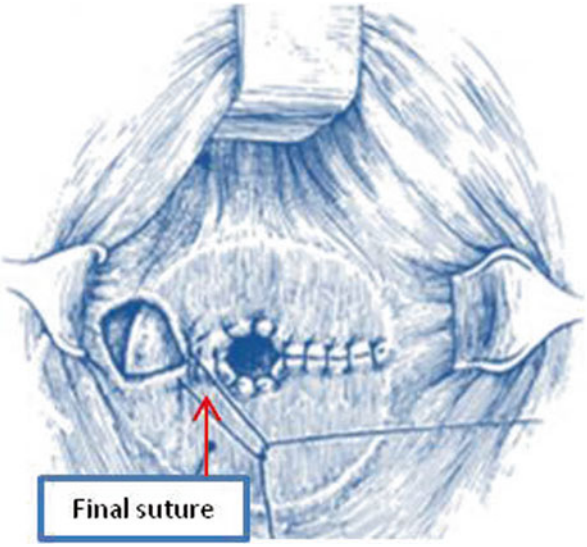


Fig. 7.60 The final suture

Mesh Complications

Elisabetta Costantini, Franca Natale

As a result of the high rates of recurrence and reoperation with native tissue repairs in the treatment of female pelvic floor problems, the placement of synthetic mesh during pelvic organ prolapse (POP) repair is used to improve durability of surgical results. A significant increase in the use of an ever-widening array of prostheses and grafts has occurred in female pelvic floor surgery over the last 30 years. While the use of such meshes may reduce the recurrence of objective symptoms when compared with repairs made with native tissue only, the occurrence of other complications is increased and the management of these complications is widely controversial because of their heterogeneity.

Mesh exposure through the vagina is the most common and consistently reported mesh-related complication especially after transvaginal POP surgeries using mesh (TVM). According to the 2011 Food and Drug Administration (FDA) report, mesh erosion can require multiple surgeries and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication. The synthetic graft that is used in the application of slings for the treatment of stress urinary incontinence has a more predictable and less severe course of complications compared with the synthetic mesh that is used for the management of POP. The 9-year cumulative rate of reoperation/revision after a mid-urethral sling (MUS) is 3.7 % with 60 % of removals/revision caused by mesh exposure. The average rate of mesh exposure in the first year after TVM placement for POP is 10.9 %. More than half of these patients require surgical excision in the operating room; some required multiple operations. Generally complications after TVM tend to be more severe, are

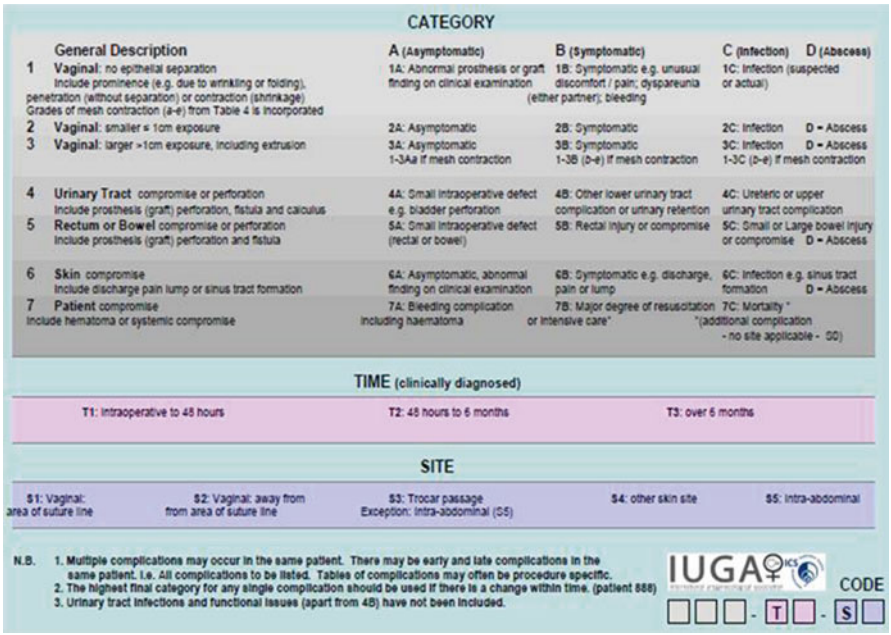


Fig. 7.61 IUGA/ICS classification of complications related directly to the insertion of prostheses (meshes, implants, tapes) or grafts in urogynecological surgery

more chronic in nature, and can be more difficult to treat. The rate of reoperation for management of complications after sacrocolpopexy (SCP) is 4.8 %.

The International Urogynecological Association (IUGA) and the International Continence Society have attempted to classify terminology and complications related to the use of native tissue or prostheses in female pelvic floor surgery, in order to simplify the decision-making process. These classifications take into account the exact site, the timing relative to the operation, the symptoms, and the general description, which are all necessary information for choosing the most appropriate therapeutical strategy. IUGA/ICS joint report made available a complete revision of the definitions and the terminology and a complete comprehensive coverage of both insertion complications and healing abnormalities. The *classification system* incorporates (a) category, (b) time, and (c) site divisions into a 6 (or seven)-digit code for any conceivable complication. The classification system includes all the complications after POP surgery without and with the use of grafts (Fig. 7.61). A well-constructed classification is necessary to reach a common language useful for clinical records application, for any database, registry, or surgical audit and finally for academic publications.

Vaginal mesh exposure, defined as a condition displaying, revealing, exhibiting, or making the mesh accessible (e.g., vaginal mesh visualized through a separation in the vaginal epithelium), is a complication which is classified as category "2" if it is small (1 cm or less) and as category "3" if it is larger (> 1 cm). Categories such as

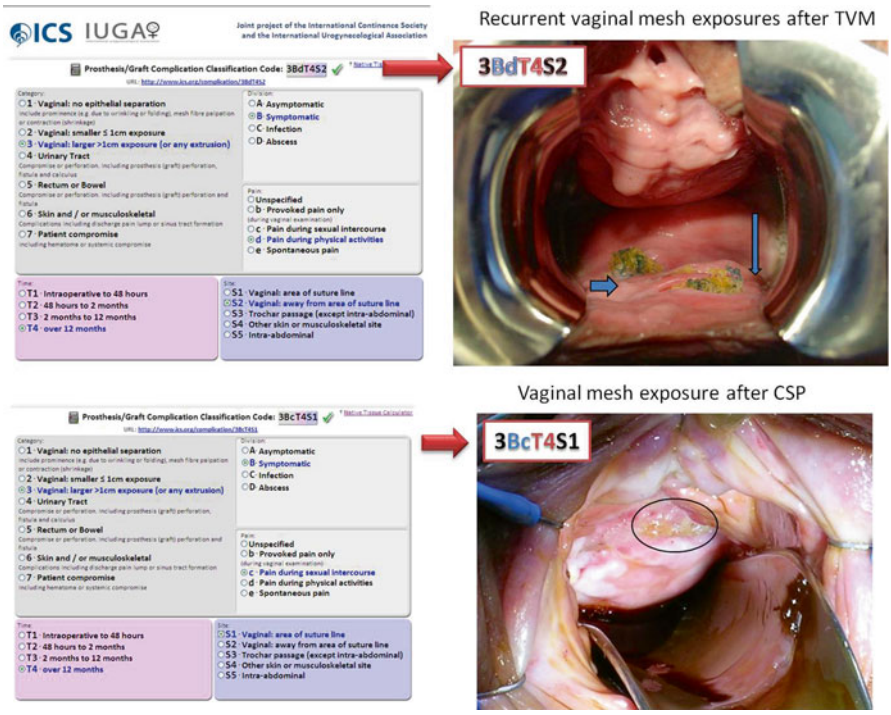


Fig. 7.62 Examples of IUGA/ICS classification (*arrows* and *circle* indicate the mesh exposures)

"2" have been broken down into several divisions, including "A" (asymptomatic), "Bc" (pain during sexual intercourse), and "C" (clinical infection). The time (T) corresponding to a complication is that of its clinical diagnosis (T1, <48 h; T2, 48 h–2 months; T3, 2–12 months; T4, more than 12 months). The selection of the site (S) divisions includes the current sites, where mesh complications have been noted (S1, vaginal area of the suture line; S2, vagina, but remote from the vaginal suture line). Figure 7.62 shows two examples of the classification.

Other classification systems were proposed; one of them, from the American Urological Association, simply classifies the erosion in simple or complex (Fig. 7.63).

About 35 % of vaginal exposures are asymptomatic and they are discovered only during routine follow-up exams. Data are similar for urethral erosion, but the percentage of asymptomatic urethral erosion is lower (about 11 %). The 66 % of whole exposures is discovered within the first 3 months after surgery. Urologists and gynecologists have to be aware that in a high percentage of cases, signs and symptoms of complication begin early after surgery, and it is a duty of the surgeon to understand and recognize them in order to offer promptly the best treatment. In some cases the patient with a mesh exposure can present a symptomatic vaginal bleeding or malodorous discharge and dyspareunia. Partner's pain during intercourse is also reported.

	Simple	Complex
Mesh type	Type 1	Type 2,3,4 expecially if removed from the market
Time to presentation	Early < 6 wks	Late ≥ 6 wks
Site of extrusion	Suturing line	Far from the suture
Depth of the mesh	deep	Into the vaginal wall
Previous excision	none	1 or more
Inflammation	No/minimal	Evident (pus)
Organ involvement	vagina	Bladder/urethra/rectum

Fig. 7.63 American Urological Association classification

Type of synthetic material

Surgical approach

- Type of incision
- Permanent sutures

Concomitant surgical procedures

- Concomitant total Hysterectomy
- Concomitant vaginal approach

Learning curve

Fig. 7.64 Risk factors for mesh-related complications

- Permanent braided sutures
- Placing sutures at the vaginal apex (often devascularized)
- Poor pre-operative vaginal estrogenization
- Concomitant total Hysterectomy (5–7 times increased erosion rate)
- Concomitant vaginal approach

Fig. 7.65 Abdominal/laparoscopic approach: risk factors

Several *risk factors* have a role in mesh-related complications (Fig. 7.64). The surgical approach is one of the most important discriminators and the risk factors change on the basis of the vaginal or abdominal/laparoscopic approach (Figs. 7.65 and 7.66). The type of incision during vaginal surgery and the use of permanent sutures on the vagina, together with some concomitant surgical procedures such as hysterectomy, are important risk factors. Learning curve is another important element as the erosion rate has been reported to be 2.9 % when surgery was performed by a consultant versus 15.6 % when surgery was performed by a fellow. The main mesh erosion risk factors in the abdominal or laparoscopic approach are

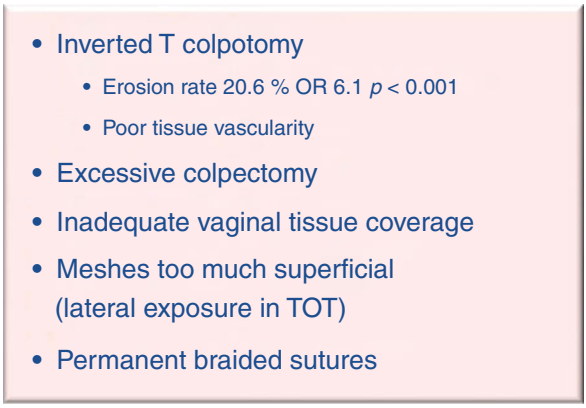


Fig. 7.66 Vaginal approach: risk factors

concomitant vaginal intervention, concomitant total hysterectomy (5–7 times increased erosion rate), poor preoperative estrogenization, placing sutures at the vaginal apex, and use of permanent braided sutures. In the vaginal approach, the main risk factors are: inverted T colpotomy (erosion rate 20.6 %), excessive colpectomy, inadequate vaginal tissue coverage, permanent braided sutures, and the placement of the mesh in a surgical plane that is too much superficial.

The *site of exposure* varies with type of surgery. In sacrocolpopexy (both abdominal or laparoscopic) usually exposure occurs at the vaginal apex, sometimes along the distal posterior vaginal wall. In the trans-obturator approach, the main site is the lateral fornix; after an inverted T colpotomy during vaginal approaches, is the midline.

Surgical Treatment

The treatment of mesh exposure is highly individualized, the choice depending on:

- The mesh type (macroporous type I monofilament polypropylene meshes are associated with lower infection rates than multifilament and polyester meshes)
- Time of presentation
- Site of the extrusion and different organ involvement (bladder, urethra, bowel)
- Depth of the mesh
- Presence of signs of inflammation/infection
- Severity of patient's symptoms
- Recurrency of the exposure/extrusion
- Patient's expectations. For example, patients who consider the possibility of recurrent prolapse following mesh exposure excision to be an unacceptable risk may prefer an initial conservative treatment.

The treatments for vaginal mesh exposure include *conservative measures* such as observation, estrogen therapy, topical antiseptics/antibiotics, abstinence from sexual intercourse, and *surgical treatments*.

Table 7.5 Pros and cons of surgical excision

Surgical excision
Cons
Risk of anesthesia
Burden of post-op recovery
Small but possibly catastrophic risk of injury to internal organs
Pros
The potential for earlier and definitive relief of symptoms

Most urogynecologists agree that a symptomatic vaginal mesh exposure must be surgically removed (partial resection or complete explantation). Total ablation of the mesh is recommended in case of mesh infection, local abscess, fistulae, and pelvic cellulitis. However, there is no precise recommendation for patients presenting with a small exposure surface area and/or asymptomatic vaginal mesh exposure and there is not randomized controlled study comparing conservative to surgical treatment. Pros and cons of surgical excision are illustrated in Table 7.5. Conservative management often involves a protracted treatment course, leading to potential frustration and distress. Regular vaginal estrogen use may not be appropriate for patients with known risks for estrogen use, severe arthritis, morbid obesity, or other functional limitations. Even when conservative therapy is chosen for initial management, some of these women ultimately undergo surgery if conservative therapy fails.

As general suggestion small asymptomatic exposure of type I polypropylene mesh into the vagina [IUGA/ICS category 2A] can be managed conservatively, through abstinence from sexual intercourse (6 weeks) and local estrogen replacement therapy associated with topical antiseptics, with the recommendation for surgeons to remain vigilant with respect to potential infections. In sexually inactive and asymptomatic patients (neither bleeding nor vaginal discharge, infection, or pain), with <3 mm exposure expectant management may be proposed (initially or following unsuccessful conservative medical treatment); though the exposure will often not heal spontaneously, it rarely progresses. Asymptomatic large vaginal mesh exposure (3A) and vaginal mesh exposure associated with infection or pain (2C, 3C, 2Bc, 3Bc) should be treated by surgical resection. Removal of the exposed mesh remains the gold standard for the treatment of symptomatic vaginal mesh exposures.

Surgical treatment includes local excision in the office, local excision in the operating room, and extensive or complete excision of the mesh (Fig. 7.67). A flowchart for the surgical treatment of simple or complex mesh exposure is illustrated in Fig. 7.68.

There is a myriad of clinical problems resulting from transvaginal mesh that clinicians must manage with little data or experience to guide them. The success rate after vaginal mesh removal is around 80–95 % but not all the patients reported complete symptom resolution. The persistence of pain and dyspareunia in 30 % of patients suggests that treatment of persistent pain may be the most difficult to achieve. Pain is related not only to mesh exposure but also to another identified mesh-related complication which is mesh contraction.

Transvaginal mesh contraction or shrinkage refers to situations where part or all of the mesh contracts after being implanted. Mesh contraction can result in

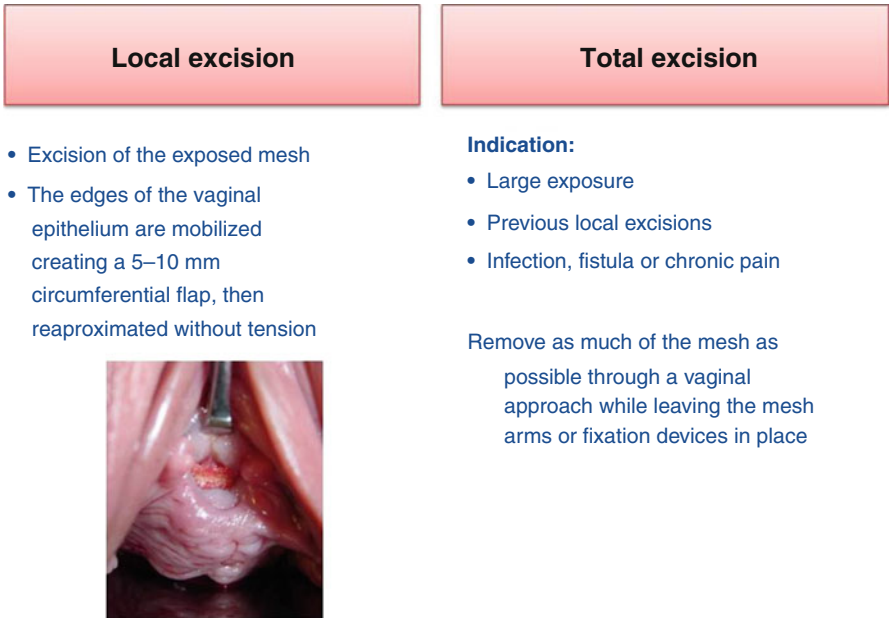


Fig. 7.67 Local or Total excision of the mesh. The intraoperative image shows a Vaginal mesh exposure after colposacropexy (3BcT4S2)

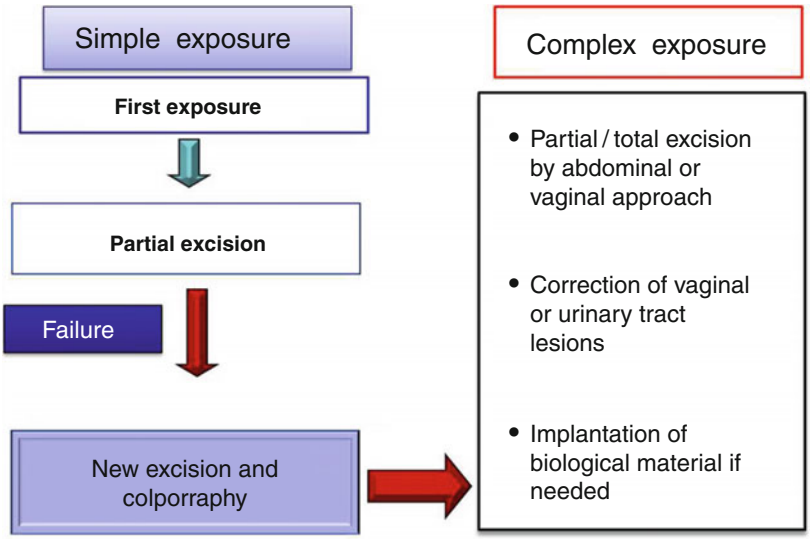


Fig. 7.68 Flowchart for simple and complex exposure treatment

severe pelvic pain, painful sexual intercourse, or an inability to engage in sexual intercourse. Symptoms of mesh contraction include vaginal shortening, vaginal tightening, and vaginal pain. Pain is thought to be due to overtensioning of the mesh

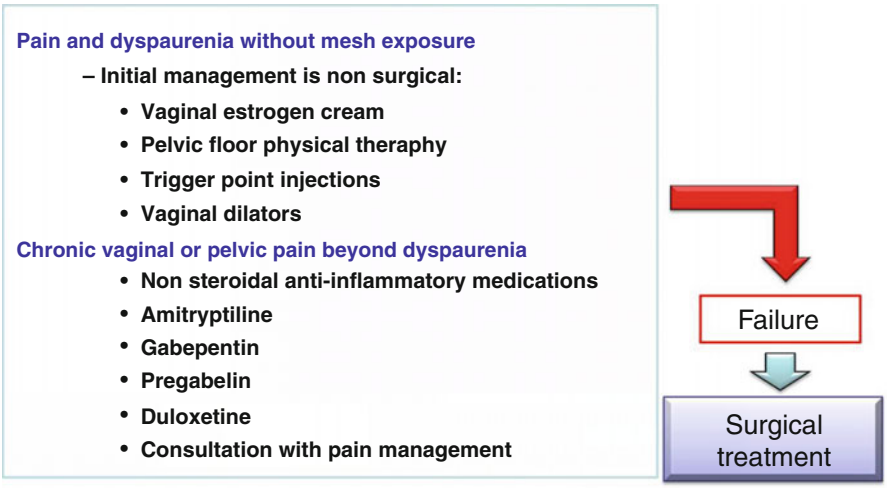


Fig. 7.69 Treatment for pain without mesh exposure

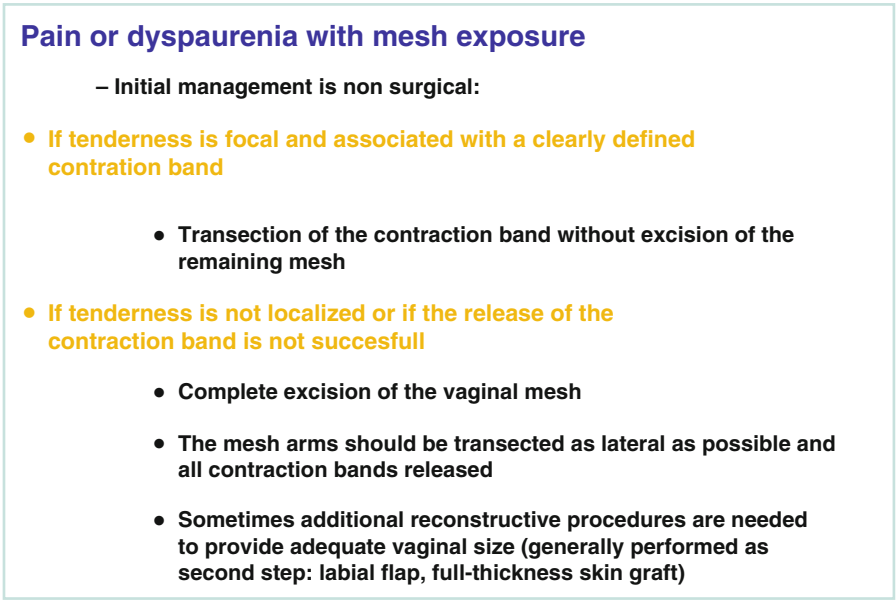


Fig. 7.70 Treatment for pain with mesh exposure

causing contraction bands or to chronic irritation to the pelvic floor muscles and associated nerves. The indications for treatment depend on the severity of the mesh contraction and the patient's QoL. The treatment of these cases is complex and can be differentiated on the basis of the presence or absence of concomitant mesh exposure (Figs. 7.69 and 7.70). Generally it starts with oral medication and surgical treatment is reserved to cases associated to mesh exposure or to patients not responding

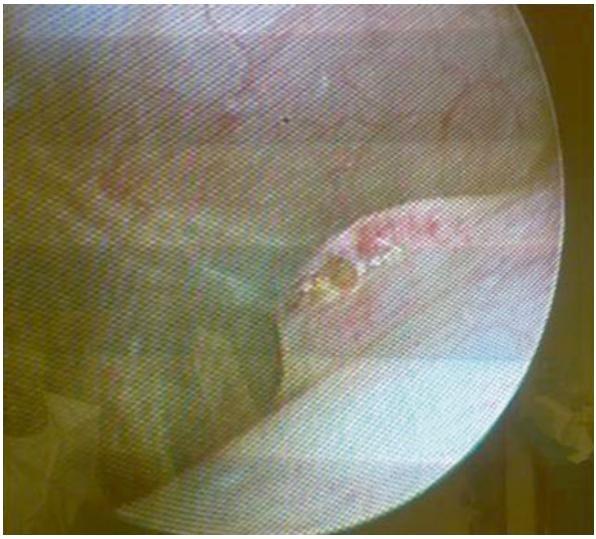


Fig. 7.71 Mesh erosion into the bladder after colposacropexy (4B T4S5 IUGA classification)

to conservative treatment (physical therapy, trigger point medications, neuropathic pain medications). Unfortunately pain not always resolves after surgical treatment.

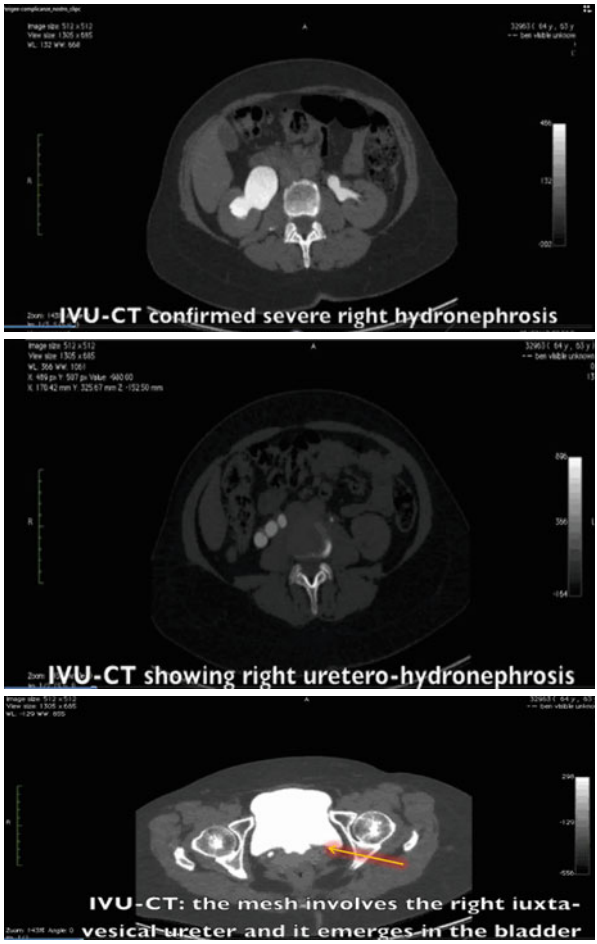
The surgical treatment for *vaginal mesh exposure after sacrocolpopexy* follows the same guidelines previously indicated. In case of simple vaginal exposure, a partial removal of the mesh is possible by the vaginal route. It's important to underline that coverage without mesh excision is not recommended because it may lead to exposure recurrence. When a total removal of the mesh is indicated because of infection of the graft or for other organ involvement, an abdominal or laparoscopic route is the best way to reach the sacrum and obtain a complete removal of the graft.

In case of *complex erosions* such as extrusion in other organs (Fig. 7.71), fistulas, and exposure recurrence, different surgical approaches requiring great surgical skill become necessary. Martius or omental flap, urethral reconstruction, and ureteral reimplantation are some of these procedures which will be tailored to the case. Figures 7.72, 7.73 and 7.74 show a patient with hydroureteronephrosis after shrinkage and mesh erosion into the bladder 2 year after anterior TVM.

Some Advice for Prevention of Mesh-Related Complications

The main problem is that all the surgical treatments for mesh-related complications may lead to other complications like fistulas, severe hemorrhage, and prolapse recurrence; for this reason *the best treatment is prevention*.

Some guidelines could be proposed. In general it is very important to prevent infection by a wide-spectrum antibiotic therapy before and after surgery and use of local estrogen therapy. The use of polypropylene grafts and avoiding concomitant anorectal surgery are recommended. Concomitant hysterectomy should be avoided in particular during TVM surgery. Other recommendations are illustrated



Figs. 7.72, 7.73 and 7.74 Hydroureteronephrosis after shrinkage and mesh extrusion into the bladder 2 years after anterior TVM (4C T4S5). *Arrow* indicate the mesh

in Fig. 7.75. During vaginal surgery, it is better to avoid T incision to prefer a retrograde dissection of the bladder and to limit the use of hemostatic hydrodissection to avoid ischemia. Furthermore it is important to maintain adequate thickness of vaginal epithelium. During sacrocolpopexy the most appropriate approach for preventing mesh exposure is closing the vaginal cuff in two layers or with a continuous introflexing suture, avoiding full-thickness stitches into the vagina, attaching meshes to distal portions of the vaginal walls and not attaching them to vaginal cuff, and finally avoiding excessive tension on the meshes.

Mesh contraction may be prevented by avoiding: (1) direct suspension of mesh with sutures, (2) compression of the bladder and rectum by the mesh and (3) high lateral tension.

In conclusion the treatment of each complication must be carefully individualized; if a surgeon chooses to use a mesh, he must complete a specific training and, most importantly, he must learn how to treat the potential complications.

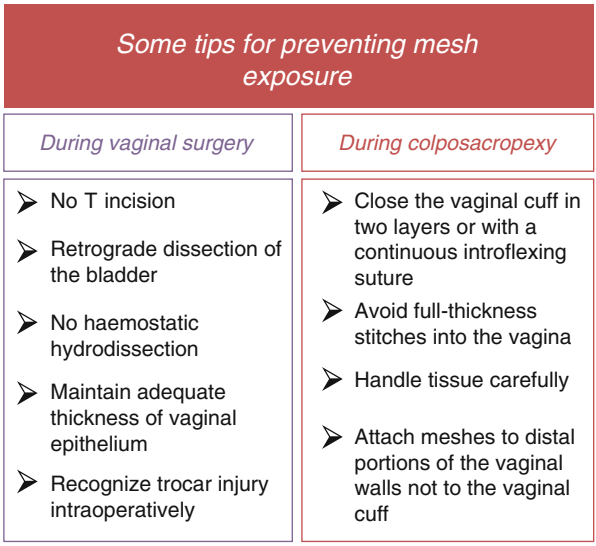


Fig. 7.75 Some guidelines to prevent mesh-related complications

Sexual Assessment

Elisabetta Costantini

Sexuality is a complex process coordinated by the neurological, vascular, and endocrine systems. Sexual satisfaction is a fundamental element of general well-being and physical and mental health has been related to greater levels of sexual activity. Female sexual dysfunction (FSD) is a multi-causal and multidimensional medical problem that adversely affects physical health and emotional well-being. It can have damaging effects on the self-esteem, sense of wholeness, and interpersonal relationships. Epidemiological surveys report a variable *prevalence* ranging from 19 to 45 %, depending on age, hormonal status, and focus on single or cumulative disorders. Regardless these discrepancies, all studies concluded that FSD is highly prevalent with an increasing incidence in elderly women. Approximately 43 % of American women (depending on age) have sexual complaints and in Europe the prevalence is around 31.1 %. The number of women who have sexual dysfunction ranges from 19 to 50 % in "normal" outpatient population and increases to 68 to 75 % when sexual dissatisfaction or problems (not dysfunctional in nature) are included. While prevalence and risk factors for male sexual dysfunction, in particular erectile dysfunction, have been intensively studied within the past decade, data regarding this issue on women are scant. Investigators identified several possible *etiologies* of FSD, which include aging, psychological, anatomical and neurological factors, hormonal status, voiding dysfunction, and cultural factors, including race and ethnicity, medications, and drug abuse. Although sexual function (SF) has been extensively studied in several medical specialties dealing with women's health, it has been largely overlooked in the field of urogynecology. Specifically, anatomical factors relating to SD gained recognition in urogynecology only recently. The

female bladder base and urethra are anatomically adjacent to the vagina; in addition to supporting the abdominal and pelvic organs and maintaining urinary and fecal continence, the pelvic floor permits intercourse and parturition and plays a role in sexual response. When voluntarily contracted, pelvic floor muscles can intensify orgasms for both men and women, so pelvic floor dysfunction may be associated with sexual problems.

Female sexual function was found to be negatively influenced or affected by the presence of lower urinary tract symptoms, with urinary incontinence (UI), and detrusor overactivity causing the greatest degree of SD. Several studies reported that 40–50 % of patients with UI report impairment of SF and recent studies demonstrated improvement in SF following treatment for UI. Similarly, multiple studies have found a correlation between pelvic organ prolapse (POP) and SD, with the higher incidence correlating with the severity of prolapse. Despite the clear relationship between pelvic floor disorders and SD, studies assessing SF following surgical repair of pelvic floor disorders have conflicting results. Whereas some authors found an improvement in SF following POP repair, others have found unchanged or increasing incidences of SD and dyspareunia. Although sexual dysfunction is recognized as a highly prevalent condition in women attending urogynecological services, only a minority of urogynecologists screen all patients for FSD. Lack of time, uncertainty about therapeutic options, and older age of the patient have been cited as potential reasons for failing to address sexual complaints as part of routine history.

Although considered as a widespread health problem, FSD continues to be underrecognized and undertreated. It is thus necessary to increase awareness and physicians' ability to communicate with female patients about sexual problems. Given that assessment by psychometric and paper-and-pencil diagnostic tools is time consuming, medical willingness to explore FSD remains low in the majority of clinical settings. Furthermore, many women may hesitate to share their sexual complaints, also because they are worried about their physicians' interest in addressing FSD. Direct questioning by physicians about sexual function, therefore, remains critical, as both males and females refrain from referring spontaneously to their sexual symptoms. Finding the correct way to ask delicate questions and to decode answers on sexual health and disease might be difficult and even embarrassing for the inexperienced physician. Standardized, validated sexual inventories might thus become a valuable help.

Definition and Classification

Sexual dysfunction is a disorder that includes manifestations ranging from unresponsiveness to any variation in intensity and quality of desire, arousal, and orgasm. Factors such as general health impairment, chronic diseases, health of relationship, adverse sociodemographic and behavioral conditions including low income, low levels of education, and stress seem to affect sexual capacity significantly. Major risk factors for FSD in women are embedded in a biopsychosocial frame (Table 7.6). Female sexual dysfunction is an overall term to describe problems across the different sexual phases and the definition is a *persistent or recurrent inability to engage*

Table 7.6 FSD and risk factors

Menopausal transition (hormonal and psychological changes)
Relationship problems
Sexual dysfunction in the partner
Depression
Urinary tract symptoms
Cancer and its treatment

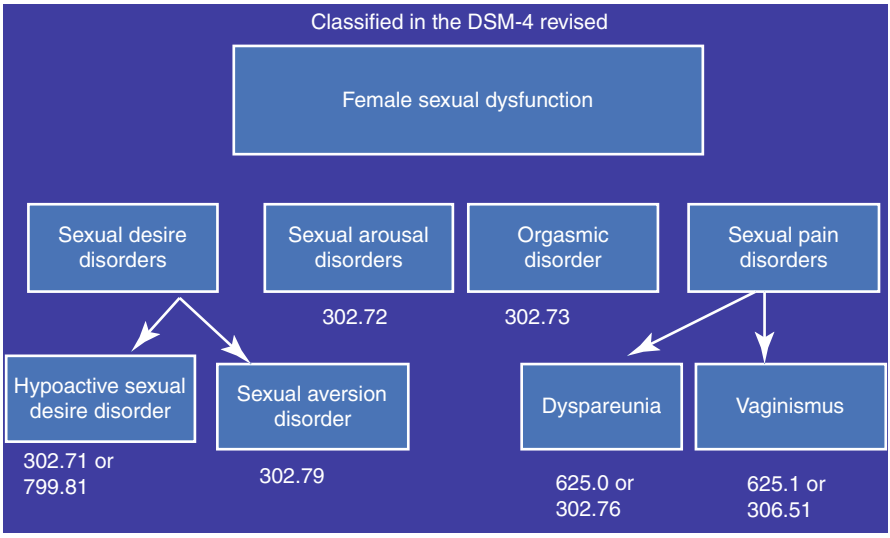


Fig. 7.76 FSD classification on the basis of DSM4 revised

in satisfying sexual activity leading to marked distress or interpersonal difficulty, excluding general medical conditions, psychiatric issues, substance abuse, and medications. FSDs are classified in four major disorders (Fig. 7.76) hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), female orgasmic disorder (FOD), and female sexual pain disorders (FPD). Often women will report difficulties within more than one of the domains, which makes it challenging to identify the treatment target and limits research in clinical trials, where it can be difficult to identify end points in which a change can be measured. Generally the different disorders are interconnected in a multidimensional problem which can be defined as the cycle of sexual dysfunction (Fig. 7.77).

Hypoactive Sexual Desire Disorder (HSDD). The hypoactive sexual desire is the lack of sexual thoughts or fantasies and it is different from sexual aversion, a phobic aversion to and avoidance of sexual contact. The percentage of women with low desire ranged from 16% in premenopausal women (aged 20–49) to 46 % in surgically menopausal women aged 50–70. In climacteric syndrome low desire is as

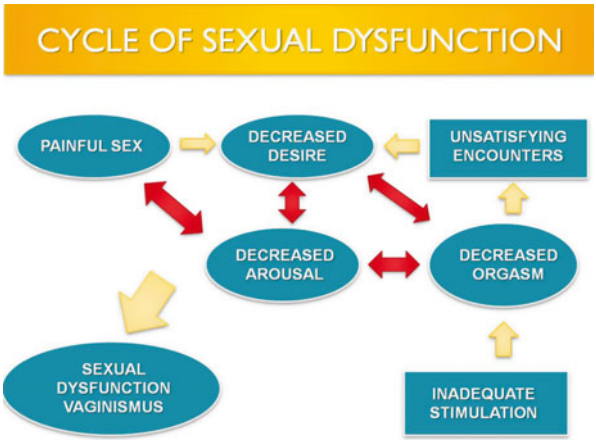


Fig. 7.77 The cycle of SD

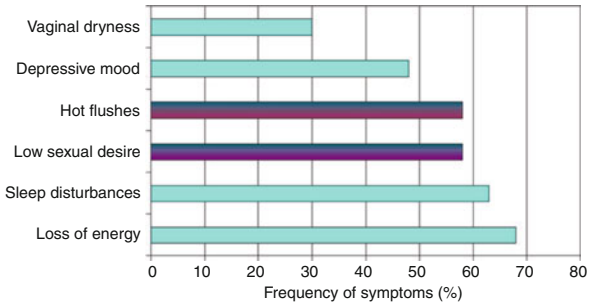


Fig. 7.78 Prevalence of low sexual desire among climacteric symptoms

common as hot flushes (Fig. 7.78). It has been hypothesized that HSDD can be triggered by an imbalance between CNS inhibitory and excitatory factors, with a reduced excitatory activity, increased inhibitory activity, or a combination of both. Disorders of desire in premenopausal patients may be secondary to lifestyle factors, medications, or another sexual dysfunction (pain or orgasmic disorder); in peri- and postmenopausal women the relationship between hormones and sexuality is unclear. Estrogen replacement therapy has been shown to correlate positively with sexual activity, enjoyment, and desire, although the findings are not universal. The mechanism of estrogen's effect on desire is probably indirect and occurs through improvement in urogenital atrophy, vasomotor symptoms, and menopausal mood disorders. What is important to underline is however that only a percentage of women consider HSDD as a distressing problem and these women should be carefully evaluated before deciding to treat the sexual problem (Fig. 7.79).

Female sexual arousal disorder (FSAD) is the inability to attain or maintain sufficient sexual excitement. It may be expressed as a lack of subjective excitement or genital response and it may be secondary to inadequate stimulation, especially in older women who require more stimulation to reach a level of arousal that was more

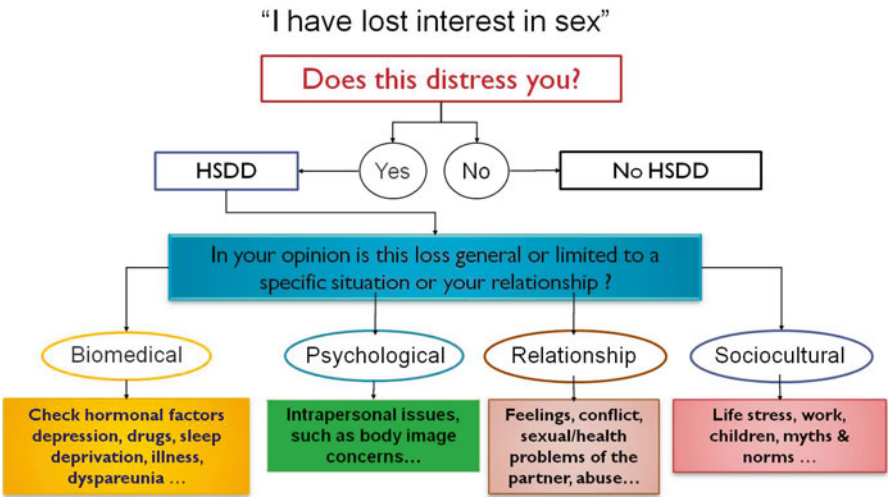


Fig. 7.79 HSDD and female distress: when the assessment is necessary

easily attained at a younger age. Urogenital atrophy is the most common cause of arousal disorders in postmenopausal women.

Female orgasmic disorder (FOD) is the difficulty in attaining orgasm following sufficient sexual stimulation and it includes anorgasmia, a condition often caused by sexual inexperience or by the lack of sufficient stimulation. Orgasmic disorders may also be psychologic (involuntary inhibition of the orgasmic reflex) or caused by medications or chronic disease.

Female sexual pain disorders (FPD) include dyspareunia (genital pain with sexual intercourse), vaginismus (involuntary spasm of pelvic musculature interfering with vaginal penetration), and noncoital sexual pain disorders.

Dyspareunia includes different situations (Fig. 7.80), and in the majority of the cases, the cause is a vestibulodynia with an estimated prevalence of 9–12 %. The condition has a substantial negative effect on a woman's daily life relationships, sexual life, quality of life, and psychological well-being. Vulvodynia is defined by the absence of relevant visible findings or an identifiable neurological disorder; its diagnosis is truly one of excluding any other mechanism that could cause the pain. This condition comprises heterogeneous pain phenotypes: provoked pain, unprovoked pain, pain localized to one region of the vulva or generalized throughout, etc. The etiology is thought to involve inflammatory and infectious factors, hypertonicity of the pelvic floor (which might be secondary to the pain), hypervigilance to body sensations, depression, and anxiety. As no good scientific data are available to guide pharmacotherapy of dyspareunia, an unmet need for an effective treatment still remains for women with this condition. Several agents have been tried and are currently in clinical use, including topical lidocaine, tricyclic antidepressants, gabapentin, pregabalin, and botulinum toxin injections, often combined with surgery, biofeedback, and cognitive behavioral therapy. However, the use of most of these treatments is based on case studies or small experimental series. *Vaginismus* may be

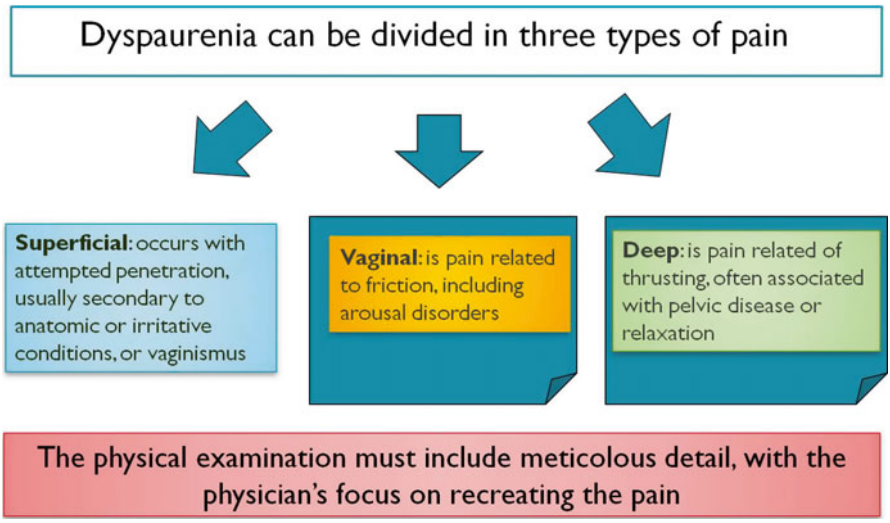


Fig. 7.80 Dyspareunia and different kinds of pain

Table 7.7 Medical conditions and FSD

Vascular disease
Diabetes (arousal disorders)
Cardiovascular disease
Arthritis
Urinary incontinence/POP

complete or situational, so that a pelvic examination might be possible while intercourse is not. It is a complex problem, often related to sexual phobias or past abuse or trauma, and its evaluation generally includes a comprehensive physical and psychological assessment.

Assessment

To assess FSD, the first step is to obtain a detailed *patient history* that defines the dysfunction; then it is important to identify causative or confounding medical or gynecologic conditions (Table 7.7) and finally it is necessary to obtain psychosocial information. Several drugs can cause FSD and should be investigated in each patient (Table 7.8). *Clinical examination* should be accurate aiming to exclude: vulvar dystrophy or dermatitis, mucosal atrophy, clitoral adhesions, herpes simplex infection, bartholinitis, episiotomy scar strictures, vaginitis, and postoperative and post-radiation changes. Furthermore pelvic organ dysfunctions such as pelvic organ prolapse (Table 7.9) and urinary incontinence should be evaluated because they have a significant impact on female sexuality. Since 1980s, several

Table 7.8 Drugs and FSD

Medications that cause:
Disorders of desire (psychoactive medications, BDZ, beta blockers, oral contraceptives, etc.)
Disorders of arousal (anticholinergics, antihistamines, SSRI, etc.)
Orgasmic dysfunction (methyldopa, trazodone, BDZ, amphetamines, etc.)

Table 7.9 Factors that might contribute to FSD in patients with POP

1. POP changes the anatomical features of vagina
2. It is a hidden disfigurement of the urogenital tract
3. It could negatively affect the woman's body image
4. It may lead to shame, embarrassment, and feeling less sexually attractive, all of which reduce quality of life
5. It may be associated with urine leakage which worsens sexual activity

assessment tools, specific to or inclusive of female sexual function, that are suitable for office-based use have been introduced. Validated questionnaires utilized to assess sexual function in women with pelvic floor dysfunction (PFD) may be generalized or condition specific. Generalized questionnaires focusing on sexual function were designed to evaluate sexual function in a general population and not specifically in women with PFD. These types of questionnaires may not be sensitive enough to detect differences due to the disease process of urinary incontinence, fecal incontinence, and/or pelvic organ prolapse in this particular population. Two general questionnaires focused on sexual function, utilized in the urogynecological literature, include the Sexual History Form 12 (SHF-12) and the Female Sexual Function Index (FSFI). The FSFI is a 19-item self-reported measurement of FSD and it analyzes six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. Each domain is scored on a scale of 0 (or 1) to 5 (Fig. 7.81). The scale has been tested to assess the impact of diverse medical conditions and treatments on sexual function and has consistently demonstrated excellent psychometric properties. It is one of the most powerful and useful diagnostic tools for diagnosing FSD and monitoring treatment. These questionnaires are condition specific and were developed, validated, and tested for use in women with PFD but do not focus on sexual function. There are two condition-specific questionnaires focused on sexual function for use in women with pelvic floor dysfunctions, the Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ) and the International Consultation on Incontinence Questionnaire Vaginal Symptoms (ICIQ-VS).

