NEURO UROLOGY
A MANUAL FOR CLINICAL PRACTICE

Bibliografia.

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NEUROUROLOGY MANUAL FOR CLINICAL PRACTICE
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The aim of the urological management of patients with neurogenic lower urinary tract dysfunction (NLUTD) is (1) to protect the upper urinary tract by achieving a safe situation in the lower urinary tract with sufficient bladder capacity, bladder filling at low pressure, emptying completely without outflow obstruction, which is of paramount importance for life expectancy; and (2) to manage urinary incontinence or possibly to restore continence, which is so important for their quality of life (QoL).

The core competence of Neuro-Urology was the management of NLUTD (“neurogenic bladder”) in spinal cord injured (SCI) patients, in patients with myelodysplasia (“spina bifida”) and with multiple sclerosis patients. Moreover, spinal cord injury was also the human model for the research of the detrusor and sphincter dysfunction caused by spinal cord lesions.

During the last three decades, however, the spectrum of neurogenic bladder patients and their management has changed considerably. What is the difference in the neuro-urological care then and now? SCI patients, those with myelodysplasia and to some extent also multiple sclerosis patients with urological problems were referred to specialized centers, where an experienced urologist took care of them. The task was very complex: In the preface of their book on “Neurological Urology,” published in 1971, the authors Ernest Bors and A. Estin Commar, at that time working at the Spinal Court Injury Center in Long Beach California (USA), state that Neuro-Urology could only be understood by combining thoughts and methods of urology, neurology, neuro-surgery, psychiatry, traumatology and rehabilitation medicine. For these reasons Neuro-Urology was not of great interest for the general urologist as most patients were treated in specialized centers.

Over the years neurologists and urologists became aware that many central and peripheral nerve lesions as well as metabolic diseases can cause significant dysfunction of the lower urinary tract. Moreover, with the ageing of our population, an increasing number of elderly persons with cerebral diseases, suffering also from LUTS need urological care. They have meanwhile become part of the daily practice of the general urologist. As the number of these patients is continuously increasing, reference centers would not have the capacity to take care of them. On the other hand, many of these, especially elderly ones, do not need a specialized center for primary care. After basic diagnostic work-up, a first-line treatment (mostly conservative) can be effectively provided by the general urologist.

This Manual should help the general urologist to manage these patients adequately. This is a joint initiative by the Brazilian Society of Urology (SBU) and the International Neuro-Urology Society (INUS). Each chapter was written by at least two authors, mostly one SBU member and one INUS member, who discussed and approved the contents in advance. Readers will be informed about LUTS characteristics depending on the underlying
neurological disease, as well as key points of medical history and physical examination, diagnostic work-up and management strategies for NLUTD. This is a quick reference book. Bibliographic references also may guide the reader in the search for additional information.

We would like to thank the unconditional support from all SBU and INUS authors, who believed in this innovative project and gave up precious time to write each one of the chapters that make up the book.

We hope this manual can increase awareness on neuro-urology through a pleasant and direct reading. The beneficiaries will ultimately be the patients suffering from NLUTD.

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Márcio Augusto Averbeck
Helmut Madersbacher
1) EPIDEMIOLOGY OF LOWER URINARY TRACT DYSFUNCTIONS IN PATIENTS WITH NEUROLOGICAL DISEASES

Authors: Riyad Al Mousa, Alfredo Canalini & Luis Augusto Seabra Rios

Introduction

Neural activity of normal micturition is controlled and coordinated by the central and peripheral nervous system. Any damage or diseases of the central or peripheral nervous system may lead to voiding dysfunction and neurogenic lower urinary tract dysfunction (NLUTD). Symptoms and signs may range from simple bothersome frequency, urgency, dysuria or incontinence to serious urinary tract infection, sepsis and possible renal failure in addition to the effect on quality of life [1].

It is challenging to describe accurately the epidemiology of NLUTD due to wide range of terminology that is used in the literature to describe NLUTD (for example neurogenic bladder, neuropathic dysfunction). The incidence depends on the primary cause, the impact is determined by the etiology and the level of CNS or peripheral nervous system injury [2]. The age at which NLUTD occurs, the rate of onset of the neurologic disorder and the patient's gender are other factors that contribute to the symptoms of NLUTD. In one study, it was reported that 8.5% of females aged 15-64 years were affected by NLUTD compared to only 1.6% of males in the same age group [3].

Several neurological conditions contribute to most of the NLUTD and we will have an overview in this chapter of these conditions and their prevalence in relation to NLUTD (see table1).

Multiple Sclerosis (MS):

MS is the most common neuro-inflammatory disorder of the CNS that affects 5 in 100,000 people in low risk areas [3,14]. NLUTD has been found in 40% to 90% of patients with MS. Disruption of the integration between the central and peripheral nervous system and neural demyelination and axonal degradation are likely the cause of NLUTD in MS patients [4]. NLUTD is often noted during the first 10 years following the diagnosis of