In conclusion questionnaires are a useful method in detecting FSD but it is important to underline that sexual function is affected by several factors, including couple relationship conflicts, socioeconomic level, sexual compatibility, and physical and psychiatric disorders of the couple. For these reasons, the importance of a multidisciplinary, collaborative approach is central in evaluating any sexual dysfunction, both organic and psychosocial issues must be considered, taking in

FSFI scoring appendix

Question	Response options
1. Over the past 4 weeks, how often did you feel sexual desire or interest?	5 = Almost always or always 4 =Most times (more than half the time) 3 =Sometimes (about half the time) 2 =A few times (less than half the time) 1 = Almost never or never

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score	Score
Desire	1,2	1–5	0.6	1.2	6.0	
Arousal	3,4,5,6	0–5	0.3	0	6.0	
Lubrication	7,8,9,10	0–5	0.3	0	6.0	
Orgasm	11,12,13	0–5	0.4	0	6.0	
Satisfaction	14,15,16	0 (or 1) –5	0.4	0.8	6.0	
Pain	17,18,19,	0–5	0.4	0	6.0	
Full scale score range				2.0	36.0	

Fig. 7.81 FSFI scoring system

consideration that whatever is the cause of a sexual dysfunction, it typically occurs in a relationship context.

Masked Stress Urinary Incontinence

Elisabetta Costantini, Antonio Carbone, Antonio Luigi Pastore

Stress urinary incontinence (SUI) is a common complaint in women with pelvic organ prolapse (POP). In fact, urinary incontinence is more common in women with prolapse than in women with normal vaginal support and it is usually associated with prolapse of the anterior vaginal wall. SUI and POP probably share some of the same etiological mechanisms.

The relation between POP and SUI is complex. Approximately 40 % of women with POP report symptoms of stress urinary incontinence while some women with POP experience SUI only with a pessary inserted, on provocative testing with reduction of the prolapse, up to half of patients with POP but without symptoms of SUI may demonstrate SUI. The reason seems to be linked to the fact that POP may actually function to kink the urethra, maintaining stress continence by causing urethral obstruction. After a successful POP surgery, the development of SUI postoperatively may result from relieving the urethral obstruction caused by prolapse, thereby unmasking a preexisting compromised urethral function. Urogynecologists have referred to this as an unmasking of occult or latent SUI.

Diagnostic Evaluation

In preoperatively continent woman with POP, the risk of "de novo" SUI is approximately estimated between 11 and 20 %, while in women with occult SUI the risk to develop postoperative SUI may even be as high as 80 %. Therefore it is important to assess SUI prior to POP surgery to adequately inform the patient and decide if additional surgical procedures are required to treat this condition. There is still controversy regarding the diagnostic evaluation of masked SUI. Physical examination and instrumental tests may be helpful to identify subjects with higher risk to develop SUI after POP surgery. *Preoperative stress test after prolapse reduction*, to mimic a repaired pelvic anatomy, may reveal the occult SUI and is often performed to predict whether a patient would benefit from a concomitant SUI procedure. Despite this, the incidence of de novo SUI after an open sacrocolpopexy without an anti-SUI procedure can be as high as 39 %; and a 25 % of de novo SUI has been reported in women who underwent mesh-augmented transvaginal POP repair without concomitant mid-urethral sling.

Urodynamic assessment after reducing POP may further contribute to show a masked SUI. Kleeman in 2006 reported that de novo SUI and urinary urgency developed only in 1.9 % of females submitted to POP surgery and previously evaluated by urodynamic with a negative stress test at cystometry. Therefore, clinicians should not base their surgical decision only on a negative report of SUI from females with POP, but they should address some clinical maneuvers or instrumental tests which can help them to unmask occult conditions.

Some of the questions that remain are what is the most effective way to look for occult SUI (which prolapse reduction method is ideal) and which specific algorithm to use.

Treatment Strategies

Up to date no general agreement exists concerning treatment strategies for women with POP and masked SUI. Some surgeons prefer to do a *concomitant anti-incontinence surgical procedure* if the patient has symptoms or any clinical evidence of SUI. Other surgeons prefer to correct the vaginal prolapse first and evaluate afterward whether an *additional anti-incontinence procedure* for unmasked SUI is indicated.

The advantage of combining POP and SUI surgery is that fewer patients may report SUI following such combination. However, this combined surgical strategy may be associated with an increased risk of complications, of which the development of bladder outlet obstruction, responsible for overactive bladder symptoms and retention, is the most important. Furthermore, combining the two procedures

Table 7.10 De novo stress urinary incontinence asymptomatic for SUI preoperatively: with occult SUI versus without occult SUI

Study	Outcome	Postoperative SUI in women with masked SUI, % (*n*/*N*)		Postoperative SUI in women without masked SUI	
		Combination surgery	Control	Combination surgery	Control
CARE trial	Objective SUI at 3 months	32 (12/38)	58 (23/40)	21 (22/106)	38 (41/109)
Sokol et al.	Objective SUI at 24 months	14 (6/43)	48 (16/39)	NA	NA
OPUS trial	UI at 12 months	35 (19/54)	60 (34/57)	28 (30/107)	41 (46/113)
Total	Objective SUI	22 (18/81)	52 (41/79)		
NNT (ARR)	Objective SUI	3.3 (30 %)		NA	

ARR absolute risk of retention, *NA* not available, *NNT* number needed to treat

may be unnecessary, as performing only POP surgery may cure SUI in about 40 % of patients.

To date data on the treatment of masked SUI remain controversial. Studies report different results not only because of the different preoperative assessment of this condition but also for the different surgical procedures used for POP repair. The prevalence of occult SUI was 27 % in the CARE trial and 33 % in the OPUS trial. The Colpopexy and Urinary Reduction Efforts (CARE) trial demonstrated that the postoperative risk of stress incontinence in stress continent women undergoing open abdominal sacrocolpopexy could be substantially reduced by the addition of a Burch colposuspension. Other RCT studies however did not confirm these results. The Outcomes Following Vaginal Prolapse Repair and Mid Urethral Sling (OPUS) trial reached similar conclusions following vaginal prolapse repair and mid-urethral sling, with lower rates of postoperative SUI after combination surgery (Table 7.10).

Sacrocolpopexy and transvaginal surgery have not been compared in a randomized trial evaluating this specific outcome, however it has been suggested that the transvaginal and transabdominal routes are related to different changes in dynamics between the anterior vaginal wall and the urethrovesical junction and, therefore, may be associated with different incidences of postoperative SUI in women with masked SUI.

All the available data did not still reduce the debate whether POP surgery repair should be combined or not with anti-incontinence surgery. If SUI has been documented in a woman preoperatively, then the benefits of a concomitant procedure to prevent SUI will probably outweigh the risks; if not, the risk–benefit ratio is less predictable. After a correct clinical assessment, the decision to perform – or not to perform – prophylactic surgery should be based on goals and desires of the patient, the skill and experience of the surgeon, and the risks and potential benefits

for a particular patient. Going to the evidence as reported by the Cochrane Collaboration Group in 2013, concomitant continence surgery at the time of POP surgery in continent women does not reduce the rate of de novo SUI, while in women with preoperative occult SUI incontinence, the rate of de novo SUI may be reduced by concomitant anti-incontinence procedure, even if approximately 20 % of women will be prevented and 80 % will have an unnecessary procedure. It is not possible to conclude that one single treatment strategy would be correct for every woman. The two options, combined POP repair and anti-incontinence procedure and wait and see strategy, should be discussed with each woman. Future research in this field should be aimed at identifying preoperative tests that could select women that are likely to be cured of SUI by prolapse surgery alone and postpone incontinence surgery until it is demonstrated that such an operation is really needed. Obviously, it has to be considered that further evaluation of these issues is necessary especially if new and larger randomized clinical trials will be developed, in which the benefit needs to be balanced against adverse effects, including the costs for the public health-care systems, which can vary between the different countries.

Neurogenic Stress Urinary Incontinence

Antonio Carbone, Giovanni Palleschi

Definition

Independently from the specific cause (inflammatory, degenerative, vascular, traumatic, iatrogenic, neoplastic), neurogenic stress urinary incontinence (SUI) is secondary to striated urethral sphincter deficiency as a consequence of a lesion which involves regions of the central and/or peripheral nervous system controlling this muscle through the pudendal nerve (Fig. 7.82) (erroneously positioned at the end of "mesh complications"). Patients with neurogenic SUI very often present also storage symptoms such as urinary urgency, frequency, and urgency incontinence, suggestive for a neurogenic detrusor overactivity (NDO) or low bladder compliance. In some cases, these symptoms may be masked by a severe SUI. Therefore, these subjects have to be carefully evaluated before planning a therapeutic protocol (Fig. 7.83), especially if surgical, to avoid failure and to prevent complications to the upper urinary tract function. In fact, in patients with mixed symptoms (urgency incontinence + stress urinary incontinence), the first approach aims to treat storage disorder and as second step SUI is treated if still necessary. In patients with severe NDO, major consideration is to be reserved to the risk of severe damage to upper urinary tract (i.e., vesicoureteral reflux) if bladder alteration is not treated before SUI surgery which may further contribute to increase endovesical pressures during

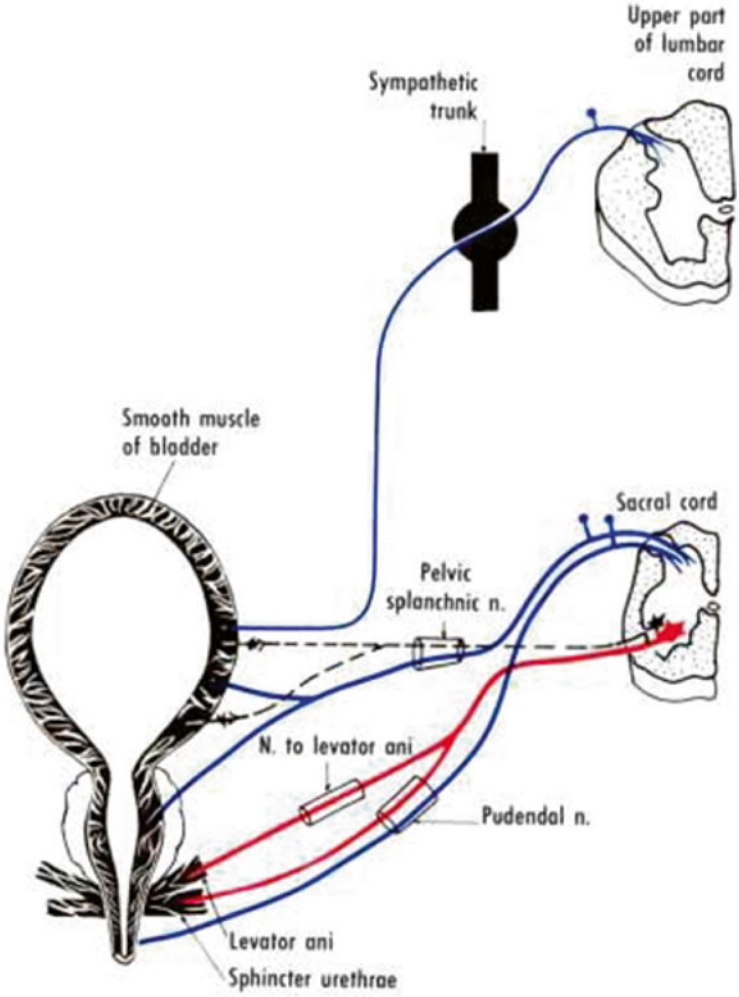


Fig. 7.82 The image shows the neurological control of the bladder and the innervation of striated urethral sphincter provided by pudendal nerve (From O'Rahilli, Capernter, Nueller and Svenson: *Basic Human Anatomy*)

filling phase, especially in case of bladder hyperactivity. As a further consideration, neurogenic implication of SUI should be considered in females with previous pregnancy and vaginal childbirth which represents an important risk factor for SUI. These conditions may be responsible for compression and stretching of the pudendal nerve contributing to the development of SUI. There is evidence that women with SUI diagnosed by urodynamics also demonstrate pudendal nerve dysfunction as evidenced by abnormal nerve conduction velocity and external urethral sphincter electromyography. Increased pudendal nerve terminal motor latency, an indicator of nerve damage or dysfunction, is correlated with vaginal delivery, advanced age, and

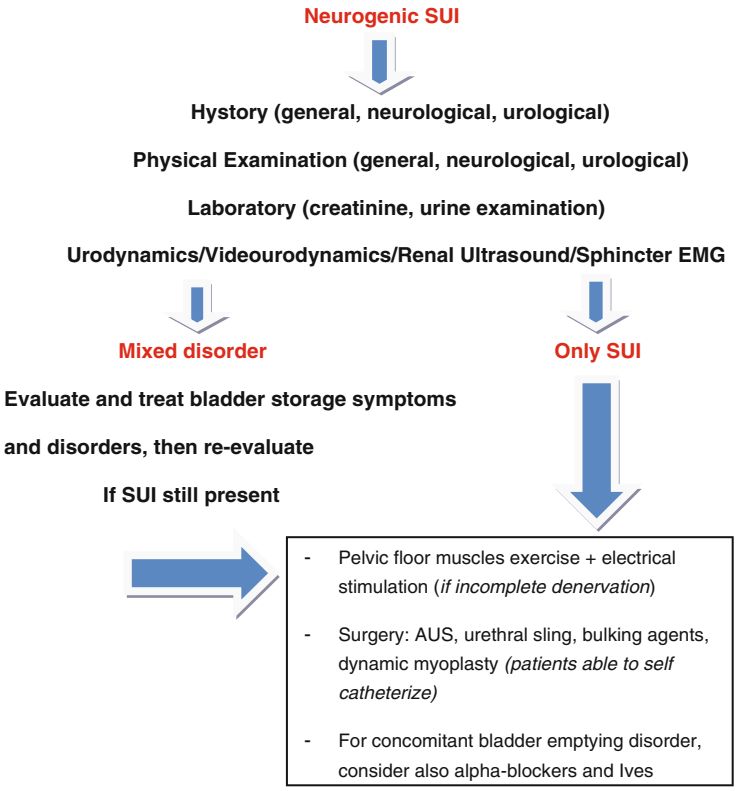


Fig. 7.83 The diagnostic and therapeutic flow chart for Neurogenic Stress Urinary Incontinence

SUI. Additionally, the external anal sphincter in these women showed abnormal fiber densities, suggesting partial reinnervation occurred following pudendal nerve injury. The underestimation of these findings in women with SUI categorized as "non-neurogenic" probably could explain unsatisfying outcomes of treatment.

Patient's Assessment

History must provide information related to pregnancy and vaginal childbirth, previous surgery, ongoing and pharmacologic treatment. Neurological diagnosis and onset of neurological and urological symptoms have to be assessed. General, vaginal, and neurological physical examination are mandatory, particularly aimed to evaluate the presence of a concomitant genital prolapse. Urodynamic study combined with sphincteric/pelvic floor electromyography is recommended to support the neurogenic origin of SUI, establish disorder severity, assess the presence of

associated bladder disorders (either of filling or voiding phase), and control the outcomes treatment. For these purposes, imaging techniques, especially cystography or videourodynamic, may improve diagnostic power and accuracy.

Treatment

In presence of neurogenic SUI, a specialized management is required. Conservative treatment with rehabilitation (pelvic floor muscle exercise) and electrical stimulation are not indicated for subjects affected by a complete denervation. Subjects with partial denervation might benefit from long-term protocols of electrical stimulation administered by a vaginal device because in these cases patients could contribute with their voluntary activity to the rehabilitation program. However, there are no studies reporting data from randomized trials. Pharmacotherapy is not recommended. Although the efficacy of various drugs has been explored to treat neurogenic SUI (adrenergic alpha-blockers, beta-3-agonists, antidepressants), no study has been yet published. For this reason, many patients with sphincteric incompetence secondary to neurogenic conditions may be considered for surgical treatment. As previously reported, combined dysfunction of bladder filling phase, as detrusor overactivity and/or low compliance, must be conservatively treated before a surgical approach for neurogenic SUI. In fact, the minimal criteria which make a patient eligible for surgical treatment of neurogenic SUI are: intrinsic sphincteric deficiency, underactive detrusor or well-controlled overactive detrusor, absence of urethral injury or pathological urethral condition (stricture), no evidence of vesicoureteral reflux, and well-stabilized neurological disease. Artificial sphincter implantation is considered one of the best surgical choices and it provides satisfying outcomes also at long-term follow-up (up to 10 years). This procedure is more used in males than in women; the long-term results are satisfying, even though there is a higher complication rate such as urethral erosion. As an alternative to artificial sphincter, good results are reported with the use of sub-urethral slings. In fact, European Urological Association Guidelines suggest that in female patients with neurogenic SUI who are able to self-catheterize, placement of an autologous urethral sling is the first choice with a high grade of recommendation (3A) while in male patients artificial urinary sphincter (AUS) is the best suggested treatment (grade of recommendation: 3A). However, all of the published studies are case series characterized by poor cohorts and without long-term data. Furthermore the studies are often not comparable because they include different surgical devices with different pre- and postoperative evaluations. Encouraging results come from the use of the dynamic myoplasty with gracilis muscle, but the experience is limited and it does not allow to consider this technique as a standard approach. Various authors report experience with bulking agents. This approach presents a large success variability in non-neurogenic population; therefore, in neurogenic cohorts its efficacy is even more unpredictable. Patients with coexisting voiding disorders can be managed by

alpha-blockers and self-intermittent catheterism. Endovesical electrical stimulation (IVES) is also considered a therapeutic option although data are absolutely preliminary and controversial.

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Chapter 8
Urinary Tract Infections

Tommaso Cai and Truls E. Bjerklund Johansen

Introduction

Humans have a huge number of microorganisms in the intestine and on the body surface. Most of the time, we live in friendly commensalism with them, but sometimes infections break out. This can be due to own microorganisms crossing physiological barriers as in honeymoon cystitis or the intrusion of foreign microorganisms as in venereal diseases.

A common feature in UTI is that the host reaction is the cause of the symptoms, as when urothelial cells are being shed from the bladder mucosa in acute cystitis or when immunological reactions counteract each other in the physiological chaos of urosepsis. The development of systemic inflammatory response syndrome into sepsis, severe sepsis, and septic shock is accompanied by a death risk of 20–40 % (Fig. 8.1, Table 8.1). While antibiotic treatment remains the cornerstone of treatment, modification of the host reaction has become an important aspect in acute cystitis as well as in urosepsis.

Diagnostics

Patient evaluation is based on a careful history, physical examination, and urine analysis.

T. Cai, MD
Department of Urology, Santa Chiara Regional Hospital, Trento, Italy

T.E. Bjerklund Johansen, MD, Dr. Med. Sci. (✉)
Oslo University Hospital, Oslo, Norway
e-mail: tebj@medisin.uio.no

Institute of Clinical Medicine, University of Aarhus, Aarhus, Denmark

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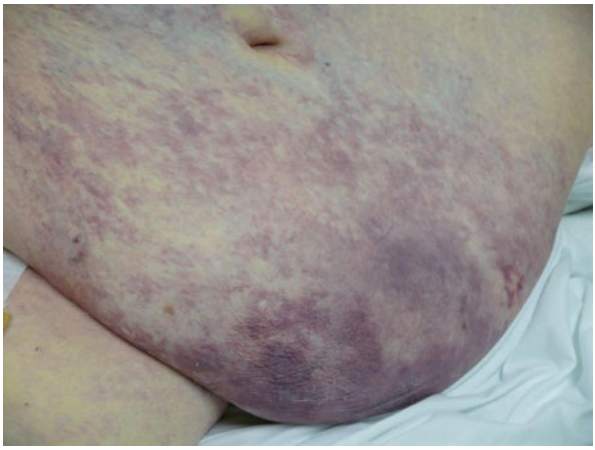

Fig. 8.1 Abdominal skin of a woman in uroseptic shock showing areas of bleeding and ceased microcirculation as a sign of physiological chaos with counteracting host reactions (Courtesy of F. Wagenlehner)

Table 8.1 Clinical presentation of cystitis (CY), pyelonephritis (PN), and urosepsis (US) and grading of severity

Clinical diagnosis	Acronym	Clinical symptoms	Grade of severity
Cystitis	*CY-1*	Dysuria, frequency, urgency, suprapubic pain; sometimes unspecific symptoms (see Table 8.1)	1
Mild and moderate pyelonephritis	*PN-2*	Fever, flank pain, CV tenderness; sometimes unspecific symptoms (see Table 8.1) with or without symptoms of CY	2
Severe pyelonephritis	*PN-3*	As PN-2, but in addition nausea and vomiting with or without symptoms of CY	3
Urosepsis (simple)	*US-4*	Temperature >38 °C or <36 °C Heart rate >90 beats min Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg (<4.3 kPa) WBC > 12,000 cells/mm^3 or <4000 cells/mm^3 or ≥10 % immature (band) forms With or without symptoms of CY or PN	4
Severe urosepsis	*US-5*	As US-4, but in addition associated with organ dysfunction, hypoperfusion, or hypotension Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria, or an acute alteration of mental status	5
Uroseptic shock	*US-6*	AS US-4 or US-5, but in addition with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured	6

The diagnosis of a urinary tract infection is based on clinical signs and the demonstration of microorganisms considered to be causing the infection. In most cases, the diagnosis is easy like in acute cystitis in a young woman, but in spinal cord injured patients with urinary catheters, the symptoms are totally different and urine findings are difficult to interpret.

Patient assessment always starts with an evaluation of severity. The clinical presentation forms correspond to grades of severity ranging from cystitis to urosepsis (Table 8.1). Severity is modified by risk factors, which can be described by means of phenotyping in a system called ORENUC (Table 8.2). Each letter in the word ORENUC refers to special patient features such as R – recurrent UTI without other known risk factor, E – extraurogenital risk factors like pregnancy, and C – presence of a catheter. According to a new classification presented by European Section for Infection in Urology (ESIU), a full section of the European Association of Urology (EAU), severity grades, and phenotyping is intended to replace the old classification into uncomplicated and complicated UTI.

Symptoms

Urinary tract infections (UTIs) often affect young people and are an important cause of reduced quality of life due to disabling symptoms. In most cases, UTIs are accompanied by typical signs and symptoms, but asymptomatic infections also

Table 8.2 Host risk factors in urinary tract infections categorized according to the ORENUC system

Category of risk factor	Examples of risk factors	Phenotype
N*O* known risk factor	Otherwise healthy premenopausal women	*O*
Risk factors for *R*ecurrent UTI, but no risk of more severe outcome	Sexual behavior (frequency, spermicide) Hormonal deficiency in postmenopause Secretor type of certain blood groups Well-controlled diabetes mellitus	*R*
*E*xtra-urogenital risk factors with risk of more severe outcome	Prematurity, newborn Pregnancy Male gender Badly controlled diabetes mellitus Relevant immunosuppression (not well defined)	*E*
*N*ephropathic diseases with risk of more severe outcome	Relevant renal insufficiency (not well defined) Polycystic nephropathy Interstitial nephritis, e.g., due to analgesics	*N*
*U*rological risk factors with risk of more severe outcome, which can be resolved during therapy	Ureteral obstruction due to a ureteral stone Well-controlled neurogenic bladder disturbances Transient short-term external urinary catheter Asymptomatic bacteriuria	*U*
Permanent urinary *C*atheter and nonresolvable urological risk factors with risk of more severe outcome	Long-term external urinary catheter Nonresolvable urinary obstruction Badly controlled neurogenic bladder disturbances	*C*

occur. For male genital infections, the clinical symptoms are not related to the severity of the infection. Asymptomatic chronic bacterial prostatitis due to *Chlamydia trachomatis* infection may cause severe complications such as decreased fertility. Generally, the symptoms of UTI depend on which part of the urinary tract that is affected. Doctors should learn the symptom language of each infection site.

Kidneys (i.e., acute pyelonephritis): upper back and flank pain; fever (not always); shaking and chills, nausea and/or vomiting (not always).

Bladder and *prostate* (i.e., cystitis and prostatitis): lower abdominal discomfort; a strong, persistent urge to urinate; a burning sensation when urinating; pelvic pressure; blood in urine (cystitis); rectal or perineal pain (prostatitis); sexual dysfunction (erectile dysfunction/premature ejaculation in case of prostatitis); in women symptoms of UTI occur without vaginal discharge or irritation.

Urethra (urethritis): Burning with urination and/or urethral discharge.

The most common clinical presentations of UTIs are outlined below.

Acute Uncomplicated Cystitis

The typical patient with acute (uncomplicated) cystitis is a female of reproductive age who presents with irritative urinary symptoms. The diagnosis can be made with a high probability based on a focused history of dysuria, frequency, and urgency in the absence of vaginal discharge or irritation. No risk factors for complicated urinary tract infections should be present.

The most common symptoms are dysuria, frequent voiding of small volumes, and urgency, sometimes hematuria and less often suprapubic discomfort or pain. In case of recurrent cystitis without other risk factors, the young patients may show psychological symptoms such as depression with a subsequent reduction in quality of life. Recently, a simple standardized self-reporting questionnaire for acute uncomplicated cystitis was presented. This is an 18-item self-reporting questionnaire, named Acute Cystitis Symptom Score (ACSS), including (a) six questions about "typical" symptoms of acute uncomplicated cystitis, (b) four questions regarding differential diagnoses, (c) three questions on quality of life, and (d) five questions on additional conditions which may affect therapy. The questionnaire has been validated and can be recommended for clinical studies and for initial diagnosis and monitoring of treatment of acute uncomplicated cystitis. Also, Clayson et al. developed a 14-item UTI Symptoms Assessment questionnaire (UTISA), to measure the severity and bothersomeness of the most frequently reported symptoms and signs of uncomplicated urinary tract infections [5]. This instrument comprises three four-item domains (urination regularity, problems with urination, and pain associated with UTI) with two additional items measuring hematuria. This questionnaire has demonstrated excellent psychometric properties and good accuracy in evaluation of severity and bothersomeness of UTI symptoms. The authors highlighted the importance of specific symptoms of UTIs that can decrease the patient's quality of life: frequency and urgency, pain or burning on urination, feeling of incomplete emptying, pain/pressure in lower abdomen, and low back pain.

Key Message
The combination of newly onset frequency and dysuria, in the absence of vaginal discharge, is diagnostic for an acute uncomplicated cystitis.

Acute Uncomplicated Pyelonephritis

The presence of flank or back pain in an otherwise healthy patient with lower urinary tract symptoms (dysuria, frequency, urgency, hematuria, suprapubic pain) is highly indicative of acute uncomplicated pyelonephritis. Moreover, these patients can sometimes present with systemic symptoms, such as nausea, vomiting, fever, chills, and abdominal pain. The history of recurrent lower urinary tract infections or a recent episode of acute uncomplicated cystitis is a risk factor of acute pyelonephritis. Other risk factors like diabetes, ureteral reflux, and incontinence may support the diagnosis of acute pyelonephritis in the presence of typical symptoms.

Key Message
The combination of newly onset frequency and dysuria, with flank or back pain, with or without systemic symptoms, in an otherwise healthy patient, is highly indicative of an acute uncomplicated pyelonephritis.

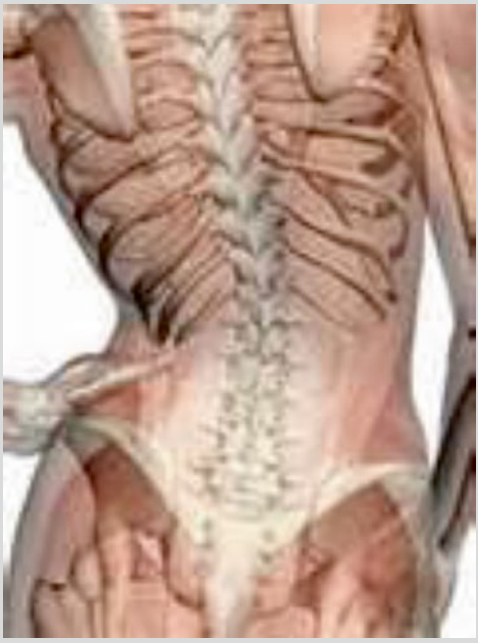

Fig. 8.2 Pain at costovertebral angle

Risk Factors, Phenotyping, and Complicated UTIs

A urinary tract infection in a patient with a structural or functional abnormality of the genitourinary tract was used to be called a complicated urinary tract infection, and the clinical presentations varied across a wide spectrum, ranging from mild lower tract irritative symptoms, such as frequency and urgency, to severe systemic manifestations, such as bacteremia and sepsis. In particular, complete urinary obstruction or trauma to the genitourinary tract with hematuria is associated with more severe clinical presentation forms. This complex picture was a main argument for the introduction of severity grades and phenotyping of risk factors thus enabling a more differentiated description of the patient and the symptoms than just a "complicated" urinary tract infection.

An important feature of the new ESIU/EAU classification is the status of asymptomatic bacteriuria which is regarded as a risk factor, not a specific type of UTI. The prevalence of asymptomatic bacteriuria is very high (almost 100 %) in patients with chronic indwelling catheters and 30–40 % in patients with a neurogenic bladder managed by intermittent catheterization.

Key Messages

- Patients with indwelling urological devices and systemic symptoms, such as fever should be suspected of having UTI even in the absence of local genitourinary signs and symptoms.
- Bacteriuria in patients with indwelling urological devices should only be treated if clinical symptoms of UTI are present.

Acute and Chronic Bacterial Prostatitis

Even if bacterial prostatitis represents a small portion of UTIs (about 10–15 %) of all urological visits in outpatient clinical setting, the impact on patient's quality of life is considerable. Patients with acute bacterial prostatitis present with typical signs and symptoms of an acute urinary tract infection including irritative and/or obstructive voiding complaints and often have additional symptoms of systemic infections like malaise, nausea, vomiting, chills, and fever and sometimes present with signs of urosepsis. They also complain of perineal and suprapubic pain, associated with pain or discomfort of the external genitalia. Chronic bacterial prostatitis represents the most frequent cause of recurrent urinary tract infections in young and middle-aged men. The initial clinical presentation of chronic prostatitis is similar to acute prostatitis, but chronic bacterial prostatitis can be a devastating disease, characterized by relapsing febrile episodes, if not treated adequately from the beginning.

Key Message
The new-onset irritative and/or obstructive voiding symptoms associated with perineal or testicular discomfort/pain are highly indicative of acute bacterial prostatitis. Moreover, all perineal discomfort/pain with or without typical signs and symptoms of urinary tract infection should be investigated in order to exclude a bacterial prostatitis due to possible future complications.

Physical Examination

The patient history and urinalysis are the most important tools for diagnosing UTIs. Even if there are no key diagnostic signs, a focused physical examination is still an important part of the diagnostic work-up. However, sometimes the physical examination is diagnostic as in cases of acute bacterial prostatitis and acute pyelonephritis.

Clinical condition	Local signs	Possible signs	Systemic signs
Acute uncomplicated cystitis	None	Suprapubic tenderness	Rarely
Acute uncomplicated pyelonephritis	Costovertebral angle tenderness	Discomfort during kidney palpation	Commonly (fever, tachycardia)
Acute bacterial prostatitis	Painful, swollen prostate	Perineal pain/discomfort Perineal pain and anal sphincter spasm	Usually (fever, nausea)
UTIs in patients with risk factors (complicated UTI)	Depending on risk factor	Not specific	Commonly (fever, tachycardia)
Prostatic abscess	Fluctuation during prostate palpation	Perineal pain/discomfort	Rarely
Chronic bacterial prostatitis	Painful prostate	Perineal pain/discomfort	Rarely

The aim of the physical examination is to assess the severity of the infection and to look for risk factors. In septic patients, one should always look for focal manifestations of circulatory failure (Fig. 8.3). In adults, the physical examination should be done in order to specifically evaluate:

- Abdomen
  - Previous surgical scars
  - Abdominal meteorism and signs of ileus
  - Costovertebral tenderness (pain elicited by blunt striking of the back, flanks, and the angle formed by the 12th rib and lumbar spine – with a fist) (Fig. 8.4)
  - Palpable renal mass
  - Dullness to percussion in the lower abdomen (bladder distension)

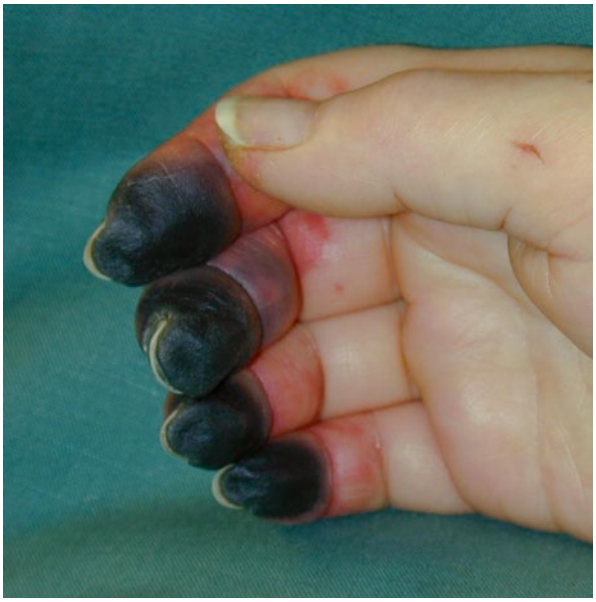

Fig. 8.3 Necrotic fingers in a young woman in septic shock due to delayed diagnosis of pyonephrosis resulting from an obstructing ureteral stone

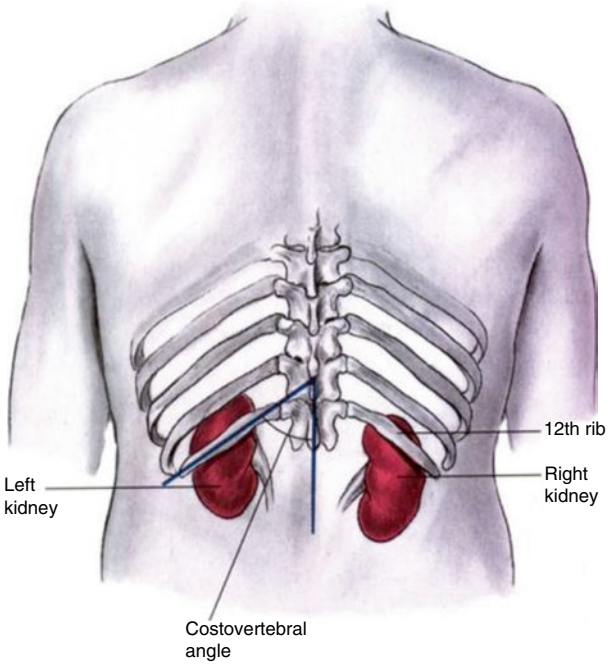

Fig. 8.4 Localization of the costovertebral angle

- In women, genitals should be evaluated for:
  - Vaginal discharges
  - Vaginal mucosa
  - Urethral secretion
  - Signs of infection of subcutaneous tissue (Fournier gangrene)
- In men, the physical examination of genitals should evaluate:
  - Urethral secretion (the penis should be examined by retracting the foreskin)
  - Testicular tenderness
  - Painful/swollen prostate
  - Perineal pain and anal sphincter spasm
  - Signs of infection of subcutaneous tissue (Fournier gangrene)
- In children, one should also evaluate the external urethral orifice.

In case of risk factors, the physical examination should be focused on genitourinary signs and symptoms related to each risk factor. In case of patients with indwelling catheter, the physical examination should always include systemic signs such as fever, nausea, and tachycardia (systemic inflammatory response syndrome).

Lab and Culture

Even if the diagnosis of UTIs can be made with a high probability based on history and physical examination, the verification of causative microorganism is the definitive diagnostic measure in UTIs. The microbiological evaluation is mandatory in cases of recurrent UTIs, in the presence of risk factors, and in patients with unusual signs and symptoms. As a rule, a urine sample should always be taken for culture before initiation of empiric antibiotic treatment. A good microbiological evaluation of a patient with UTIs requires that the urine specimen is appropriately collected, that a uropathogen is isolated, and the number of organisms is counted.

Sampling Technique

There is general consensus about the importance of using a midstream, clean-caught urine specimen to diagnose UTIs, although some authors found no significant difference in numbers of contaminated or unreliable results between specimens collected with and without preparatory cleansing.

Dipstick

In most cases of UTIs without risk factors, the urine dipstick testing has the same sensitivity and specificity, convenience, and cost-effectiveness, as conventional

urinalysis and urine microscopy. This is due to the fact that nitrites and leukocyte esterase are the most accurate indicators of UTIs in symptomatic patients. A diagnosis of UTI can be safely made in patients with typical symptoms who are found to have a positive urine dipstick test or urinalysis, without obtaining a urine culture.

It is important to know that nitrite tests may be negative if the UTI is caused by a non-nitrate-producing pathogen such as *Enterococci*, *S. saprophyticus*, and *Acinetobacter* and if the urine is too dilute. Pyuria is frequently present in patients with lower urinary tract infection and always in those with acute pyelonephritis. However, the absence of pyuria does not exclude a urinary tract infection in patients with typical symptoms. Nitrites and leukocyte esterase may be negative in urine of patients with bacterial prostatitis.

Urine Culture

Urine cultures are highly recommended for:

- Patients with suspected acute pyelonephritis
- Patients with symptoms that do not resolve or that recur within 2–4 weeks after therapy
- Patients with atypical symptoms
- Patients with suspected bacterial prostatitis
- Patients with suspected UTIs and systemic signs or symptoms

In the emergency room setting, it is recommended to take a urine sample for microbiological evaluation before starting empirical treatment in patients thought to be at high risk of pyelonephritis or bacteremia/urosepsis, as well as in those expected to have uncommon or resistant organisms. Routine posttreatment urinalysis or urine cultures in asymptomatic patients are not necessary.

Each clinical presentation requires specific sampling and microbiological assessment in order to isolate the bacterial strains and localize the infection site.

Clinical condition	Sample to obtain	Additional samples
Acute uncomplicated cystitis	Midstream urine	None
Acute uncomplicated pyelonephritis	Midstream urine	Blood
UTIs with risk factors (complicated)	Midstream urine	Blood
Acute bacterial prostatitis	Midstream urine	Blood In mild cases, only samples may be obtained by using Meares-Stamey test
Prostatic abscess	Samples obtained by using Meares-Stamey test	Blood/secretion from surgical drainage
Chronic bacterial prostatitis	Samples obtained by using Meares-Stamey test	None

Acute Uncomplicated Cystitis

A colony count of greater than or equal to 10^3 CFU/ml of a uropathogen in midstream urine is now the commonly accepted microbiologic diagnostic criterium for acute uncomplicated cystitis. Some authors argue that more than 10^2 colony-forming units per mL in women with typical symptoms of UTI represent a positive culture. Moreover, it is well known that about 10–20 % of symptomatic women have negative urine cultures, and yet the clinical response to treatment of these women is similar to women with positive urine cultures. An important aspect to consider is the potential role of contamination of voided specimens by periurethral microorganisms in premenopausal women. In fact, when cultures do not yield *Escherichia coli* in women with symptoms of cystitis, the usefulness of midstream urine cultures is debatable. In such cases, the presence of *Escherichia coli* in midstream urine was highly predictive of bladder bacteriuria even at very low counts, but *Enterococci* and group B *streptococci* were not predictive of bladder bacteriuria at any colony count. This aspect is important to take into account in order to avoid unnecessary antibiotic therapy.

Key Messages
- In women with typical symptoms of a UTIs, a count >102 colony-forming units per mL represent a positive culture.
- In women with symptoms suggestive of cystitis, a midstream portion of voided urine is recommended, but if *Enterococci* and group B *streptococci* are detected, more attention is due.

Acute Uncomplicated Pyelonephritis

Up to 95 % of episodes of acute uncomplicated pyelonephritis are associated with greater than or equal to 10^5 CFU/mL of a uropathogen. However, due to the fact that some patients with acute uncomplicated pyelonephritis have lower colony counts, it is proposed that a quantitative count of greater than or equal to 10^4 CFU/mL may be considered as significant bacteriuria. Although blood cultures are commonly performed for patients with febrile UTIs, the role of blood culture in diagnosis of acute uncomplicated pyelonephritis is controversial. Many authors argue that blood cultures do not provide useful information for the clinical management of acute uncomplicated pyelonephritis, and it may therefore not be routinely performed.

Key Messages
In acute uncomplicated pyelonephritis, blood culture may not be routinely performed.

UTI with Risk Factors (Complicated UTI)

Significant bacteriuria in a UTI with risk factors is defined by counts of $\geq 10^5$ cfu/mL and $\geq 10^4$ cfu/mL, in the midstream urine of women and men, respectively. If a straight catheter urine sample is taken, $\geq 10^4$ cfu/mL can be considered relevant. The requirement for pyuria is ≥10 white blood cells per high-power field (×400) in the resuspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. A dipstick method can also be used for routine assessment, including a leukocyte esterase test, hemoglobin, and a nitrite reaction.

Pyuria only as identified by urinalysis or a positive leukocyte esterase dipstick test is consistent with, but not diagnostic of, urinary tract infection. On the contrary, a urinalysis without pyuria may reliably exclude symptomatic urinary infection due to the high negative predictive value of pyuria. In all cases, however, a urine specimen for culture should be obtained before the initiation of antimicrobial therapy in order to identify the infective organism and its susceptibilities. Moreover, a count of at least 10^5 cfu/mL is required for microbiological verification of symptomatic UTI in patients on intermittent catheterization or with indwelling catheters.

Key Messages
A urine specimen should be obtained for culture and susceptibility testing before starting antimicrobial therapy in every episode of urinary tract infection in patients with risk factors.

Bacterial Prostatitis

Acute Bacterial Prostatitis The Meares-Stamey test is not recommended during the early phase of acute bacterial prostatitis. Hence, midstream urine culture is the only laboratory evaluation of the lower urinary tract and usually shows typical uropathogens. Blood cultures should also be taken in case of SIRS. Even if elevated levels of PSA have been described in more than 70 % of men with acute bacterial prostatitis as a consequence of increased vascular permeability and disrupted epithelium of the gland, the role of PSA in the differential diagnosis and evaluation of acute bacterial prostatitis is not clear.

Chronic Bacterial Prostatitis The Meares-Stamey four-glass test is, however, the standard method of assessing inflammation and the presence of bacteria in the lower urinary tract in men presenting with prostatitis symptoms. This test not only gives information about bacterial strains and susceptibility but also gives useful data to plan treatment in abacterial prostatitis. Moreover, the Meares-Stamey test is the best way to localize the infection site. Unfortunately, very few urologists use the four-glass test in routine diagnostic work-up. Therefore, the two-glass pre- and post-prostatic massage test is a valuable alternative to the preferred Meares-Stamey test for diagnosing prostatitis. Other laboratory testing is not routinely needed.

The four-glass test comprises the following samples: first-void early morning urine (VB1), midstream urine (VB2), expressed prostatic secretion (EPS), and post-

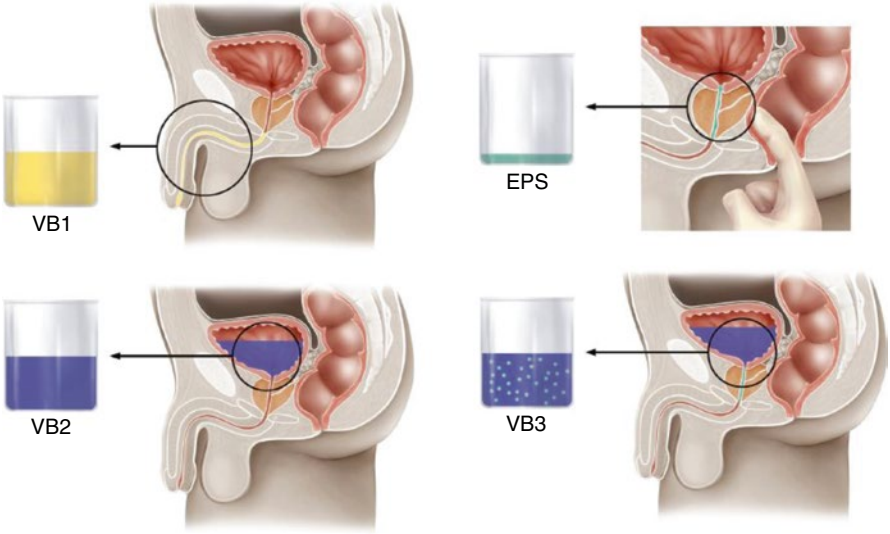

Fig. 8.5 The Meares-Stamey test

prostatic massage urine (VB3) (Fig. 8.5). The four-glass test can be considered positive for bacterial prostatitis if the bacterial load in EPS or in VB3 was at least 1000 CFU/mL and at least ten times higher than in VB1 and VB2.

Key Messages

- Midstream urine culture is considered the only laboratory evaluation needed in patients with suspected acute bacterial prostatitis.
- However, in the case of SIRS, blood cultures should also be taken.
- The two-glass pre- and post-prostatic massage test is a reasonable alternative to the preferred Meares-Stamey four-glass test for diagnosing chronic bacterial prostatitis.

Imaging

The role of imaging in UTI is to detect conditions that need to be resolved immediately (i.e., pyonephrosis), to detect conditions that can be corrected to prevent recurrences (i.e., obstruction and reflux), and to diagnose pyelonephritis in children.

Urinary Tract Infections

Imaging is rarely indicated in diagnosis and management of UTIs in adult women. Imaging should be considered in acute cystitis and acute pyelonephritis when urological and nephrological risk factors are suspected, in patients who present with atypical symptoms, and in those who do not respond to appropriate antimicrobial therapy. Imaging may reveal a renal abscess or an obstructing stone.

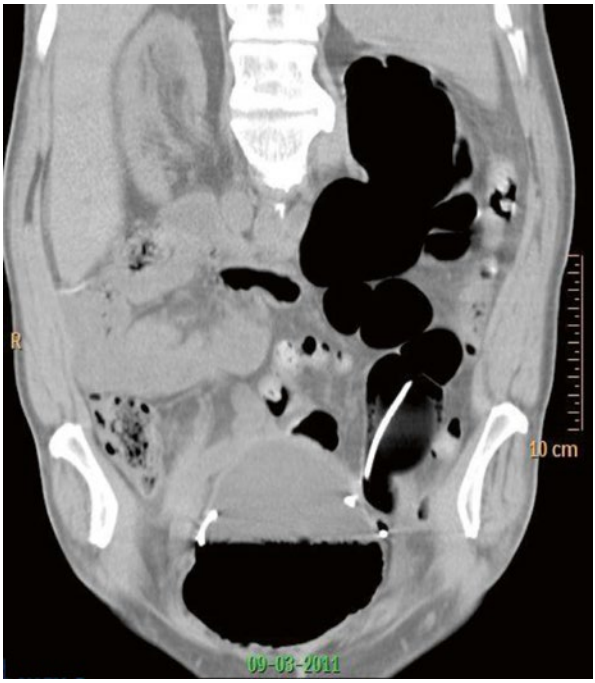

Fig. 8.6 CT scan of a severe case of emphysematous ureteropyelonephritis due to a left-out ureteral stent

The preferred modalities in adults are ultrasonography of the urinary tract and/or computed tomography (CT) scan with contrast. CT may also be used to diagnose subcutaneous gas-producing infections as Fournier gangrene. Bladder ultrasonography is helpful in diagnosing post-void residual volumes. Plain kidney ureter and bladder films still have a role in patients with a history of stones in the urinary tract and in the case of emphysematous pyelonephritis (Fig. 8.6). Renography should be considered if kidney function needs to be assessed. In patients with a history of considerable radiation exposure, MRI of kidneys may replace CT.

Bacterial Prostatitis

Imaging is indicated in patients with suspected prostatic abscess and in those who fail to respond to appropriate antimicrobial therapy. The preferred modalities are transrectal ultrasound (TRUS) or MRI of the prostate. The main aim is to rule out and sometimes drain a prostatic abscess. In patients who do not respond to appropriate antibiotic therapy and in particular in immunocompromised patients, TRUS should not be postponed for >48 h. CT scans and magnetic resonance imaging offer no advantage over TRUS, unless the abscess has penetrated, the confines of the prostate gland or further abscess foci are suspected. TRUS can be performed in patients with acute bacterial prostatitis without increasing the risk for urosepsis. In patients with chronic bacterial

prostatitis, TRUS should be performed also in order to evaluate concomitant prostatitic disease such as BPH or seminal vesciculitis. The role of prostatic calcifications in diagnosis and management of bacterial prostatitis is controversial. There is currently no indication to evaluate the presence, location, size, and number of prostate calcifications in patients with chronic bacterial prostatitis unless in extreme cases.

Treatment

Daily Life Changes as Prophylaxis

UTIs have a high prevalence in the population, especially among otherwise healthy young sexually active women and may cause considerable morbidity and expenses. Preventive measures of these events are therefore desirable. Having a mother with a history of UTI and having had UTI during childhood put patients at greater risk of developing UTI themselves in adult age.

Among all UTIs, acute cystitis is that more suitable to respond to daily life changes. Recommendations on preventive measures have to be based on the most common behavioral risk factors associated with UTIs. In young women, most behavioral risk factors for cystitis and pyelonephritis are related to sexual activity. These are:

- Frequency of sexual intercourse
- Spermicide use
- Getting a new sexual partner
- Having more than one sexual partner

While sexual intercourse is a strong predictor of UTI in young women, studies in postmenopausal women have yielded inconsistent and weak relations. Moore et al., recently, showed absent or only moderately increased risks of UTI related to sexual intercourse in postmenopausal women.

Other behaviors that are thought to increase the risk of UTI are reduced fluid intake, habitually delaying urination, delaying postcoital urination, wiping from back to front after defecation, douching, and wearing occlusive underwear. Some factors are associated with higher risk of getting a second UTI: hormonal status, bowel function, number of previous UTI episodes, and type of pathogens isolated.

Even if there are no good studies that have evaluated the impact of behavioral changes in the prevention UTIs, some strategies are highly recommended:

- Reducing use of spermicides
- Reducing sexual activity
- Early postcoital micturition
- Increasing daily fluid intake
- Regularize the bowel function

Due to the low cost of daily life changes, all women with a second episode of UTI should be counseled about the pathogenesis of UTIs and how behavior modification might be useful in reducing one's risk.

Key Messages
- All safe strategies to prevent recurrent UTIs that avoid the use of antimicrobials are highly desirable.
- Education and counseling with the aim of behavioral modification should be offered to all women with more than one episode of UTI.

Antimicrobial Treatment of Urinary Tract Infections

In everyday clinical practice, a diagnosis is frequently made and treatment is started without the results of urine culture. However, even if empirical therapy is still recommended, it is very important to take into account that in geographic areas or in age groups where antimicrobial resistance is high, preemptive culturing (a culture secured prior to instituting empirical therapy) is recommended.

Empirically based treatment means that we know beforehand which pathogen is the most likely in the current situation and what is the most probable susceptibility.

The aim of antimicrobial treatment is to relieve the patients' symptoms, eradicate the pathogen, and preserve kidney function. However, systemic antibiotic treatment affects all microorganisms in our body. Unfortunately, some bacteria are able to develop resistance to antibiotics and to reattack the host.

Recommendations on which antibiotic to use are based on general pathogen susceptibility, pharmacokinetic and pharmacodynamics properties of the antibiotic, and evidence form clinical studies. Pharmacokinetics refers to concentrations of antibiotics being obtained in the serum, and pharmacodynamics refers to the concentrations being obtained at the site of infection. The aim is to achieve a certain concentration for a certain length of time. Too low dosing will facilitate development of resistance. Recommendations on empirical antimicrobial treatment are shown in Table 8.3.

If risk factors are present, as described in the ORENUC phenotyping, the severity of the clinical situation might be upgraded and the empiric antibiotic treatment adjusted accordingly. Some practical advices can be found in the textbox below:

State-of-the-Art Expert Advice on Antibiotic Treatment of UTI
- Determine the clinical presentation of the infection, check for risk factors, and determine the severity grade.
- Check the resistance rates to the most commonly used antibiotics in your country.
- Clarify if the infection is community acquired or health care acquired.
- Clarify which is the most likely pathogen and if inherent resistance is likely.
- Chose the most relevant antibiotic from Table 8.3.
- Adjust treatment according to culture results as soon as they are available.
- In febrile infections, continue treatment until 3–5 days after defeverescence.

Table 8.3 Recommended antimicrobial therapy in acute urinary tract infections without risk factors (uncomplicated)

Antibiotics	Daily dose	Duration	Comments
Severity grade 1 (*acute cystitis*)			
First choice			
Fosfomycin trometamol	3 g single dose	1 day	
Nitrofurantoin macrocrystal	100 mg bid	5 (−7) days	Avoid in G6PD deficiency
Pivmecillinam	400 mg tid	3 days	
Alternatives			
Ciprofloxacin	250 mg bid	3 days	Not during pregnancy
Levofloxacin	250 mg qd	3 days	Not during pregnancy
Norfloxacin	400 mg bid	3 days	Not during pregnancy
Ofloxacin	200 mg bid	3 days	Not during pregnancy
If local resistance pattern is known (*E. coli resistance <20 %*)			
TMP	200 mg bid	5 days	TMP not in the first trimester of pregnancy
TMP-SMX	160/800 mg bid	3 days	SMX not in the last trimester of pregnancy
Severity grade 2 (*mild and moderate pyelonephritis*)			
Ciprofloxacin	500–750 mg bid	7–10 days	
Levofloxacin	500 mg qd	7–10 days	
Levofloxacin	750 mg qd	5 days	
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)			
Cefpodoxime proxetil	200 mg bid	10 days	
Ceftibuten	400 mg qd	10 days	
Only if the pathogen is known to be susceptible (not for initial empirical therapy):			
Trimethoprim/sulphamethoxazole	160/800 mg bid	14 days	
Co-amoxiclav[a,b]	0.5/0.125 g tid	14 days	
Severity grade 3 (*severe uncomplicated pyelonephritis*)			
Initial empirical parenteral antimicrobial therapy			
Ciprofloxacin	400 mg bid	Fluoroquinolones are contraindicated during pregnancy Re: duration, kindly see below under alternatives	
Levofloxacin[a]	250–500 mg qd		
Levofloxacin	750 mg qd		

(continued)

Table 8.3 (continued)

Antibiotics	Daily dose	Duration	Comments
Alternatives			
Cefotaxime[b]	2 g tid	After improvement, the patient can be switched to an oral regimen using one of the above mentioned antibacterials (if active against the infecting organism) to complete a 1–2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated	
Ceftriaxone[a,d]	1–2 g qd		
Ceftazidime[b]	1–2 g tid		
Cefepime[a,d]	1–2 g bid		
Co-amoxiclav[b,c]	1.5 g tid		
Piperacillin/tazobactam[a,d]	2.5–4.5 g tid		
Gentamicin[b]	5 mg/kg qd		
Amikacin[b]	15 mg/kg qd		
Ertapenem[d]	1 g qd		
Imipenem/cilastatin[d]	0.5/0.5 g tid		
Meropenem[d]	1 g tid		
Doripenem[d]	0.5 g tid		
Severity grade 4, 5, and 6 (the sepsis syndrome)			
Any of the drugs recommended for severity grade 3, usually in combination with gentamicin			

[a]Lower dose studied, but higher dose recommended by experts
[b]Not studied as monotherapy in acute uncomplicated pyelonephritis
[c]Mainly for gram-positive pathogens
[d]Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible)

Prevention of Recurrent UTI (rUTI)

Recurrent UTI is said to occur when a patient has more than three episodes of microbiologically verified UTIs in 1 year or two episodes within 6 months. A reinfection should be differentiated from a relapse which means that an infection with the same pathogen occurs within 2 weeks after completion of antibiotic treatment of a UTI. In the ORENUC system, phenotype R means that all other risk factors are excluded. Recurrent UTI is common among young, healthy women. Several preventive measures are available.

Behavioral Modifications

Sexual intercourse is highly associated with rUTI in young and old women alike. Spermicide use and a new sex partner add to the risk. Several other behaviors are also thought to increase the risk of rUTI. These include reduced fluid intake, habitually delaying urination, delaying postcoital urination, wiping from back to front after defecation, douching, and wearing occlusive underwear. Their association with UTI is, however, not proven in clinical trials. Micturition training and biofeedback accompanied by long-term antibiotic prophylaxis have significant effect on rUTI in children, but no corresponding studies are available in adults.

Hormonal Replacement

In postmenopausal women, local, vaginal estrogen replacement is thought to strengthen the mucosa and influence the local bacterial flora by stimulating the growth of *Lactobacillus* sp. which prevents the growth of Enterobacteria that are urinary tract pathogens. Studies have showed a trend toward preventing UTI recurrences, but vaginal irritation is common.

Immunoactive Prophylaxis

Immunoactive prophylaxis is thought to stimulate the innate immune system. Three routes of administration have been tested: oral, vaginal, and parenteral.

OM-89 (Uro-Vaxom®) are tablets for oral administration which contain a dried lysate of several bacteria and have a good safety profile. The drug has been shown to be more effective than placebo in several randomized trials but has not yet been compared with antimicrobial prophylaxis.

Urovac® is a vaginal vaccine that has been shown to reduce UTI recurrence and to increase time to reinfection. Two parenteral immunotherapeutic products have been studied in phase II studies, StroVac® and Solco-Urovac®. Both have been shown to be effective when administered with a booster cycle of the same agents.

Probiotics

Vaginal application of *Lactobacillus crispatus* has been shown to reduce the rate of recurrent UTI in premenopausal women, while oral lactobacilli prophylaxis did not decrease UTI recurrence. Clinically proven probiotics for UTI prophylaxis are currently not universally available.

Cranberry

Cranberry containing proanthocyanidin A is able to decrease the binding capacity of P-fimbriae of *Escherichia coli* to the mucosa in a dose-depending manner. Previous studies have suggested that cranberry (*Vaccinium macrocarpon*) was useful in reducing the rate of lower UTIs in women, but a recent meta-analysis comprising 4473 participants showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI.

D-Mannose

D-mannose is a sugar thought to inactivate fimbria which is a virulence factor of *E. coli*. In a prospective randomized placebo-controlled clinical trial, it could be demonstrated

Non-antimicrobial approaches to prevent recurrent UTIs

	When	How	Mechanism	Evidence
Sexual behavioral changes	Premenopausal women	Education and counseling	Reduce the bacterial passage through the urethra	Some evidence from studies
Use of topical estrogen	Postmenopausal women	Topical vaginal estrogens	Reconstitution of vaginal flora	Randomized placebo-controlled studies
Cranberry products	All women (especially in young women)	Oral administration	Block adherence of *E. coli* to uroepithelial cells via the proanthocyanidin type A	Conflicting evidence – no evidence for cranberry powders
Probiotics	All women	Oral administration	Reconstituting vaginal lactobacilli	Randomized studies
Immunoprophylaxis	All women	Oral administration	Stimulates urinary tract immunological defense	Meta-analysis

that a daily dose of 2 g d-mannose was significantly superior to placebo and as effective, but better tolerated than 50 mg nitrofurantoin in preventing recurrent UTI.

Antimicrobial Prophylaxis

Due to the risk of resistance, antimicrobial prophylaxis should only be given after other preventive measures have failed. Prophylaxis can be given continuously (daily, weekly) for longer periods of time (3–6 months), or as a single postcoital dose. Recurrences tend to occur in clusters and it is advisable to pay attention to the time intervals when the duration of prophylaxis is decided. Furthermore, many women

The most commonly used regimens for antimicrobial prophylaxis of rUTI include:

- Continuous regimens:
  - Nitrofurantoin (macrocrystal) 50 or 100 mg once daily
  - Fosfomycin trometamol 3 g every 10 days
  - During pregnancy:
    - Cephalexin 125 or 250 mg
    - Cefaclor 250 mg once daily
- Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy.

with recurrent UTI can safely diagnose themselves and administer short-course regimens of an antimicrobial agent.

The choice of antibiotics should be based upon the identification and susceptibility pattern of the organism causing the rUTI, the patient's history of drug allergies, and the ecological collateral effects including bacterial selection of resistance by the chosen antimicrobial. The spectrum of antibiotics is the same as for sporadic acute UTI (Table 8.3).

Recently, several concerns have been raised against antimicrobial prophylaxis of rUTI. Oral fluoroquinolones and cephalosporins are no longer recommended due to the risk of ecological side effects. There are warnings against long-term prophylactic use of nitrofurantoin because of pulmonary and hepatic side effects. Increase of *E. coli* resistance against trimethoprim and resistance in ESBL-producing *E. coli* to fosfomycin underlines the need for non-antimicrobial preventive measures.

An important aspect is whether or not to treat persistent asymptomatic bacteriuria in young women after UTI. Recently, Cai et al. found that the antibiotic treatment of asymptomatic bacteriuria in young women with recurrent UTI is not only unnecessary, but harmful. They found that in women who had undergone antibiotic treatment, the rate of *E. coli* decreased over time, whereas the prevalence of *E. faecalis* increased gradually, suggesting that *E. coli* might be an important biological defense mechanism that effectively interferes with the establishment of other important enteric pathogens, such as *E. faecalis*.

The use of antimicrobial prophylaxis might appear highly effective in reducing the risk of recurrent UTI in a short time perspective, but a non-antimicrobial approach should always be tried first in order to avoid long-term antimicrobial side effects with selection of resistant strains.

Alternative Preventive Measures

Natural Antibiotics and Disinfectants There are several components of our infection defense system acting as natural antibiotics and disinfectants. Antimicrobial peptides (AMPs) are produced by several species as a key component of the natural defense system. AMPs protect against bacteria, fungi, parasites, viruses, and even cancer cells. Keratinocytes in the perianal region produce psoriasin, a substance which destroys enteric bacteria. This is an intriguing new field of research, but so far there are no data from clinical studies.

Phytotherapy Phytotherapeutic drugs have been shown to have inflammatory, antioxidative, antibacterial, diuretic, and spasmolytic effects. Well-designed studies have been performed showing the phytotherapeutic drug Canephron^{R} to have similar protective effect as antimicrobial prophylaxis against rUTI. The initial results warrant follow-up with double-blind clinical studies.

Bladder Instillation Intravesical instillation of hyaluronic acid (HA) or chondroitin sulfate (CS) has been attempted to strengthen the intravesical GAG (glycosaminoglycan) layer and thereby prevent rUTI. In a recent small double-blind, placebo-controlled trial, intravesical instillations of HA-CS were given during a five-month

period. Compared with placebo, HA-CS instillations significantly reduced the recurrence rate over a 12-month period, and there were no severe side effects. However, further intravesical instrumentations are not recommended for the management of uncomplicated rUTI.

Surgery

Surgery has a double role related to urinary tract infections:

- Treatment of acute infections
- Prevention
  - Of recurrences
  - Of hospital acquired infections

Treatment of Acute Infections

The role of surgery in acute situations rests on the old principles: wherever there is pus, you should drain it (ubi pus ibi evacua), and that retention might cause infection. An important feature of the urinary tract is the reflux from the renal pelvis to

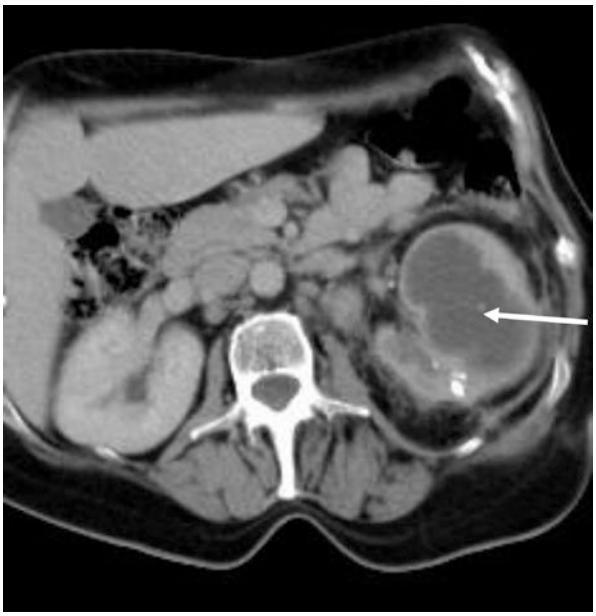

Fig. 8.7 CT scan showing left-sided pyonephrosis in a young woman (*arrow*)

the veins through the pyelovenous and pyelolymphatic drainage which occurs when the pressure in the renal pelvis exceeds a certain limit.

In the most serious acute conditions like severe pyelonephritis and urosepsis, one should always look for dilatation of the upper tract, and drain it with a nephrostomy tube if pyonephrosis is suspected (Fig. 8.7). The reason why symptoms usually improve very fast is that the pyelovenous reflux of microorganisms is stopped.

Renal or perirenal abscesses should be drained outside the abdominal cavity. The peritoneum is a dialysis membrane and microorganisms may easily penetrate to the systemic circulation. Spread of infection may cause intra-abdominal adhesions and ileus at a later time. If open surgery is needed to drain an abscess, the surgical field will become infected. The surgeon should therefore ensure large drainage tubes and consider the old war surgical principle of delayed primary closure of the skin a week or so later.

Prevention of Recurrences

Prevention of recurrent UTI in children is a cornerstone of pediatric urology. We used to think that there was an etiological relationship between reflux causing ureteral dilation, causing infections, and causing renal failure, but recent studies indicate that there might be a common inborn defect behind all four conditions. Reflux may be prevented by periureteral instillation of blocking materials like collagen and ureteral reimplantation.

In adults, urology prevention is about removal of infection stones and relief of obstruction at all levels of the urinary tract. It is difficult to define a critical threshold for residual urine in patients with recurrent UTI and prostatic enlargement due to benign prostatic hyperplasia. The decision on when to do a transurethral resection (TURP) should be based on clinical experience and supported by urodynamic evaluation. One hundred milliliters might sometimes be enough to cause recurrent infections. One should be hesitant to do a TURP if recurrent UTI is thought to stem from chronic bacterial prostatitis.

Prevention of Hospital-Acquired Infections (HAUTI)

Some measures to prevent HAUTI lie on the level of the hospital and some lie on the personal level of the surgeon.

Hospital Level

The prevalence of HAUTI varies form 7 to 21 % in urology departments. This is a big problem, especially as more and more patients are coming in for elective surgery without having any symptoms. Prevention of HAUTI rests on:

- A recognition of the contamination status of the procedure
- The patient's risk factors for developing infection
- Antibiotic prophylaxis (ABP)

Each contamination category has a certain peril of infection. Risk factors modify this peril. ABP should be decided according to the most likely pathogen, the resistance situation in the hospital, and the pharmacokinetic and pharmacodynamic properties of the antibiotic. Antibiotics used for prophylaxis should not cause collateral damage. This means development of resistance in causative pathogens and spread of resistance to other microorganisms is called cross-resistance and is a point of growing concern. As a rule, ABP should not extend beyond 24 h, and the most potent antibiotics should not be used for prophylaxis, but should be reserved for treatment in case infection occurs. This situation is already setting limits for urological practice in certain countries, especially in prostate biopsies and stone surgery.

The Surgeon Level

The single most important measure to prevent hospital-acquired urinary tract infections is to take out urinary catheters and stents (Fig. 8.6). As a rule, prophylaxis can never compensate for a poor surgical technique. Unfortunately, some surgeons have more complications than others.

The surgeon should strive for perfection in surgical technique and avoid damaging tissue and leaving dead tissue behind. Tissues must be handled gently with forceps, avoiding too extensive electrocoagulation and big ligatures. Consider carefully the blood supply to intestinal segments. One single improper suture may cause leakage and infection and ruin the result of an extensive procedure. Try and prevent hematomas, if necessary with drains, but never use a suction drain after opening the urinary tract. Leakage usually stops after 11 days. Learn the pathophysiology of sepsis and the clinical signs of imminent septic shock. Follow recommendations on basic hygienic principles.

Recommended Further Reading

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Chapter 9
Male Lower Urinary Tract Symptoms (MLUTS)

Odunayo Kalejaiye, Hashim Hashim, and Matthias Oelke

Background

Introduction

Lower urinary tract symptoms (LUTS) are common in the ageing male and represent a significant burden on both the patient and the health-care system worldwide. There are a large number of high-quality trials and guidelines to support clinical practice. In this chapter, we will be exploring the assessment of men with voiding LUTS and the recommended medical and surgical therapies, as well as their outcomes. Treatment of storage LUTS is being discussed in other chapters.

Prevalence and Bother

The two largest contemporary population surveys to investigate the prevalence and bother of LUTS are the EpiLUTS and EPIC studies. The overall prevalence of any

O. Kalejaiye, MBBS, BSc, FRCS (Urol)
Southmead Hospital, Bristol, UK

Bristol Urological Institute, Southmead Hospital,
3rd Floor Learning & Research, Southmead BS10 5NB, UK

H. Hashim, MBBS, MRCS, MD, FEBU, FRCS (Urol) (✉)
Bristol Urological Institute, Southmead Hospital,
3rd Floor Learning & Research, Southmead BS10 5NB, UK
e-mail: h.hashim@gmail.com

M. Oelke, MD, FEBU
Department of Urology, Hannover Medical School,
Carl-Neuberg-Str. 1, Hannover 30625, Germany
e-mail: Oelke.Matthias@mh-hannover.de

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LUTS was estimated to be 62.5 % in the EPIC study. This increases with age from 51.3 % in men under 40 years to 80.7 % in men aged over 60 years. Storage symptoms are the most common symptoms with 51.3 % of men reporting this compared with 25.7 and 16.9 % who reported voiding and post-micturition symptoms, respectively. The most common storage symptoms are nocturia (48.6–69.4 %) and urgency (10.8–22.4 %). There is an overlap between storage, voiding and post-micturition symptoms. It is estimated that 9–10 % will present with a combination of voiding and storage symptoms and 24.2 % with all three symptom groups. In addition, 62.5 % will present with one or more LUTS. Understandably as the number of LUTS increases, the proportion bothered significantly by their symptoms also rises. Although storage symptoms remain the most bothersome and prevalent symptoms, voiding symptoms are more likely to be the reason for referral to secondary care. In addition, voiding symptoms are more likely to be treated initially as treatment is often prostate focused.

Definitions

LUTS was a term coined in the late 1990s to dissociate urinary symptoms from the assumed source of their origin, traditionally perceived to be the prostate in men. In 2002, the International Continence Society (ICS) divided LUTS into three groups with symptoms defined from the patient's perspective. The groups are:

- Storage: urgency, frequency, nocturia, urgency and urinary incontinence
- Voiding: slow stream, hesitancy, intermittency, straining and terminal dribbling
- Post-micturition: feeling of incomplete emptying and post-micturition dribble

Aetiology

The underlying aetiology of LUTS is multifactorial with causes being split into urological and non-urological causes. For this chapter, we will focus on the urological causes; however, when assessing the patient in the office, it is also important to consider all the non-urological causes. The urological causes may be broadly divided into:

- Bladder: overactive bladder (OAB), impaired contractility and detrusor underactivity (DUA) during voiding, bladder tumour, cystitis and neurogenic bladder dysfunction
- Prostate: benign prostatic enlargement (BPE), bladder outlet obstruction (BOO) or benign prostatic obstruction (BPO), benign prostatic hyperplasia (BPH) and prostatitis
- Others: urethral stricture, ureteral stones, foreign body and ketamine abuse

Assessment

Objectives

The correct management is dependent on eliciting all the individual's symptoms, determining the degree of bother of each symptom and managing expectations (see Tables 9.1 and 9.2). The reason for presentation is another key aspect of the consultation. Men may present for a variety of reasons not always associated with symptom bother, i.e. public health campaigns and anxiety about the association of their symptoms with prostate cancer. Lastly, it is important to exclude underlying significant pathologies and establish the clinical profile of their condition.

Table 9.1 History and examination

Symptoms	Storage versus voiding versus post-micturition Duration Severity: i.e. incontinence episodes Degree of bother Which symptom is most bothersome Any treatment previously trialled Impact on quality of life Any precipitating factors
Drug history	Diuretics, herbal formulations, illicit drug use (especially ketamine)
Co-morbidities	Diabetes mellitus/insipidus Previous surgery: penile, prostatic or rectal (e.g. for inflammatory bowel disease) Previous trauma Neurological disorders: Parkinson's, multiple sclerosis, cerebrovascular accident, spinal cord injury, disc prolapse, spina bifida Cardiorespiratory disease: heart failure, sleep apnoea Renal disease

Table 9.2 Examination

Examination	Abdomen
	  Urinary retention
	  Surgical scars
	External genitalia
	  Phimosis
	  Meatal stenosis
	  Balanitis xerotica obliterans
	  Penile cancer
	Digital rectal examination
	  Anal tone, sensation
	  Prostate: size, irregularity, tenderness, bogginess
	  Rectal mass
	Perineal/lower limbs: motor and sensory function

Symptom Questionnaires

There are several available questionnaires which are validated in a variety of languages. They are usually sensitive to changes in symptoms and therefore can be used to monitor responses to treatment. The most widely used questionnaire is the International Prostate Symptom Score (IPSS). This eight-item questionnaire has seven symptom and one quality of life (QoL) questions. The symptom questions assess four voiding and three storage symptoms for the previous month (see Fig. 9.1). The response options range from 'not at all' (0 points) to 'almost always' (5 points). The minimum score is 0 and the maximum score 35. The symptom severity is determined based on the basis of the total symptom scores as:

- Asymptomatic: 0 points
- Mildly symptomatic: 1–7 points
- Moderately symptomatic: 8–19 points
- Severely symptomatic: 20–35 points

The QoL scores range from 0 to 6. The main limitation of the IPSS is the lack of assessment of incontinence. This means that LUTS severity may be underestimated.

International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

This validated questionnaire resulted from the ICS-BPH study. This 11-item questionnaire assesses a large spectrum of LUTS and bother scores for individual symptoms.

Bladder Diary

These are useful adjuncts in providing information about patients' drinking and voiding habits. A bladder diary records volumes voided and their times, incontinence episodes, pad usage, fluid intake and degree of urgency. Information about fluid intake allows counselling regarding fluid reduction at specific times of the day and avoidance of stimulants. The diary may also be used to diagnose nocturnal polyuria (nocturnal urine production >20 % in young individuals and >33 % in elderly of the total 24-h urine production) or 24-h polyuria (24-h urine production >40 ml/kg bodyweight). Frequent small-volume voids may indicate OAB. The time between voids may be utilised in counselling in bladder training techniques. Lastly, the maximum volume voided may be useful when performing invasive urodynamics in guiding volumes to which the patient's bladder can be filled. This also provides information about bladder capacity.

International Prostate Symptom Score (I-PSS)

Patient Name: Date:	Not At All	Less Than 1 Time In 5	Less Than Half The Time	About Half The Time	More Than Half The Time	Almost Always	YOUR SCORE
1. Incomplete Emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you have finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream Over the last month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	Once	Twice	3 times	4 times	5 or more	YOUR SCORE
7. Nocturia Over the past month how many times did you most typically get up each night to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total I-PSS Score							

Quality of Life due to Urinary Symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly unhappy	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

The I-PSS is based on the answers to seven questions concerning urinary symptoms. Each question is assigned points from 0 to 5 indicating increasing severity of the particular symptom. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

Although there are presently no standard recommendations into grading patients with mild, moderate or severe symptoms, patients can be tentatively classified as follows: **0 - 7 = mildly symptomatic; 8 - 19 = moderately symptomatic; 20 - 35 = severely symptomatic.**

The International Consensus Committee (ICC) recommends the use of only a single question to assess the patient's quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of BPH symptoms on quality of life, it may serve as a valuable starting point for doctor-patient conversation.

Fig. 9.1 International Prostate Symptom Score (IPSS)

Bright et al. have recently illustrated that the validated ICIQ-bladder diary is as reliable when completed over 3 days versus 4 days. They recommend the 3-day version.

Urinalysis

This is an inexpensive tool to exclude underlying pathologies such as diabetes, UTI, renal disease or urogenital malignancy. The European Association of Urology (EAU) expert panel recommends its use, although there is no strong evidence for its use in LUTS.

Prostate-Specific Antigen (PSA)

The serum PSA concentration may be used as a surrogate for prostate volume. A prostate volume >30 mL is associated with 3 times greater risk of acute urinary retention (AUR) and BPO-related surgery. The PSA thresholds for volumes greater than 30 mL are:

- 1.3 ng/mL for ages 50–59 years
- 1.5 ng/mL for ages 60–69 years

Recent studies have also used PSA to predict the likelihood of BPO; a PSA >4 ng/mL was shown to have an 89 % chance of being associated with BPO. The EAU currently recommends that the PSA should only be measured if it will change the patient's management or in those at risk of disease progression.

Renal Function Measurement

There is a very low risk of renal impairment in men with LUTS, less than 1 % in the Medical Therapy of Prostatic Symptoms Study (MTOPS). However, renal impairment is associated with an increased risk of complications following TURP.

The EAU recommends renal function should be checked if:

- Renal insufficiency is suspected.
- Hydronephrosis is seen on imaging.
- Surgical therapy is being considered for LUTS.

Post-void Residual (PVR) Measurement

This can be measured by transabdominal ultrasound, bladder scan or catheterisation. It can be calculated by $height \times width \times length \times 0.7$.

There are a variety of available formulae for calculating PVR, usually varying in the multiplication factor used in the formula. A high PVR was found to be associated with an increased risk of symptom progression in both MTOPS and ALTRESS. A significant PVR may be associated with BOO/BPO and/or DUA. EAU recommendation: PVR measurement should be part of routine assessment.

Uroflowmetry

This is a non-invasive urodynamic test which produces a visual representative of the strength of urinary flow. It evaluates the function of the lower urinary tract. It is a quick test which may be easily performed and interpreted in the office.

The key parameters of the test are:

- Maximum urinary flow rate (Q_{max})
- Voided volume (VV)
- PVR
- Flow pattern

Ideally, uroflowmetry should be performed twice to maximise the reliability of the results, especially when flow parameters are pathological, and the voided volume should exceed 150 mL. The flow pattern may provide suggestions regarding a diagnosis:

- Bladder outlet obstruction: reduced Q_{max}, prolonged tail
- Urethral stricture: reduced Q_{max} with plateau flat trace
- Detrusor underactivity: reduced Q_{max}, intermittent, fluctuating flow

A normal flow trace is bell shaped with Q_{max} attained with 3–10 s. Q_{max} may be affected by age, voided volume, bladder contractility and urethral resistance. The values give an indication of probability of BOO/BPO (Table 9.3). Q_{max} >15 mL/s can exclude BOO/BPO in 97 % of patients and is associated with a poorer outcome after TURP; therefore, Q_{max} >15 mL/s is one of the indications for performing invasive urodynamics prior to prostate surgery in symptomatic patients.

Invasive Urodynamics (UDS)

This invasive test involves the insertion of intravesical and rectal catheters which allows for simultaneous bladder filling, vesical and rectal pressure measurements and the

Table 9.3 Risk factors for bladder outlet obstruction

Q_{max} (mL/s)	% Obstructed
≥15	3
<15	59
≥10	28
<10	69

calculation of detrusor pressure. The test consists of filling and voiding phases. It allows for the diagnosis of bladder detrusor overactivity (DO) during filling and BOO and/or DUA during voiding which may significantly affect management. BOO and DUA may be determined using the bladder outflow obstruction index (BOOI, previously known as the Abrams-Griffiths number) and bladder contractility index (BCI), respectively (Fig. 9.2). BOO is characterised by increased detrusor pressure and reduced flow, while DUA is characterised by reduced detrusor pressure and flow during the voiding phase. The importance of establishing a UDS diagnosis is that in men with 'clinical' BOO, 57–61 % may have DO, 29 % BOO and 11 % DUA. The prevalence of DUA in men with LUTS ranges between 11 and 40 %. A study by Cannon et al. revealed that there are no UDS or symptomatic gains from TURP in men shown to have DUA. Lastly, the other advantage of invasive UDS prior to surgery is in determining the presence of preoperative DO which, after bladder outlet surgery, may result in DO incontinence. This allows for better patient counselling prior to surgery (Table 9.4).

Others

- Ultrasound: only if large PVR or history of urolithiasis (EAU 2014) (Tables 9.5 and 9.6)

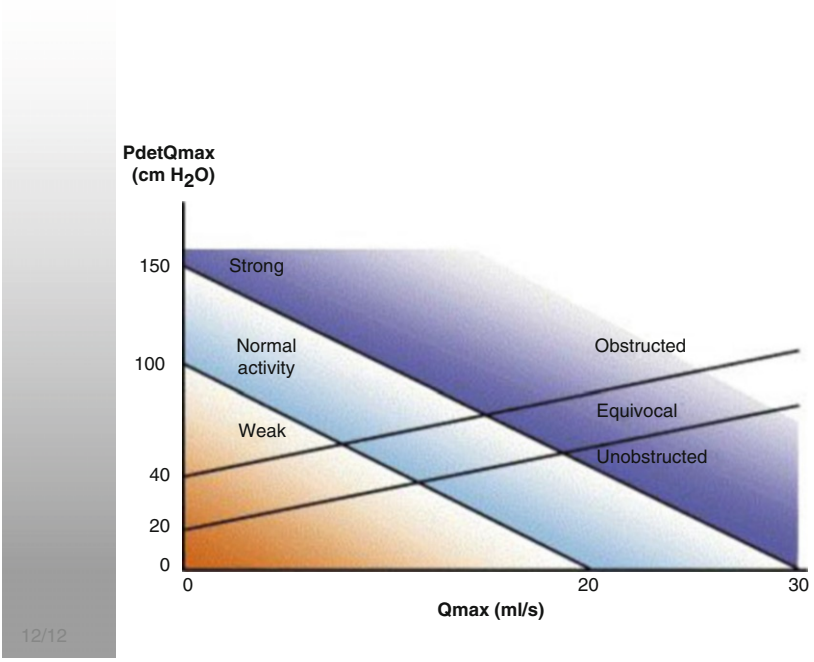

Fig. 9.2 Composite Bladder outlet obstruction index (BOOI) and Bladder contractility index (BCI) nomograms. (Hashim Hashim et al. *Eur Urol* 2007;4:1186–94)

Table 9.4 EAU recommendations for invasive urodynamics

Voided volume on uroflowmetry ≥150 ml
$Q_{max} \geq 15$ ml/s
Age <50 years or >80 years
PVR >300 mL
Suspicion of neurogenic bladder dysfunction
Bilateral hydronephrosis
Previous radical pelvic surgery
Previous failed invasive treatment

Table 9.5 Predictors for progression of LUTS/BPO

Predictor	Risk increase
Age >70 years	8
PSA >1.4 ng/mL	3
IPSS >7	3
Q_{max} <12 mL/s	4
Prostate volume >30 mL	3
PVR >50 mL	3
Prostatic inflammation	
Failure to respond to medical treatment	

Table 9.6 Complications of LUTS/BPO

Complication	Risk
Symptom progression	17–40 %
Acute urinary retention	1–2 %/year
UTI	0.1–12 %
Bladder stone	0.3–3.4 %
Renal impairment	<2.5 %
Urinary incontinence	<1 %
Haematuria	10 %

Conservative Treatment of Male LUTS

The origin of LUTS in adult men, as described above, is multifactorial and shifted away from the prostate (BPH, BPE or BPO). Although the prostate may be responsible for LUTS in some men, different organs or structures can also cause or contribute to LUTS in others, for example, the urinary bladder, pelvic floor, central or peripheral nervous system and even the kidney in case of nocturia due to nocturnal polyuria. It is sometimes difficult or even impossible to detect the primary origin of LUTS in individual patients. Therefore, symptomatic therapy of LUTS with conservative treatment modalities, regardless the exact cause, should always be the first and an essential part of the treatment in all patients without absolute indications for surgery. Conservative treatment modalities consist of:

- Education: explanation of the anatomy of the lower urinary tract, physiology of urine storage and voiding and pathologies which can lead to LUTS, instructions concerning drinking volumes as well as fluid types and explanation of the

correlation between fluid volume intake and voiding frequency (www.patients.uroweb.org/library-bpe/).

- Reassurance: explanation that not (bladder or prostate) cancer is the cause for LUTS.
- Lifestyle advice: is diverse, should be applied according to the predominant complaint and includes:
  - Reduction of the fluid volume in cases of excessive fluid intake, emptying the bladder before going to bed or when urinary frequency is most inconvenient (e.g. during travels or going out in public)
  - Avoidance of, or moderation in, caffeinated and/or alcoholic beverages which can have a diuretic or irritant effect on the bladder
  - Distraction techniques (e.g. penile squeeze, breathing exercises, perineal pressure or mental tricks) to take the mind off the bladder or toilet and to control bladder storage symptoms, i.e. the brain controlling the bladder and not the other way round
  - Bladder retraining to encourage men to hold on when they have urgency in order to increase bladder capacity and increase the time between voids
  - Providing assistance in cases of cognitive dysfunction or impairment of dexterity and mobility
  - Reviewing medications (for other indications than LUTS) and optimising the time of administration or replacement in case of urinary adverse events (e.g. diuretics)
  - Treatment of constipation
  - Use of relaxed or double-voiding techniques, pelvic floor muscle exercises with or without biofeedback support
  - Urethral milking or use of absorbents to cope with post-micturition dribble
- Periodic monitoring: regular follow-up examinations of the patient with re-evaluation of LUTS, the prostate and pathologies which have been identified and quantified during initial workup, offer to return to the clinic in case of symptom deterioration.

Conservative treatment has shown to significantly reduce LUTS to a greater extent than standard care when three self-management sessions were offered. Approximately 64 % of men do well with conservative treatment over a period of 5 years. Conservative treatment has level 1b evidence (randomised-controlled trials, RCTs), and the EAU guidelines on male LUTS recommend this treatment approach for patients with mild (to moderate) symptoms in the absence of complicated LUTS, absolute indications for surgical treatment or parameters of disease progression. Physicians should always offer conservative treatment prior or concurrent to drug treatment (grade of recommendation A).

Drug Treatment of Male LUTS

If symptom relief has been insufficient with conservative treatment modalities alone and the patient still suffers of LUTS, drug treatment can be added. There are

currently five different drug classes available which have been licensed for the treatment of male LUTS and can be used either alone or in combination:

- α-Adrenoceptor antagonists (α-blockers)
- 5α-Reductase inhibitors (5ARI)
- Muscarinic receptor antagonists (antimuscarinics)
- Phosphodiesterase type 5 inhibitors (PDE5i)
- Arginine-vasopressin analogues (desmopressin)

Approved drug classes, drugs within the different classes, the key pharmacokinetic features and recommended daily doses are listed in Table 9.7. This chapter focuses only on the drugs which have been analysed by the NICE, EAU and AUA guidelines.

In some European countries, phytotherapy is also popular and has a market share as high as 50 % of the national male LUTS market. However, plant extracts are a heterogeneous group of drugs, not universally available, and can contain different concentrations of active ingredients when comparing the extract of different producers and even different brands of the same producer. Additionally, it has yet not been clarified which active ingredient is responsible for LUTS improvement. Phytotherapy was excluded from the NICE, EAU and AUA guidelines due to methodological reasons but may be a viable treatment option for some men with mild to moderate LUTS who refuse using chemical drugs. Therefore, phytotherapy could be used to support conservative treatment.

The prescription of one drug of the above-mentioned five chemical drug classes depends on baseline values determined during systematic assessment of the patient and is largely dependent on the type of symptom (storage, voiding, storage + voiding or nocturnal polyuria), concomitant erectile dysfunction, prostate volume and the patient's willingness to use the drug long term. The flow diagram (Fig. 9.3) illustrates the evidence-based drug treatment of male LUTS with key results of the initial diagnostic tests, as described in the EAU guidelines on male LUTS in the year 2013.

α-Adrenoceptor Antagonists (α-Blockers)

The urinary bladder, bladder neck and prostate contain α_1-adrenoceptors in high density which can increase, after noradrenaline stimulation, smooth muscle tone. The effect on smooth muscle cells in the bladder outlet is primarily mediated by α_{1A}-adrenoceptors. In contrast, α_{1B}- and α_{1D}-adrenoceptors are mainly located in blood vessels, central nervous system and in the urinary bladder proximal to the bladder outlet and may also contribute to LUTS. α-Blockers act by reversible inhibition of these α_1-adrenoceptors, thereby reducing the tone of smooth muscle cells of the prostate and bladder neck and, eventually, reducing BPO and LUTS. However, the effect on BPO is only modest and does not fully explain the effects of α-blockers; other factors may therefore be responsible for LUTS reduction, such as central nervous effects.

Table 9.7 Drug classes, drugs within the classes, key pharmacokinetic properties and standard doses of drugs licensed for the treating of male LUTS (license text added next to the drug class) [Oelke M et al. *Eur Urol*. 2013;64:118–40]

Drug (class)	t_{max} [h]	$t½$ [h]	Recommended daily dose
α_1-Adrenoceptor antagonists (for treating signs or symptoms of BPH)			
Alfuzosin IR	1.5	4–6	3×2.5 mg
Alfuzosin SR	3	8	2×5 mg
Alfuzosin XL	9	11	1×10 mg
Doxazosin IR	2–3	20	1×2–8 mg
Doxazosin GITS	8–12	20	1×4–8 mg
Silodosin	2.5	11–18	1×4–8 mg
Tamsulosin MR	6	10–13	1×0.4 mg
Tamsulosin OCAS	4–6	14–15	1×0.4 mg
Terazosin	1–2	8–14	1×5–10 mg
5α-Reductase inhibitors (for treating benign prostatic enlargement due to BPH)			
Dutasteride	1–3	3–5 weeks	1×0.5 mg
Finasteride	2	6–8	1×5 mg
Antimuscarinic drugs (for treating OAB/storage symptoms)			
Darifenacin	7	12	1×7.5–15 mg
Fesoterodine	5	7	1×4–8 mg
Oxybutynin IR	0.5–1	2–4	3–4×2.5–5 mg
Oxybutynin ER	5	16	2–3×5 mg
Propiverine	2.5	13	2–3×15 mg
Propiverine ER	10	20	1×30 mg
Solifenacin	3–8	45–68	1×5–10 mg
Tolterodine IR	1–3	2–10	2×1–2 mg
Tolterodine ER	4	6–10	1×4 mg
Trospium IR	5	18	2×20 mg
Trospium ER	5	36	1×60 mg
B3 agonist (for treating OAB/storage symptoms)			
Mirabegron	3.5	50	1×50 mg
Antidiuretic (for treating nocturnal polyuria)			
Desmopressin tbl.	1–2	3	1×0.1–0.4 mg orally before sleeping
Desmopressin oral lyophilisate (MELT)	0.5–2	2.8	1×60–240 μg* sublingually before sleeping
Phosphodiesterase 5 inhibitors (for treating signs or symptoms of benign prostatic hyperplasia with or without erectile dysfunction)			
Tadalafil	2 (0.5–12)	17.5	1×5 mg

LUTS lower urinary tract symptoms, *BPH* benign prostatic hyperplasia, *ER* extended release, *GITS* gastrointestinal therapeutic system, *IR* immediate release, *MR* modified release, *OAB* overactive bladder, *OCAS* oral controlled absorption system, *SR* sustained release, t_{max} time to maximum plasma concentration, $t½$ elimination half-life, * equivalent to tablet doses of 0.1–0.4 mg

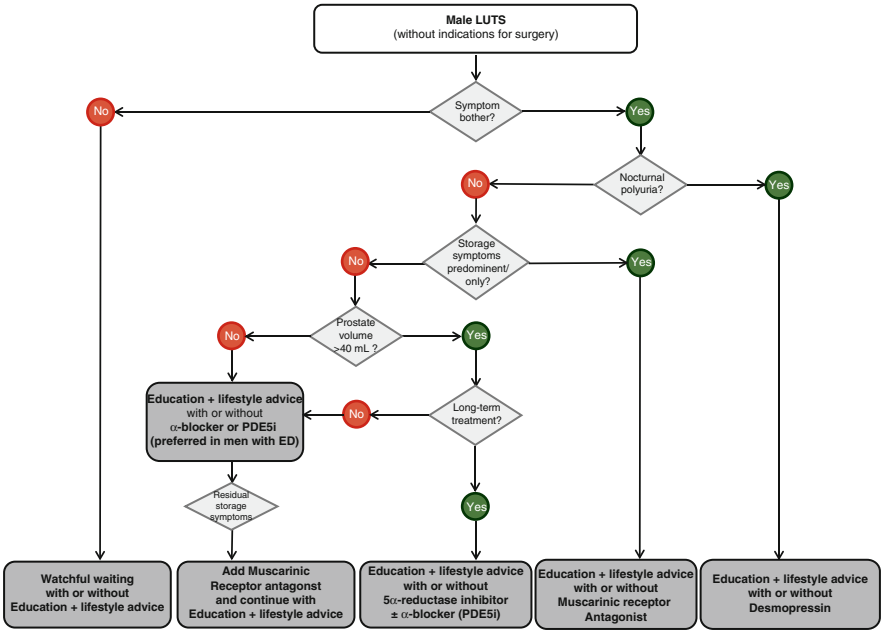

Fig. 9.3 Treatment algorithm of male LUTS with conservative treatment options and drugs, EAU guidelines on male LUTS, including BPO. *PDE5i* phosphodiesterase type 5 inhibitor, *ED* erectile dysfunction [Oelke M et al. *Eur Urol*. 2013;64:118–40]

α-Blockers are available in different formulations (Table 9.7) and have become the most popular drug class for the treatment of male LUTS during the past 25 years. Primary candidates for α-blocker therapy are men with bothersome moderate-to-severe voiding or voiding + storage LUTS. Reasons for this first-line treatment choice are obvious:

- α-Blockers can be administered in the majority of symptomatic men because the majority suffer of voiding or voiding + storage symptoms.
- They are efficacious after a few days.
- They significantly and substantially reduce storage and voiding LUTS within weeks (IPSS decrease by 30–40 % on average after placebo run-in and up to 50 % in open-label trials).
- About 60 % of men experience a clinically meaningful LUTS reduction within the first treatment month.
- They significantly improve maximum urinary flow rate (Q_{max}) within hours (by 20–25 %).
- Work independent of patients' age, prostate volume and initial symptom severity.
- Have long-lasting effects on symptoms, thereby reducing symptomatic disease progression.
- They are able to significantly improve health-related quality of life and decrease bother from LUTS.

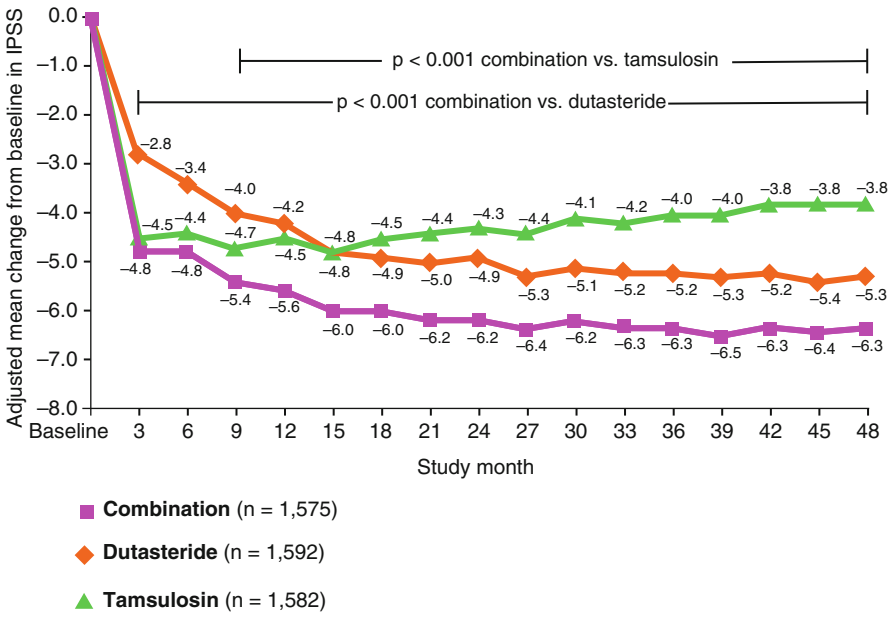

Fig. 9.4 IPSS reduction with combination therapy using α-blocker (tamsulosin 0.4 mg once daily) together with 5α-reductase inhibitor (dutasteride 0.5 mg once daily) compared to α-blocker and 5α-reductase inhibitor monotherapies (CombAT study). Combination therapy is significantly more efficacious than both monotherapies, starting at treatment month 3 for dutasteride and month 9 for tamsulosin monotherapy [Roehrborn CG et al. *Eur Urol*. 2010;57:123–31]

All available α-blockers have a significant impact on LUTS in adult men in the short-term (≤3 months) and long-term RCTs (≥12 months). No α-blocker has consistently shown superiority over other α-blockers despite differences in α_1-adrenoceptor subtype inhibition; therefore, all α-blockers are considered to be equally efficacious. However, α-blockers do not influence prostate size or PSA concentration and do not consistently reduce PVR in RCTs. Additionally, α-blockers (tamsulosin) seem to have reduced long-term efficacy in men with prostate volumes ≥40 mL (Fig. 9.4). α-Blockers have level 1a evidence (meta-analyses) and grade A recommendation in the EAU guidelines on male LUTS.

Although there are no relevant differences between the different α-blockers and formulations in terms of efficacy, the adverse event profiles are substantially different. Consequently, the choice of the α-blocker in the individual patient is largely dependent on the expected adverse event profile.

Cardiovascular Adverse Events

Cardiovascular tolerability (e.g. [orthostatic] hypotension, dizziness or asthenia) is a great concern for many α-blockers, especially for α_1-subtype unselective blockers

and when administered as immediate-release formulation. Doxazosin and terazosin are unspecific for α_1-adrenoceptor subtypes and lower blood pressure significantly, especially upon treatment initiation ('first dose hypotension'); consequently, these α-blockers have to be dose titrated when immediate-release formulation is used. The doxazosin extended-release formulation GITS (gastrointestinal therapeutic system) and alfuzosin formulations have a better tolerability profile but still lower blood pressure significantly. In contrast, tamsulosin reduces blood pressure less frequently. Nevertheless, in a recently published study of first-time users of tamsulosin in the USA (compared to users of 5ARIs), tamsulosin had significantly higher rates of severe hypotension during the first two treatment months. The hazard ratio for severe hypotension requiring hospital admissions was 2.12 for the first and 1.51 for the second treatment month but was no longer significant afterwards. Consequently, it is recommended to use α-blockers after meals and in the evening to prevent rapid lowering of blood pressure (or the clinical consequences of blood pressure decrease) and to prescribe extended-release formulations. In contrast to the other α-blockers, silodosin is highly selective for the α_{1A}-adrenoceptor subtype and does not significantly affect the blood pressure, as shown in phase III trials.

Abnormal Ejaculation

α-Blockers in general do not adversely affect libido or erectile function but may alter ejaculation. It was long believed that ejaculation disorders (reduced semen volume or dry ejaculation) were caused by retrograde ejaculation but recent studies have demonstrated that α-blockers cause (relative) anejaculation as no sperm cells were detected in the bladder after ejaculation. Of all available α-blockers and formulations, only tamsulosin and silodosin have consistently shown to cause anejaculation which occurred in RCTs with silodosin 8 mg once daily in up to 28 % of patients. However, post hoc analyses have shown that anejaculation was often associated with a more pronounced LUTS reduction and high-treatment persistence. Therefore, anejaculation seems to be a good predictor of LUTS treatment response and satisfaction. Anejaculation is no special threat for the patient and is reversible. As the majority of men are in their mid-60s or older when treated for voiding LUTS, (relative) anejaculation and subsequent infertility are often no major issues for this patient group anymore.

Intraoperative Floppy Iris Syndrome (IFIS)

Ocular adverse events have first become evident in the year 2005 when three phenomena during cataract surgery were described in tamsulosin users: (1) an iris that flutters and billows to normal intraoperative fluid movements, (2) prolapse of iris tissue to surgical incisions and (3) progressive intraoperative miosis despite standard preoperative pupil dilation. This triad has also been described for almost all α-blockers (including those for the treatment of arterial hypertension, e.g. prazosin,

indoramin or labetalol) and, interestingly, also for drugs with partial α-adrenoceptor blocking abilities (e.g. antipsychotics, antidepressants, benzodiazepines, serenoa repens) as well as finasteride. IFIS can occur in one eye only, may be incomplete (appearance of only 1 or 2 phenomena of the triad), can be seen in both men and women and can be seen even after a long time after cessation of α-blocker therapy. Preliminary results suggest that IFIS is irreversible and a consequence of pharmacologic inhibition of the smooth musculature of the iris and smooth muscle atrophy due to drug accumulation in the iris pigment. Although IFIS is not life threatening, precautions should be taken in patients who are scheduled for cataract surgery, such as delaying α-blocker use, prescribing PDE5i instead and performing cataract surgery only by an experienced ophthalmologists (overview and recommendations of the American Academy of Ophthalmology).

5α-Reductase Inhibitors (5ARIs)

The hormonal environment of the prostate and prostate growth is mainly regulated via testosterone which is converted to the active androgen dihydrotestosterone by the enzyme 5α-reductase located in prostatic stromal cells. In the male body, two isoforms of 5α-reductase have been detected: 5α-reductase type 1 with major activity in the liver and skin (hair follicles) and minor activity in the prostate and 5α-reductase type 2 with predominant expression and activity in the prostate. Inhibition of the enzyme 5α-reductase (by 5ARIs) reduces the intraprostatic dihydrotestosterone concentration, induces apoptosis of prostatic epithelial cells and reduces prostate size by approximately 18–28 % after 1–4 years and serum PSA concentration by about 50 % after 6–12 months of treatment. Prostate size reduction can significantly lower the BPO grade and eventually improve LUTS. Because the serum PSA concentration is used for prostate cancer screening and detection, serum PSA concentration has to be multiplied by 2 during 5ARI treatment.

Two 5ARIs have been licensed for the treatment of male LUTS due to BPE: finasteride inhibits 5α-reductase type 2 only, whereas dutasteride inhibits both 5α-reductase types 1 and 2 ('dual inhibition') (Table 9.7). Although dutasteride reduces serum dihydrotestosterone concentration to a greater extent than finasteride (95 % vs. 70 %), the intraprostatic concentration of dihydrotestosterone is reduced to a similar level with both 5ARIs (~85–90 %). No relevant differences in terms of efficacy or adverse events have been detected between the two drugs.

Reduction of LUTS versus placebo is first seen after several months of treatment; the time of onset is mainly determined by the initial prostate volume. The larger the prostate at baseline, the faster the effects on LUTS become evident. 5ARIs are usually not more efficacious than placebo in men with prostate volumes <40 mL. After treatment duration of 2–4 years, 5ARIs reduce LUTS (IPSS) by approximately 15–30 % and increase Q_{max} by 1.5–2.0 mL/s. In direct comparison to α-blockers, 5ARIs reduce LUTS slower and less effectively; however, 5ARIs (dutasteride) were able to reduce LUTS to a greater extent than α-blockers (tamsulosin) after a

treatment duration of 15 months if initial prostate volume was >30–40 mL (Fig. 9.4); the longer the treatment, the stronger the effects of dutasteride were versus tamsulosin (after 4 years: IPSS −5.3 vs. −3.8, Q_{max} +2.4 vs. +0.7 and quality of life [BPH Impact Index] −1.8 vs. −1.2). Therefore, long-term treatment with 5ARIs is necessary to significantly reduce LUTS and improve quality of life.

5ARIs are currently the only drug class which can prevent disease progression with regard to acute urinary retention or need for prostate surgery. BPH disease progression and acute urinary retention appear especially in older men with enlarged prostates (see section assessment and Table 9.5). Several trials have proven that both 5ARIs can significantly reduce acute urinary retention after minimum treatment duration of 6–12 months (relative risk reduction 57–68 % after 1–4 years). In the CombAT trial, in which dutasteride was compared against tamsulosin (and combination treatment) for a total duration of 4 years only in men with prostate volumes >30 mL, dutasteride was able to significantly reduce acute urinary retentions already after 8 months. BPO-related surgery is reduced with 5ARIs by 34–70 % after 1–4 years of treatment; the large variation between the numbers is possibly reflecting the missing standardisation when to perform surgery in patients without urinary retention. The EAU guidelines on male LUTS recommended using 5ARIs only in patients with moderate-to-severe LUTS, prostate volumes >40 mL and men who are willing to use 5ARIs for at least 1 year. 5ARIs have level 1a evidence and grade A recommendation.

Adverse events of 5ARIs are mainly related to sexual function and include decreased libido, erectile dysfunction and ejaculation disorders (e.g. retrograde ejaculation, reduced semen volume or anejaculation). Patient-reported sexual adverse events appear in RCTs in low frequency (<10 %) and especially during the first 1–2 years of treatment, but open-label studies suggest higher frequencies in real-life practice. Similar to anejaculation in patients with α-blockers, the majority of sexual adverse events are no major issue for patients with ARIs. Interestingly, the addition of PDE5i (tadalafil 5 mg once daily) can antagonise the sexual adverse events during 5ARI therapy (finasteride 5 mg once daily). Additionally, gynecomastia and nipple pain are reported by patients with 5ARIs with low frequency (approximately 1–2 % of study participants). Long-term trials with 5ARIs have also detected (slightly) increased rates of breast cancer (4/3047 cases of the MTOPS study), but the relationship between 5ARIs and male breast neoplasia is currently unknown. The same is true for the development of high-risk prostate cancers in patients treated with 5ARIs.

Muscarinic Receptor Antagonists (Antimuscarinics)

The main neurotransmitter of the urinary bladder is acetylcholine which binds to muscarinic receptors on the surface of the bladder urothelial and smooth muscle cells in order to initiate detrusor contractions. There are five different muscarinic receptor subtypes in the human body ($M_{1–5}$) of which only M_2 and M_3 are mainly

expressed in the bladder. Reversible inhibition of muscarinic receptors (by antimuscarinics) decreases muscarinic receptor stimulation and, consequently, increases the threshold for urothelial receptor depolarisation (afferent loop) and smooth muscle cell contraction (efferent loop). Measurable urodynamic effects of antimuscarinics are, besides others, increased bladder capacity, reduction of the amplitude as well as frequency of involuntary detrusor contractions and (slight) decrease of detrusor contraction power. Although approximately 80 % of muscarinic receptors of the human bladder are M_2 subtypes, only the M_3 receptor subtype (~20 %) seems to be involved in detrusor contractions in healthy humans. All available antimuscarinics (Table 9.7) inhibit to a variable amount M_2 and M_3 receptors, and some have also inhibitory function on calcium channels and α-adrenoceptors (e.g. propiverine).

Based on the mechanism of action, antimuscarinics are particularly useful for the treatment of bladder storage symptoms, such as urgency, frequency and urgency incontinence. Approximately 45–50 % of adult men with LUTS have storage symptoms, of which 10 % of men have them alone and 35–40 % in combination with voiding symptoms. Antimuscarinics have been evaluated for the treatment of LUTS in men with bothersome moderate-to-severe storage and voiding symptoms (alone or in combination with α-blockers). The greatest amount of data on the treatment of male LUTS or male OAB exists with the three antimuscarinics, fesoterodine, solifenacin and tolterodine, but it is assumed that there is a class effect and all antimuscarinics exhibit similar effects in this patient group. Muscarinic receptor antagonists have level 1b evidence and grade B recommendation in the EAU guidelines on male LUTS.

The majority of participants investigated in RCTs or post hoc analyses were men without BOO. It was demonstrated that antimuscarinics can significantly:

- Reduce daytime and 24-h frequency.
- Suppress urgency episodes, urgency intensity and urgency-related voiding.
- Reduce urgency urinary incontinence.
- Improve scores of disease-specific questionnaires (e.g. IPSS or IPSS-QoL) of which some are specifically addressed to bladder storage symptoms/OAB (e.g. patient perception of bladder condition [PPBC], overactive bladder questionnaire [OAB-q] or patient perception of intensity of urgency scale [PPIUS]).

Improvement of LUTS with antimuscarinic monotherapy (tolterodine) seems to be more pronounced and significantly superior in men with serum PSA concentrations <1.3 μg/L. Because serum PSA is a proxy parameter for prostate volume, tolterodine is especially efficacious and useful in men with smaller prostates (<30 mL).

Adverse events of antimuscarinics in men are mainly related to M_2 and M_3 muscarinic receptor inhibition outside of the bladder (e.g. in salivary glands, intestine or vessels). These adverse events are typical for antimuscarinics, have already been described for female OAB and are not different in frequency or severity in men. Compared to placebo, the following adverse events appear with a higher frequency in men treated with antimuscarinics: most frequently dry mouth, followed by dizziness, constipation, nasopharyngitis, blurred vision and voiding difficulties. Based

on the mechanism of action of antimuscarinics and M_2 as well as M_3 receptor inhibition in the bladder, it is possible that a decrease of detrusor contraction power could significantly increase PVR and provoke (acute) urinary retention. Although some RCTs have shown a (slight) decrease of Q_{max} and a (slight) increase of PVR/urinary retention, others could not confirm this finding or even observe opposite effects. It was shown in one post hoc analysis of pooled data of two fesoterodine studies that especially older men (≥66 years of age) during the first weeks of treatment using the higher dose (8 mg once daily) have a (slightly) increased risk to develop PVR or urinary retention. It therefore appears safe to use antimuscarinics in men but it is still recommended to control PVR during the first treatment weeks to detect PVR increase. Additionally, patients should be informed about the symptoms and signs of (acute) urinary retention.

Phosphodiesterase Type 5 Inhibitors (PDE5i)

Nitric oxide is an important neurotransmitter in the human body and also involved in the signal transmission of the urinary bladder. Nitric oxide stimulates the synthesis of cyclic guanosine monophosphate (cGMP) in the cell where it activates protein kinases and ion channels which are responsible for (detrusor) smooth muscle cell relaxation. The effects of PDE are stopped by PDE isoenzymes which catalyse the hydrolysis of cGMP to inactive molecules. PDEi increase the intracellular concentration of cGMP by blocking the hydrolysis and, therefore, prolong the relaxing effects on smooth muscle tone of the urinary bladder, prostate and urethra. Of the 11 PDEs in the human body, especially PDE4 and PDE5 are expressed in the lower urinary tract and transition zone of the prostate. Next to relaxation of the smooth musculature of the bladder outlet, other mechanisms of action may also contribute to the clinical effects of PDE5i, such as modulation of autonomic innervation of the bladder, downregulation of the Rho-kinase activity in the prostate and increase of blood flow in pelvic organs. However, the exact mechanism of action of PDE5i still remains to be determined.

Of the PDE5i in clinical use, RCTs have been performed with sildenafil, tadalafil and vardenafil (Table 9.7). While all oral PDE5i are used for the treatment of erectile dysfunction, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS (with or without erectile dysfunction). Clinical studies have shown that approximately 60–70 % of elderly men with LUTS also have erectile dysfunction; therefore, PDE5i (tadalafil) seems to be especially suitable for co-morbid patients with bothersome moderate-to-severe LUTS and erectile dysfunction. PDE5i have level 1a evidence and grade A recommendation in the EAU guidelines on male LUTS. PDE5i have shown in RCTs to subjectively significantly improve:

- Storage and voiding LUTS (IPSS decrease 17–37 %) as early as 1 week after start of treatment
- Nocturia (nocturnal voiding frequency)

- LUTS over a period at least 12 months
- Quality of life (IPSS-QoL, BPH Impact Index)
- Treatment satisfaction (TSS-BPH scale)
- Erectile and ejaculatory function in those men with erectile dysfunction at baseline (IIEF-questionnaire)

Treatment effects of tadalafil are independent on pre-existing erectile dysfunction and similar to the α-blocker tamsulosin; however, treatment satisfaction is greater with tadalafil versus placebo or tamsulosin. Treatment effects (and adverse events) are not influenced by baseline parameters, such as age, LUTS severity, prior α-blocker or PDE5i use, baseline serum testosterone concentration or prostate volume. However, it is important to realise that PDE5i have not demonstrated to objectively influence prostate volume, PVR, Q_{max} (only in one RCT and in subgroups) or disease progression.

Adverse events of PDE5i in studies of men with LUTS are nearly identical to studies in men with erectile dysfunction. Adverse events include headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, back pain, hypotension, syncope, tinnitus and altered vision (blurred or discoloration). All adverse events appear with low frequency, are reversible and usually do not cause harm to the patient. The appearance of priapism or (acute) urinary retention is unlikely, and both adverse events have not been seen in RCTs in patients with LUTS. Caution is advised in men with coronary or cerebral artery diseases who use potassium channel openers or the α-blocker doxazosin or terazosin (for the treatment of arterial hypertension) because PDE5i can cause hypotension which, together with other blood pressure-lowering drugs, can lead to myocardial infarction or cerebrovascular strokes.

Arginine-Vasopressin Analogues (Desmopressin)

Arginine-vasopressin (AVP) is a hormone secreted by the hypothalamus in a circadian rhythm which can increase blood pressure by binding to V1 receptors in blood vessels and retain water by binding to the V2 receptor of the renal collecting duct. Stimulation of the V2 receptor leads to cAMP- and protein kinase A-mediated activation of aquaporin channels which are responsible for reabsorption of water in the kidney, thereby decreasing urine excretion and increasing urine osmolality.

Desmopressin is a synthetic AVP analogue with V2 receptor-binding activity only, avoiding V1 receptor-induced vasoconstriction. Vasopressin is available as tablet or MELT formulation (Table 9.7) and has been used for the treatment of diabetes insipidus or nocturnal enuresis for decades. Lately, desmopressin has also been licensed for the treatment of nocturia, in those under the age of 65, due to nocturnal polyuria (i.e. nocturnal urine production >33 % of the 24 h urine production). It was shown in adult men with nocturia that more than 80 % had nocturnal polyuria of whom 20 % had nocturnal polyuria alone and more than 60 % had

nocturnal polyuria in combination with decreased functional bladder capacity due to LUTS/BPE or BPO. Desmopressin should be taken before going to sleep at night. Additionally, the patient has to be instructed to avoid drinking fluids 1 h before until 8 h after using desmopressin. Clinical effects (i.e. decrease of urine excretion) are apparent for approximately 8 h. Desmopressin has level 1b evidence and grade A recommendation in the EAU guidelines on male LUTS.

Dose titration of desmopressin is recommended, starting with 0.1 mg tablets and escalating until 0.4 mg (or equivalent doses when using the MELT formulation) in intervals of at least 1 week. Desmopressin showed in RCTs the following significant effects:

- Reduction of diuresis by 0.6–0.8 mL/min (~40 %)
- Decrease of the frequency of nocturnal voids by 0.8–1.3 (~40 %)
- Reduction of the night-time urine volume
- Increase of the hours of undisturbed sleep and the time until the first void at night by 1.6–2.1 h
- Improvement of the quality of sleep as well as health-related quality of life

Desmopressin effects are more pronounced in patients with more severe nocturnal polyuria compared to those with a less severe condition. However, the 24-h diuresis with desmopressin is unchanged as diuresis is increased after the antidiuretic effects of the drug have diminished in the morning; therefore, retained water during night time is excreted during the daytime. Clinical effects of antidiuresis at night with desmopressin are stable over an observational period of 12 months and return to baseline values once desmopressin treatment should be stopped again.

Nocturia has been identified to be the leading cause for sleep disturbance and sleep fragmentation, causes daytime fatigue, impacts daily activities and deteriorates psychomotor performance, cognitive function and mood. Nocturia can also cause depression, immune suppression, increases vulnerability for cardiovascular diseases and may contribute to the development of diabetes mellitus type II. Additionally, nocturia ($\geq$2 times per night) significantly increases accidents, falls and fractures. It is expected that antidiuretic treatment with desmopressin can also prevent patients from these consequences of nocturia, although studies to demonstrate these beneficial effects have not been conducted for most of the parameters. However, studies could show that patients feel fresher in the morning and have less daytime fatigue after using desmopressin.

Adverse events with desmopressin are rare and usually mild in nature. The most frequently seen adverse events with desmopressin are headache, diarrhoea, nausea, abdominal pain, dizziness, dry mouth and hyponatraemia (serum sodium concentration <130 μmol/L). In long-term trials (12 months), peripheral oedema (2 %) and arterial hypertension (5 %) were also documented. Of all adverse events, only hyponatraemia is potentially dangerous as it could cause nausea, vomiting, headache, short-term memory loss, confusion, lethargy, restlessness, muscle weakness, cramps, seizures, decreased consciousness and coma. Hyponatraemia, not necessarily associated with symptoms or signs, appears during desmopressin treatment in men and women in 5–7.6 %. However, hyponatraemia predominantly develops in

women and patients aged ≥65 years. Studies in experimental animals and humans have suggested that women have a higher sensitivity of vasopressin to the V2 receptor in the kidney, leading to a fivefold higher risk of hyponatraemia in women aged >50 years. Therefore, equivalent doses of desmopressin result in lower overall efficacy in men compared to women but also lower risk of hyponatraemia, suggesting no major threat of developing hyponatremia in men with the standard doses between 0.1 and 0.4 mg once daily (or equivalent doses of the MELT formulation). Known risk factors for developing hyponatraemia are, besides age and gender, low serum sodium concentration at baseline (at the bottom of the normal serum sodium range of 135–145 μmol/L) and higher basal 24-h urine volume per bodyweight. Although the risk of hyponatraemia appears to be low in men, it is still recommended to monitor serum sodium concentration at baseline and days 3, 7 and 30 of treatment. Once the patient is on a stable dose and serum sodium has not decreased, it is recommended to check serum sodium concentration every 3–6 months. If the dose of desmopressin needs to be escalated, the same time intervals for monitoring serum sodium concentration should be chosen again.

α-Blocker + 5ARI Combination Therapy

The simultaneous use of an α-blocker and a 5ARI aims to combine the beneficial effects of both drug classes which are, besides others, fast, substantial and long-lasting symptom relief with α-blockers and decrease of prostate volume as well as the ability to prevent (acute) urinary retention or the need for prostate surgery with 5ARIs. Combination therapy is more efficacious in relieving LUTS (including nocturia) or improving Q_{max} than the α-blocker or 5ARI alone (Fig. 9.4). However, prostate volume is not more reduced with combination therapy than monotherapy. Superiority of combination therapy has been demonstrated in several trials for several α-blockers and for both dutasteride and finasteride. Compared to monotherapy, LUTS decrease with combination therapy is significantly more efficacious after >1 year of treatment but, however, is dependent on initial prostate volume or PSA concentration (as a proxy parameter of prostate volume); men with prostates >40 mL (or serum PSA concentration >1.6 μg/L) have a faster symptom reduction than men with smaller prostates. For patients who completed the study period in the CombAT study, mean change in IPSS from baseline until the end of year 4 was significantly higher for the combination therapy compared to tamsulosin or dutasteride alone (Fig. 9.4). Decrease of IPSS-QoL score was significantly greater for the combination treatment (−1.5) compared to tamsulosin (−1.1) or dutasteride (−1.3). Q_{max} improvement was also significantly higher for combination treatment (2.4 mL/s) compared to tamsulosin (0.7 mL/s) or dutasteride (2.0 mL/s). There was a tendency towards a continuous decrease of IPSS and continuous increase of Q_{max} for dutasteride monotherapy and combination treatment over time, whereas both parameters worsened with tamsulosin monotherapy after 15–18 months (Fig. 9.4). Interestingly, PVR significantly decreased in the treatment arms containing dutasteride but not with tamsulosin alone. The EAU guidelines on male LUTS recommend

combination treatment with an α-blocker and a 5ARI in men with bothersome moderate-to-severe LUTS, enlarged prostates and reduced Q_{max} (men likely to develop disease progression), but combination therapy only seems useful when treatment duration exceeds 12 months. Combination therapy has level 1b evidence and grade A recommendation.

SMART was an RCT that evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after 6 months. After discontinuation of the α-blocker, almost three quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS ≥20) at baseline showed symptom deterioration and, therefore, seem to benefit from longer combination therapy.

Prevention of disease progression (i.e. IPSS increase ≥4 points, (acute) urinary retention and need for prostate surgery but also the appearance of urinary incontinence, urinary tract infection or renal insufficiency) is also more pronounced with combination therapy compared to α-blocker or 5ARI monotherapy. Two long-term studies evaluated the ability of combination therapy to reduce disease progression, the MTOPS trial (using placebo, doxazosin, finasteride or combination for a mean follow-up of 4.5 years) and the CombAT trial (using tamsulosin, dutasteride or combination for a follow-up of 4 years). MTOPS, which included men with the entire range of prostate volumes without any lower limit, showed that combination therapy was significantly more efficacious in reducing disease progression than placebo, α-blocker and 5ARI alone but the risk of disease progression was similar with doxazosin compared to finasteride (Fig. 9.5). At the end of the study, disease progression occurred in 17 % of men with placebo, 10 % with doxazosin, 10 % with finasteride and 5 % with combination therapy. Overall, combination therapy significantly reduced the overall risk of disease progression by 66 % versus placebo and was also significantly better than the monotherapies with doxazosin or finasteride versus placebo (39 % and 34 %, respectively). Additionally, finasteride alone and in combination but not doxazosin was able to significantly reduce the disease progression parameters of acute urinary retention and need for prostate surgery. The CombAT study, which included only men with prostate volumes >30 mL, confirmed that combination therapy was significantly more efficacious than monotherapy with tamsulosin or dutasteride in terms of prevention of disease progression. The time to first clinical progression was significantly longer with combination therapy which, after 4 years, reduced the relative risk of BPE disease progression by 44.1 % compared to tamsulosin and by 31.2 % compared to dutasteride. Compared to tamsulosin monotherapy, combination therapy was significantly more efficacious in reducing the relative risk of acute urinary retention and need for prostate surgery by 67 % and 71 %, respectively. Compared to dutasteride monotherapy, combination therapy reduced the relative risk of acute urinary retention and need for prostate surgery by 18.3 % and 31.1 %, respectively, but this risk reduction with combination therapy was not significantly lower than with dutasteride monotherapy. Taken together the results of combination therapy, this treatment approach is especially useful for patients who are likely to develop BPE disease progression; patients suitable for combination therapy can be identified by careful assessment and evaluation of symptoms and signs of BPE disease progression (see section assessment and Table 9.5).

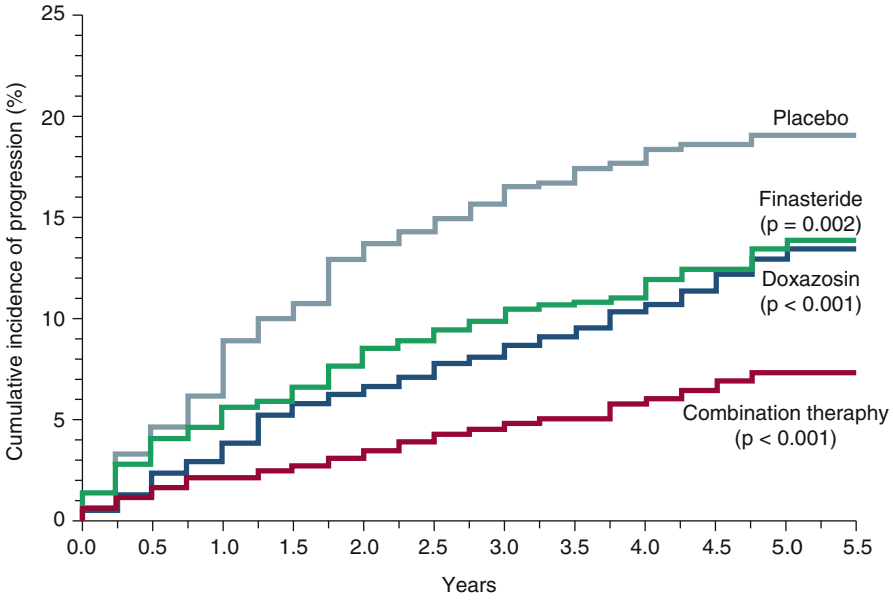

Fig. 9.5 Cumulative incidence of BPE disease progression with placebo, α-blocker (doxazosin), 5α-reductase inhibitor (finasteride) and combination therapy (doxazosin + finasteride). BPH disease progression is significantly reduced with doxazosin, finasteride or combination therapy versus placebo. Doxazosin mainly inhibited LUTS deterioration, whereas finasteride mainly inhibited (acute) urinary retention and need for prostate surgery (MTOPS study) [McConnell JD et al. *New Eng J Med*. 2003;349:2387–98]

The types of adverse events are identical to those of α-blockers or 5ARIs, but the frequency is higher for combination therapy, especially for erectile dysfunction, dizziness, postural hypotension, asthenia, decreased libido, abnormal ejaculation, peripheral oedema and dyspepsia. Therefore, physicians have to weigh the treatment benefits against potential adverse events in the individual patient before initiation of combination therapy.

α-Blocker + Antimuscarinic Combination Therapy

The simultaneous use of an α-blocker and an antimuscarinic aims to combine the beneficial effects of both drug classes which are, besides others, fast, substantial and long-lasting relief of voiding symptoms with α-blockers and fast, substantial and long-lasting relief of storage symptoms with antimuscarinics. Therefore, this combination therapy is especially useful in patients with both storage and voiding LUTS. As α-blockers are also able to reduce storage symptoms in some patients (˜35 %), it is recommended to use combination therapy only when α-blockers have failed to adequately reduce storage symptoms in patients suffering with both storage and voiding symptoms, and they are still bothered (add-on therapy). It was shown in the SATURN study that combination

therapy of an α-blocker (tamsulosin) together with an antimuscarinic (silodosin in different doses) does not add any additional effects if the patients suffer only or predominantly of voiding symptoms. However, if the patient has substantial storage and voiding LUTS, combination therapy is significantly more efficacious in reducing 24-h daytime and night-time voiding frequency, urgency intensity, total urgency-frequency score (TUFS), urgency urinary incontinence episodes and IPSS total as well as IPSS storage sub-score compared to α-blocker monotherapy or placebo. Additionally, voided volume and health-related quality of life scores improve significantly with combination therapy compared to α-blocker monotherapy or placebo. The TIMES study indicated that LUTS improvement with combination therapy works independent of prostate volume (or serum PSA concentration as a proxy parameter). Treatment effects with combinations of α-blocker (tamsulosin) and an antimuscarinic (solifenacin) are maintained for at least 12 months. A urodynamic study demonstrated that bladder contractility index and voiding efficiency remained unchanged with combination therapy using tamsulosin 0.4 mg and solifenacin 6 or 9 mg once daily. The EAU guidelines on male LUTS recommend using combination therapy in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with either monotherapy. Combination therapy has level 1b evidence and grade B recommendation.

The types of adverse events are identical to those of α-blockers or antimuscarinics. The most frequently reported adverse event in all trials on combination therapy is dry mouth. Some adverse events appear with increased frequency (e.g. dry mouth, dizziness or ejaculation disorders) and cannot be explained by simply adding the individual frequencies of α-blockers and antimuscarinics. Increase of PVR and the rate of (acute) urinary retention are also important issues for α-blocker and antimuscarinic combination therapy. Although PVR is significantly increased in some RCTs investigating combination therapy, studies have rarely shown a clinically relevant PVR increase or increased rates of (acute) urinary retention. The NEPTUNE II study investigated the long-term use of combination therapy and found a low retention rate (1.1 % at month 12), which is similar to the retention rate of the symptomatic male population without treatment. A recently published meta-analysis of pooled data from 7 RCTS with more than 3,600 patients concluded that combination therapy reduces Q_{max} (weighted mean difference −0.59 mL/s) and increases PVR (weighted mean difference 11.6 mL) compared to α-blocker monotherapy but the risk of (acute) urinary retention is low (101 patients needed to harm one patient). It therefore appears safe to use combination therapy in adult men with LUTS but, nevertheless, PVR should be monitored especially during early treatment.

Surgical Therapies

Monopolar Transurethral Resection of the Prostate (mTURP)

This remains the ‘gold’ standard treatment for BPO with the longest outcome data. It involves the removal of prostate tissue using monopolar electrocautery passed through inert, optically clear and non-conductive irrigation fluid. Electrical current

passes from an active electrode on the resectoscope loop to the prostate, through the body before exiting via a return electrode placed on the skin. The most common irrigating fluid used is glycine; the others in use include ethanol and mannitol. The current recommendation is that prostate sizes should be 30–80 mL, although this reflects expert opinion only. Three systematic reviews of all available RCTs have suggested that antibiotic prophylaxis significantly reduces bacteriuria, fever, sepsis and need for further antibiotics post-TURP. There was a trend towards a higher efficacy with a short course compared with a single dose. EAU guidelines recommend UTIs should be treated prior to surgery.

Efficacy

A historic meta-analysis from 1999 of 29 RCTs revealed a mean reduction in LUTS of 70 % and mean increase in Q_{max} of 125 % post-TURP. In addition, a more contemporary analysis has again shown excellent outcome data. This involved 20 RCTs published between 2000 and 2009 with an overall sample size of 954 patients and a maximum follow-up of 5 years. There was an improvement in mean Q_{max} of 162 %, reduction in mean IPSS of 70 %, mean reduction in QoL scores of 69 % and mean reduction of PVR of 77 %. Similar results have been replicated in many other studies with follow-up of 8–22 years suggesting that mTURP results are durable long term.

Adverse Effects

- Retreatment rates: 14.7 % at 8 years
- TUR syndrome: 0.8 %
- Transfusions: 2.9–8.6 % (2 % in contemporary series)
- Urethral strictures: 3.8–9.3 %
- Bladder neck contractures: 1.9–9.2 %
- Urinary incontinence: 2.2 %
- Retrograde ejaculation: 65.4 %
- Erectile dysfunction: 6.5 %

Transurethral Incision of the Prostate (TUIP)

This involves one or two lateral incisions in the prostate at the 4 and 7 o'clock positions. The incision extends from below the ureteric orifice to the level of the verumontanum down to the prostatic capsule. No prostatic tissue is resected. The procedure is performed with a Collings knife, resection loop or laser. This is recommended by some authors especially in young men with small prostates (<30 mL). The efficacy is comparable or slightly inferior to mTURP; however, the re-intervention rates are higher compared to TURP (15.9 % vs. 2.6 %). Transfusion and retrograde ejaculation rates are lower than with TURP.

Bipolar Transurethral Resection of the Prostate (bTURP)

This modification of the traditional mTURP involves the passage of current between the active and return electrodes both attached to the resectoscope. Current passes from the active electrode (loop) to the saline irrigation fluid resulting in excitation of sodium ions and tissue resection. As saline irrigation fluid is used, the risk of TUR syndrome may be abolished allowing larger prostates to be resected. There are five types of bipolar devices currently available which differ in the way their current is delivered to achieve coagulation, cutting or vaporisation. There are two modalities of action:

- Resection
- Vaporesection

Efficacy

A meta-analysis of 17 RCTs has shown no significant differences in the short-term efficacy (up to 12 months) between m- and bTURP with respect to IPSS, QoL, Q_{max} and re-intervention rates. The main advantages found with bTURP are the shorter hospital stay and catheterisation times as well as reduced post-operative retention, transfusion and TUR syndrome rates.

Open Prostatectomy (OP)

This is the oldest surgical treatment for moderate-to-severe LUTS due to large prostates, usually defined as >80 mL but dependent on the resection speed of the individual surgeon. This open procedure may be performed via the perineal, retropubic or suprapubic routes. The obstructive adenoma is enucleated using the index finger either from inside the bladder (Freyer's procedure) or through the anterior prostatic capsule (Millin's procedure). Although efficacious in long term, it may be associated with higher short-term morbidity than endoscopic procedures; it is estimated that it makes up less than 5 % of all prostatectomies being performed in the UK currently.

Efficacy

Studies on OP have revealed durable long-term results with a reduction in LUTS of 63–86 %, improvements in QoL scores of 60–87 %, a mean rise in Q_{max} of 375 % and reduction of PVR by 86–98 %. These compare very favourably with TURP. In addition, three recent RCTs have demonstrated similar outcomes between Holmium laser enucleation, photoselective vaporisation of the prostate (PVP) and OP in the treatment of large prostates. EAU guidelines recommend OP or Holmium laser enucleation as the first-line treatment of LUTS/BPO in men with prostates greater than 80 mL. Although, performing a TURP on one lobe and then repeating the

process on the other lobe at a later time is also an option which may involve two anaesthetics but, however, may have less morbidity.

Adverse Effects

- Mortality: <0.25 %
- Transfusion rates: 7–14 %
- Re-intervention rates: 0–6.7 %
- Urinary incontinence: 10 %
- Urethral strictures: 1.7–6 %
- Bladder neck strictures: 3.3–5 %.

Holmium Laser Enucleation (HoLEP) and Holmium Laser Resection of the Prostate (HoLRP)

The Holmium laser has a wavelength of 2140 nm, an absorption distance of 0.4 mm and is absorbed by water and water containing tissues. This minimises the area of tissue coagulation and necrosis to 3–4 mm. The main advantages are that it may be utilised in variably sized prostates, maximal prostatic tissue is removed and sent for histological analysis and may be used in men on anticoagulation. A laser fibre is inserted via a laser bridge down a resectoscope. The procedure aims to replicate an open prostatectomy. Once a lobe has been enucleated, it is placed in the bladder, shred and retrieved with the use of a morcellator. The main disadvantage of the procedure is the longer learning curve required compared with a TURP. The NICE Institute currently recommends that this treatment modality may be offered but at a centre specialising in the technique or where a mentorship programme is in place.

Efficacy

HoLEP compares favourably with mTURP, bTURP and OP in meta-analysis and systematic reviews. Functional outcomes with respect to IPSS, Q_{max} and PVR were either equivalent or favoured HoLEP. Complication rates with respect to re-intervention and strictures were equivalent. HoLEP was associated with reduced catheter and hospital times but longer operating times. HoLEP has satisfactory results in the medium term (3–8 years).

Adverse Events

- Dysuria was the most common adverse event.
- Re-interventions: 1.4 % at 6 years follow-up.
- Urethral strictures: 3.3 %.
- Bladder neck strictures: 1.7 %.

- Transfusion rate: 0 %.
- Urinary incontinence: 1.5 %.

Greenlight Laser Vaporisation

This is a 532 nm laser. The two types are the potassium titanyl phosphate (KTP) and lithium triborate (LBO) which are derived from neodymium: yttrium-aluminium-garnet (Nd:YAG). The Nd:YAG wavelength is reduced from 1064 to 532 by the addition of KTP/LBO crystals to a laser converter. The laser energy is absorbed by haemoglobin and results in vaporisation which leads to immediate tissue removal. There are currently three green light lasers in use which differ in their power output, fibre design and energy application:

- 80 W (KTP)
- 120 W HPS (LBO)
- 180 W HPS (LBO)

The main advantages of this technique are that it is easier to learn, safe in anticoagulated men, has minimal fluid absorption and less retrograde ejaculation versus TURP and HoLEP. However, it is a slow procedure with relatively less tissue removed versus TURP or HoLEP and tissue for pathological investigation is not available.

Efficacy

A meta-analysis from 2012 of nine RCTs compared the 80 and 120 W with TURP. They found no significant difference between the two modalities with respect to Q_{max} and IPSS. However, three RCTs had sufficient 12-month data to be included. In the literature, follow-up time remains variable and short. The longest RCT using 120 W HPS had 36 months follow-up. There were comparable improvements in IPSS, Q_{max} and PVR. However, the percentage reduction in PSA and prostate volume was greater with TURP. The re-intervention rate was significantly higher with greenlight. A meta-analysis comparing the 120 W laser with mTURP found comparable functional outcomes at 12 months. Greenlight is associated with longer operating times, shorter catheter and hospital times but lower risk of transfusion. The recent prospective, randomised non-inferiority study on the 180 W with a 12-month follow-up demonstrated non-inferiority to TURP for mean IPSS, mean Q_{max} and complication-free rate. The early re-intervention rate was three times higher after TURP; however, the overall re-intervention rate was not significantly different between the two groups.

Adverse Events

- Re-intervention rates: 9.6–11 %
- Urinary incontinence: 11 %

- Transfusions: 0–0.3 %
- Urethral strictures: 3.7 %
- Bladder neck strictures: 7.4 %

Thulium:Yttrium-Aluminium-Garnet (Tm:YAG) Laser

This is a 2000 nm wavelength laser which is absorbed by water. It has a continuous wave mode which allows for the smooth incision of tissue. There are four techniques utilised in prostate removal:

- Vaporisation (ThuVaP)
- Vaporesection (ThuVaRP)
- Vapoenucleation (ThuVEP): HoLEP-like approach
- Laser enucleation (ThuLEP): blunt dissection

Efficacy

This is the newest laser technique with a limited number of RCTs comparing it with TURP. The main study outcomes have shown comparable improvements in voiding parameters, i.e. Q_{max}, PVR and QoL. However, a 4-year randomised-controlled study revealed that some of these parameters may not be maintained. The main advantages of thulium are that it is associated with a reduction in operating time, hospital stay and catheter times.

Adverse Events (Follow-Up 9–12 Months)

- Strictures (ThuVaRP): 1.9 %
- Bladder neck strictures: 1.8 %
- Re-intervention rates: 0.7–1 %

Prostatic Stents

Prostatic stents were introduced approximately 25 years ago and may be a useful alternative to long-term indwelling urethral catheters. Long-term catheters may be associated with reduction in QoL, risk of catheter-related infections as well as the ongoing costs of the catheters and staff required for their upkeep. Prostatic stents require functioning detrusor to facilitate bladder emptying and aim to maintain urethral patency. The main advantage of these stents is that they are relatively easy to insert and may be inserted under local anaesthesia in a clinical setting. Stents are either temporary or permanent. The permanent stents (Urolume Wallstent) are

biocompatible and allow epithelisation which means that they are eventually embedded in the urethra. They are less liable to encrustation and infection but removal may be difficult and often cannot be undertaken in clinic. Temporary stents are biostable or biodegradable, do not epithelise and provide short-term relief. Biodegradable stents may be inserted to allow the temporary relief of BPO until medication has a chance to reduce prostate volume. There are multiple stents currently available, all of which differ in their method of deployment. Unfortunately, the studies are generally poor quality and heterogeneous. At present, NICE and AUA do not include prostatic stents in their guidelines. The EAU recommends their use as an alternative to catheter in men unfit for surgical treatment. Prostatic stents have been used intermittently over the years by urologists but have been generally not used and have proven unpopular in the long term due to problems with encrustations and difficult removal.

Efficacy

- IPSS reduction: 10–19 points
- Mean Q_{max} increase: 3–13.1 mL/s
- Spontaneous voiding: 84–93 %

Adverse Events

- 5-year failure rates: 27–50 %
- Migration: 15 %
- Urinary incontinence: 22 %
- Haematuria: 19 %

Prostatic Urethral Lift (UroLift™)

This technique manipulates the properties of the urethra, prostate and its capsule. The compliant urethra is surrounded by the compressible prostate which in turn is supported by the tough prostatic capsule. This means that the application of an implant between the urethra and capsule lifts the urethra towards the capsule thereby expanding the urethral lumen. The implants are permanent and attached to a suture. They separate occlusive prostatic lobes and are usually placed at the 2 and 10 o'clock positions. Once an appropriate tension is attained, the excess suture is trimmed. Prostate size determines the number of implants used; however, 4–6 are usually deployed. The UroLift™ delivery system is preloaded with the implant components, a syringe and 19-gauge needle. This procedure is performed under cystoscopic guidance with regional, local or general anaesthesia. Several studies have evaluated the use of this new technology with the main exclusion being large prostates (>80–100 mL) and large or obstructing median lobes. A large median lobe

is believed to be technically more challenging to treat. At present, NICE, EAU and the American Urological Association (AUA) do not include prostatic stents in their guidelines.

Efficacy

In a retrospective review of 102 men across five countries with a median follow-up at 1 year found that symptom relief was achieved as early as 2 weeks. Mean improvements at 12 months were:

- IPSS: 52 %
- QoL: 53 %
- Q_{max}: 51 %

A multicentre double-blind crossover study published this year found a mean IPSS improvement of 122 % greater than sham at 3 months. Q_{max} had a stepwise improvement. The LIFT study, a multicentre randomised study with a 1-year follow-up included 206 men and compared the UroLift™ with a sham procedure. They found an 88 % greater improvement in IPSS over sham at 3 months, a reduction in voiding and storage symptoms and a significant improvement in Q_{max}. The improvements were significant at 3 months and maintained at 1 year. An additional benefit was the preservation of sexual function.

Adverse Events

- Mild and resolved within 2 weeks
- Most common:
  - Dysuria (36 %)
  - Haematuria (26 %)
  - Pelvic pain/discomfort (21 %)
  - Urgency (10 %)
- Progression to TURP: 6.5 %

Prostate Artery Embolisation (PAE)

The purpose of PAE is to cause apoptosis and necrosis with resultant shrinkage. This is a new radiological minimally invasive technique. It requires precise knowledge of prostatic anatomy and arterial supply. The prostate arteries have highly variable origins between the left and right sides of the same patient and also between different patients. The prostate has a dual supply:

- Anterolateral (from superior vesical): supplies BPH nodules
- Posterolateral

The anterolateral branch is usually the preferred vessel to embolise. In 50–60 %, there is anastomosis between the prostate artery and surrounding arteries which may result in the inadvertent injury to surrounding structures. The prostate artery may arise from the same artery or independently to give two arteries. In most studies, PAE is performed under local anaesthesia with most men discharged on the same day or after a very short hospital stay. The approach is femoral with either unilateral or bilateral embolisation. Unilateral embolisation is usually due to procedure failure on one side as a consequence of atherosclerosis or tortuosity of the vessel. The endpoint is usually interruption of flow, reflux and gland opacification.

Efficacy

Most of the studies are small and with poor quality. However, Pinheiro et al. have published one of the largest series. This was a single-centre cohort study of 365 men with moderate-to-severe LUTS at a mean follow-up of 14 months. The best outcomes were observed in men with large prostates (>100 mL) and severe symptoms (IPSS >20). Clinical success rates were 84.9 % at 3 months, 77.2 % at 18 months and 74.3 % at 24–42 months. There was a 24 % clinical failure rate. They also observed mean reductions in IPSS, QoL and prostate volume of 10.9, 2.8 and 16.2 %, respectively. The same group also evaluated the use of PAE in men with acute urinary retention with indwelling catheters. Their initial clinical success was 90 % at 3 months with 4 men having failed catheter removals. However, 3 of them had successful catheter removal after repeat PAE. Antunes et al. assessed UDS findings in 11 men with urinary retention treated with PAE. Prior to PAE, all the men had UDS proven BPO (BOOI > 40). After treatment with PAE:

- BOOI >40: 30 %
- BOOI 20–40: 40 %
- BOOI <20: 30 %

An RCT comparing PAE with TURP found greater improvements in IPSS, QoL, Q_{max} and PVR at 1 and 3 months associated with TURP. There were more adverse events associated with PAE.

Adverse Events

- UTI: 9.8 %
- Transient haematuria: 13.1 %
- Transient haematospermia: 6.6 %
- Transient rectal bleeding: 8.8 %
- Inguinal haematoma: 7.4 %
- Acute urinary retention: 1.6 %
- 1 documented case of bladder ischaemia

Botulinum Toxin A (BTX-A)

The prostate is innervated by sympathetic and parasympathetic efferents and sensory afferents. The secretory role of cholinergic nerves is mediated by muscarinic receptors. The activation of these receptors plays a role in the growth of the normal prostatic tissue and the development of BPH. Acetylcholine (ACh) activates the muscarinic receptor. BTX inhibits release of ACh at the neuromuscular junction which may therefore result in disruption of the neural pathway and subsequently symptom relief. It has proven benefit in the treatment of OAB especially in neuropathic detrusor overactivity. BTX may be injected into the prostate under local anaesthesia transrectally or transperineally.

Efficacy

A recently (2014) updated systematic review on the use of BTX in men with LUTS/BPE has found no significant changes in IPSS, Q_{max} and prostate volume when compared with placebo. There were significant changes in PSA and PVR. The main limitation of the review was that there were few studies included which had a high level of evidence. The largest level 1 trial to date by Marberger et al. included 374 men. There was a high placebo response but no significant difference between placebo and BTX. Only one study reviewed the use of BTX in men with retention who were unfit for surgery. 81 % were able to void after injection of 200 units of BTX-A. The systematic review concluded that the evidence was contradictory and BTX should not be used. A post hoc analysis by Marberger et al. revealed a significant reduction in IPSS versus placebo in men who had previously used α-blockers.

Adverse Events

The incidence of adverse events was similar across the placebo and treatment groups. These events were thought to be due to the procedure rather than BTX. Adverse events included haematuria, haematospermia, urinary urgency, dysuria and UTI.

Transurethral Microwave Therapy (TUMT) and Transurethral Needle Ablation (TUNA™)

Both these techniques are minimally invasive and may be performed under local anaesthesia or sedation in the clinical setting. They involve delivery of heat to the prostate either via microwave radiation (TUMT) or radiofrequency energy (TUNA™) in order to create coagulation necrosis. Both techniques have been shown in systematic reviews and meta-analyses to be efficacious and safe but inferior to results obtained from TURP. TURP is also associated with lower retreatment rates. However, most of the studies have limited follow-up data.

Robotic Prostatectomy

This is a technique usually reserved for the management of prostate cancer. However, there are now small series using the technique to treat very-large-volume BPH. The results reveal this is feasible with good efficacy results and minimal complications. Although the procedure costs are high when compared with open prostatectomy, there may be saving with regard to in-hospital stay. This is an exciting new robotic procedure; however, it will require a learning curve and will probably need to be reserved for high-volume surgeons. In the perspective of alternative techniques for the removal of large prostates, there is currently no place for robotic prostatectomy for the treatment of BPE.

Conclusions

LUTS/BPO remains a significantly bothersome chronic disease worldwide and is one of the most common complaints presenting to urologists. The patients may present with a variety of symptoms, anxieties and co-morbidities. Some will be worried by the concern that their symptoms are due to prostate cancer. Others will be embarrassed by symptoms such as incontinence or assume that surgical treatment of the prostate is the only way to treat their condition. The correct assessment of these patients is vitally important to determine the likely underlying correctable or non-correctable causes, which men are likely to progress, and the patient's expectation of treatment outcome. When counselling men, it is again important to stress the importance of lifestyle changes and the side effects of the various medical treatments. Although there is excellent evidence for both medical and surgical therapies, they are not without risks. Each patient must be treated on an individual basis when deciding on the most appropriate treatment. In men with LUTS who wish to preserve sexual function, consideration must be given to the PDEi tadalafil (Cialis™), UroLift™ or PAE; the patient may be willing to sacrifice some of the efficacy of TURP for their sexual function. There is a large variety of surgical options now available with growing evidence base for their use as alternatives to TURP. HoLEP and monopolar and bipolar TURP are considered at least equivalent in terms of outcomes. However, surgical experience with new technologies may lag as surgeons become as proficient in their use as they are in the performance of the 'gold' standard TURP. In addition, surgical options offered to men may be affected by the available funding and equipment.

Points of Interest
Lower urinary tract symptoms remain an important and common condition which urologists must have an efficient strategy for managing. This strategy must involve the use of evidence-based definitions which allow us to determine the underlying pathogenesis and determine exactly what a patient means

by the symptoms he describes. It is vital to remember the LUTS are often not due to prostatic pathology. The history and examination of the patient remains a critical part of the assessment. This must include a review of their current medications and conditions which may affect or cause symptoms such as diabetes mellitus or neurological dysfunction. It is possible that the urologist may be the clinician initially diagnosing these non-urological conditions. Simple adjuncts often provide a vast amount of information for the clinician which must not be overlooked. The bladder diary allows the assessment of the patient's drinking habits, bladder capacity, degree of frequency and nocturia. In addition, bladder diaries along with questionnaires allow the patient to take a more active role in their own management. Although invasive urodynamics has a role in the assessment of LUTS, this should be reserved for specific patients where there is uncertainty in the diagnosis or there is a specific question which needs an answer. UPSTREAM is a study currently recruiting which is comparing invasive urodynamics with non-invasive urodynamics in the selection of patients for TURP; the results will be eagerly awaited.

The management of LUTS may be divided broadly into conservative, medical and surgical. Conservative management should not be ignored as there is some evidence to suggest its usefulness in patients with mild symptoms. It is especially useful in those keen to avoid drugs who are self-motivated. There are now a multitude of drugs with good efficacy. However, the real challenge appears to be in choosing the correct combination for a specific patient. An example would be a man with predominant storage symptoms or another with erectile dysfunction and lastly one at high risk of disease progression. The patient plays a critical role in these decisions as the expectations must as always be balanced with treatment of adverse events. The vast variety of surgical technologies now available highlights the innovation and growing interest in this area. The more traditional monopolar TURP is now being eclipsed by bipolar TURP which has equivalent outcomes at least in short-term follow-up. In addition, bipolar has advantages with respect to lower rates of transfusion, TUR syndrome and hospital stay. There is growing interest in the use of the laser with a variety of modalities now available. However, follow-up is short and more data is still required. As post-operative sexual function becomes more important and patient preoperative morbidity grows, we may observe techniques such as the prostatic urethral lift (UroLift™), prostatic embolisation and prostatic stents gaining a more important role in selected patients. The evidence for their outcomes though limited remains promising. Lastly, as experience with robotic surgery grows, this technology may expand into the treatment of benign prostatic pathology. This is an exciting time in LUTS management with new studies challenging how we assess patients and determining the efficacies of new techniques.

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Chapter 10
Urethral Disorders

Tricia L.C. Kuo, Nadir Osman, and Christopher Chapple

Introduction

The urethra is a vascular tube that conveys urine out from the bladder. A thorough understanding of basic anatomy and physiological function of the male and female urethra is essential to understand the impact of urethral disorders and their treatment. In this chapter we discuss the clinical anatomy of the male and female urethra as well as urethral disorders commonly encountered in urological practice.

Anatomy

The male and female urethra differ quite significantly in terms of anatomy, physiology and function. As such, the types of pathology that can affect either sex also vary.

The female urethra is approximately 4 cm in length. It is composed of epithelium surrounded by lamina propria and a thin layer of circular smooth muscle. Beneath is a thick longitudinal layer of smooth muscle which runs along the entire length. Striated muscle extends over the distal two-thirds in a horseshoe configuration forming the external urethral sphincter (EUS). The proximal one-third of the female urethra is lined by urothelium and the distal two-thirds by non-keratinised stratified squamous epithelium.

T.L.C. Kuo, MBBS, MRCS, MMed, FAMS
Department of Urology, Singapore General Hospital, Singapore, Singapore

N. Osman, MBChB (Hons), MRCS • C. Chapple, BSc, MD, FRCS (Urol), FEBU, DHC (✉)
Department of Urology, Royal Hallamshire Hospital, Sheffield, UK
e-mail: c.r.chapple@sheffield.ac.uk

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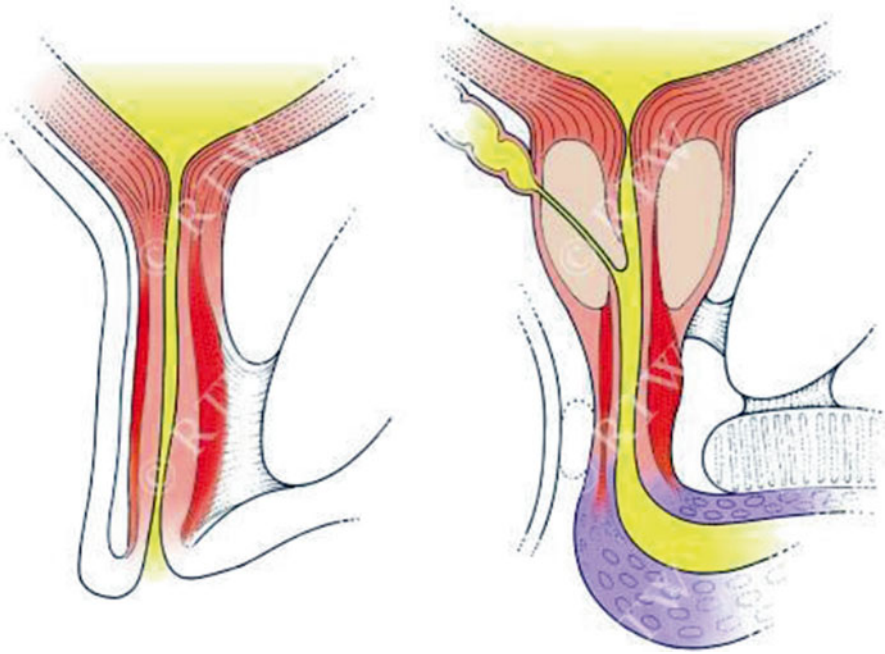


Fig. 10.1 Differences between female and male urethral sphincter mechanisms

The male urethra may be divided into proximal (posterior) and distal (anterior) segments. The proximal portion consists of the prostatic and membranous segments, and the distal portion consists of the bulbar, pendulous/penile and glandular/navicular fossa segments.

Males have two distinct sphincter mechanisms – the bladder neck mechanism which extends from the internal meatus down to the verumontanum and the distal sphincter which extends up to the verumontanum from the bulbomembranous junction. The two mechanisms are distinct and functionally independent (Fig. 10.1).

Physiology and Function

Sensory innervation of the bladder is conveyed to the spinal cord in the pelvic and hypogastric nerves. This involves sensory nerves in the suburothelial plexus, myelinated (A) and unmyelinated (C) fibres. (A) fibres respond to passive distension and active contraction, whereas C fibres respond to noxious stimuli. The cell bodies are located in the dorsal root ganglia (DRG) at S2–3 and T11–L2 spinal segments. Bladder afferent activity thus ascends from the spinal cord to the pontine micturition centre (PMC) and cerebral cortex.

The motor innervation of the lower urinary tract (LUT) comes from both the parasympathetic and sympathetic branches of the autonomic nervous system.

The parasympathetic preganglionic fibres are located in the S2–4 spinal segments, and these synapse with postganglionic cell bodies in the detrusor, bladder neck and urethra. Activation of the parasympathetic fibres causes detrusor contraction and relaxation of the smooth muscle of the bladder neck and urethra. Sympathetic cell bodies are located in T10–12 and L1–2. The preganglionic fibres synapse with postganglionic fibre in the hypogastric plexus. The predominant effect is inhibition of the parasympathetic pathways. The somatic supply to the pelvic floor muscles and external sphincter originates from S2-4 and conveyed by the pudendal nerve.

There are important gender differences with regard to bladder neck sphincter mechanism function. The male bladder neck has a well-developed layer of inner circular smooth muscle along with an outer layer of longitudinal smooth muscle. It has a relatively rich adrenergic innervation (contraction prevents retrograde ejaculation), and its functional competence is considered so reliable as to sufficiently maintain continence in the presence of damage to the EUS. The female bladder neck is less well developed with the predominant orientation of fibres being longitudinal and the principle innervation being cholinergic. Consequently its functional competence is less reliable.

Anatomical/Structural Versus Functional Disorders

A wide variety of pathology can affect the urethra and can be broadly classified in a variety of ways, e.g. congenital or acquired, male or female, anatomical/structural abnormalities or functional abnormalities. A structural and anatomical classification is detailed in Tables 10.1 and 10.2.

Whilst it is not possible to address all the different urethral pathologies, the common conditions will be discussed in detail in this chapter.

Table 10.1 Structural/anatomical classification of urethral disorders

Disorders of the male urethra	Disorders of the female urethra
Congenital	Congenital
Duplication of the urethra	Distal urethral stenosis in childhood (urethral spasm and dysfunctional voiding)
Urethral stricture (rare)	
Posterior urethral valves	
Anterior urethral valves	
Hypospadias	
Urethrorectal and vesicorectal fistulas	
Epispadias	
Acquired	Acquired
Urethral stricture	Urethritis (acute and chronic)
Urethral stenosis	Urethral caruncle
Urethritis and infections	Urethrovaginal fistula
Urethral carcinoma	Urethral diverticulum
	Urethral stricture (rare)

Table 10.2 Functional classification of urethral disorders

Functional disorders	*Disorders of sensation*	Hypersensitive sensation or pain due to inflammation
		Decreased sensation
	Disorders of motor function	
	During storage	Incompetent or underactive/absent
	During voiding	Obstruction due to non-relaxation or overactivity, e.g. detrusor-urethral dyssynergia (detrusor bladder neck dyssynergia or detrusor sphincter dyssynergia)

Male Urethral Disorders

Urethral Strictures

Introduction

The term "urethral stricture" refers to an abnormal narrowing of any segment of the urethra surrounded by the corpus spongiosum and implies varying degrees of ischaemic spongiofibrosis. The term "urethral stenosis" is reserved for narrowing of the membranous urethra, the prostatic urethra and the bladder neck as they are not invested by corpus spongiosum (in contrast to the term "urethral distraction defect" as seen with a pelvic fracture urethral injury) [1].

Acquired urethral strictures are more common in men. These can be subcategorised into iatrogenic, traumatic, inflammatory and idiopathic causes [1]. Fenton et al. found that the majority of strictures were idiopathic (34 %) and iatrogenic (32 %) in a review of 175 stricture patients with a total of 194 strictures [2]. Inflammatory and traumatic causes were found in only 20 % and 14 % of patients, respectively. The most commonly involved site was the bulbar urethra (52 %).

Clinical Presentation

Key points in the history include:

- Presenting symptoms – obstructive symptoms (e.g. poor flow, urinary retention), storage symptoms, haematuria, dysuria
- History of trauma, previous instrumentation (e.g. difficult urethral catheterisation) or transurethral procedures
- History of sexually transmitted diseases or urinary infections
- Current status of erectile and ejaculatory function
- Previous treatment, e.g. urethral dilatation or urethrotomy, hypospadias repair, intermittent self-dilatation (ISD)

A directed physical examination should assess the following:

- Difficulties with positioning of patient, i.e. lithotomy position (especially after trauma)

- External genitalia – condition of tissues, previous fibrosis/scarring and lichen sclerosis (LS), previous circumcision, fistula, signs of ongoing infection
- Abdominal examination – suprapubic scars, presence of a suprapubic catheter
- Digital rectal examination

Evaluation and Follow-Up

Patients should undergo comprehensive symptomatic evaluation at presentation and follow-up [3, 4]. The recently published patient-reported outcome measure (PROM) for urethral stricture surgery provides a standardised and validated method of assessing outcomes and consists of a lower urinary tract symptom (LUTS) construct (6 questions), a separate LUTS-specific quality-of-life (QoL) question and Peeling's voiding picture. The post-operative PROM is supplemented by 2 questions addressing overall patient satisfaction (Appendix A).

Retrograde urethrogram (RUG) is recommended as a reliable, accessible and versatile means to both diagnose and stage urethral stricture. It should be combined with voiding cystourethrography (VCUG) to achieve a synergistic approach to the evaluation of the entire urethra [5]. It remains the standard method to ascertain the location and length of a stricture and any associated urethral pathology, e.g. false passages, fistulae and calculi.

Cystoscopy is recommended by the SIU/ICUD committee as the most specific procedure for the diagnosis of urethral stricture. It is a good adjunct in the staging of anterior urethral stricture, particularly to confirm abnormal or equivocal findings on imaging studies. For pelvic fracture-related urethral distraction defect, cystoscopy is highly recommended for assessment of the bladder neck and posterior urethra [5].

Ultrasonography is another potential adjunctive investigational tool. In addition to ascertaining the length and location, ultrasound can also provide information regarding degree of spongiofibrosis and concomitant pathology, e.g. diverticula, fistulae, stones, false passages and periurethral abscesses [6–8]. Previous retrospective reviews have shown that intraoperative ultrasound changed the surgical approach in 19 % and was integral in deciding between two possible approaches in 26 % of patients [9]. This is suggested as a supplement to the standard approach for most reconstructive surgeons, i.e. an intraoperative decision based on the visual assessment of the anatomy, calibre of the urethra and its vascularity.

The value of uroflowmetry in assessing a stricture preoperatively or for the post-operative follow-up is of limited value. It is the norm to have a patient present with a very tight stricture at the first instance, as they usually have normal bladder function that compensates. In 1968, Smith reported that the effective diameter of the unobstructed male urethra was 11 Fr gauge. Hence, until the stricture narrowed beyond this point, there would be no significant interference with flow, and hence, patients would not be necessarily aware that there was a significant problem [10].

Treatment

In 1974, Sachse introduced direct vision internal urethrotomy (DVIU) to treat urethral strictures by incising with the use of a cold knife [11]. Both urethrotomy and dilatation work by disrupting the stricture, and rely upon adequate tissue vascularity for healing without re-narrowing.

A nationwide survey of practising members of the American Urological Association was performed in 2007 and found that the most commonly used procedures for treatment of urethral strictures were dilatation (used by 92.8 % of surveyed practitioners), optical internal urethrotomy (used by 85.6 %) and endourethral stents (used by 23.4 %). It was noted that for a long bulbar urethral stricture or short bulbar urethral stricture refractory to internal urethrotomy, only 20–29 % of respondents would refer to another urologist, whilst 31–33 % would continue to manage the stricture by minimally invasive means despite predictable failure [12].

Steenkamp et al. compared internal urethrotomy to dilation in a randomised controlled trial and found no difference in efficacy between the two methods. Recurrence rates were noted to be higher for strictures of increasing length. They thus recommended dilation or internal urethrotomy (DVIU) for strictures shorter than 2 cm, primary urethroplasty for those longer than 4 cm, and a trial of dilation or urethrotomy for those 2–4 cm in length [13]. Therefore, SIU/ICUD guidelines recommend that primary DVIU/dilation be used as first-line treatment for short (<1–2 cm), single bulbar urethral strictures (Grade A) [14].

Generally, a third DVIU/dilation is not recommended, except if necessitated by patient comorbidities, choice or economic resource (Grade A). This is evidenced by a previous study that showed that after a third dilation or urethrotomy for stricture recurrence at 3 and 6 months, the stricture-free rate at 24 months was 0 ($p<0.0001$) [15].

Permanent urethral stenting is not recommended for patients with strictures who are considered to be candidates for urethral reconstruction. There is evidence that subsequent failure of a permanently implanted stent represents a major surgical challenge [16].

Urethroplasty for the anterior urethra consists of a range of operations such as excision and primary anastomosis (EPA) and the different types of substitution urethroplasty. The type of urethral reconstruction depends on several factors. The length, location and aetiology (e.g. lichen sclerosis) and previous interventions all have impact on the final outcome.

A recent analysis of 17 articles comprising a total of 1234 patients over 35 years (1975–2010) found that overall success of EPA was 93.8 %. Reported complications were <5 %, and there was no evidence of persistent loss of sexual function. Other possible complications include fistula, chordee, postmicturation dribbling and recurrence. Thus, EPA should be carried out for patients with short bulbar strictures, especially if expected success rates of other procedures are <90 % [17].

Care needs to be taken in the assessment and subsequently when performing an anastomotic reconstruction of the anterior urethra. In general, only strictures <3 cm were considered for anastomotic procedure. Mobilisation of the urethra and corporal separation allows gain of several more centimetres (Fig 10.2).

Mobilisation of the bulbar urethra should not extend beyond the penoscrotal junction to prevent chordee. In this context, one should perform an augmentation (substitution) if the stricture is too long. Likewise, it is rare to be able to perform an anastomotic urethroplasty for the penile urethra due to the risk of producing a chordee. The exception would be in the case of an acute penile fracture.

Augmentation urethral reconstruction can be either one-stage or two-stage procedure. There are three potential options to a one-stage procedure – an onlay augmentation, an augmented anastomotic or a tube augmentation procedure. Whereas, a two-stage procedure includes excision of the stricture and reconstruction of the roof strip. The second stage tubularisation is carried out at least 3–6 months later, but further evaluation at 2 months is essential to identify what revision, if any, of the first stage is necessary [19].

A systematic review of graft augmentation urethroplasty techniques for treatment of anterior urethral strictures showed there was no significant difference between the average success rates for the dorsal and ventral onlay procedures, 88.4 % and 88.8 % at 42 and 34 months, respectively. The lateral onlay procedure has only been described in 6 patients and is reported to have a success rate of 83 % at 77 months. For penile stricture disease, the success rate for a two-stage procedure was significantly better than the one-stage technique (90.5 % versus 7.5 %, respectively) [20].

Oral mucosa is the most versatile augmentation (substitution) material. Oral mucosa has privileged immunology, with preclinical work showing less fibrosis compared to skin. This mucosa is wet and is unlikely to be affected by lichen sclerosis.

Bioengineered buccal mucosa grafts are likely to have a future role for patients with long and complex strictures. Particularly for redo cases where oral mucosa has already been used, then the supply may be limited. Autologous cell-seeded

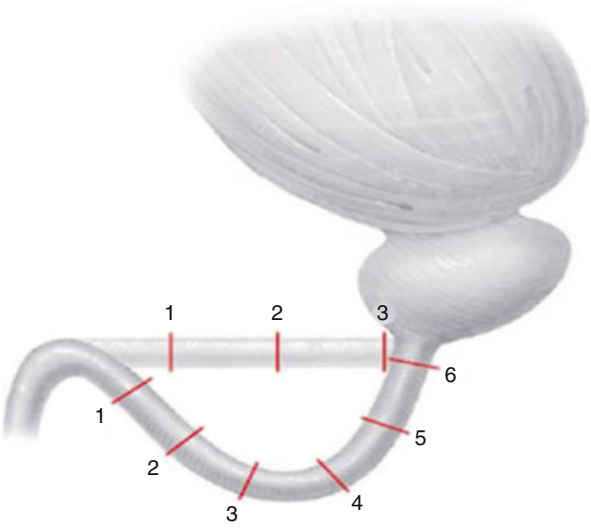


Fig. 10.2 Diagrammatic representation of the additional length (in cm) gained by separation of the corpora cavernosa [18]

grafts are not dependent on ingrowth of epithelial cells and show some promise. Tissue-engineered oral mucosa was reported in five men. All patients had complex strictures secondary to lichen sclerosis. Initial graft take was 100 %. However, at 3 years, three patients had intact graft, albeit with the need for instrumentation [21].

Pelvic Fracture Urethral Injuries (PFUI)

Classic signs of blood at the meatus, inability to void and a distended bladder after a traumatic incident are the classic signs but may not always be present. Other signs include a butterfly sign or perineal/scrotal haematoma and a high riding prostate on per rectal examination. It is particularly important to exclude the coexisting rectal injury which is seen in up to 5 % of cases.

Posterior urethral injuries associated with pelvic fracture are best considered as pelvic fracture urethral distraction injury (PFUDD). This term was introduced by Turner-Warwick [22]. However, a large percentage of such injuries are partial and do not necessarily result in "distraction" or "separation". Therefore, the terminology of PFUI has replaced PFUDD.

Some types of pelvic fracture are associated with a higher risk of posterior urethral injury. The highest risk of urethral injury was found in cases with straddle fracture when combined with diastasis of the sacroiliac (SI) joint (24 times more than the rest of the pelvic fractures); this was followed by straddle fracture alone (3.85 times) and Malgaigne's fracture (3.4 times) [23].

Ideally a retrograde urethrogram should be performed in all patients suspected of having a PFUI. The urethrogram should be performed with 45° oblique views with the downside leg externally rotated and flexed at the knee. The downward obturator fossa should be completely closed on the scout film to confirm appropriate positioning. This is followed by the injection of 15–20 ml of contrast under fluoroscopic guidance. However, in polytrauma patients, this may be logistically difficult. In addition, extravagated contrast can confuse later CT findings.

There are two accepted treatment methods in the acute setting. Early closed realignment over a catheter can be done using blind or endoscopic techniques. The second and safest approach recommended for the majority of cases is the placement of a suprapubic catheter and an interval perineal urethroplasty 3–6 months later. It is well established that immediate open retropubic urethroplasty and open catheter realignment result in significantly higher incontinence and impotence rates and hence are not recommended (Grade A) [24].

The progressive perineal approach is the means to which an end-to-end bulbomembranous anastomosis (BMA) can be achieved in stepwise fashion. These are:

1. Bulbar urethral mobilisation
2. Separation of the crura in the midline
3. Inferior pubectomy
4. Supracrural rerouting

When adequate access to the membranous urethra and the bladder neck cannot be accomplished with the above four steps, an abdominoperineal approach could be used, with or without transpubic exposure.

The success rate of uncomplicated bulbomembranous anastomosis (BMA) is quoted at 90–98 % [25–29]. However, this very much depends on the competence of the surgeon, experience of the tertiary unit and severity of the surgery. Surgical complications include erectile dysfunction and incontinence.

Female Urethral Disorders

Urethral Diverticulum

Introduction

Urethral diverticula (UD) are outpouchings of the urethral wall which occur almost exclusively in women between the ages of 30 and 60. The actual prevalence is unknown but is estimated to be around 1–6 % in the general populace, increasing to as much as 40 % in women with lower urinary tract symptoms (LUTS) [30, 31].

Most UD are postulated to arise after infection of the paraurethral glands [30]. Other possible causes may be trauma, childbirth or iatrogenic injury. Paraurethral glands have ducts draining into the urethra and are located in the posterolateral position along the whole urethral length. Their main function is the secretion of mucin which acts as a mucosal sealant. Infection of urethral gland leads to obstruction of the ducts and abscess formation. These abscesses then point and often rupture into the urethral lumen, after which the tract epithelialises and a diverticulum forms. The connection between the diverticulum and the urethra is termed the ostium.

UD are usually distributed along the 3 or 9 o'clock positions of the urethra [32]. They can have simple or complex configurations whereby the sac wraps partially or completely around the urethra [33]. Ostia typically open into the urethral lumen at the 6 o'clock position. Untreated UD can result in stone formation and benign or malignant neoplasms (although associated malignancy is extremely rare).

Clinical Presentation

UD present a major diagnostic challenge due to the non-specificity of the presenting symptoms [34]. These symptoms typically comprise storage LUTS, dysuria, urethral pain, pelvic pain and dyspareunia. In addition patients may complain of stress or urgency urinary incontinence, voiding difficulties or retention of urine and urethral discharge or bleeding. The classically described triad of dysuria, dyspareunia and dribbling is actually uncommon. Due to the non-specificity of symptoms, there is often a delay in diagnosis [35]. Confusable conditions include bladder pain syndrome and recurrent urinary tract infection, which can coexist along with UD and is usually attributed to stagnation of urine.

Vaginal examination may reveal a periurethral swelling or be entirely normal particularly if the diverticulum is anteriorly placed. Examination during an acute infective exacerbation may demonstrate significant tenderness. Milking the sac may produce urine or discharge per urethra. Hardness of the swelling may indicate a stone or malignancy. Identification of stress urinary incontinence, urogenital prolapse and urethral hypermobility is important as their presence may influence the surgical approach.

Evaluation

Routine urinalysis (± urine microscopy and culture) is essential to assess for infection or haematuria. Urethroscopic examination may allow visualisation of the ostium in up to 60 % of cases [36]. A zero degree lens will provide the best visualisation of the whole lumen.

We advise the use of urodynamics preoperatively in all patients to assess baseline urinary tract function. Voiding cystourethrography during a videourodynamic study was previously considered the study of choice for diagnosis of UD but has now been superseded by newer imaging modalities. It has low diagnostic accuracy (around 65 %), as the ostium may be stenotic or the flow down the urethra may be too weak to allow the sack to fill with contrast.

Ultrasound can be performed transvaginally, transabdominally and less commonly transurethrally, to demonstrate a UD. Transvaginal and transurethral ultrasound provides better detail although are more invasive. Although very rapid and inexpensive, ultrasound for the identification of UD is user dependent and requires a high degree of expertise to identify the relevant surgical anatomy.

In contrast to ultrasound, post-micturition magnetic resonance imaging (MRI) is easier to perform and interpret. It is currently considered the best investigation for identifying and defining UD [37]. Surface or endoluminal coils (placed in the rectum or vagina) can be used, the advantage of the latter is the superior signal to noise ratio and better image resolution [38]. T2-weighted images provide the best mode of identifying UD. Both sagittal and coronal views are needed for surgical planning. It is also essential that images are taken post-voiding.

Classification System

A comprehensive classification system, termed the LNSC3 system, for UD was proposed by Leach et al. It describes the following aspects of UD: location, number, size, site of connection with urethra, configuration and continence state [39] (Table 10.3).

Treatment

Conservative management is indicated for asymptomatic patients, those who are minimally symptomatic and those not wanting to undergo surgery. The mainstay of conservative treatment is urethral antibiotic prophylaxis as necessary.

Table 10.3 LNSC3 classification system

L	Location	Distal, middle or proximal urethra
		+ or − extension behind bladder neck
N	Number	Single or multiple
S	Size	Centimetres
C1	Configuration	Single, multiloculated or saddle shaped
C2	Communication	Site of communication with urethra: distal, mid or proximal
C3	Continence	Is stress incontinence present or not

If surgery is being considered, a videourodynamic study is recommended preoperatively to provide an objective assessment of bladder and urethral function as patients often have coexistent problems such as stress incontinence and detrusor overactivity [40]. Surgery for UD is challenging due to its extension through part of the urethral sphincter mechanism, which makes incontinence a significant risk. The tissues around the UD are often inflamed and fibrosed due to recurrent infection leading to a lack of clear planes. Surgery is best deferred until any infective flare-ups have been adequately treated. The best surgical approach is a transvaginal excision with urethral sphincter reconstruction which should only be performed in experienced hands. The procedure is usually performed in the lithotomy position although with more complex and proximal diverticula, the prone position provides optimal access [41]. Apart from de novo or worsening stress incontinence, other risks of surgery include urethrovaginal fistula and dyspareunia. A Martius flap can be used to reduce the risk of fistula formation and to facilitate any subsequent incontinence surgery which may be needed. We would not advise the use of techniques such as marsupialisation of a UD or incision of the ostium as both are associated with high morbidity.

Urethrovaginal Fistula

Urethrovaginal fistula is rare. In developed nations, they usually arise as a result of iatrogenic injury (e.g. surgery for stress incontinence, prolapse and urethral diverticula). In developing nations, the most common cause by far is obstructed labour. Less frequent causes include vaginal cancer, radiation therapy and pelvic fracture. Recently with the increasing use of synthetic mesh in incontinence surgery, mesh erosion has emerged as a new cause of fistulae.

Clinical Presentation

Clinical presentation is dependent on the size and location of the fistula [42]. The patient may be continent if the fistula is in the distal urethra, but usually patients with a fistula complain of urine passing involuntarily out per vagina. Fistula located proximally or in the mid urethra may lead to leakage intermittently or in certain positions.

Evaluation

It is important to document the number and location of fistulae. This is best done via a combination of examination under an anaesthetic (EUA) and cystoscopy. Imaging may be helpful.

Treatment

If diagnosed within the first 2–3 weeks following iatrogenic trauma, operative repair is recommended. After this window of opportunity, if the patient is dry with a urethral catheter in situ, then there is a chance that drainage alone may lead to spontaneous healing. Should the fistula tract fail to close after a period of 30 days, it is unlikely to close spontaneously [43].

Surgical management is associated with a significant risk of stress urinary incontinence, as the sphincter mechanism is usually damaged due to the injury that caused the fistula. The traditional approach is transvaginal. Utmost care must be taken to avoid too much dissection around the fistulous tract, which may further damage the urethral sphincter mechanism. Martius flap interposition between the urethral and vaginal closure is recommended to reduce the risk of recurrence and facilitates future placement of an autologous fascial sling should the patient develop postoperative stress incontinence.

Female Urethral Stricture

Introduction

Urethral stricture in females is rare, representing 4–13 % of the causes of bladder outlet obstruction in women [44]. Obstruction in women is in itself an uncommon urodynamic finding in women presenting with urinary tract symptoms (2.7–8 %) [45]. The pathogenesis of female urethral strictures is poorly understood, and the postulated aetiological factors include trauma, infection and prior instrumentation. There are currently no accepted standardized definitions or diagnostic criteria.

Clinical Presentation

Patients typically complain of voiding lower urinary tract symptoms (LUTS) but may also have storage LUTS and a feeling of incomplete bladder emptying, particularly if post-void residuals are elevated.

Evaluation

First-line investigations include uroflowmetry and measurement of post-void residual volumes (PVR). Some authors make the diagnosis using urethral calibration

placing the threshold in terms of a diagnostic calibre anywhere in the range of 14 Fr to 20 Fr. On urodynamic testing, stricture would be suggested by a high-pressure, low-flow pattern along with radiological evidence on urethrography of a narrowed urethral segment and ballooning of the proximal non-strictured urethra. An MRI scan may demonstrate an associated diverticulum or fistula.

Treatment

First-line management is usually urethral dilatation which can be considered to have a mean success rate of around 47 % at mean follow-up of 43 months [46]. Urethrotomy is not recommended in women due to the significant risk of damage to the urethral sphincter mechanism. Recently there has been increased interest in reconstructive surgery for female urethral strictures. Urethral reconstruction can be undertaken through dorsal, ventral or a circumferential approach using grafts (e.g. vaginal or buccal mucosa) or using labial flaps. The available literature suggest that reported success rates in excess of 80 % can be achieved using these approaches with a low risk of stress incontinence in expert hands [46]. The low risk of stress incontinence can probably be explained by the fact that most strictures are located distally where the sphincter mechanism is at its thinnest.

Summary

Urethral disorders have a varied pathophysiology and clinical presentation. A key to diagnosis is having a high degree of clinical suspicion and utilisation of appropriate specialised investigations. The treatment depends on the patient presentation, disease pathophysiology and the resources available. In view of their relative rarity, complex cases should be treated at high-volume tertiary centres.

Points of Interest

- Urethral disorders have a varied pathophysiology and clinical presentation.
- Assessment of urethral pathology often requires specialised investigations and recently includes patient-reported outcome measures (PROM) particularly for urethral strictures.
- Determinants of type of procedure for treatment of urethral stricture depend on stricture location, length, degree of spongiofibrosis, previous intervention and surgeon experience.
- Urethral diverticula present a diagnostic challenge. Surgery is recommended for symptomatic patients.
- Majority of urethral diverticula can be approached via a transvaginal approach, with the patient in a prone position. A Martius flap reduces the risk of fistulation.
- Female urethral strictures are rare and can be treated first with urethral dilatation, with consideration for urethral reconstruction if recalcitrant.

Appendix A

Thank you for completing this questionnaire. The following questions are designed to measure the effect that urethral strictures have on patients' lives.

Some questions may look the same but each one is different. Please take time to read and answer each question carefully, and tick the box that best describes your symptoms over the past 4 weeks.

If you currently have a urethral or suprapubic catheter (a catheter through the lower abdomen) please start at page 4.

1 Is there a delay before you start to urinate?

- Never ☐
- Occasionally ☐
- Sometimes ☐
- Most of the time ☐
- All of the time ☐

2 Would you say that the strength of your urinary stream is...

- Normal ☐
- Occasionally reduced ☐
- Sometimes reduced ☐
- Reduced most of the time ☐
- Reduced all of the time ☐

3 Do you have to strain to continue urinating?

- Never ☐
- Occasionally ☐
- Sometimes ☐
- Most of the time ☐
- All of the time ☐

4 Do you stop and start more than once while you urinate?

- Never ☐
- Occasionally ☐
- Sometimes ☐
- Most of the time ☐
- All of the time ☐

5 How often do you feel your bladder has not emptied properly after you have urinated?

- Never ☐
- Occasionally ☐
- Sometimes ☐
- Most of the time ☐
- All of the time ☐

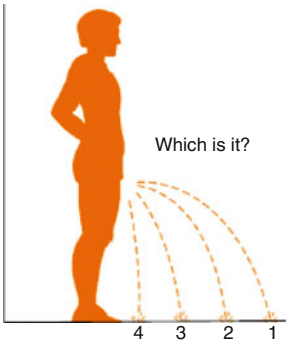
6 How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

- Never ☐
- Occasionally ☐
- Sometimes ☐
- Most of the time ☐
- All of the time ☐

7 Overall, how much do your urinary symptoms interfere with your life?

- Not at all ☐
- A little ☐
- Somewhat ☐
- A lot ☐

8 please ring the number that corresponds with the strength of your urinary stream over the past month



(From Peeling 1989)

9 Are you satisfied with the outcome of your operation?

- yes, very satisfied ☐
- yes, satisfied ☐
- No, unsatisfied ☐
- No, very satisfied ☐

10 If you were unsatisfied or very unsatisfied is that because:

- The urinary condition did not improve ☐
- The urinary condition improved but there was some other problem ☐
- The urinary condition did not improve and there was some other problem as well ☐

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usal Activities *(e.g. work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have modarate pain or discomfort ☐
- I have extreme pain or discomfort ☐

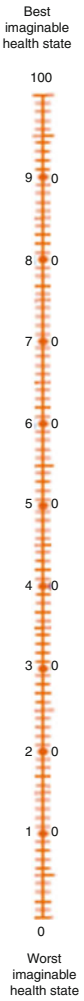
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extermely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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Chapter 11
Reconstructive Surgery

Dirk De Ridder, Jan Moritz Laturnus, and Karl-Dietrich Sievert

Management of Vesicovaginal Fistula

Dirk De Ridder

What Do the Guidelines Say?

The evidence on the treatment of vesicovaginal fistula is limited. While an initial attempt can be made by placing a transurethral catheter for 2–3 weeks in the hope that the fistula will close spontaneously, surgical repair will usually be necessary. There is no evidence that the timing of the repair makes a difference to the chances of successful closure of the fistula. There is no clear advantage of vaginal, abdominal, transvesical, or transperitoneal approaches. Laparoscopic and robotic approaches have been described but without showing any clear advantage over traditional approaches. Interposition grafts can be used, but there is little evidence to support their use. Urethro-vaginal fistula can be complicated by persisting stress incontinence, urethral strictures, or urethral shortening necessitating long-term follow-up. Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient [1, 2].

D. De Ridder, MD, PhD (✉)
Department of Urology, UZ Leuven campus Gasthuisberg, Leuven, Belgium
e-mail: dirk.deridder@uzleuven.be

J.M. Laturnus
Department of Urology, University Hospital Lübeck, Germany
e-mail: jan.laturnus@uksh.de

K.-D. Sievert, MD, PhD, FACS, FRCS (✉)
Department of Urology and Andrology, SALK University Clinic and Parccelsus Private Medical University (PMU), Salzburg, Austria
e-mail: k.sievert@salk.at; kd_sievert@hotmail.com

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Clinical Practice

In developed countries, most of the fistulas are seen as complications of gynecological surgery after radiotherapy. In developing countries, obstetric trauma is the main cause. In the developed world the surgical experience is limited to small series of patients using a variety of surgical approaches, while in developing countries fistula surgeons often have operated on more than 10,000 women mostly by a vaginal route. There is a high need to share this vast experience with the urological community in the developed world. A surgeon should choose the approach he or she is most experienced in. There is no advantage of one approach over another.

Clinical Diagnosis

In most cases, the fistula can be seen or felt during clinical examination. The surgeon needs to assess the location and size, number of fistula, amount of scarring, position of the uterus, eventual urethral involvement, and status of in the outpatient clinic the mid compartment and posterior wall. The exact status can be difficult to assess at the outpatient clinic due to pain and discomfort. In many cases, the clinical examination will have to be repeated once the patient is under anesthesia.

Radiation fistula can progress over time. One should allow 6–12 m before a formal repair. Often derivative surgery will be necessary in these cases.

Vaginal Fistula Repair

Gaining Access and Exposure

The position of the patient on the operation table should allow good access to the vagina. Usually the lithotomy position is used, but in some centers and the knee-elbow position is advocated. Traction sutures or Scott retractors as well as adapted specula are necessary for a good surgical exposure. An episiotomy can be necessary. A transurethral catheter, preferably silicone catheter 16–18 French, will be remain in the patient to drain the bladder for at least 2 weeks. The blue dye tests can be repeated in the OR using this catheter, to ensure the correct identification of the fistula and to assess the number of fistulas.

Incision, Dissection, and Mobilization of the Other Fistulas

Several types of vaginal incisions have been described depending on the position of the fistula and accessibility of the vagina.

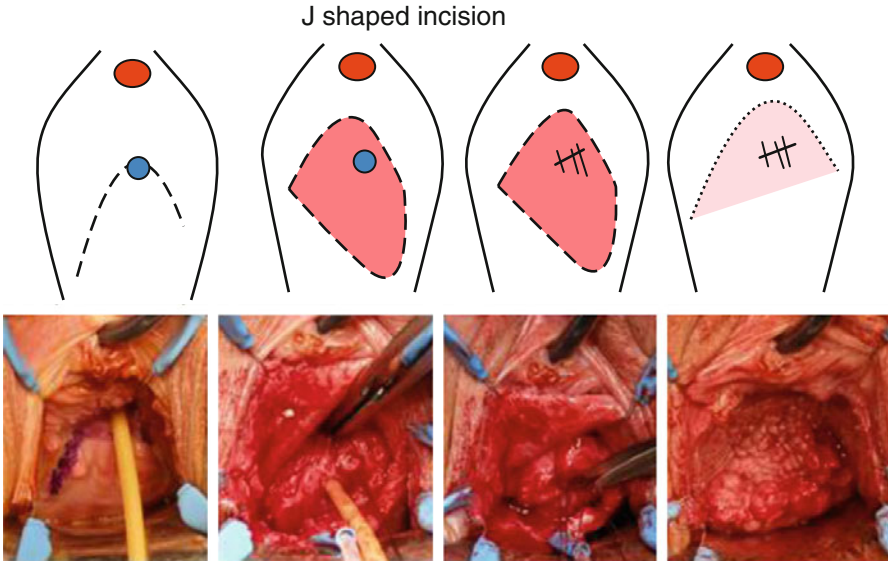

Fig. 11.1 J-shaped incision for small fistula. The tip of the J should encompass the fistula. Flaps can be used to cover the fistula suture line

Latzko Incision This incision will circumcise the fistula and close the anterior and posterior wall over the fistula in one or two layers. The vaginal wall is then closed separately. This is a nice incision for high vaginal fistulas. The limited reduction in vaginal length will not cause sexual dysfunction.

J-Shaped Incision An incision in the shape of a J is made with the fistula lying in the top of the curvature of the J. The arms of the J can be directed anteriorly or posteriorly in such a way that ample mobilization of an anterior and posterior flap of the vaginal tissue is possible. The mobilization should be carried out in such a way that a tension-free closure of the fistula becomes feasible (Fig. 11.1).

Inverted Y Incision This incision is used for larger fistula. The incision starts at the posterior rim of the fistula and can be extended to the lateral walls of the vagina. The circumferential incision is then extended to the midline of the anterior vaginal wall allowing the development of two anterolateral flaps. This incision allows wide mobilization of the fistula tract and even of the urethra. The flaps can be used after the fistula closure to cover the fistula suture line (Fig. 11.2).

Ensure that the ureters are identified and eventually protected by placing ureteral catheters. If fistulas are located at the bladder neck, proximal urethra, or mid-urethra, make sure to maintain the urethral length as much as possible and think consider adding an autologous sling to prevent postoperative stress incontinence.

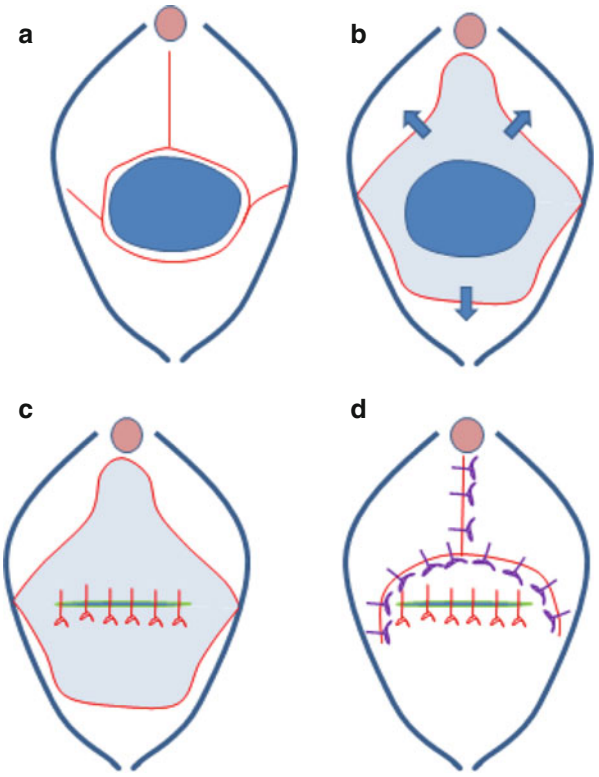

Fig. 11.2 (**a**) The large fistula is incised at the base. The incisions extend to the lateral vaginal wall and are extended in the midline of the anterior vaginal wall. (**b**) Dissection of the vaginal wall allows the formation of two anterolateral flaps, and a posterior flap and allows for wide mobilization of the fistula. (**c**) The fistula is closed in a tension-free way and the repair is watertight. (**d**) The flaps are used to cover the fistula suture line without creating an overlap between the suture lines

Closing of the Fistula

For the obstetric fistula, several consensus meetings have been held on the optimal closure of the fistula. Absorbable sutures 2/0 are recommended. Strong bites in the detrusor and serosal layers are necessary to close the fistula, but there is no need to close the urothelium separately. A single layer of separate sutures of 4–5 mm apart is sufficient to close the fistula. After closure, the bladder should be filled with blue dye to check for watertight closure. Eventually, supporting sutures can be used to stabilize the bladder neck. A Martius flap is optional in most cases [3].

Achieving and Maintaining Continence

Fistulas involving the bladder neck area or mid-urethra have a higher risk of persisting incontinence, despite a successful closure of the fistula. The urethral support mechanisms and the external urethral sphincter might be damaged as a consequence of the fistula, fibrotic process, or fistula repair. The larger the

fistula, the more vaginal scarring and the smaller the bladder capacity, the higher the risk for postoperative incontinence. The surgical principles in these cases are the same as for other fistulas, but some additional measures can be taken. The urethral length should be maintained as much as possible. If the urethral length is less than 2.4 cm or if the urethral defect is more than 4 mm, an incontinence procedure should be added. If performed, postoperative incontinence can be reduced by approximately 50 %. Either a sling procedure can be added or a bladder neck suspension can be performed. For the sling procedure, only autologous material should be used. A sling can be created from fibromuscular tissue in the lateral vaginal wall or can be constructed out from the rectus or fascia lata. In the bladder neck suspension, non-absorbable sutures are used to suspend the bladder neck area in a fixed position [4].

Postoperative Care

Bladder drainage should be continued for 10–14 days, in most cases. In smaller fistulas that were easy to repair, shorter catheterization periods might be possible. When draining the bladder, silicone catheters are preferred since these have a larger internal diameter for the same external diameter and are less likely to be blocked by blot clots. A high fluid intake should be maintained to prevent clot formation. There is no need for antibiotics during the catheterization periods. Nursing staff should be trained and supervised adequately to ensure that catheters are not blocked, which could lead to a rupture of the fistula repair.

Abdominal Approach

Abdominal fistula repair can be done open, laparoscopically, or robotically. Extravesical and transvesical techniques have been described. The principles remain the same: identify the fistula, separate the bladder wall from the vaginal wall, and mobilize the fistula well enough to allow tension-free closure. Omentum can be used as interposition material.

Points of Interest

- Most vesicovaginal fistulas can be managed by a vaginal approach, but abdominal, laparoscopic, or robotic repairs are also feasible.
- Wide mobilization of the fistula to allow tension-free and watertight closure is of the utmost importance.
- The timing of fistula surgery can be individualized, except for radiation fistula, where a longer waiting time (6–12 m) is advocated.

Bladder Augmentation

Karl-Dietrich Sievert and Jan Moritz Laturnus

General Introduction

Many patients with small-capacity, high-pressure, or unstable or low compliant bladders will be managed with conservative measures. A small but significant minority of these patients will require surgical intervention, the therapeutic goals of which are to provide urinary storage while preserving renal function, continence, resistance to infection, and convenient voluntary and complete emptying.

Augmentation cystoplasty increases bladder capacity and decreases detrusor overactivity by enlarging the bladder with the addition of a bowel segment and possibly by disrupting the detrusor. Many different surgeons have carried out augmentation for many reasons, using many different types of tissue. The stomach, ileum, cecum, and ascending and sigmoid colon have all been used as tubular or detubularized, simple or complex segments.

The classic, augmentation enterocystoplasty has been performed in patients with neurogenic voiding dysfunction, but it has been shown to be effective for patients with neurogenic and non-neurogenic detrusor overactivity or patients with a reduced bladder compliance/capacity.

What Do the Guidelines Say?

EAU

"Replacing or expanding the bladder by intestine or other passive expandable coverage will reduce bladder compliance and at least reduce the pressure effect of detrusor overactivity. The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed."

"In order to treat refractory detrusor overactivity, bladder augmentation is recommended. Detrusor myectomy is an acceptable alternative (LE: 3, GR: A)."

Fourth International Consultation on Incontinence

"Children: For detrusor overactivity/poor compliance, botulinum toxin and bladder augmentation may be performed."

"Men: 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."

"Women: 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)."

Clinical Practice

In a large majority of patients with refractory detrusor overactivity or reduced bladder compliance/capacity, augmentation enterocystoplasty is effective, provided that these principles are followed:

1. Achieving a large bladder capacity.
2. Detubularization of the intestinal segment by incising the antimesenteric bowel wall.
3. Half-sphere reconfiguration of the bowel segment.
4. Wide anastomosis between the reconfigured bowel and the bladder is performed.

Many patients require intermittent self-catheterization after augmentation and need to be prepared to do this prior to consenting to the operation.

Background

Outcome

Augmentation cystoplasty is reported to have a 0–2.7 % mortality. The deaths that were reported were caused by pulmonary embolus, myocardial infarction, and adult respiratory distress syndrome after postoperative pancreatitis. Surgical early complications include a 3–5.7 % rate of adhesive small bowel obstruction requiring operative intervention, a 5–6.4 % incidence of significant wound infection (including dehiscence), and a 0–3 % reoperation rate for bleeding.

Failure of augmentation enterocystoplasty to resolve the underlying lower urinary tract problem was reported in 5–42 % of patients. Failure rates are higher with idiopathic detrusor instability, where long-term symptomatic success was reported in as few as 53–58 % of patients, compared with the 92 % success reported in neuropathic patients. In view of this, bowel augmentation may be the treatment of choice in patients with neuropathic bladders, while autoaugmentation may be the surgical intervention considered first in cases of detrusor instability.

Complications

Typical complications are recurrent infections, stone formation, perforation or possible malignant changes, intestine metabolic abnormality, mucus production, and impaired bowel function.

Recommendations for Follow-Up

Depending on the underlying diagnosis, the follow-up interval may vary between a few months but should not exceed 2 years. The follow-up protocol should consist of a physical examination, regularly performed urine analysis, and a checkup of the upper urinary tract. Also blood gases and folic acid should be checked frequently.

Diagnostics

All patients need to have sufficient intellect to understand the proposed surgery, its pros and cons, and the requirement of lifelong surveillance. They need to be motivated to learn and comply with intermittent catheterization, cope with the physical and emotional stress of what is a significant operation, and (in the case of patients with neuropathy), be prepared for the requirement to perform subsequent procedures to achieve acceptable continence.

First the patient history, with concentration on past and present symptoms and conditions for urinary, bowel, sexual, and neurological functions and a systematic physical examination, is mandatory before further diagnostic tests should be initiated. A history of psychiatric illness should be investigated in all patients, especially those with no neuropathy, as those patients tend should be obtained to have poor outcomes from any surgical intervention. For those with a history of any bladder pathology.

Hypersensitivity in non-neuropathic patients indicates a probably unsuccessful augmentation, especially if intermittent catheterization is required afterward.

Additionally a 24-h bladder diary (recording should be done for three consecutive days) is strongly recommended to evaluate the underlying bladder dysfunction thoroughly. An assessment of the patient's quality of life (QoL) can be helpful because of the effect on QoL of any therapy used. For example, there is an easy and validated generic tool, known as Visual Analogue Scale (VAS), for symptom bother.

A urodynamic investigation should also be done. This is the only method that can objectively assess the (dys-)function of the lower urinary tract and therefore gives an objective indication to justify an operation. A cystoscopy to measure the bladder capacity (functional and anatomic) and to exclude any bladder malignancies or a subvesical obstruction is also advisable. After a bladder augmentation the upper urinary tract is at risk, so a complete evaluation of both upper and lower urinary tracts is required before treatment. IVU or renal ultrasonography of the upper urinary tract and serum creatinine and radioisotope renal studies provide information about total and differential renal function and the presence of upper tract obstruction.

Technique

Bladder Augmentation

The objective of augmentation enterocystoplasty is the construction of a low-pressure diverticulum, which will absorb the involuntary contractions and high pressures generated by the abnormal detrusor and increase both the capacity and compliance of the bladder.

Sigmoidocystoplasty and ileocystoplasty have become standard techniques, but there is renewed interest in alternative techniques due to the relatively high morbidity of intestinal cystoplasty.

The ideal ileal segment is 25 cm long and located 25 ± 40 cm from the ileocecal valve, as this produces the least metabolic disturbance. The ileal patch is always detubularized.

A sigmoid segment is generally detubularized as a straight patch or a cup patch and is the usual alternative to the ileum for a straightforward augmentation. The sigmoid has several advantages; its thick muscular wall, large lumen, and abundant mesentery guarantee adequate bladder capacity and maneuverability. The disadvantages of sigmoid cystoplasty are the higher risks of UTI due to the colonic commensal bacteria colonization, more mucus production, and a theoretically higher long-term risk of malignancy.

There are many different techniques described in the literature to avoid inclusion of intestinal mucosa in the urinary tract. Gastrocystoplasty, vesicomyotomy, seromuscular augmentation, and various alloplastic or biodegradable materials or in vitro cultures of autologous urothelium are only some of the possible options. Although encouraging animal and human results have been reported, each technique is associated with its own limitations and disadvantages. While intestinal cystoplasty remains the standard, several alternative techniques show promise, but only gastrocystoplasty, ureterocystoplasty, and seromuscular augmentation should be considered clinically useful.

Bladder Reconstruction

Only in case of bladder diverticula or in certain instances when the native bladder plate is too diseased and cannot undergo augmentation, there is need for bladder reconstruction with resection of the diverticulum or using a neobladder as a substitute.

Point of Interest

- In small children bladder augmentation is commonly performed with a colon/sigmoid segment. In children, colonic anastomoses are less prone to problems.
- Many different tissues and techniques to perform bladder augmentation. Standard: ileum cystoplasty.

Case Study

A boy of 16 years with ataxia telangiectasia and B non-Hodgkin's lymphoma developed at the age of 13 a severe hemorrhagic cystitis. The cause of the hemorrhagic cystitis was the medication with cyclophosphamide because of an allogenic stem cell transplantation. In addition he had to undergo a ureterocutaneostomy on both sides.

After 3 years the patient a bladder capacity of 50 ml was recorded; the ultrasound study showed both kidneys without any pathologic findings. Normal serum creatinine. No subvesical obstruction was detected in cystoscopy.

A bladder augmentation was planned with reimplantation of both ureters back into the augmented bladder to achieve better quality of life.

Augmentation was performed using an ileal W-shaped augment, of which both proximal lumens of the ileum were kept intact, whereas the rest was detubularized and afterward augmented to the remaining bladder wall. The proximal captured ureters of the former ureterocutaneostomy were implanted in an end-to-side, reflexive technique. (Please see below the figure X-ray documents, and the bilateral remaining ureters, which were not removed in the initial surgery when the ureterocutaneostomy was performed.)

At week eight the boy had a bladder capacity of 500 ml and was able to empty the bladder by voluntary voiding (no need for self-catheterization). The ultrasound study shows both kidneys and a residual free augmented bladder and normal serum creatinine. Normal serum creatinine.

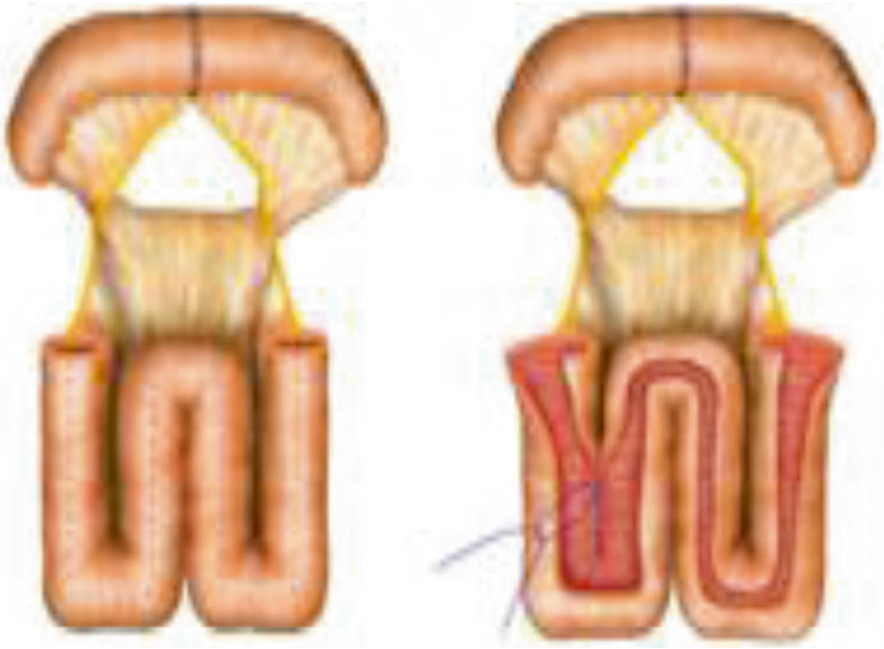

Figure 1a: Terminal Ilium positioned in a w shape which will be opened longitudinal to become the augment of the bladder (Figure 1b)

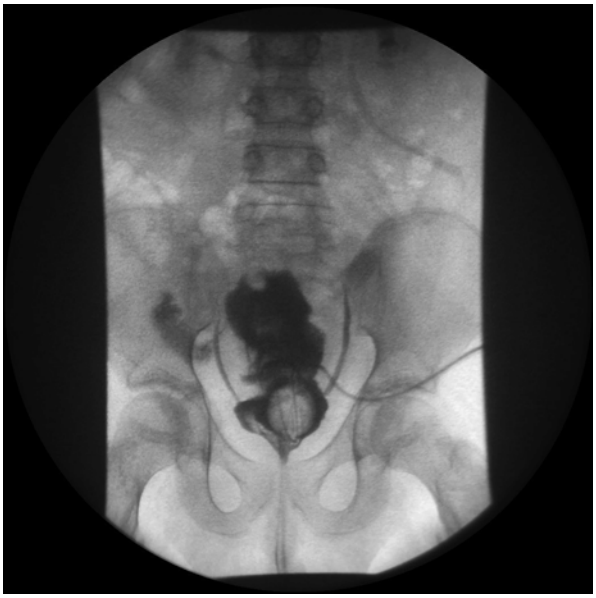

Figure 2: Xrays of the abdomen after augmentation

Different to this picture both ends (lumen) of 4–5 cm were kept intact to have the ureters of each side implanted in a side-to-end fashion.

The rest of the W was detubelarized and shaped to become the new dome of the remaining bladder.

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Chapter 12
Erectile Dysfunction

Emmanuel Weyne and Maarten Albersen

What Do the Guidelines Say?

The EAU guidelines on male sexual dysfunction were last updated in March 2013, now almost 2 years ago. Since no major changes have been pushed through in the evaluation and treatment of erectile dysfunction (ED) in the last 2 years, these recommendations remain valid and will be further commented on in this chapter. In line with the structure of this chapter, the main recommendations of the EAU expert panel include the following.

Background and Epidemiology

ED is a highly prevalent condition, especially in the aging male. ED is linked to various other diseases out of which, importantly, cardiovascular disease. While not included in this table, ED is further associated to lower urinary tract symptoms, which has important treatment implications in men suffering from both conditions.

	LE
Erection is a neuro-vasculo-tissular phenomenon under hormonal control.	2b
ED is common worldwide.	2b
ED shares risk factors with cardiovascular disease.	2b
Lifestyle modification (intensive exercise and decrease in BMI) can improve erectile function.	1b
ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
ED is common after radical prostatectomy, irrespective of the surgical technique used.	2b
ED is common after external radiotherapy and brachytherapy.	2b

E. Weyne, MD • M. Albersen, MD, PhD (✉)
Department of Urology and Andrology, University Hospitals Leuven, Leuven, Belgium
e-mail: maartenalbersen@hotmail.com

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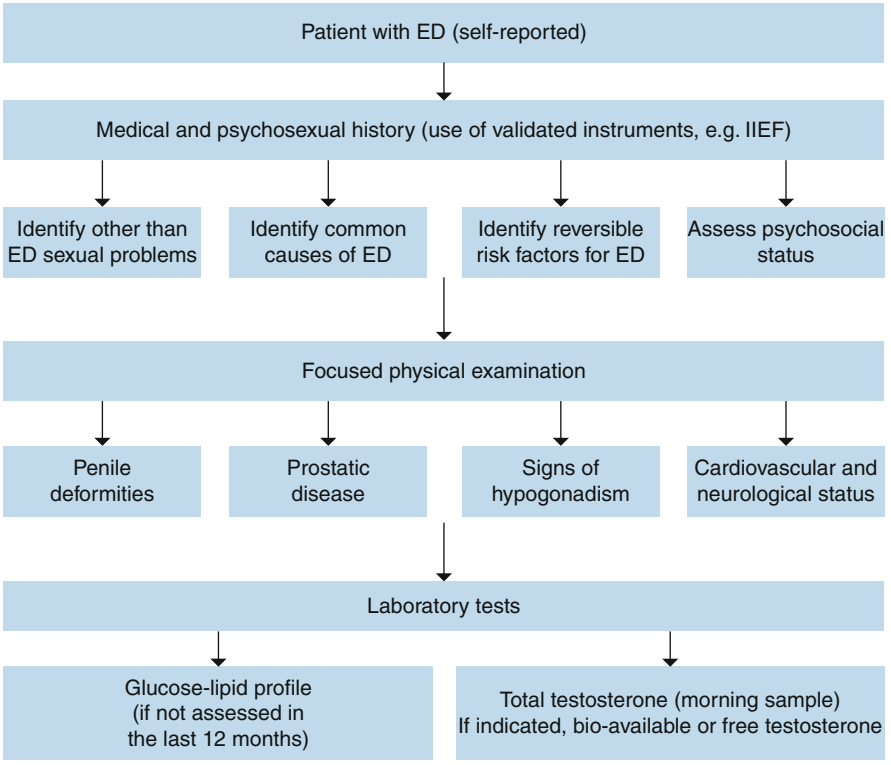
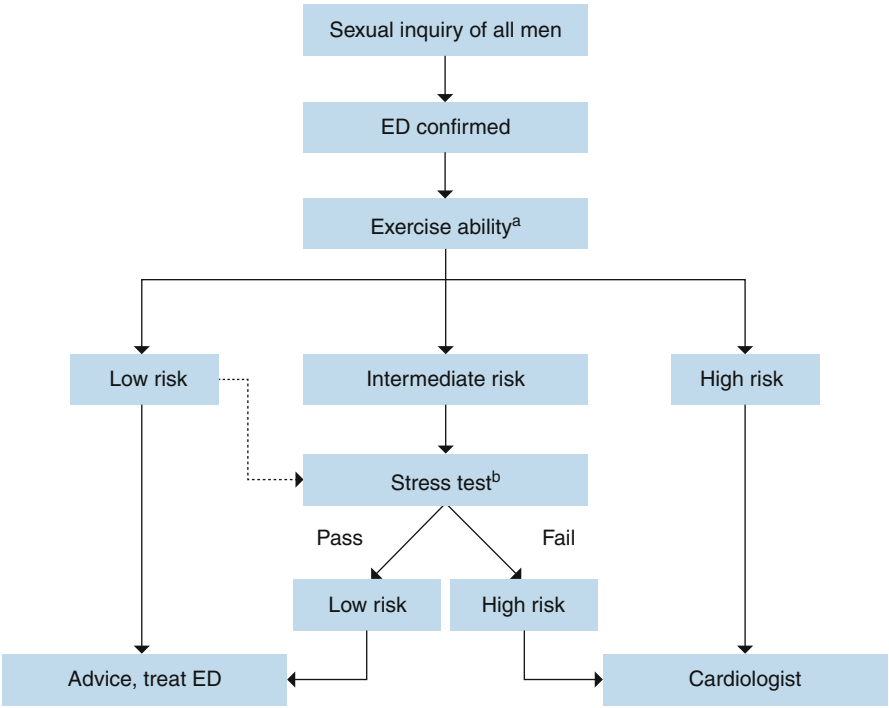
Clinical Practice: Diagnostic Evaluation

The diagnostic workup of ED patients consists not only of the identification of potential reversible causes for the ED but also includes an examination directed toward identifying underlying and comorbid conditions (diabetes, hypogonadism, prostatic diseases, and neurological or cardiovascular impairments) which should be treated separately.



Clinical Practice: Diagnostic Evaluation, Cardiovascular Risk Assessment

Patients who present with ED have a high prevalence of cardiovascular disease. ED precedes cardiovascular incidents by approximately 3 years and therefore the diagnosis of ED should trigger a cardiovascular risk assessment, which helps to triage those patients who need cardiologists' evaluation before continuation of ED assessments and treatment.



[a]*Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.*
[b]*Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.*

Clinical Practice: Diagnostic Evaluation Summary

	LE	GR
Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality.	3	B
Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED.	4	B
Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and lifestyle factors that can be modified.	4	B
Specific diagnostic tests are indicated by only a few conditions.	4	B

Clinical Practice: Treatment Summary

As a general rule of thumb, every patient presenting with ED can receive PDE5-inhibitors. Failure to respond to PDE5 inhibitors should trigger a discussion on correct use and further evaluation toward why this therapy is insufficient. Generally, vacuum devices, intracavernous injection therapy, and intraurethral applications of

alprostadil either in pellet form or in cream form are second choices if there is no response to initial oral therapy or whenever there are contraindications for PDE5 inhibitors use. The issue of penile rehabilitation strategies after radical pelvic surgery is debatable and whether or not treatment should be given as soon as possible after surgery does, in the opinion of the authors, does not warrant a grade A recommendation. This will be further discussed in this chapter. An excellent review on this issue is included in the suggested reading section at the end of this chapter. Low-intensity focused linear shockwave therapy is shortly discussed in the guidelines but evidence is limited and therefore this option was not included in the general treatment recommendation table.

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1a	A
Pro-erectile treatments have to be given at the earliest opportunity after RP.	1b	A
When a curable cause of ED is found, it must be treated first.	1b	B
PDE5Is are first-line therapy.	1a	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.	3	B
A VED can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

Background

Erectile dysfunction (ED) was defined by the NIH Consensus Development Panel on Impotence as the persistent inability to attain and maintain an erection sufficient for sexual intercourse. While premature ejaculation is probably the most prevalent, ED is without a doubt the most studied male sexual dysfunction and a highly prevalent sexual complaint in men presenting to their healthcare providers. Notwithstanding variations in definitions and methodology, various large-scale studies substantiate the high global prevalence of ED.

Epidemiology

The Massachusetts Male Aging Study (MMAS) is a prospective observational longitudinal study of health in randomly selected men. It investigates the effects of aging on male sexual health, among other domains. This landmark study reported a combined prevalence of minimal, moderate, and complete ED of no less than 52 % in US men. The prevalence of complete ED tripled from 5 to 15 % between subject ages 40 and 70 years. In the European Male Ageing Study (EMAS), a collaborative

effort of eight European centers investigating the effects of aging on general and sexual health in a male population aged 40–79 with a mean age of 60 years old, about one-third of the entire EMAS sample reported ED. The prevalence of ED was higher in the older age groups, peaking at 64 % in men over 70 years of age. However, it appears from the results of the EMAS study that although patients in older age groups are more frequently affected by the disease, they tend to be less bothered with the presence of ED. With the rapidly expanding aging population and the increase in life expectancy, an increase in the prevalence of ED is expected in the years to come. It is estimated that in 10 years, about one in ten men of the worldwide population will be older than 65 years of age. By then, the number of men suffering from ED will reach 322 million worldwide.

Comorbid Conditions and ED as a Harbinger of Cardiovascular Disease

While ED does not pose direct threat to physical health, it can have dramatic effects on personal sense of well-being and has a significant impact on the quality of life of patients and their sexual partners. Besides this impact, ED is also an independent predictor of cardiovascular morbidity and mortality. It is frequently postulated that "the penis is the antenna of the heart," and as such, the complaint of ED should always trigger further questioning and investigation to identify underlying cardiovascular disease or other comorbidities. These other comorbidities are often related to the cardiovascular risk profile and include diabetes mellitus, metabolic syndrome, and smoking. Iatrogenic ED is not uncommon and can be the result of pelvic surgical procedures or the use of various medications. Besides these underlying issues, it is of particular importance to the readers of this book to be aware that community-based, preclinical and clinical data demonstrate a strong and consistent association between LUTS and ED, suggesting that elderly men with LUTS should be evaluated for ED and vice versa. Therefore ED merits consideration from both the primary care physician and the specialist as an important health concern in se and as a potential sentinel for serious health conditions. In this chapter we will discuss the pathophysiology of erectile dysfunction in men and the essentials in ED evaluation and ED treatment.

Prerequisites for Normal Erections and Pathophysiology of ED

Sex drive is the initiator of penile erection, and therefore, intact libido, mood, and psychosocial circumstances are capital to normal erectile function. Penile erection requires neural transmission of pro-erectile impulses, being the efficacious delivery of the neurotransmitter nitric oxide (NO) to the smooth muscle in the corpus cavernosum. Furthermore, an intact arterial blood supply is key to supply the cavernous

erectile tissue with oxygenated blood. The end organ, the corpus cavernosum, should be in good health, containing healthy smooth muscle and being elastic to successfully expand and compress the subtunical venous plexus during the rigid phase of erection. Lastly, hormonal balance should be in order as testosterone is a key mediator of libido but also keeps the peripheral effectors, such as cavernous smooth muscle and cavernous nerves, in good shape. ED can develop as result of a failure in one of these systems or, as is commonly the case, a multilevel failure. ED is typically defined as neurogenic, vasculogenic, hormonal, anatomical/structural, drug induced, or psychogenic. A summary of prevalent causes of ED is given in Table 12.1.

Clinical Practice: Diagnosis

History Taking

ED is often multifactorial in origin and is therefore best managed with a holistic approach that includes lifestyle modification, pharmacological management, and importantly counseling of both the patient and his partner. It is of particular importance to encourage open and honest communication between the patient and his partner. All of the above are best facilitated in the context of a trusting patient/provider relationship. Therefore it is critical to establish a comfortable and confidential atmosphere when addressing issues in sexuality with patients. It can be recommended to display literature in the consultation – and waiting rooms indicating a private and nonjudgmental approach toward sexual dysfunctions and more specifically ED. Cultural and ethical beliefs can be a hurdle in communication on sexual functioning and this should be taken into account when evaluating the ED patient.

The initial evaluation of ED should include a complete medical, psychosocial, and sexual history. A thorough medical assessment is mandatory in the evaluation of erectile complaints, with the aim of identifying comorbid or underlying diseases.

Cardiovascular Disease

In the Princeton III consensus, a leading document on the relationship between ED and cardiovascular disease, it is stated that:

- ED not only shares risk factors with cardiovascular disease but also is, in itself, an independent marker of increased cardiovascular risk (ACCF/AHA class Ia).
- ED is a marker of significantly increased risk of cardiovascular disease, coronary artery disease, stroke, and all-cause mortality.

Table 12.1 Comorbid conditions and causes for ED

Vasculogenic	Cardiovascular disease; atherosclerosis
	Hypertension
	Diabetes mellitus
	Hyperlipidaemia
	Smoking
	Major surgery (retroperitoneum)
	Radiotherapy (retroperitoneum)
Neurogenic – central causes	Multiple sclerosis
	Multiple atrophy
	Parkinson's disease
	Tumours
	Stroke
	Intravertebral disk disease
	Spinal cord disorders
Neurogenic – peripheral causes	Diabetes mellitus
	Alcoholism
	Uremia
	Polyneuropathy
	Surgery (pelvis or retroperitoneum, radical prostatectomy)
Anatomical/structural	Peyronie's disease
	Penile fibrosis (following pelvic radiotherapy or pelvic surgery)
	Penile trauma (penile fracture)
	Congenital curvature of the penis
	Micropenis
	Hypospadias, epispadias
Hormonal	Primary hypogonadism (e.g., late-onset hypogonadism)
	Secondary hypogonadism/hypogonadotrophic hypogonadism (e.g., hyperprolactinemia)
	Hyper- and hypothyroidism
	Cushing's disease
Drug or substance induced	Antihypertensives (thiazides and beta-blockers are most common)
	Antidepressants
	Antipsychotics
	Antiandrogens
	Antihistamines
	Recreational drugs/smoking
Psychogenic	Generalized type (e.g., lack of arousability and disorders of sexual intimacy)
	Situational type (e.g., partner-related or performance-related issues or due to distress)

Table 12.2 Cardiovascular risk assessment in ED patients

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, <3 risk factors for CAD (excluding sex)	≥3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (>2, <6 weeks)	Recent MI (<2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD coronary artery disease, *CHF* congestive heart failure, *LVD* left ventricular dysfunction, *MI* myocardial infarction, *NYHA* New York Heart Association

Incident ED was found to be an independent marker of cardiovascular events (1.5× relative risk) and all-cause mortality (1.2× relative risk) additional to conventional risk factors (e.g., age, weight, hypertension, diabetes, hyperlipidemia, and cigarette smoking). Since ED commonly occurs in the presence of silent CAD, the complaint of ED should always trigger further questioning and clinical examinations aimed at the identification of underlying cardiovascular disease. Typically, a time window between ED onset and the occurrence of a coronary artery disease event is 2–5 years (class Ia); thus ED provides an excellent opportunity for cardiovascular risk reduction. It is thus evident that the ED patient is entitled to a thorough analysis of classical cardiovascular risk factors such as smoking, dyslipidemia, hypertension, and a positive family history for cardiovascular events. A cardiovascular anamnesis allows stratification of patients in low-cardiovascular-risk, intermediate-risk, and high-risk group and to identify those who need a cardiologist's evaluation before resuming sexual activity (see the flow diagram in "what do the guidelines say"). Cardiovascular conditions and their risk categories are detailed in Table 12.2.

Other Comorbidities

A detailed history taking on overall health status and general well-being can provide clues for the presence of conditions concurrent with, and contributing to, ED. More specifically, signs and symptoms of possible underlying conditions such as depression, diabetes, late-onset hypogonadism, metabolic syndrome, and medication/surgically induced causes of ED should be assessed. Furthermore, since there is a clear

relationship between LUTS and ED, an assessment of voiding function can be offered to patients presenting with ED. This can either or not be done with a questionnaire such as the international prostate symptom score (IPSS), as detailed elsewhere in this book. Information about the association between ED and tobacco use can be an important tool in helping patients decide to quit use of tobacco products. A thorough review of current medications may reveal agents that are known to cause or exacerbate ED (e.g., antidepressants, antiandrogens, thiazides, and β-blockers). It is also important to assess for use of nitrate donors, which are absolute contraindications for therapy with phosphodiesterase-5 (PDE5) inhibitors. The goal of history taking should not only be to understand the specific erectile condition but to also identify possible reversible or treatable underlying disorders.

Sexual History Taking and Questionnaires

An adequate sexual history should include information about current sexual relationships, the emotional status of the patient and the partner, and the exact nature of the particular sexual concerns unique to the couple. Issues of sexual orientation and gender identity should also be noted. Descriptive measures such as rigidity and duration of nocturnal erections, erections during masturbation, and erections following sexual arousal should be discussed, as they can give clues about the etiology of ED. The onset of the problem and any situational factors that ameliorate or exacerbate ED should be determined. In this regard, situational ED, sudden-onset ED, the persistent presence of nocturnal erections, and good erectile function during masturbation hint toward an important psychogenic component of the ED, whereas non-situational ED, ED with gradual onset, and loss of naturally occurring nocturnal erections are strong clues for a predominantly organic cause of the disease. Since a psychogenic component – such as performance anxiety – often superposes onto an organic cause, the distinction in real-life clinical practice may not always be this clear. Problems with arousal, ejaculation, and difficulty reaching orgasm should be discussed since these may be signs of concomitant sexual dysfunctions such as premature and retarded ejaculation or anejaculation and/or hypogonadism. The impact of ED and other sexual dysfunctions on both general well-being and sexual satisfaction should be discussed, as well as issues of partner interest in and satisfaction with sex. It is imperative that the healthcare provider taking the sexual history displays a nonjudgmental and open attitude toward the patient and his partner.

The use of validated questionnaires such as the International Index of Erectile Function (IIEF) can be useful as an “icebreaker” to initiate the conversation about ED. Numeric scores obtained from instruments such as this may also be helpful in assessing the severity of ED, in screening for other sexual dysfunctions, and in evaluating treatment outcome. These metrics, however, should not be regarded as a replacement for direct assessment of sexual history. The IIEF was developed by Raymond Rosen and coworkers and consists of 15 questions and is likely the most widely used self-reported inventory to provide a standardized measure of erectile function and assesses five separate domains at different stages of the male sexual

response cycle: sexual desire (2), erectile function (6), orgasmic function (2), intercourse satisfaction (3) and overall satisfaction (2). The IIEF score was shown to have strong internal consistency and adequate test-retest reliability. A five-item short form of the IIEF has been developed and validated along with a diagnostic classification into ED severity scales. This short form, also called the Sexual Health Inventory for Men (SHIM), or the IIEF-5, provides a rapid solution for standardizing ED severity assessment in daily clinical practice.

Clinical Examination

General Considerations Before Starting Clinical Examination

For many patients a first sexual clinical examination can be experienced as embarrassing and confronting, whereas others see it as a potential reassurance and relief. Therefore it is important to perform the exam in the most comfortable setting possible. This will not only lead to more comfort for the patient but will also yield more consistent and reliable clinical findings. Think about how stress augments the adrenergic tonus and can confound clinical examination for ED, especially in young men with a psychogenic factor. Explaining to patients upfront the course of the examination is important, as well as stressing how this will help to find a diagnosis and eventual treatment. If the patient is too stressed and unable to relax, deferring the examination is a good option. So when doing a sexual physical examination, it should, again, be performed in a quiet environment with the necessary attention for the concerns of the patient toward the exam.

Physical Examination in the ED Patient

General Non-genital Exam

The physical exam starts with a brief overall health assessment. This should include length and weight measurement to calculate body mass index (BMI) (kg/m^2). Waist circumference can serve as an alternative to counsel patients on risk of obesity and metabolic syndrome. Inquiring about pants size can easily follow this up. Blood pressure and heart rate must be measured if they have not been assessed in the previous 3–6 months. Palpation of peripheral pulsations and carotid auscultation can be performed. Physical proportions, pubic and general hair growth, pitch of the voice, and presence of gynaecomastia are assessed.

Neurologic Exam and Spinal Cord Reflexes

Tactile and pinprick sensation in the perineal and lower limb dermatomes can be assessed. Different reflexes can be tested to evaluate the integrity of the spinal cord

when abnormalities are suspected but this is not advised routinely. The perianal reflex or anal wink is the reflexive contraction of the external anal sphincter upon stroking the skin around the anus (S2–S4). The bulbocavernosus reflex consists of (firmly) squeezing the glans penis, resulting in the contraction of the bulbocavernous muscle located between the scrotum and anal sphincter (S2–S3). This reflex can be provoked in 70 % of healthy men, but the general validity of the bulbocavernous reflex has been challenged. By the same maneuver the bulbo-anal reflex can be assessed when squeezing the glans provokes a contraction of the anal sphincter (S3–S4).

Genital Exam

Penis

The penis should be checked for abnormalities. Flaccid penile size is variable but ranges from 5 to 10 cm. There is no standardized technique for measuring penile length but there appears to be consensus that penile length should be measured on the dorsum of the penis. A good technique has been described by Wessells where the patient is evaluated in supine position. The glans is grasped and pulled to full stretch at 90° from the plane of the body. A rigid ruler can be used to press down on the fat pad to the pubic bone, and then the penis is measured dorsally to the corona or meatus depending on physician preference. The penis may seem smaller in obese men because it is partially buried in the prepubic fat (buried penis). A very short penis or micropenis can be seen in a number of genetic disorders with hypogonadotropic/hypergonadotropic hypogonadism or androgen resistance, e.g., Klinefelter and Kallmann syndromes. The glans should be inspected for any scars, ulcers, nodules, or sign of inflammation (balanitis). To inspect for urethral discharge, open the meatus by compressing the glans gently between index finger and thumb. The foreskin should be checked for phimosis, a condition in which the foreskin cannot be retracted over the glans. Sometimes a short frenulum (frenulum breve) is observed that can be bothersome for adolescents during intercourse and causes a ventral deviation of the glans in erect state. The penis should be palpated to detect fibrous plaques lying under the skin that indicate Peyronie's disease. In most cases they can be found on the dorsum of the penis and are accompanied with a curvature during erection. Correct assessment of penile curvature can only be done during the rigid phase of erections. This implies that the physician either injects the penis with a vasoactive drug like alprostadil in the office or relies on pictures taken by the patient at home. While photographic images of the erect patients are most often sufficient, the examination of a pharmacological-induced erection can be helpful in the planning of (complex) surgery or for the detection of venous leak by duplex ultrasound.

Testes

Bilateral positioning of normal-sized testis in the scrotum should be confirmed. If one or more testes are absent, the patient has maldescended testis or cryptorchidism. In 90 % of the cases, the undescended testis can be palpated in the inguinal canal.

Sometimes it can be difficult to distinguish an undescended testis from a retractile testis. In the latter case the normal testis is normally developed but is pulled up by the cremasteric reflex during clinical examination. Retractile testes are more common than truly undescended testes and do not require operation. These problems, however, are rarely primarily found in adult life. A normal testicular volume is between 12–20 ml and can be measured using an orchidometer or ultrasound. Small, firm testes can be found in Klinefelter syndrome. The testis should be palpated to look for nodules or masses. A painless testicular swelling can constitute of a hydrocele that is typically clear on transillumination.

Digital Rectal Exam

There is a strong relationship between LUTS due to BPH and sexual dysfunction. Therefore, it is suggested that men with LUTS should be evaluated for SD and vice versa. Furthermore it is not uncommon for medical treatment for BPH to cause ED, ejaculatory dysfunction, and sexual desire impairment. A rectal examination should be performed in every patient older than 40 years. Furthermore digital rectal examination is advised in all men who may be possible candidates for testosterone replacement therapy. DRE can assess the form and size of the prostate that is enlarged in BPH. The presence of noduli or a firm irregular zone warrants further investigations for prostate cancer.

Physical Exam in Patients with Suspected Hypoganidsm

The signs and symptoms of hypogonadism vary depending on age of onset, duration, and severity of testosterone deficiency. Prenatal or prepubertal onset leads to delayed or incomplete sexual development and absence of secondary sex characteristics: small genitalia, failure to achieve muscle mass in spite of vigorous exercise, lack of a beard, and failure of the voice to deepen. Furthermore an eunuchoid proportion can be seen in prepubertal hypogonadism; the lower body segment (floor to pubis) is more than 2 cm longer than upper body segment (pubis to crown) and the arm span is more than 5 cm longer than height. In adolescents the development of appropriate sexual maturation according to age can be assessed by the Tanner scale. Patients with Klinefelter syndrome typically have small firm testes. In patients with postpubertal onset, clinical examination reveals a loss of pubic and axillary hair growth, a decreased muscle mass and increased waist circumference, gynecomastia, and small or shrunken testes. Hyperprolectinemia due to a prolactinoma of the pituitary gland can be accompanied by galactorrhoea or visual field defects (bitemporal hemianopsia) in rare cases.

Laboratory Testing

Recommended laboratory tests include a complete blood count and measurements of fasting serum glucose, a lipid profile, and free and total testosterone, particularly

in patients with signs of hypogonadism. Additional hormonal testing is only required when low testosterone levels are detected. Baseline PSA screening is advised in patients over 40 years of age or when ED is accompanied by lower urinary tract symptoms.

Specific Diagnostic Testing

Radiological testing, nocturnal penile rigidity testing, vascular and neurological functional testing, and penile Doppler ultrasound are available for further diagnostic workup of ED. These tests are not routinely indicated in the primary care setting but may be ordered by urologists or sexual medicine specialists in certain cases. Specifically in young men with primary ED, history-specific investigations such as intracavernosal injection of vasoactive drugs with color Doppler or duplex of the penile arteries may be helpful to rule out vascular etiology of ED, which may be correctable. Furthermore, color Doppler ultrasound and duplex sonography may assist in diagnosing venous leakage in specific clinical situations. Nocturnal penile tumescence (NPT) measurements have been used in the differential diagnosis of organic ED vs. psychogenic ED but nowadays have no role in the routine evaluation of ED.

Clinical Practice: Treatment

General Considerations before Starting Pharmacological Treatment

Both the patient's and partner's understanding of ED and results of the diagnostic tests should be reviewed before treatment is initiated so that a rational selection of treatment options and expectations can be provided. Current pharmacological treatments for ED do not "cure" ED but can generally be relied upon to greatly improve erectile function. Setting realistic treatment goals and granting permission and legitimacy to alternative means of sexual intimacy that do not rely on penetrative sexual intercourse should be a goal of therapy. Few ED patients will be able to regain full medically unassisted potency, but most should be able to experience restoration of satisfying sexual encounters, either with or without the use of pharmacotherapy.

Underlying reversible conditions (obesity, medical comorbidities, relationship issues) should be addressed and treated before or simultaneously with initiating specific ED-directed treatment. Lifestyle changes such as exercise and smoking cessation should be suggested where applicable. Referral to exercise physiologists, nutritionists, or personal trainers may be of some benefit in these situations. For the treatment algorithm in the EAU guidelines, please see the section "what do the guidelines say."

Pharmacological Treatment: Phosphodiesterase Type 5 Inhibitors

PDE5-specific inhibitors (PDE5-inhibitors) are nonhydrolyzable analogs of cGMP and exert their beneficial effects on smooth muscle relaxation by binding and blocking the catalytic site of this enzyme. By inhibiting the degradation of cGMP, these drugs produce an intracellular accumulation of cGMP in smooth muscle cells lining the walls of the arteries and arterioles perfusing the spongy tissue in the corpus cavernosum, resulting in relaxation of these smooth muscle cells, increased blood flow, and penile tumescence only when there is a release of endogenous NO or, in other words, only during sexual stimulation or arousal.

In current treatment guidelines, PDE5-inhibitors are recommended as the preferred first-line pharmacotherapy for ED. Several trials have established on-demand efficacy rates of 60–70 % in the general population, and postmarketing data confirms excellent safety profiles of the four compounds currently available (sildenafil, vardenafil, tadalafil, and avanafil). The currently available drugs differ from each other in time to onset of action and duration of action (sildenafil and vardenafil up to 5 h, avanafil somewhat longer and with a rapid onset of action, and tadalafil up to 24–36 h). The choice of appropriate drug is based on patient and partner preference guided by physician advice.

Before initiation of treatment, patients should be informed that sexual stimulation is essential for the efficacy of the drugs. The most common reason for PDE5-inhibitor failure is incorrect usage and therefore this information can change the outcome of the therapy. In general, it is recommended to start with the highest dose available and lower the dose according to effects and side effects. The unique pharmacokinetic properties of tadalafil have led to the approval of this drug as a daily treatment for ED at 2.5- and 5-mg doses; this regimen may be best for patients who have frequent intercourse or those who desire to separate the act of taking the drug from sexual interactions. Furthermore, as detailed below, men with concomitant LUTS and ED are good candidates for daily dosing of PDE5-inhibitors as there is a good effect of these drugs on both complaints.

Phosphodiesterase 5 inhibitors are relatively contraindicated in patients with unstable angina pectoris, recent myocardial infarction, certain arrhythmias, and poorly controlled hypertension. As stated above, according to the Princeton III consencus, these patients should undergo cardiovascular examination and treatment for their heart-related condition before initiating ED treatment. Furthermore, patients treated with nitrates or nitrate donors should not take PDE5Is, and use of PDE5Is with certain α-blockers may result in postural hypotension.

The most common adverse events from PDE5 inhibitors include headache, facial and ocular hyperemia, nasal congestion, myalgia, dyspepsia, and back pain. Congestion and flushing are more common with sildenafil relative to the other PDE5 inhibitors, whereas myalgias and dyspepsia are more strongly associated with tadalafil and vardenafil, respectively.

Of the patients who do not experience an initial response to PDE5 inhibitors, a large proportion may be converted to responders through counselling on proper dosing technique and through dose escalation. Some others can be converted to responders by switching from an on-demand dosing to the daily regimen. Since the efficacy of PDE5 inhibitors depends on the integrity of the NO pathway and the endogenous bioavailability of NO, patients in whom this pathway is disturbed will benefit far less from PDE5 inhibitors compared with the "general" ED population. Disease states that diminish NO availability include denervation of the erectile tissue after radical prostatectomy, severe diabetes, and downregulation of NOS expression, as may be seen in atherosclerosis, metabolic syndrome, aging, and hypogonadism.

Pharmacological Treatment: Intracavernous Injection of Vasodilating Compounds

Before the advent of PDE5Is, intracavernous and intraurethral administration were the only nonsurgical treatment options for ED. Prostaglandin E1 or alprostadil is the most commonly used compound and exerts its effects independent of the NO-cGMP pathway, making this treatment an excellent option for patients who do not experience response to PDE5 inhibition. Intracavernous PGE1 therapy has relatively high rates of satisfaction if the patient is well counselled and knows what to expect. Papaverine is also available for intracavernous injection, although its role is limited to combination therapy (commonly referred to as bimix or trimix). Similarly, vasoactive intestinal polypeptide and phentolamine are, either or not combined, available in some countries for intracavernous injection therapy. Alprostadil is also available for intraurethral administration as a pellet (medicated urethral system for erection [MUSE]) and is currently being launched in cream to be applied in the urethral meatus.

Adverse events from these therapies include priapism, variable degrees of pain with injection in approximately half of patients, and penile fibrosis after long-term use. Each drug has their own adverse event profile, and therefore the drug of choice is tailored to the patient's and physician's preference and experience. A healthcare provider should be present to instruct patients on the proper technique of intracavernous drug administration, to determine an effective dose, and to monitor patients for side effects, especially prolonged erection. Patients are advised to consult their physician if they experience prolonged penile pain or an erection lasting up to or more than 4 h, because aspiration of cavernous blood may be necessary for penile decompression. Patient education and timely follow-up will likely decrease the occurrence of improper injection and treatment failure. Relative contraindications to injection therapy include a history of priapism or bleeding disorders. Before initiation of therapy, patients follow a short in-office training program. MUSE and meatal application of PGE1 cream have side effects in common with intracavernous

PGE1, although they are less likely to cause priapism and may have marginal efficacy in many cases. Topical application of PGE1 and MUSE are both associated with urethral burning or pain and vaginal irritation in the partner, and condom use can therefore be considered.

The Vacuum Erection Device

For some patients this may be a primary option, for example, those not willing to use drugs or those who have contraindications. It is also a good option for patients who suffer from veno-occlusive dysfunction, who may not benefit from PDE5 inhibitors or injection therapy. This device creates negative pressure around the penis, thereby initiating passive engorgement of the sinusoidal spaces and creating an erection. Maintenance of erection is facilitated by application of a rubber cuff worn around the base of the penis. Although effective in up to 90 % of patients, the resulting cold and congested penile erection renders this option unattractive to many, especially younger patients. Some patients will prefer the purchase of the VED as this is a one-time investment, whereas this is not the case for pharmacological treatments. Side effects are relatively minor and include bruising, some discomfort, and ejaculatory obstruction. It is advised to limit the use of the constriction band to 30 min to avoid skin necrosis.

Surgery

Implantation of a penile prosthesis, which can be either inflatable or malleable, is indicated for men in whom pharmacologic therapy is not effective. Noninflatable penile prostheses have the advantages of lower cost, better mechanical reliability, and ease of use by the patient. On the other hand, inflatable devices resemble best the natural states of flaccidity and erection. Patient education about inflation and deflation techniques is not necessary. The surgical technique is quite straightforward and an absolute antiseptic approach is imperative. Implantation of a penile prosthesis has satisfaction rates of 70–90 %, but patients should be aware of the definitive and irreversible nature of this surgery; that is, when the patients is not satisfied or complications occur, after removal of the device, other therapeutic options are not effective anymore. Adverse events include mechanical failure after several years of use, 6–16 % at 5 years (depending on the type of device) and up to 50 % after a 10-year interval, infection (1–3 %), and, rarely, erosion. Patients should be aware that penile shortening is not uncommon. For the prevention of adverse outcomes, perioperative prevention of infections is key; therefore the patient should be free of urinary tract infection, and he should have no infections elsewhere. Wounds, cutaneous lesions, and dermatitis in the operative field should be healed before surgery, and antibiotics providing Gram-negative and Gram-positive coverage should be administered preoperatively and

continued for 24–48 h postoperatively. Shaving and skin preparation is done immediately before surgery and a no-touch technique can be employed.

Other surgical options available for ED include penile revascularization and venous ligation. Outcomes of these surgeries in the general population of patients with ED are poor. These surgeries should be reserved for a select group of primarily young patients and should be performed in specialized centers only.

Specific Treatment Situations

Lower Urinary Tract Symptoms and ED

A strong and independent association between LUTS suggestive of BPH and ED has been widely evidenced in several clinical epidemiologic studies. They share pathophysiological mechanisms which may include microvascular disease impairing the function of pelvic innervation, (macro)vascular disease inducing chronic pelvic ischemia, increased andrenergic tonus, and decreased NO signalling. Although the efficacy of the most commonly used treatments for LUTS/BPH is well defined, the negative impact of these treatments on sexual function – in particular, on ED – has triggered the search for new treatment options. Tadalafil is now the most extensively investigated PDE5 inhibitor which has proven efficacy both on LUTS and ED, when administered in a daily fashion, in men displaying both these complaints. It is now recommended in the EAU guidelines that this option is to be considered in this specific patient population.

Premature Ejaculation and ED

It has been postulated by the expert panel on PE treatment of the international society for sexual medicine (ISSM) that in PE developing secondary to other conditions, the underlying condition should be treated first. Therefore, in patients who suffer from both these male sexual dysfunctions, ED should be treated first and then the effect on PE should be reevaluated.

Peyronie's Disease and ED

When a penile plaque or curvature is diagnosed during the workup of ED, both conditions should be thoroughly discussed with the patient. In essence, ED is a problem associated with Peyronie's disease and all typical treatment options for ED are acceptable. The efficacy of PDE5 inhibitors in Peyronie's disease patients seems to be similar to that in "general" ED patients. Two phases of the disease can be distinguished. The first is the acute inflammatory phase, which may be associated with pain. The second is the fibrotic phase, identified by formation of hard palpable

plaques that can be calcified, which results in disease stabilization. With time, penile curvature is expected to worsen in 30–50 % of patients or stabilize in 47–67 % of patients. Spontaneous improvement has been reported by only 3–13 % of patients and is more likely early in the disease. Pain tends to resolve with time in 90 % of men, usually during the first 12 months after disease onset. In the acute phase, no oral or local therapies are recommended as the results of the studies on conservative treatment for Peyronie's disease are often contradictory because of several methodological problems that make it difficult to provide recommendations in everyday real life. In spite of this, many different treatments such as oral vitamin E and Pentoxifylline are used in everyday clinical practice. Daily dosing of PDE5 inhibitors has been shown in small unpublished series to have a beneficial effect both on ED and on PD severity and curvature. Results of studies in larger peer-reviewed series are awaited before any definitive conclusions can be made on this treatment. The role of conservative (nonsurgical) treatment in men with stable/chronic disease has not yet been adequately defined. Recently, local injection of collagenase, combined with manipulation of the plaque, has shown benefit in large-scale phase 2 and 3 trials which has led to the recent approval of collagenase for the treatment of Peyronie's disease both in Europe and the USA. Other options include surgical options, which include tunical plication procedures, Nesbitt's procedure, and plaque incision or excision and grafting. Grafting procedures have been associated with worsening of ED, and therefore, concurrent placement of an inflatable penile prosthesis should be considered in the patient with severe Peyronie's disease curvature and ED. The main indication for surgery is Peyronie's disease in which the curvature hinders sexual intercourse.

ED Following Radical Pelvic Surgery (Radical Prostatectomy)

(Temporary) denervation of the smooth muscle and endothelium in the penis is believed to have detrimental effects on the quality of the erectile tissues via the loss of spontaneous nocturnal and sexual activity-induced diurnal erectile activity. This renders the penis in a continuous flaccid state and exposes the tissues in the corpus cavernosum to a chronic state of relative hypoxia. This relative hypoxia is believed to result in apoptosis of endothelium and smooth muscle and subsequently fibrosis by activation of pro-fibrotic cytokines such as transforming growth factor beta. The concept of "penile rehabilitation" following radical prostatectomy was invented by Montorsi and colleagues and describes the theoretical benefits of penile oxygenation at regular intervals. Initially, a trial showed benefit of 3× weekly dosages of intracavernous vasoactive substances on recovery of spontaneous erectile function in a small cohort of patients. Initial studies testing the same concept with regular (daily) dosing of PDE5 inhibitors were positive on the effects of orally administered penile rehabilitation therapy, but the conclusions of these studies have to be interpreted with caution as a result of methodological flaws. Later, two large-scale randomized, double-blind, double-dummy designed studies comparing daily dosing with tadalafil of vardenafil with dosing

on demand showed no beneficial effects of regular dosing, and primary endpoints of these studies were not reached. Thus, despite many well-designed studies attempting to demonstrate efficacy of rehabilitative approaches, there currently is not enough evidence to incorporate it into the standard of care in the post-prostatectomy patient to rehabilitate erectile function. On the other hand, no significant harm of rehabilitation has been demonstrated provided the patients understand the side effects and costs of the proposed treatment. It is generally assumed that penile rehabilitation should be initiated early after the surgery, and therefore it is essential to discuss the option of a penile rehabilitation regimen with the patient prior to the surgery. As there is no clear benefit of one strategy over another, it is up to the discretion of the patient, supported by objective information provided by the surgeon, what rehabilitation strategy is most appropriate in each individual situation. In addition, we do believe that appropriate counselling and sexual rehabilitation is essential after pelvic surgeries resulting in ED. However this "sexual rehabilitation" should consider not only penile rehabilitation (if desired) but also psychosexual counselling and guidance for the couple to get their sex life back on track, being it either or not with the use of penetrative sex.

Points of Interest

- ED is a prevalent condition and the most common sexual complaint in men consulting their healthcare provider.
- ED is related to various comorbid conditions including diabetes, hypogonadism, prostatic diseases, and neurological and cardiovascular impairments.
- ED is the antenna of the heart: ED precedes cardiovascular incidents by approximately 3 years. Therefore, every ED patient should get a cardiovascular risk assessment and, if necessary, a referral to the cardiologist for further examination.
- Evaluation of the ED patient should be holistic and include the partner. Primary focus is the symptom of ED but also identification of underlying diseases if present.
- Treatment of the ED patient starts with counseling and setting realistic expectations.
- A trial with phosphodiesterase type 5 inhibitors is the first choice in most patients and should be preceded by a discussion on correct usage and the need for sexual stimulation in order to have an effect.
- Second- and third-line options are intracavernous and intraurethral administration of vasoactive substances and implantation of a penile prosthesis.
- Primary ED, ED post-radical prostatectomy, ED in Peyronie's disease, ED in patients with premature ejaculation, and ED in patients with lower urinary tract symptoms need specific adaptations in diagnostic and therapeutic approach.

Further Reading

Albersen M, et al. The future is today: emerging drugs for the treatment of erectile dysfunction. Expert Opin Emerg Drugs. 2010;15(3):467–80. A review on what to expect from the future therapies for ED.

Corona G, et al. EMAS Study Group. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). J Sex Med. 2010;7(4 Pt 1):1362–80. One of the capital studies on the epidemiology of ED.

Fode M, et al. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int. 2013;112(7):998–1008. Mikkel Fode and coworkers critically revise the evidence for post-prostatectomy penile rehabilitation and conclude that better documentation for current penile rehabilitation and/or better rehabilitation protocols are needed: "One must be careful not to repeat the statement that penile rehabilitation improves erectile function after RP so many times that it becomes a truth even without the proper scientific backing."

Lue TF. Erectile dysfunction. N Engl J Med. 2000;342(24):1802–13. Excellent review on all aspects of ED by one of the pioneers of ED research.

Nehra A, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78. The Princeton III consensus: first emphasizing the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED, and second highlighting the link between ED and CVD, which may be asymptomatic and may benefit from cardiovascular risk reduction.

Chapter 13
Retention and Bladder-Emptying Disorders

Victor Nitti and Aqsa Khan

Background

Incomplete bladder emptying and urinary retention can cause a number of bothersome lower urinary tract symptoms including voiding symptoms (hesitancy, slow stream, incomplete emptying), storage symptoms (frequency, nocturia, incontinence, urgency), and urinary tract infections. In more severe cases of urinary retention and elevated bladder storage pressures, upper urinary tract decompensation can result. To properly understand the myriad of disorders that can cause urinary retention, it is important to have an understanding of the anatomy and voiding physiology. In essence, bladder-emptying disorders can result from bladder outlet obstruction, detrusor underactivity, or a combination of both.

In this review we aim to discuss the physiology of voiding and the pathophysiology and causes of incomplete emptying, to better define the difference between detrusor underactivity and bladder outlet dysfunction. We will also discuss algorithms for diagnosis and management of patients with incomplete emptying.

Physiology and Pathophysiology

Physiology of Voiding

Voiding physiology is complex and multifactorial with neurologic, endocrine, muscular, and cognitive components (Fig. 13.1). In its resting state, urine

V. Nitti, MD (✉) • A. Khan, MD
Department of Urology, New York University, New York, NY, USA
e-mail: Victor.Nitti@nyumc.org

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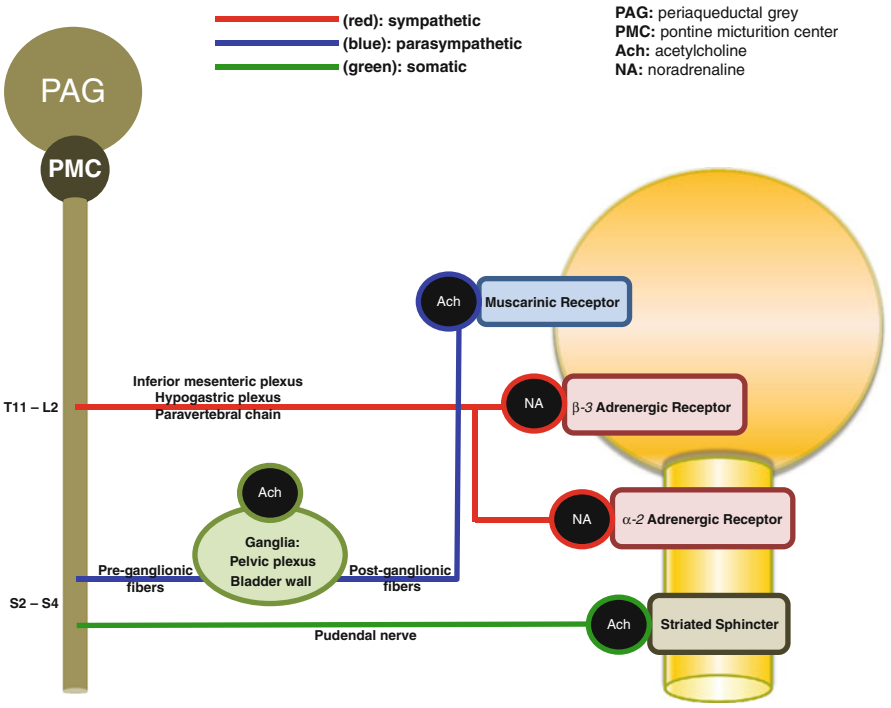

Fig. 13.1 Physiology of voiding

storage in mediated by the sympathetic nervous system, with stimulation of beta-3 adrenergic receptors that relax the bladder smooth muscle and the alpha-1 receptors to contract urethral smooth muscle. Somatic motor neurons travel through the pudendal nerve to innervate and maintain contraction of the external urethral sphincter striated muscle. Once there has been adequate filling, there is an increase in intensity of the afferent input via the pelvic nerves, which then stimulates the spinobulbospinal reflex pathway to activate the pontine micturition system. The parasympathetic system is thereby activated, reflexively inhibiting the sympathetic and somatic systems, resulting in relaxation of the outlet and stimulation of M3 muscarinic receptors to induce detrusor contraction. Additionally, there are other less studied cerebral pathways involving the periaqueductal gray matter and cognitive brain centers that influence sensation and voluntary voiding.

Ultimately, in order to properly empty, the bladder needs to generate a contraction strong enough to overcome the resistance of the outlet. Problems with this coordination, either caused by dysfunction of the bladder due to a reduction in the strength and/or duration of a detrusor contraction (detrusor underactivity), the outlet due to increased resistance or obstruction (bladder outlet obstruction), or both can cause incomplete bladder emptying.

Pathophysiology of Incomplete Bladder Emptying

Dysfunction of the outlet causing obstruction has been well studied. Chronic outlet obstruction has been associated with many changes to the morphology of the bladder, including changes to the extracellular matrix, electrical gap junctions, and smooth muscle enzymes and mitochondria. Obstruction has been shown to lead to a rapid hypertrophy of the bladder smooth muscle and an increase in collagenous connective tissue deposits, but with decreased myosin concentration, which ultimately results in a decreased force of contraction. It is theorized that obstruction results in acute ischemia, thereby affecting all components of the bladder that embody its viscoelastic properties (epithelium, connective tissue, vasculature, and smooth muscle), resulting in acute muscle dysfunction. The degree of dysfunction is thought to be related to the degree of tissue hypertrophy and not necessarily the duration of the obstruction. However, the bladder has amazing ability to regenerate and has shown evidence of recovery as early as fourteen days after obstruction.

Primary dysfunction of the bladder without obstruction, on the other hand, is not as well understood. A number of changes have been found to impact the bladder secondary to aging, ischemia, and comorbidities. Diabetic neuropathy has been shown to affect the innervation to the bladder, dull the sensory input, and induce changes to the physiology of detrusor smooth muscle. In cases of chronic overdistention, there can also be subsequent reversible or irreversible changes to the detrusor muscle cells. Studies focusing on the effect of aging on the bladder have demonstrated decreased ratios of detrusor muscle to collagen and changes in the quantity of muscle and collagen with aging.

A number of theories exist to try to explain the development of bothersome symptoms from incomplete bladder emptying. It has been postulated that the detrusor is organized into circumscribed modules controlled by a peripheral myovesical plexus, interstitial cells, and intramural ganglia. Bladder outlet obstruction may cause reduced blood flow, causing a transient or permanent ischemia that then affects sensitive nerve terminals and leads to denervation to certain modules. Supersensitivity then develops in the affected muscle modules, causing a reflexive excitation. Eventually the denervation progresses to an extent that the detrusor no longer functions and decompensates. These secondary changes that occur may explain why treatment will not always cause a resolution of symptoms. Other studies looking at smooth muscle proteins Connexin 43 and 26, the most predominant subtypes in the bladder, have found that increased fluid pressure from urine retention caused four- to fivefold increase in their levels, noticed as early at 7–9 h after obstruction. There have also been found to be increases in alpha-1 adrenergic receptor subtypes, particularly subtype alpha-1 d, now being identified as having a marked role in the development of irritative symptoms that are associated with bladder outlet obstruction.

Definitions Related to Urinary Retention and Bladder-Emptying Disorders

It is important to emphasize the value of having a common understanding of the terminology for purposes of reporting results and developing guidelines for treatment. The International Continence Society produced a report in 1988 to standardize definitions for a variety of lower urinary tract symptoms and conditions, which has subsequently been updated a number of times. Most recently in 2002 they published an updated report including urodynamic study findings. Appendix 1 reviews definitions from the report as they pertain to retention and bladder-emptying disorders.

"Lower urinary tract symptoms (LUTS)" now serves as a global term that applies to the variety of symptoms that may be representative of any bladder, urinary outlet, pelvic floor, endocrine, or neurologic abnormalities related to storage of urine and voiding. We are discovering that LUTS have a similar prevalence between men and women, and this prevalence increases in both groups with age. The EPIC study, a large multicenter survey study of 19,165 individuals 18 years or older in five countries using the 2002 ICS definitions for LUTS, found 64.3 % reported of at least one lower urinary tract symptom, with higher prevalence of storage symptoms in women compared to men (59.2 % vs. 51.3 %) and the opposite was true for voiding symptoms (men vs. women 25.7 % vs. 19.5 %). The overall presence of overactive bladder symptoms was 11.8 %, and the rate increased with age in both men and women.

Causes of Incomplete Bladder Emptying

Multiple potential sources contribute to incomplete bladder emptying (Fig. 13.2) and can be differentiated into dysfunction of the bladder or dysfunction of the bladder outlet.

The ICS 2002 defines detrusor underactivity (DU) as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span." A movement toward the use of the term "detrusor underactivity (DU)" has been advocated to encompass this spectrum of diseases and to replace prior terminology used such as "impaired detrusor contractility," "underactive bladder," "detrusor areflexia," "hypotonic bladder," and "detrusor/bladder failure." Detrusor underactivity is impressed upon because it places the focus of the condition more on the symptoms rather than the etiology, which, as we will discuss, are broad and quite variable, resulting from neuropathic, myogenic, or pharmacologic sources. Currently there is not an accepted definition for the clinical syndrome associated with DU. It has been suggested that the term underactive bladder (UAB) syndrome could be applied to the "clinical syndrome that accompanies detrusor underactivity." The problem with this definition, as opposed to the overactive bladder syndrome (OAB), is that the symptoms associated with DU are variable and nonspecific. Osman et al. suggested that UAB

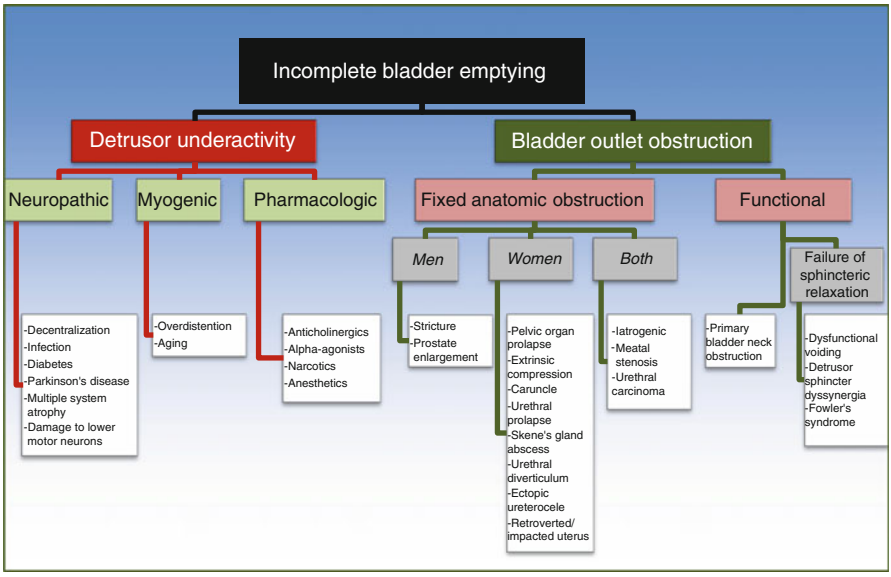

Fig. 13.2 Causes of incomplete bladder emptying

could be defined as "reduced sensation of the need to void (the opposite of urgency) that may be associated with frequency and nocturia or reduced voiding frequency often with a feeling of incomplete bladder emptying and incontinence that may predominate at nighttime." This definition has its obvious limitations.

Bladder outlet dysfunction, also coined as "bladder outlet obstruction (BOO)," may be a result of a fixed anatomic obstruction. Less obviously, it may be due to a functional abnormality in which no distinct structural abnormality is present, but rather the patient "functionally" has obstruction due to a neurological, myogenic, or psychological condition.

Detrusor Underactivity (DU)

Neuropathic Causes Medical conditions including diabetic neuropathy and infections with HIV, herpes simplex virus, tertiary syphilis, or post-infectious polyneuritis causing Guillain-Barre are known to be causes of impaired detrusor function from neurological dysfunction. Parkinson's disease is routinely found to cause detrusor overactivity but has been demonstrated to present with detrusor underactivity or acontractility. This has also been demonstrated in patients that suffer from upper motor neuron damage, particularly with hemorrhagic or cerebellar infarcts. Other spinal pathology primarily involving damage to lower motor neurons exiting from the lumbosacral vertebrae or sub-sacral lesions, such as from spinal cord injury, multiple sclerosis, trauma, or pelvic surgery, may result in detrusor underac-

tivity or areflexia or poor urethral sphincter function. Consideration should also be given to cases of disk herniation, spinal stenosis, myelodysplasia, and cranial or spinal arteriovenous malformations as possible contributors.

Myogenic Causes As discussed previously, it is postulated that ischemic detrusor denervation subsequently affects the entire myovesical plexus. The normal process of aging has also been associated with morphological changes to the detrusor muscle. Urodynamic studies have noted a loss of bladder contractility and voiding efficiency with increasing age. MRI imaging of the inula, the brain center that is responsible for processing visceral sensation, notes a diminished response to bladder filling in aging asymptomatic humans. In cases of chronic urinary retention, prolonged overdistention of the bladder results in changes to smooth muscle contractile function.

Pharmacologic Causes Pharmacological influences on voiding are known to be very powerful. Despite their use for lower urinary tract symptoms, antimuscarinics may be overly effective in inhibiting detrusor function, resulting in incomplete emptying. Other classes of medications that impact bladder emptying include narcotics and alpha-agonists (phenylephrine, pseudoephedrine, clonidine).

Numerous studies and case reports have found asymptomatic or symptomatic postoperative urinary retention (PUR) following administration of regional or general anesthesia. Soon et al. reported a rate of urinary retention of 39.3 % and UTI in 24 % of patients who underwent surgery for hip fracture, with higher risk associated in those with longer hospitalization and higher 2-year mortality. This may have significant implications for those that require hardware for their repairs. Another study utilizing bedside ultrasound in the post-anesthesia care unit (PACU) in patients that underwent thoracic, vascular, abdominal, ENT, or orthopedic surgery found 44 % of the patients had bladder volumes of greater than 500 mL. If treated within one to two hours, however, volumes of 500–1000 mL were not harmful. Similar studies have found incidences of PUR in the PACU of 16 %. Factors predictive of PUR include age greater than 50, intraoperative fluids greater than 750 mL, bladder volume of greater than 270 mL on entry to PACU, male gender, obstructive preoperative symptoms, spinal/epidural anesthesia, prolonged postoperative analgesia, and anesthesia time greater than two hours.

Childbirth has also been associated with overdistention and possible overdistention injury. A recent study evaluating 8000 consecutive births found a 0.05 % incidence of prolonged voiding dysfunction. It has also been suggested that labor exceeding 700 min increases the risk for postpartum voiding dysfunction.

In cases in which the bladder has acute distention for a prolonged period of time, defined as "a bladder filling volume at the time of diagnosis of at least 120 % of a normal bladder capacity, which has lasted at least 24 h," a new term has been introduced, "acute prolonged bladder overdistention" (ApBO), thought to be a consequence of spinal or epidural anesthesia, extensive pelvic or orthopedic surgery, or prolonged childbirth. It is often asymptomatic, leading to delayed treatment. ApBO differs from acute distention that is due to anatomic obstruction, which often initially is characterized by causing significant symptoms.

Bladder Outlet Obstruction (BOO)

Fixed Anatomic Obstruction Differing etiologies exist between men and women that may serve as an anatomic source of obstruction. In men, benign prostatic enlargement (BPE) causing benign prostatic obstruction (BPO) is the most common and well studied. Urethral strictures, although may develop in women, are far more common in men. They may be affiliated with a history of sexually transmitted disease, balanitis xerotica obliterans, trauma, or an iatrogenic cause such as urethral catheterization or transurethral surgery. Obstructive female urethral pathology may be due to urethral prolapse, diverticulum, or caruncle. Other possible causes of obstruction may include pelvic organ prolapse, Skene's gland abscess, a retroverted or impacted uterus during pregnancy, or extrinsic compression from, for example, a pelvic malignancy. Etiologies common to both genders include meatal stenosis, urethral carcinoma, or anti-incontinence surgery.

The latter is the most common cause of outlet obstruction in women. An estimated 2 % incidence of bladder outlet obstruction following surgery for stress urinary incontinence has been quoted in women based on data evaluating post-op urinary retention; however this may be an underestimation, as many women may have subclinical obstruction resulting in significant symptoms but no significant voiding dysfunction. Rates of voiding dysfunction, mainly obstruction, have been reported up to 33 % after autologous slings, 22 % after Burch, 20 % after retropubic, and 7 % and 4 % respectively for transvaginal needle suspension and tension-free vaginal tape. Suggested risk factors for postoperative obstruction include prior anti-incontinence surgery, concomitant pelvic organ prolapse, a lack of detrusor contraction on preoperative UDS, as well as a post-void residual greater than 100 mL and peak flow of less than 20 mL/s.

In men, a recent study of 117 patients that underwent artificial urinary sphincter (AUS) noted an increased incidence of postoperative urinary retention following transcorporal AUS placement. This was found in 32 % compared to 8 % of those that had a 4 cm or larger cuff placed in traditional fashion. Of those with a transcorporal AUS, 27 % versus 2 % of the traditional AUS underwent suprapubic tube placement. The overall urinary retention rate after AUS was 15 %. The mean duration of post-op catheterization was 6.5 days but lasted up to 6 weeks in some patients with suprapubic tube. They did report a lower rate of cuff erosion in those that had transcorporal cuff placement.

Functional Obstruction Functional causes of outlet dysfunction are as a result of a poorly relaxing outlet rather than a fixed anatomic obstruction, caused either at the level of the bladder neck or the urethra and pelvic floor.

Primary bladder neck obstruction (PBNO) is when the bladder neck fails to open adequately during voiding. The two requirements for this diagnosis are lack of anatomic obstruction and lack of increased striated sphincter activity. It was initially thought to be an entity diagnosed most commonly in men ages 21–50, but more recently there has been increasing recognition of this condition in women as well. There is minimal data on its prevalence in children. It has been hypothesized to be due to either failure of degradation of mesenchymal elements, with incorporation of connective tissue and subsequent smooth muscle hypertrophy, or underlying neurologic pathology.

Failure of the sphincter or pelvic floor to relax can be a result of three conditions. One cause is thought to develop as a habitual contraction of the pelvic floor and/or urethral sphincter during micturition, perhaps in young children who have pelvic floor discomfort (from possibly abuse or constipation) or as a response to urinary urgency. These patients are often diagnosed as having dysfunctional voiding, which is characterized by variable contractions throughout a void that prevent normal emptying. It is now being recognized as also developing in adults that present with a myriad of voiding complaints, thought to be a compensatory response to detrusor overactivity by urethral sphincter contraction throughout voiding that then becomes habit. Often patients with dysfunctional voiding present with very bothersome storage and voiding symptoms. If a patient has an underlying neurological condition (e.g., spinal cord injury, multiple sclerosis) and have the same symptoms and study findings, the patient will be diagnosed with detrusor sphincter dyssynergia (DSD). This can further be subclassified into lack of coordination by the external sphincter (detrusor external sphincter dyssynergia; DESD), which may occur by supracervical lesions, or by the internal sphincter (detrusor internal sphincter dyssynergia; DISD), which occur with lesions that occur at or above the takeoff of the sympathetic efferents at T11–L2 (Fig. 13.1). Additionally, the presence of DESD and DISD can coexist together.

Fowler's syndrome differs from dysfunctional voiding and DSD as patients are asymptomatic and are often in retention at time of diagnosis. It is a rare condition found in young women, typically postmenarche and in the second and third decades of life, with long-standing detrusor inhibition from a chronically non-relaxing external urethral sphincter. The original paper describing Fowler's syndrome in 1988 made an association to polycystic ovaries because 14 of the 22 patients with abnormal EMG activity had the condition, which thereby postulated a hormonal cause. There is poor data to support this as of yet.

Clinical Practice: Diagnosing Incomplete Bladder Emptying

The proper workup and evaluation of the patient is important to identify patients at risk, offer appropriate therapies in a timely fashion, and avoid unnecessary tests and treatments. Regardless of the etiology of incomplete emptying, the subsequent symptoms that develop may be debilitating despite very minimal objective findings, or the opposite may occur in which upper tract dysfunction is identified in a patient who has minimal to no symptoms. The goals of evaluation should be to establish a diagnosis, to define the characteristics of the patient's storage and emptying, and to identify patients at risk for long-term sequelae.

History

In addition to obtaining a routine history from the patient, one needs to take care to elicit additional information relevant to developing a differential diagnosis. A

clear elucidation of the nature, acuity, and duration of the urinary symptoms is crucial, whether they have storage symptoms (frequency, nocturia, urgency, or incontinence), voiding symptoms (slow stream, splitting of spraying of the stream, intermittency, hesitancy, straining, or terminal dribbling), or post-void symptoms (a sensation of incomplete emptying or post-void dribbling). A history of diabetes, stroke, infection, trauma, prior abdominal, back, or pelvic surgeries, prolonged anesthesia or childbirth, or abdominal or pelvic radiation history should be obtained. Additional information regarding any abnormal childhood voiding patterns and history of recurrent urinary tract infections (and associations to infection such as intercourse) are important to assess, as well as gastrointestinal symptoms of constipation, diarrhea, or fecal incontinence. Also important to gather is a sexual history, inquiring about a history of sexually transmitted diseases, dyspareunia, or a history of abuse. In women, a thorough gynecological history including pertinent history during deliveries, symptoms of prolapse, menopause, and prior gynecologic surgeries need to be ascertained. If a patient has been seen by other practitioners or had prior surgeries, it is very helpful to obtain reports on labs and imaging and prior operative notes. Finally, it is important to understand the patient's home situation and their functional status, as it may impact your treatment choices.

In patients who are not at risk of upper tract deterioration or recurrent urinary tract infections, the guiding force to management is going to be the degree of bother to the patient. A number of validated questionnaires are available to obtain an initial assessment and are also helpful to use through the course of management to assess for improvement or worsening of symptoms. Lepor et al. administered the American Urological Association Symptom Index (AUASI) survey to 750 men and women and found that aging men and women both have symptoms and rates of symptoms that are largely equivalent to each other, thereby suggesting that the AUASI is not BPH specific. It has also been found to be helpful in assessing lower urinary tract symptoms in women independent of incontinence.

Physical Exam

In addition to performing a routine physical exam, particular attention should be paid to particular aspects of the exam. A palpable or percussible bladder during the abdominal exam is important to gauge. The back should be examined for vertebral pathology or costovertebral angle tenderness. Hard stools, fecal impaction, masses, and anal sphincter tone need to be assessed during the rectal exam. A thorough neurological exam and an assessment for lower extremity edema should be noted. The meatus should be noted for abnormalities. In men, palpation of the penis for plaques or masses and examination of the prostate to ascertain size or for tenderness or masses are important. In women, assessment for pelvic organ prolapse, for pain during palpation of the levator complex, or for urethral or vaginal masses that may be suggestive of a cyst, abscess, or diverticulum is warranted.

Diagnostics

A number of studies can be utilized in the assessment of the patient. The information gained from the history and physical should help to guide the practitioner to what studies should be ordered, so as to avoid a potentially unnecessarily costly and invasive workup. However in certain patients, of primary concern should be the assessment of risk, which includes upper tract deterioration or development of urinary tract infections.

Post-void Residual (PVR) A post-void residual will be the first test that indicates urinary retention. It can be performed with a bedside bladder scan or ultrasound, or if those are unavailable or it is unclear if it is accurate, a catheterization may be necessary. Portable ultrasonographic devices have been found to be largely comparable to catheterization.

No value for PVR has been established as defining abnormal bladder emptying. A range of values have been quoted for men as considered incomplete bladder emptying, including 150 mL, 200 mL, or 300 mL. Abrams et al. cited that PVRs of 300 cc are the lowest threshold after which the bladder becomes suprapubically palpable based on urodynamic findings. The UK National Institute for Health and Clinical Excellence proposed using a PVR of greater than one liter. AURO.it (Italian Association of Urologists) Guidelines for BPH define a pathological PVR "more than one-third of total bladder capacity." A combination of these criteria proposed by Negro et al. suggests using a PVR of >300 mL in those who can void and a PVR of >1000 mL in those who are unable to void.

For women, the literature most often quotes a PVR of >100 mL to be "elevated." One study using these criteria in urogynecology clinic found a PVR in those with urgency and frequency without incontinence was 5 % and 10 % and in those with urgency incontinence an overall incidence of 9 %. Another study utilizing a post-void residual of 100 mL or greater in women with symptoms of urgency, frequency, and urgency incontinence found 19 % of patients to have elevated PVR; risks were increased in older age, prior incontinence surgery, history of multiple sclerosis, greater AUASI, vaginal parity greater than 2, greater pad use, and stage 2 or greater vaginal prolapse.

It is important to interpret post-void residual data in the context of the patients symptoms and, when available, urodynamic findings. For example, an "elevated" post-void residual in a patient with poor or decreased compliance likely has more clinical significance than the same PVR in a patient with a compliant bladder.

Uroflow A uroflow helps to gather information on flow rates, time to void, and presence of abdominal straining with voiding. The voided volume added to the post-void residual may be indicative of a large capacity bladder but may not be accurate if the patient is not at capacity when they void. Maximum flow rates are helpful and will be discussed in greater detail when used in the setting of urodynamic evaluation.

Labs A urine dipstick may help to evaluate for a urinary tract infection. In patients that have concern for a urine infection, either because of the dipstick findings or

symptoms, a urine sample should be sent for urinalysis and/or culture. Assessment for proteinuria may also be performed. Patients that have concern for upper tract dysfunction should have a basic metabolic panel in order to check serum creatinine, electrolytes, and GFR.

Imaging Upper tract imaging is important in those with a significantly elevated post-void residual or concern for upper tract dysfunction. A renal and bladder ultrasound may assess for hydronephroureterosis. It may also be able to identify bladder stones and for thinning of renal parenchyma. The same information may be obtained from a non-contrast CT scan, but a US does not expose the patient to radiation, and can measure ureteral jets and a post-void residual. A contrast CT will not provide additional information in regard incomplete emptying and should not be performed in those with renal dysfunction. An MRI is helpful in cases of pelvic and urethral pathology in women, such as to assess for urethral diverticulum. In addition to identifying urethral pathology, it is helpful to assess extrinsic factors as well, such as Mullerian duct remnants or leiomyoma. A dynamic MRI may also help assess degree of prolapse but is an expensive study that may not provide any additional information about bladder emptying than less expensive studies. Patients on dialysis should not receive gadolinium due to the risk of nephrogenic systemic fibrosis.

Cystourethroscopy Cystoscopy in and of itself does not make a diagnosis of obstruction but can help to determine the cause or anatomy of the obstruction. Indications for cystoscopy include evaluation for any masses or lesions that may be a source of symptoms in patients with a risk of malignancy or for those that also endorse gross hematuria. In those with concern for stricture, this allows evaluation of the urethra. The prostate can also be grossly assessed for obstructing lobes or prominent median lobes. Those that have had prior surgery on the bladder, urethra, or prostate can be assessed for scarring or obstructing masses. It allows the practitioner the ability to visually assess for urethral angulation and distention ability and assess for anatomical variants (diverticuli or masses) or foreign bodies.

Urodynamics The definitive study to evaluate for the cause of incomplete bladder emptying is urodynamics. A vast amount of information can be obtained from the study, including presence or absence of sensation, capacity, compliance, involuntary contractions, generation of detrusor pressures, storage pressures, urinary flow rates, and post-void residual. It is important to remember that discomfort or anxiety during the exam may impair the results. If feasible, there may be a role for ambulatory urodynamics to try to assuage this issue. Urodynamics is not perfect, however, as there may be a number of variables that affect the study, including catheter size or test anxiety; however it is the best study available to evaluate for detrusor contractile dysfunction with simultaneous pressure-flow analysis and quantify the degree of obstruction.

Fluoroscopy at the time of urodynamics can be exceedingly helpful in identifying obstruction and at what level it exists, particularly in women. This is particularly helpful when trying to differentiate between functional causes of bladder outlet obstruction. In primary bladder neck obstruction, the obstruction is at the

bladder neck, while in dysfunctional voiding or detrusor external sphincter dyssynergia, the obstruction is at the external sphincter and may reveal a "spin top" urethra. We have found fluoroscopy to be the best identifier for obstruction independent of max flow and detrusor pressures. Additionally, the presence and grade of vesicoureteral reflux can be assessed, as well as any abnormalities of the bladder (diverticulum, trabeculations, or filling defects) and urethra (stricture or diverticulum).

Voiding Cystourethrogram Even in the absence of multichannel urodynamics, the fluoroscopic images obtained from a voiding cystourethrogram can provide a large amount of information, namely, for the level of obstruction, the presence of vesicoureteral reflux, or anatomic bladder or urethral abnormalities.

Nomogram Over the past decade, a number of nomograms have been developed to define obstruction; however their application is largely for the evaluation of men. In 1997, the International Continence Society published a nomogram recommended for use in older men with obstructive LUTS based on the results of studies from the Abrams-Griffiths and Schafer nomograms which was coined the "provisional ICS method for definition of obstruction." Utilizing the Bladder Outlet Obstruction Index (BOOI) from the Abrams-Griffiths nomogram, measured by the equation BOOI = Pdet @ Qmax – 2(Qmax), men are divided into three groups: obstructed if BOOI >40, equivocal if BOOI 20–40, and unobstructed if BOOI <20. The bladder contractility index (BCI) is derived from the Schaefer nomogram and is calculated by the formula BCI = PdetQmax + 5(Qmax) and defines contractility as strong if >150, normal if 100–150, and weak if <100.

Women do not yet have clearly defined urodynamic criteria that may be indicative of obstruction, likely because the prevalence and causes of obstruction are quite different. Variable criteria have been suggested for women, including peak flows of less than 12 mL/s, as well as values for detrusor pressure at peak flows of greater than 20cmH_2O to greater than 50cmH_2O. The Blaivas-Groutz nomogram defines obstruction as those that have a maximum flow rate less than 12 mL/s, with our without radiographic evidence of obstruction, in the presence of a sustained detrusor contraction greater than 20 cmH_2O, and/or an inability to void. It has been shown, however, to overestimate the prevalence of obstruction in women. Utilizing variants of these criteria, Choi et al. evaluated lower urinary tract symptoms in women and defined "voiding difficulty" at a Qmax less than or equal to 15 mL/s. If on urodynamics the detrusor pressure at peak flow was >20 cmH_2O, they were subclassified as having bladder outlet obstruction, and if it was <20 cmH_2O, it was defined as detrusor underactivity. Using this criteria, of 1415 women that presented to urology offices, 102 (12.8 %) complained of voiding difficulties and had peak flows under 15 mL/s. Of these, 89 women (87.2 %) showed bladder outlet obstruction, and 13 (12.8 %) showed detrusor underactivity. We have found that pressure flow dynamics in obstructed women are quite variable and the diagnosis requires an individualized rather than a nomogramic approach. That is why we favor the videourodynamics criteria.

Clinical Practice: Treatments and Techniques

Treatment of the patient should be driven by two factors: risk and symptoms. The following figure categorizes the approach to the patient with concern for incomplete bladder emptying and should be considered when determining the aggressiveness of the workup and treatment for the patient (Fig. 13.3). Initial assessment should be approached with a history, a physical exam, and an evaluation of a post-void residual (PVR). As discussed, a set value for an acceptable post-void residual is still undetermined. Based on various prior recommendations and guidelines, one may consider cutoff values of 300 mL in men and 100 mL in women as limits for elevated post-void residual; however this will be based on the patient, their comorbidities, and the practitioner's judgment. Any patient with risk of additional problems including upper tract deterioration or recurrent urinary tract infections should be strongly advised to undergo some treatment to drain the bladder. Those without risk can then be further stratified by degree of bother and offered treatment based on the cause of their incomplete emptying.

Once a patient has been classified into a risk and symptom category, an appropriate workup can be initiated to determine the cause. The treatments will vary depending on the cause. For those that are unbothered and not in any risk, they should be offered an option to do no therapies and monitor them biannually to annually. Conservative therapies include double or triple voiding, intermittent catheterization, or indwelling catheterization. These may also be employed in those with significant comorbidities that may make them poor surgical candidates or that refuse invasive therapies.

Bladder Dysfunction

Unfortunately, most causes of bladder dysfunction are irreversible, particularly neuropathic and myogenic causes. Early intervention and optimal management of neurological disorders may help to delay detrusor dysfunction, but ultimately it may

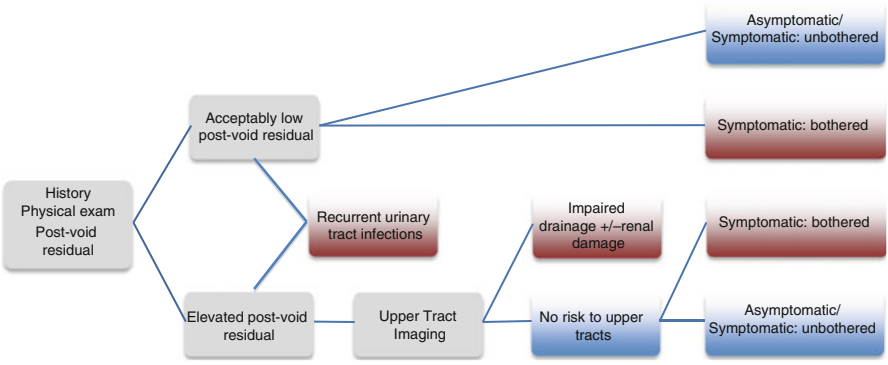

Fig. 13.3 Approach to incomplete bladder emptying

be unavoidable. Strict control of comorbidities and fluid management may assist in preventing progression of deteriorating function. The degree of bladder dysfunction from pharmacological causes varies based on the mechanism of action of the drug, as well as the metabolizing potential by the patient. There is no established time frame as to when the bladder may regain function. The patient should be treated with conservative therapies and/or catheterization with frequent assessment for return of detrusor function.

A number of oral drugs have been attempted to stimulate detrusor activity with no significant efficacy. These drugs include alpha-adrenergic antagonists, muscarinic receptor agonists (e.g., bethanechol), and prostaglandin E. Sacroneuromodulation has also been studied extensively in animal models, and emerging data in humans is demonstrating stimulation of sacral efferents and its modification on the reflex between bladder and urinary sphincter.

A number of investigational therapies are being studied, including gene therapy using nerve growth factor-encoded herpes simplex virus and stem cell therapy with muscle-derived cells from skeletal muscle, both of which are showing some promise in improving contractility and bladder emptying in rats. Nerve growth factor (NGF) is a neurotrophic protein that is necessary for normal function of sensory and sympathetic neurons and has been found to be protective of neurons from various neurotoxins. It has been extensively studied in animal models in being an important peptide for neurotrophic support for the lower urinary tract. It has been demonstrated that exogenous administration of NGF has a protective effect on diabetic rat bladders. Studies replacing NGF and other neuroprotective agents such as alpha-lipoic acid have showed promise.

Often in cases of patients with detrusor underactivity, even though it is not the primary cause, treatment is focused on the outlet (e.g., bladder neck incision or resection, urethral stricture repair or dilation, prostatectomy, transurethral resection, or sphincterotomy). The goal is to help promote emptying by reducing outlet resistance, even though resistance may not be "abnormal." It is critical that patients are counseled appropriately prior to performing any outlet procedure as there are risks associated with many of these procedures, and the procedures are not addressing the underlying etiology of their voiding dysfunction.

Bladder Outlet Dysfunction

Fixed Anatomic Obstruction In those with a fixed anatomic obstruction, there is high likelihood of improving emptying by removing the obstruction. With chronic long-standing obstruction, however, the detrusor also may have irrecoverable function. It is beneficial to have assessed for this prior to treatment for purposes of counseling, as well as appropriate treatment choices to offer the patient.

In men with obstructive or bothersome prostatic enlargement, management with medications is often the first course of action. In patients who fail medical therapy or which for surgical treatments, procedures to unobstruct the outlet can be

performed. These may be performed abdominally (prostatectomy) or transurethrally (transurethral resection of the prostate, greenlight vaporization, holmium laser enucleation). A recent meta-analysis comparing minimally invasive BPH management to traditional TURP found less improvement in symptom scores for patients that had transurethral needle ablation, laser coagulation, and transurethral microwave treatment than traditional transurethral resection of the prostate, although there was still overall a reduction in the IPSS by 3 points. Compared to TURP, these patients otherwise had less blood loss, lower stricture rate, and lower incontinence rates and were less likely to have loss of ejaculation. Laser coagulation, although shorter than TURP, had higher urinary retention rates and post-op UTI than the other treatment modalities. Transurethral needle ablation procedures were longer but had shorter hospital stays. Minimally invasive procedures had a higher need for reoperation.

Strictures may be dilated if short; however recurrent or long strictures may require a urethroplasty. Meatoplasty can be performed in those with meatal stenosis. Urethral carcinoma should be dealt with per oncology guidelines, which will be based on grading and depth of invasion and a number of patient factors.

Anatomic abnormalities in women may also require a procedure to treat, including repair of urethral diverticulum, caruncle, or prolapse, drainage of a Skene's gland abscess and removal of the cyst, and reduction of pelvic organ prolapse either with a pessary or with surgery. In those that have undergone anti-incontinence surgery, up to 30 % with an autologous sling may need to undergo sling lysis, 42 % with long-term catheterization, and urethal dilation in up to 8 %. Loosening or cutting of transvaginal tapes (TVTs) has found to have excellent results with restoration and normal voiding in almost all patients and marked improvement in storage and voiding symptoms. The rate of recurrent SUI after sling lysis is currently unknown.

Functional Obstruction Once a patient has been found to have a functional cause of obstruction, it is important to decipher which of the three causes they have, as the therapies vary for each other.

In those with primary bladder neck obstruction, alpha-blocker therapy is not unreasonable. It may act as both a diagnostic and therapeutic modality prior to proceeding with a transurethral incision of the bladder neck, which would be the next step.

In patients that have failure of the sphincter to relax, those with dysfunctional voiding may benefit from physical therapy and biofeedback in order to "relearn" how to void with proper coordination. Other therapies that have been implemented include Botox injections into the external urethral sphincter, sacroneuromodulation, and muscle relaxers. It may also benefit the patients to possibly undergo psychotherapy, especially in those with a history of abuse.

In patients with a neurological cause that prevents their sphincter from relaxing (DSD), one can also attempt botulinum toxin injections in the external urinary sphincter. Other options include sphincterotomy. The risks, however, of treating the outlet in patients with a neurological condition include making them incontinent. In some patients, it may be best to treat them with intermittent catheterization or, in

those with functional impairment, indwelling catheter (either transurethral or suprapubic) or a urinary diversion. A continent diversion may be considered in those that have good dexterity of their upper extremities and hands.

In patients diagnosed with Fowler's syndrome, the treatment of choice is sacroneuromodulation. Its postulated mechanism of action is retraining of the nerve input to the pelvic floor, which will allow its relaxation and thereby permitting the bladder to contract again.

Conclusion

Disorders of incomplete bladder emptying and urinary retention are in essence due to either failure of either the detrusor (detrusor underactivity) or of the outlet (bladder outlet obstruction). They are quite bothersome to a large population of patients and can cause additional concerns when contributing to recurrent urinary tract infections and/or upper tract deterioration. The diagnostic tests and treatments options are numerous; therefore it is important to approach these patients with a good understanding of possible causes and the roles for different tests. The gold standard study to determine the cause of incomplete emptying is urodynamics and should be utilized when there is not a clear etiology. Treatments for bladder outlet obstruction are numerous and should be offered after a complete and thorough assessment. Treatments for detrusor underactivity are unfortunately limited. Although there is promising research on a variety of investigational therapies, further work will be required to understand and treat this condition.

Point of Interest

- The physiology of voiding is intricate and complex, with a vast potential for disruption of normal voiding patterns.
- In order to properly empty, the bladder needs to generate a pressure of adequate strength and duration to overcome the resistance set by the outlet. Dysfunction of the bladder to generate the pressure needed or of the outlet to allow passage of urine results in incomplete bladder emptying.
- Underlying pathophysiological processes are important to understand as this may be a means for development of new therapies.
- It is important to have a common understanding of terminology applied to the genitourinary tract for purposes of reporting results and developing treatment guidelines.
- The workup is crucial to properly diagnose and to implement an effective treatment strategy. A thorough history and physical exam are then supplemented by studies, including post-void residual, uroflow, labs, imaging, and, the gold standard, urodynamics with our without fluoroscopy. Nomograms can be helpful to standardize the evaluation of

patients but are better served in men as there are not yet good criteria developed in women.
- Causes of bladder dysfunction are of neuropathic, myogenic, or pharmacologic etiologies. Of these three, only pharmacologic therapies are likely reversible. There is a role for sacroneuromodulation for acontractile detrusor.
- Causes of bladder outlet dysfunction are by either a fixed anatomic obstruction or a functional obstruction, the latter of which is from a failure of either the bladder neck or the sphincter and pelvic floor to relax. Treatment of bladder outlet dysfunction depends on the cause. Fixed anatomic obstruction can be surgically or medically treated. Primary bladder neck obstruction can have a trial of alpha-blocker or proceed to TUIBN. Dysfunctional voiding often involves "re-training" the bladder to void normally. Fowler's syndrome is treated with sacroneuromodulation.

Appendix 1: ICS 2002 Definitions of LUTS as They Pertain to Urinary Retention and Bladder-Emptying Disorders

International continence society subcommittee standardization of terminology in lower urinary tract function (2002)	
Terminology	**Definition**
Normal detrusor function	A voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span and in the absence of obstruction. For a given detrusor contraction, the magnitude of the recorded pressure rise will depend on the degree of outlet resistance
Lower urinary tract symptoms (LUTS)	The subjective indicator of a disease or condition as perceived by the patient, caregiver, or partner that may lead him/her to seek help from healthcare professionals *Storage symptoms*: *frequency*, *nocturia*, *urgency*, *urinary incontinence* *Voiding symptoms*: *slow stream*, *splitting or spraying*, *intermittency*, *hesitancy*, *straining*, *terminal dribble* *Post micturition symptoms*: *feeling of incomplete emptying*, *post-micturition dribble*
Detrusor underactivity	A contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span
Acontractile detrusor	One that cannot be demonstrated to contract during urodynamic studies
Bladder outlet obstruction	The generic term for obstruction during voiding and is characterized by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure *Further stated that bladder outlet dysfunction has been* "*defined for men but*, *as yet*, *not adequately in women and children*"

(continued)

Appendix 1 (continued)

Dysfunctional voiding	Voiding characterized by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals *It has also be termed* "*non-neurogenic neurogenic bladder*," "*idiopathic detrusor sphincter dyssynergia*," *or* "*sphincter overactivity voiding dysfunction*"
Detrusor sphincter dyssynergia	A detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. Occasionally, flow may be prevented altogether *Occurs in patients with a supra-sacral lesion and is uncommon in lesions of the lower cord*
Non-relaxing urethral sphincter obstruction	Usually occurs in individuals with a neurological lesion and is characterized by a non-relaxing, obstructing urethra resulting in reduced urine flow *Found in sacral and infra-sacral lesions. This term replaces* "*isolated distal sphincter obstruction*"
Acute retention of urine	A painful, palpable, or percussible bladder, when the patient is unable to pass any urine *In certain circumstances pain may not be a presenting feature* (*herniated vertebral disk*, *post-anesthesia*, *postpartum*)
Chronic retention of urine	A non-painful bladder, which remains palpable or percussible after the patient has passed urine. Such patients may be incontinent *Implies a significant residual urine* (*a minimum figure of 300 mL has been previously mentioned in men*)
Benign prostatic obstruction	A form of *bladder outlet obstruction* and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic enlargement, due to histologic benign prostatic hyperplasia
Benign prostatic hyperplasia	A term used (and reserved) for the typical histological pattern which defines the disease
Benign prostatic enlargement	Prostatic enlargement due to histologic benign prostatic hyperplasia *The term* "*prostatic enlargement*" *should be used in the absence of prostatic histology*

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Chapter 14
Practical Catheter Management

Shirley Budd

Catheters are a common method of bladder drainage for obstructive voiding or incomplete bladder emptying. Presuming that a clinical rationale has been proven identifying that a Foley catheter has been assessed as the best method for bladder drainage, this chapter will identify evidence-based practical ideas to support management of the problematic indwelling catheter. This includes explanations and solutions to catheter-associated UTI (CAUTI), bypassing and expelled catheters, the non-draining catheter including catheter encrustation, pain associated with catheters and general problems associated with catheter insertion and removal. Practice that is advised and not advised is detailed.

Assess the patient for potential problems to provide proactive care.

A risk assessment should include an assessment to identify bladder and bowel dysfunction. Assess the patient's medical conditions, the medication they are taking and the effect these may have on catheter function. A health and social assessment to include fluid intake, types of fluid, diet, and bowel function, abilities of self-care, cognition, mobility, dexterity, eyesight and environment enables proactive care and treatment. Poor fluid intake, constipation and neuropathy will cause problems for catheter management before you have even decided they need a catheter.

Catheter management should involve a multidisciplinary team. It is usually the jurisdiction of a nurse to provide catheter insertion, daily care, assessment and patient education.

Remove the catheter as early as possible. Assessing for catheter removal is identified as an effective nurse-led protocol to reduce CAUTI.

S. Budd, MSc
SEQOL Wiltshire, Continence Advisory Service, Swindon, UK
e-mail: SABudd56@hotmail.co.uk

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Reasons for catheterisation: use the acronym HOUDINI (make the catheter disappear) to empower nurses to remove catheters:

*H*aematuria visible
*O*bstruction/inability to empty bladder
*U*rological surgery or gynae procedures
*D*ecubitus ulcer/open sacral wound
*I*nput/output fluid monitoring haemodynamic instability
*N*ursing care only/end of life care to promote comfort
*I*mmobility

CAUTI

Catheter-associated UTI is the most prevalent nosocomial infection. The design of a Foley catheter results in a number of challenges. The balloon causes a sump of urine collecting below the eyelets. The catheter is a foreign body onto which bacteria adhere and create a self-protecting biofilm as a cause of bacteriuria and symptomatic CAUTI.

Wherever possible assess for using a catheter valve negating the need for a drainage bag to promote bladder filling and emptying and increase flushing of bacteria out with urine.

Assess for suprapubic catheterisation if CAUTI is recurrent and/or a cause of bacteraemia.

Apply aseptic non-touch technique (ANTT) at catheter insertion and change by maintaining sterility and not touching key areas of the catheter.

Effective hand washing and application of clean gloves have been proven to reduce CAUTI. Ensure hands are washed before and after any contact with the patient or provision of catheter care. Alternatively apply alcohol hand rub using the same hand washing technique to cover all areas of the hands when appropriate, e.g. lack of facilities in a patient's home and hands visibly clean.

Teach patients and carers hand hygiene requirements and skills.

Give fluid and dietary advice including required fluid volume; patient should aim to drink 2.5–3 l or until urine looks clearer and paler. Avoid caffeinated drinks if sensitive to caffeine.

Maintain the closed drainage system by adhering to manufacturers guidelines of 5–7 days to reduce CAUTI.

Only if the patient is unwell as a result of CAUTI should urine samples be taken to ascertain the appropriate antibiotic. Take samples aseptically from the sample port on the drainage bag. Do not use antibiotics to treat bacteriuria. The biofilm on the catheter protecting the bacteria prevents antibiotic effectiveness. Do not use antiseptic bladder washouts. This promotes resistant bacteria.

If antibiotics are required to treat symptomatic CAUTI, the patient should take 24/48 hours of antibiotics then the catheter should be changed depending on length of time catheter has been in-situ. This allows time for antibiotics to start to work and helps to prevent bacteraemia.

Consider antibiotic prophylaxis for patients who have a history of symptomatic urinary tract infection after catheter change or for patients who experience trauma.

Urine Is Bypassing Around the Outside of the Catheter or the Catheter Is Expelled with the Balloon Inflated or Deflated

Proactively assess risks to predict and resolve bypassing of urine around the outside of the catheter and urethral leakage when there is a suprapubic catheter as well as catheter expulsion with the balloon inflated. This is a common occurrence for any patient with neuropathic and idiopathic overactive bladder symptoms (OAB).

Proactively assess and treat OAB symptoms and bowel management. If not resolved, plan for insertion of suprapubic catheter.

Drainage bags should remain at a level below the patient's bladder to prevent backflow of urine within the drainage bag tubing. Avoid traction and a piston effect with the catheter moving up and down the urethra by appropriate drainage system fixation and regularly emptying the urine drainage bag when the bag is about one half to two thirds full. Use of supportive thigh straps, leg sleeves, bag stands and hangers reduces potential risks from traction and the piston effect of the catheter.

Manage the challenge of balloon deflation of silicone catheters. Some manufacturers provide a syringe of sterile water with 5 % glycerine such as the L.IN.C medical Uniball catheter.

Do not use a 30 ml balloon to promote catheter retention. Large heavy balloons may cause tissue necrosis in the bladder and increase irritation and CAUTI risk. A larger balloon is also noted to cause bladder irritation and bypassing of urine and may still be expelled resulting in damage to the bladder neck and urethra.

Do not over- or underinflate catheter balloons as this is in breach of manufacturer licence and is likely to cause the balloon to fall onto one side, resulting in irritation, bypassing and expulsion.

The Catheter Has Stopped Draining

One of the main problems associated with catheterisation is the non-draining catheter. Before making a decision about treatment, it is essential to identify the cause. If the catheter has blocked for the first time and the fault is not with the drainage system or constipation, then the catheter should be changed and the non-draining catheter examined by cutting it open. On examination the clinician may identify that there are three options identified about the catheter. There may be nothing in the catheter, mucous or a gritty-/toothpaste-type blockage within the catheter lumen which may be visible around the outside of the catheter.

Option 1: There is mucous or debris in the catheter lumen. This is likely to occur where the patient is elderly and/or immobile.

There is little evidence identified to treat this problem identifying an area for research. To support catheter maintenance, ensure patient understands how much fluid they need to drink, at least 30ml/kg or 2.5–3 l or until urine looks clearer and paler. If the catheter continues to block, try saline bladder washout inserted as a sterile solution. Assess for suprapubic catheter as this allows for a larger catheter charrière gauge.

Option 2: There is nothing in the catheter. Assess the urine quality and fluid intake. Can the patient feel the vacuum is released when the drainage bag is detached? The problem is likely to be caused by hydrostatic pressure related to the drainage bag being more than 30 cm from the bladder. This causes the catheter eyelets to be drawn into the delicate bladder mucosa which may cause damage to the bladder walls. Bring the catheter bag closer to the bladder. Try a shorter tube leg bag or possibly a Teleflex Medical belly bag (note, manufacture guide use is up to 28 days).

Option 3: There is crystallisation/encrustation in the catheter lumen and possibly around the eyelets. Evidence identifies that about 50 % of patients will be "blockers". There is little evidence to say that any of the Foley catheters available on prescription are better at resisting encrustation. However, patients are unique individuals and so it is worth trying a different type of catheter including a hydrogel-coated catheter, silicone or silver alloy catheter. The main point is to manage and map the catheter life span and frequency of catheter blockage using a catheter diary. Then change the catheter routinely more frequently prior to the anticipated blockage date.

If this is not feasible based on patient assessment, then it is appropriate to use catheter maintenance solutions. Getliffe identified that two sequential 50 ml citric acid solutions to treat the catheter are more effective. Using the Optiflo system by Bard with a bellows design promotes treating the catheter, minimising the contact with the bladder mucosal lining. However, evidence identified in a Cochrane review is not robust and use of citric acid solutions should be monitored and minimised whenever possible.

Managing encrustation requires catheter maintenance, not bladder washout. Routinely assess the appearance externally and internally of the catheter. If the catheter continues to be unmanageable, assess for bladder stones. If the catheter is long term and the patient is a "blocker", then the patient should be assessed for a suprapubic catheter which allows for a larger charrière gauge catheter.

Assess catheter for external signs of encrustation on the outside of the catheter following catheter removal. Possibly use Solution R, 6 % citric acid to dissolve encrustation prior to removal of catheter. Also note encrustation developing around the balloon may result in a stone cast of the balloon falling off when balloon is deflated.

Pain Associated with Catheters

There are many reasons for pain affecting the catheterised patient including difficulty inserting the catheter. The following are management options:

Ascertain where the discomfort is. Is the correct size of catheter used? Always insert the smallest catheter possible, 12 to 14Ch for men and 12Ch for women. A catheter where the gauge is too large is a risk for men potentially developing infection and strictures due to compression of the urethra and paraurethral gland.

Ensure adequate volume of lubrication used during the catheterisation procedure: 11 ml for male catheterisation and 6 ml for female catheterisation. If using anaesthetic antiseptic gel ensure gel remains in urethra for 3 to 5 minutes to allow time for the anaesthetic and antiseptic to work. Warn patients there might be a transitory period where anaesthetic lubricant may cause stinging. Check patient allergies and medical conditions.

Be aware of available catheter materials as a patient may experience allergic reaction to latex or discomfort depending on material used.

When inserting the catheter into the urethra, ensure it is well advanced into the bladder, preferably up to the bifurcation of the valve and drainage bag point for male catheterisation. Wait until urine is draining before balloon inflation. Inflate the balloon slowly, checking all the time that the patient is comfortable.

Following male catheterisation ensure foreskin, if present, is drawn back down over glans penis. If this is not done, paraphimosis may occur where the prepuce creates a tight band around the penis, resulting in oedema, pain and trauma. Ease the foreskin back. A cold compress may help.

Vaginal atrophy results in loss of elasticity and moisture of the mucosa, increasing trigone sensitivity potentially resulting in catheter-related problems such as trauma, bypassing and discomfort. Consider topical oestrogen.

If the discomfort is at the urethral meatus, try anaesthetic gel and nonsteroidal anti-inflammatory drug pain relief.

Assess for catheter valve.
Consider suprapubic catheterisation.
Constipation can cause discomfort pressing on the catheter and bladder.

Points of Interest

Loss of suprapubic catheter tract at catheter change is potentially a risk for people with neuropathy conditions and symptoms. This risk assessment identifies patients who will need prompt catheter insertion following catheter removal.

To reduce the risk of losing the cystostomy site, be organised: applying aseptic non-touch technique (ANNT), prepare a catheter removal field and a catheter insertion field layout, all equipment maintaining sterility. This enables prompt catheter replacement.

If you are not able to insert a Foley catheter, insert an ISC/nelaton catheter, which is firmer, and tape into place to keep the tract open whilst waiting for reinsertion of a foley catheter rather than suprapubic catheter.

Not able to see the female urethra? Dilate female urethral meatus with lubricating gel. Open labia and pull up gently to reveal urethral meatus. Try placing a pillow under the buttocks to tilt the pelvis forward. If the patient is unable to adopt supine position, with feet flat on couch, try side lying. Another health-care professional is likely to be required to support the upper leg.

Catheter balloon does not deflate. If equipment is thought to be faulty, try another syringe. Do not pull on the syringe; this might collapse the deflation channel. Apply slight tension to start the deflation process then allow the balloon to deflate itself. Avoid use of creams and talcum powder as these can block the deflation channel. Never cut any part of the catheter whilst in situ. The catheter may slide up into the bladder.

Balloon cuffing may occur with silicone catheters and is likely to be worse the longer the catheter remains in situ. This causes difficulty in removing the catheter as the balloon forms a doughnut ring. In urethral catheterisation, this may be a problem for men and may be a problem when removing a suprapubic catheter. Try removing the catheter proactively between 6 and 8 weeks. Possibly use L.IN.C Medical silicone suprapubic catheter which has an integral balloon and so should deflate flat. If there is not any latex allergy, try hydrogel-coated latex catheter.

If silicone catheter is resisting removal, allow time for silicone to relax into a softer shape. If this does not work, instil small-volume sterile water for injection: 0.5–1 ml to soften the shape of the cuffing. If it is a suprapubic catheter, tape the catheter to the abdomen, to ensure catheter does not just fall out, and leave for 1–2 h. This allows more time for the silicone cuff to relax. You are likely to need to pull firmly. Alleviate patient anxiety by education, support and encouraging relaxation.

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Chapter 15
Nocturia

Karel Everaert, An-Sofie Goessaert, and Marie-Astrid Denys

What Do the Guidelines Say?

Current guidelines and recommendations for the diagnosis and treatment of nocturia are included in the guidelines for male lower urinary tract symptoms and benign prostate obstruction, urinary incontinence, overactive bladder, and neurogenic bladder dysfunction. Despite the recognition of the multifactorial etiology, bothersome nocturia is often considered as a symptom associated with other diseases, and not as a distinct condition that requires an individualized treatment. The development of specific guidelines on the management of nocturia is scheduled by the European Association of Urology (EAU).

Clinical Practice

The general perception among caregivers and patients is that nocturia is not harmful, little bothersome, and part of the normal aging process. Guidelines for general practitioners confirm this assumption. Consequently, patients do not complain of nocturia, and caregivers do not see the need to evaluate the symptoms or to find the underlying cause. Furthermore, desmopressin is the only evidence-based pharmacological treatment that is indicated for nocturia. The potentially fatal side effects, if the required precautions are not taken into account, make caregivers reluctant to prescribe this and, consequently, any medication to treat nocturia.

K. Everaert, MD, PhD (✉) • A.-S. Goessaert, MD • M.-A. Denys, MD
Nopia Research Group, Department of Urology, Ghent University Hospital, Ghent, Belgium
e-mail: karel.everaert@ugent.be

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Background

Definition

The ICS (International Continence Society) defines nocturia as the complaint that an individual has to wake at night one or more times to void, with each void preceded and followed by sleep. Getting up once at night is considered as little bothersome, while two nocturia episodes are reported as moderately bothersome, with increasing bother as the number of nocturnal voids increases.

Epidemiology

The prevalence of nocturia increases with age and is similar in both genders. Over one-third of young people (<40 years) report at least one void per night, and even 15 % have to wake up twice or more to void at night. In older persons (>65 years) the prevalence increases to 70–90 % for one nocturia episode, and 30–60 % report at least 2 voids per night.

Intraindividual fluctuations in prevalence, spontaneous resolution, and correlations with body mass index (BMI >25 in women, BMI >30 in men) and drinking habits have been described.

Causes

Nocturia is the result of disturbances in the circadian rhythms of the kidney, bladder, and sleep pattern, which can lead to nocturnal polyuria, 24 h polyuria, reduced functional bladder capacity, and/or sleep disorders.

Nocturnal Polyuria (NP)

Nocturnal polyuria, or the production of an abnormally large volume of urine during sleep, is present in 60–80 % of patients. It is the most important cause of nocturia and commonly defined as a nocturnal diuresis greater than 33 % of 24 h diuresis (NP33 definition), as long as the 24 h urine production is within normal ranges. However, many other definitions are used to define NP:

- Ratio of nocturnal diuresis to 24 h diuresis:
  - Nocturnal diuresis/24 h diuresis >20 % in younger adults (ICS definition)
  - Nocturnal diuresis/24 h diuresis >33 % in older adults (ICS definition)
  - Nocturnal diuresis/24 h diuresis >35 %

- Cutoff values for nocturnal diuresis:
  - Nocturnal urine production >0.9 ml/min
  - Nocturnal urine production >1.3 ml/min
  - Nocturnal urine production >1.5 ml/min (= 90 ml/h)
- Ratio of nocturnal diuresis to body weight:
  - Nocturnal urine volume >6.4 ml/kg
  - Nocturnal urine volume >10 ml/kg

There are many causes of NP that should be considered when carrying out further investigations (see section "Pathophysiology").

24 h Polyuria

Patients with a 24 h diuresis exceeding 40 ml/kg body weight suffer from 24 h polyuria. The main causes of 24 h polyuria are diabetes mellitus, diabetes insipidus, or polydipsia. The latter can be primary when the excessive fluid intake is because of cultural, social, or psychological reasons or secondary when the body has to compensate for circulatory collapse.

Reduced Functional Bladder Capacity (RFBC)

A reduced functional bladder capacity can be either global or nocturnal. Although there is no strict definition for reduced bladder capacity up till now, it is believed to be present in 30–50 % of nocturia patients. The nocturnal bladder capacity index can be used to define RFBC (see section "Frequency volume chart (FVC)"). It is associated with pathologies of the filling phase of the bladder such as overactive bladder syndrome and/or the emptying phase of the bladder such as lower urinary tract obstruction and bladder hypocontractility. There are also non-urological causes such as pharmacological agents and learned voiding dysfunctions.

Sleep Disorder

Nocturia is one of the primary causes of sleep disturbance. The proportion of adults with nocturia as primary cause of nocturnal awakenings increases with age: 40 % of younger adults (18–44 years) and 77 % of older adults (>65 years). Questionnaires to assess sleep quality show a correlation between the severity of nocturia and a lower sleep quality. This sleep fragmentation is associated with impaired functioning, quality of life, health, and productivity. Nocturia not only induces sleep disorders, it can also be induced by sleep disorders. The best known sleep disorder that results in nocturia is the obstructive sleep apnea syndrome. Its therapy with continuous positive airway pressure (CPAP) treats the sleep apnea but at the same time also reduces the amount of nocturia episodes.

Pathophysiology

Nocturnal Polyuria (NP)

The rate of urinary output is regulated by complex interactions between urine concentrating and diluting mechanisms. This can only be achieved with an intact cardiovascular, endocrinological, neurological, and renal system. When evaluating disorders in diuresis, it is important to dissociate water diuresis from osmotic diuresis because they are regulated by totally different mechanisms. Water diuresis is the excretion of water without osmoles (free water), while osmotic diuresis is the excretion of osmoles (e.g., sodium, urea, glucose) together with water. An increase in (nocturnal) urine production can originate from abnormalities in glomerular filtration, osmotic diuresis, and water diuresis (Fig. 15.1).

Glomerular Filtration

The glomerulus receives its blood supply from an afferent arteriole of the renal circulation and drains into an efferent arteriole. The resistance of these arterioles is autoregulated and determines the fraction of blood plasma that is filtered through the glomerular capillaries into the Bowman's capsule, which empties the filtrate into the proximal tubule.

An increase in intravascular volume and blood pressure (e.g., in patients with cardiac failure, hypertension, obesity, reabsorption of peripheral edema, polydipsia) can lead to an increase in glomerular filtration, which also affects osmotic and water diuresis.

In healthy controls, there is a circadian rhythm with a decrease (15–30 %) in glomerular filtration during the night. A subgroup of patients with NP shows an increase in nighttime glomerular filtration. This is called glomerular hyperfiltration.

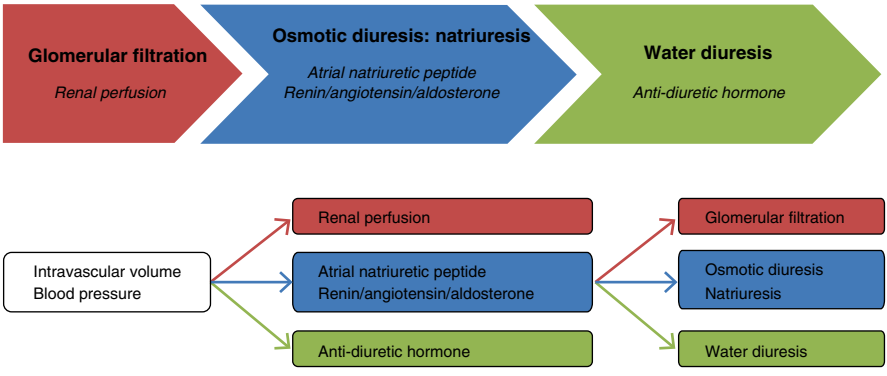

Fig. 15.1 Pathophysiology of nocturnal polyuria

Osmotic Diuresis

Endocrinological, neurological, renal, and cardiovascular stimuli are responsible for the reabsorption of the majority (95–99 %) of the filtered osmoles together with water. This process mainly takes place in the proximal tubule but also in the loop of Henlé and the distal tubule of the kidney. Natriuresis is the most important type of osmotic diuresis in the pathophysiology of NP. It is regulated by salt dietary intake and several hormones, including the atrial natriuretic peptide (ANP) and the renin-angiotensin-aldosterone system (RAAS). Other types of osmotic diuresis are glucosuria in patients with diabetes mellitus and excretion of urea due to a high-protein diet or hepatic diseases.

An increase in intravascular volume and blood pressure (e.g., in patients with cardiac failure, hypertension, obesity, reabsorption of peripheral edema, polydipsia) not only stimulates glomerular filtration but also rises the secretion of ANP and inhibits the RAAS, both leading to an increase in natriuresis.

In healthy controls, there is a circadian rhythm with a decrease in nocturnal natriuresis. Some patients with NP, especially older persons, have an absent or even inversed circadian rhythm in natriuresis.

Water Diuresis

In order to decrease water excretion and increase urine osmolality, different endocrinological, neurological, renal, and cardiovascular stimuli are responsible for the reabsorption of free water in the collecting duct of the kidney.

The most important regulator is the antidiuretic hormone (ADH), vasopressin. In response to hyposmolality or an increase in intravascular volume and blood pressure (e.g., in patients with cardiac failure, hypertension, obesity, reabsorption of peripheral edema, polydipsia), the secretion of ADH is inhibited and water diuresis is stimulated.

In healthy controls, there is a circadian rhythm with an increase in ADH during the night, leading to a decrease in water diuresis. A subgroup of patients with NP lacks this circadian rhythm and shows an increased nocturnal water diuresis.

24 h Polyuria

In 24 h polyuria the same mechanisms as in NP play a role. However, in this case, a disturbance in circadian rhythm does not only occur at night but also during daytime.

- Glomerular hyperfiltration as underlying mechanism for 24 h polyuria can occur due to polydipsia or cardiac failure. For a detailed description, see section “Glomerular filtration”.

- Osmotic diuresis in 24 h polyuria is usually caused by glucosuria. Normally all glucose is reabsorbed by the kidneys; however, in untreated or poorly treated diabetes mellitus, the elevated blood glucose levels result in excretion of glucose in urine which leads to excessive water loss.
- Diabetes insipidus is characterized by increased water diuresis over 24 h, regardless of fluid intake. Central diabetes insipidus is caused by a deficiency of ADH, whereas nephrogenic diabetes insipidus is caused by an insensitivity of the kidneys to ADH.

Reduced Functional Bladder Capacity

The pathophysiology of an RFBC depends on the cause. Overactive bladder syndrome is caused by disturbances in the nerves, smooth muscle, and urothelium. Prostate enlargement and bladder, prostate, or urethral cancer resulting in lower urinary tract obstruction can lead to bladder decompensation with increased mass, decreased compliance, and cholinergic denervation. As bladder contractions occur in a response to cholinergic stimuli, any cholinergic medication, for example, beta-blockers and cholinesterase inhibitors, can increase voiding frequency and reduce bladder capacity.

Sleep Disorders

The pathophysiological mechanism of sleep apnea leading to nocturia is based on the hypoxemia due to airway obstruction stimulating ANP release, leading to natriuresis and nocturnal polyuria.

Impact

Nocturia is a major cause of sleep fragmentation and associated with a reduction in quality of life, impairment of daily activities and productivity at work, additional comorbidities (falls, traffic accidents, cardiovascular diseases, metabolic syndrome), and mortality. Although many experts consider nocturia to be clinically significant only when patients void at least twice during the night, the need to get up once to void is often related to disruption of the deep sleep (slow wave sleep) within the first 3 h of sleep, which is considered to have the most impact on quality of life. The first hours of undisturbed sleep are the best parameter to evaluate the impact of Nocturia.

Diagnostic Evaluation

A complete diagnostic evaluation is invaluable to initiate an adapted and individualized treatment. All patients with bothersome nocturia need to complete a frequency volume chart and a questionnaire on sleep quality and lower urinary tract symptoms

to diagnose the underlying cause(s) of nocturia: NP, 24 h polyuria, RFBC, and sleep disorders. Patients with NP or 24 h polyuria should have an additional evaluation with a renal function profile to evaluate abnormalities in glomerular filtration, osmotic diuresis, and water diuresis.

Frequency Volume Chart (FVC)

Patients have to record voided volumes, volume and type of fluid intake, and the time of going to bed and getting up in the morning during 3 days. In case of urinary incontinence, the frequency of urinary leaks has to be reported together with (an indication of) the quantity and the circumstances (e.g., coughing, sneezing, hand-washing) (Fig. 15.2).

A lot of information can be deducted from an FVC (Table 15.1). When considering calculations with volumes, the first morning void of day 1 is excluded but the first morning void of day 2 is included. When considering calculation with frequencies, the first morning void of day 1 is included and the first morning void of day 2 is excluded.

Nocturnal Polyuria

Various definitions for NP can be used when analyzing an FVC (e.g., NPi33 or NUP90). In order to adapt treatment according to the underlying cause, we suggest to perform a renal function in all patients with NP.

24 h Polyuria

In patients with a 24 h diuresis exceeding 40 ml/kg body weight, the most common disorders should be considered by evaluating:

- Fluid intake (polydipsia)
- Glucose or HbA1c and osmotic diuresis on RFP (diabetes mellitus)
- Water diuresis on RFP (diabetes insipidus)

Further diagnosis and treatment have to be organized by an internal medicine practitioner.

Reduced Functional Bladder Capacity

Because there are no cutoff values for a normal bladder capacity, the diagnosis of an RFBC is based on the NBCI (Table 15.1). Further urological investigation with uroflowmetry, ultrasonography, and urodynamics is recommended to explore the cause of the RFBC (e.g., outlet obstruction, hypocontractility of the bladder, overactive bladder syndrome).

Hour	DAY 1: ...../...../.....			DAY 2: ...../...../.....			DAY 3: ...../...../.....		
	TIME OF WAKING UP DAY 1:.....H			TIMEOF WAKING UP DAY 2:.....H			TIME OF WAKING UP DAY3:.....H		
	A	B	C	A	B	C	A	B	C
6									
7									
8									
9									
10									
11									
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	GOING TO SLEEP DAY 1: ..... H WAKING UP AFTER DAY 1:.....H MORNING VOID AFTER DAY 1:.....ML			GOING TO SLEEP DAY 2:.....H WAKING UP AFTER DAY 2:.....H MORNING VOID AFTER DAY 2:.....ML			GOING TO SLEEP DAY 3:.....H WAKING UP AFTER DAY 3:.....H MORNING VOID AFTER DAY 3:.....ML		

Fig. 15.2 Frequency volume chart. *Column A*: Write down the voided volumes of each micturition during 3 × 24 h (in ml). Do not forget to note the volume of the first morning void of the next day, the time of going to bed with the intention to sleep and the time of waking up in the morning. *Column B*: Measure the involuntary urine loss: weight of wet diaper – weight of dry diaper. If that is not possible, give an indication of the estimated urine loss: N1 = some drops of urine; N2 = leakage that requires a new diaper. Describe the situation of the urine leakage (e.g. during coughing, laughing, following urgency, etc.). *Column C*: Note the amount (in ml) and type of fluid intake (e.g. water, alcohol, coffee, soft drinks, etc.)

Questionnaires on Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions used to measure sleep quality over the past month in the following 7 domains: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) use of sleeping medication, and (7) daytime dysfunction (Addendum 1). The 19 items are combined to form 7 component scores, each of which are scaled from 0 (no difficulty) to 3 (severe difficulty). The sum of scores

Table 15.1 Information deducted from an FVC

	Unit
Diurnal voiding frequency Daytime voiding frequency Nighttime voiding frequency	Number
Diurnal urine production Nocturnal urine production (NUP)	ml
Diurnal diuresis rate Nocturnal diuresis rate	ml/min
Functional bladder capacity (FBC) = maximal voided volume in 24 h Mean FBC daytime = mean of voided volumes during daytime Mean FBC nighttime = mean of voided volumes during nighttime	ml
Mean hours of sleep	h
Diurnal fluid intake	ml
Frequency of diurnal incontinence episodes Frequency of nocturnal incontinence episodes	Number
Mean volume of incontinence	g
Nocturia index (NI) = NUP/FBC → Nocturia if >1	/
NP33 definition: NP index (NPi) = NUP/24 h diuresis → NP if >33 %	%
NUP90 definition = NUP/h of sleep → NP if >90 ml/h	ml/h
Nocturnal bladder capacity index (NBCI) = actual – predicted number of voids (= NI-1) → RFBC if >1.3	/

Table 15.2 Renal function profile

Start	8 urine collections: 1 collection every 3 h							
Micturition	U1	U2	U3	U4	U5	U6	U7	U8
6–8 h	9–11 h	12–14 h	15–17 h	18–20 h	21–23 h	00–2 h	3–5 h	6–8 h

yields a global score which ranges from 0 to 21, with scores above 5 reflecting poor global sleep quality. A polysomnography is recommended when a sleep disorder (e.g., obstructive sleep apnea syndrome) is suspected.

Renal Function Profile (RFP)

A renal function profile is a 24 h test based on the collection of a urine sample every 3 h to analyze diuresis rate, osmolality, and sodium, urea, glucose, and creatinine concentrations (Table 15.2). The voided volume at the time of sample collection has to be registered, as well as volumes of any interim micturition. This test starts in the morning with the first sample 3 h after the first morning micturition. Urinary sample

U1 is collected between 9 and 11 am, U2 between 12 and 2 pm, U3 between 3 and 5 pm, U4 between 6 and 8 pm, U5 between 9 and 11 pm, U6 between 12 and 2 am, U7 between 3 and 5 am, and U8 between 6 and 8 am. A blood sample is taken to determine plasma osmolality, sodium, urea, glucose, and creatinine.

The RFP makes it possible to identify the pathophysiological mechanism(s) of NP. Since there are no cutoff values yet, circadian rhythms are analyzed by comparing the individual values of the 8 urine samples or by comparing the mean daytime and nighttime results.

Glomerular Filtration

The rate at which blood is filtered through all of the glomeruli, and thus a measure of the overall renal function, is the glomerular filtration rate (GFR). This is calculated by using the creatinine clearance, creatinine concentration in the urine sample (U_{Cr}), voided volume of the urine sample (V), and plasma concentration of creatinine (P_{Cr}):

$$\text{Creatinine clearance} = \left(U_{Cr} * V\right) / P_{Cr}$$

An episode of glomerular hyperfiltration during the night can cause NP.

Osmotic Diuresis

Osmotic diuresis can be evaluated by comparing total osmotic clearance or individual clearance of sodium, urea, etc. When there is no blood sample available, comparing urinary excretion also provides valuable information.

Clearance

The clearance of an osmole is the volume of plasma cleared of osmotically active particles per unit time. The overall osmolar clearance is calculated by using the concentration of osmolality in the urine sample (U_{osm}), voided volume of the urine sample (V), and plasma osmolality (P_{osm}):

$$\text{Osmolar clearance} = \left(U_{osm} * V\right) / P_{osm}$$

The clearance of an osmole X is calculated by using the concentration of X in the urine sample (U_x), voided volume of the urine sample (V), and plasma concentration of X (P_x):

$$\text{Clearance of } X = \left(U_x * V\right) / P_x$$

Urinary excretion

As there is a higher rate of osmolar excretion with higher voided volume, all calculations are corrected with the creatinine concentration in the urine sample (U_{Cr}):

$$\text{Osmolar excretion} = U_{\text{osm}} / U_{\text{Cr}}$$

U_{osm} = concentration of osmolality in the urine sample

$$\text{Urinary excretion of } X = U_{\text{x}} / U_{\text{Cr}}$$

U_{x} = concentration of X in the urine sample

Mainly nocturnal increases in natriuresis cause NP, but also disturbances in urea and glucose excretion can contribute to the development of NP.

Water Diuresis

Water diuresis can be evaluated by comparing free water clearance. When there is no blood sample available, comparing urinary osmolality also provides valuable information.

Clearance

The free water clearance is the difference between the voided volume of the urine sample (V) and the osmolar clearance. It is the volume of free water subtracted from (positive free water clearance) or added to (negative free water clearance) the plasma per unit time:

$$\text{Free water clearance} = V - \text{Osmolar clearance}$$

Urinary excretion

Urinary osmolality (U_{osm}) is a parameter to measure urine concentration. It can range from 50 to 1400 mosm/kg, but the mean 24 h osmolality should be 500–800 mosm/kg. A large value indicates concentrated urine; small values indicate diluted urine.

Smaller values due to a reduced effect of ADH and therefore a higher free water excretion or water diuresis can be observed in patients with NP. Patients with 24 h polyuria and a low 24 h osmolality should be referred to an internal medicine practitioner to exclude diabetes insipidus.

Management

Managing nocturia needs to be based on an approach that targets the underlying cause(s) and takes into account the individual bother (Fig. 15.3). Notice that only desmopressin has a level of evidence (LE) of 1 for the treatment of nocturia.

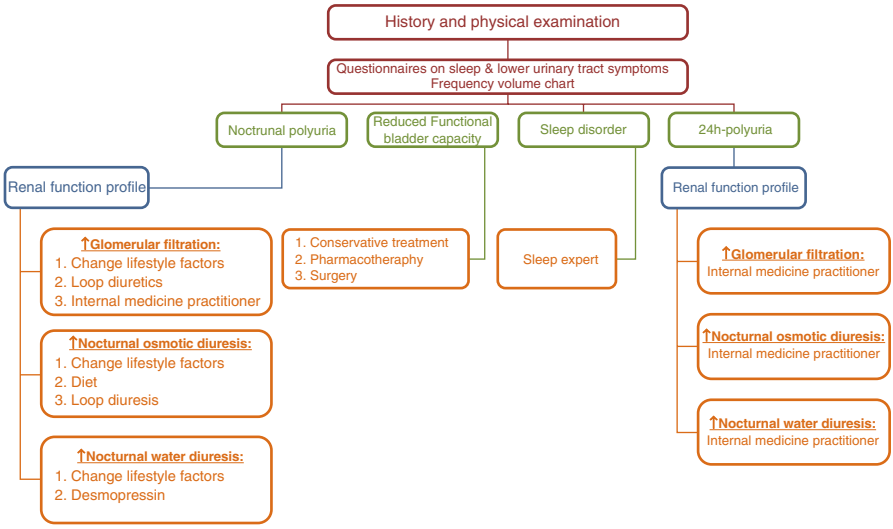

Fig. 15.3 Nocturia assessment. It targets the underlying causes as well as the individual bother

Nocturnal Polyuria

General measures to change lifestyle factors have to be considered in all patients with NP:

- Limit the daily fluid intake to 1.5–2 l.
- Restrict fluid intake in the evening, especially caffeine and alcohol intake.
- Take afternoon naps and elevate the legs to prevent fluid accumulation.
- Wear compression stockings to prevent fluid accumulation.
- Perform positional changes before going to bed.

Glomerular Filtration

Reducing glomerular filtration can be obtained by treating the underlying cause (e.g., hypertension, cardiovascular diseases) by an internal medicine practitioner.

Intake of short-acting loop diuretics (e.g., furosemide) 5–6 h before going to bed can stimulate diuresis during the day instead of the night. A decrease in nocturnal voiding frequency is demonstrated in older men with lower urinary tract symptoms. It can safely be combined with desmopressin and alpha-blocker. Always be aware of adverse effects such as postural hypotension, fluctuations of glycemia, and electrolyte disturbances. Especially in older persons, the levels of creatinine, sodium, chloride, potassium, magnesium, and calcium should be checked at baseline, after 3 days and after 7 days of treatment, and after every change in dosage.

Osmotic Diuresis

Salt (or protein) restriction might be a treatment option in patients with an increased nocturnal natriuresis (or urea excretion), but it has not yet been evaluated in patients with NP. A study in patients with nephrogenic diabetes insipidus showed a reduction in urine output of 20–50 % after the combination of salt restriction and intake of hydrochlorothiazide/amiloride or hydrochlorothiazide/indomethacin (LE 3).

Administration of short-acting loop diuretics (e.g., furosemide) 5–6 h before going to bed in order to stimulate diuresis during the day instead of the night is also a treatment to consider (see section "Glomerular filtration").

Water Diuresis

Desmopressin (solid tablet, 0.2–0.4 mg, or orally disintegrating tablet, 60–240 μg) is a synthetic analogue of the endogenous ADH and currently the only proven pharmaceutical treatment for nocturia caused by NP (LE 1). A better efficacy and safety profile is found in women with an even lower dose of 25 mg ODT. It lowers the nocturnal urine production and improves sleep quality by prolonging the initial sleep period of patients. The beneficial effects have been confirmed on short and long term. Patients have to take it 1 h before going to bed and must not drink 1 h before until 8 h after the intake in order to avoid water intoxication. Adverse effects (e.g., headache, abdominal pain, nausea) are limited. However, there is a risk for potentially fatal hyponatremia, especially in women and individuals older than 65 years. Therefore, the levels of sodium and creatinine need to be checked before initiating the treatment:

- Sodium <135 mmol/l: do not start desmopressin.
- Sodium >135 mmol/l: start with the lowest dose of desmopressin.
- Check sodium levels after 3 days, 7 days, 30 days, and 6 months.
- Check sodium levels after changing the dose.
- Check sodium levels after intake of other medications that can affect sodium levels (e.g., diuretics, antidepressants, antipsychotics, anticonvulsants).

Starting this treatment in patients older than 65 years requires a hospitalization to monitor adverse effects and electrolyte disorders. Polypharmacy is a major problem in this population, and concomitant use of medications that lower sodium levels increases the risk for adverse events.

24 h Polyuria

For this cause of nocturia, the patient has to be treated by an internal medicine practitioner.

Reduced Functional Bladder Capacity

Treatment of an RFBC depends on the underlying cause. It may consist of conservative measures such as bladder training or timed voiding. Pharmacological treatment with anticholinergics, beta-agonists, alpha-blockers, 5-alpha-reductase inhibitors, and phosphodiesterase inhibitors (tadalafil) has been tested in selected populations (LE 2). Surgery is required for specific pathologies (e.g., transurethral resection of the prostate, sacral neuromodulation).

Sleep Disorder

For this cause of nocturia, the patient has to be treated by a sleep expert.

Combining Therapy

A combination of treatments is recommended if there are multiple causes for nocturia.

Points of Interest

- The use of an FVC is mandatory to evaluate the cause of nocturia. It provides a direction for further diagnostic investigations and management of nocturia. Nevertheless, only ¼ of GPs and ½ of urologists use an FVC to evaluate patients with nocturia. Increasing the awareness and stimulating education is imperative.
- The use of an RFP is useful to diagnose the underlying cause of NP and 24 h polyuria and can direct us toward the optimal treatment. Future research is required to prove this.
- A better knowledge of desmopressin will decrease the resistance and fear to use this medication. For example, a better knowledge of safety estimation using age, gender, and baseline sodium levels is important. To increase safety, prescribers also have to be aware of other medications that can cause hyponatremia when initiating desmopressin.
- Trials to prove the efficacy and safety of combined treatment are needed in the future.

Addendum 1: Pittsburgh Sleep Quality Index (PSQI)

Instructions

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

During the past month:

1. When have you usually gone to bed?
   ……
2. How long (in minutes) has it taken you to fall asleep each night?
   ……
3. When have you usually gotten up in the morning?
   ……
4. How many hours of actual sleep do you get at night?
   ……

(This may be different than the number of hours you spend in bed.)

5. During the past month, how often have you had trouble sleeping because you:	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
(a) Cannot get to sleep within 30 min				
(b) Wake up in the middle of the night or early morning				
(c) Have to get up to use the bathroom				
(d) Cannot breathe comfortably				
(e) Cough or snore loudly				
(f) Feel too cold				
(g) Feel too hot				
(h) Have bad dreams				
(i) Have pain				
(j) Other reasons (please describe, including how often you have had trouble sleeping because of this reason(s): ..……)				
6. During the past month, how often have you taken medicine (prescribed or over the counter) to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				

8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Scoring

	Scoring system	Score
1. Subjective sleep quality	#9 score	0–3
2. Sleep latency	#5a score + #2 score (15 min = 0; 16–30 min = 1; 31–60 min = 2; >60 min = 3) → if sum is equal 0 = 0; 1–2 = 1; 3–4 = 2; 5–6 = 3	0–3
3. Sleep duration	#4 score → >7 = 0; 6–7 = 1; 5–6 = 2; <5 = 3	0–3
4. Habitual sleep efficiency	(Total # of hours asleep)/(total # of hours in bed) × 100 → 85 % = 0; 75–84 % = 1; 65–74 % = 2; <65 % = 3	0–3
5. Sleep disturbances	Sum of scores #5b to #5j → if sum is equal 0 = 0; 1–9 = 1; 10–18 = 2; 19–27 = 3	0–3
6. Use of sleeping medication	#6 score	0–3
7. Daytime dysfunction	#7 score + #8 score → if sum is equal 0 = 0; 1–2 = 1; 3–4 = 2; 5–6 = 3	0–3
Global score	**Add the 7 component scores together**	**0–21**

Further Reading

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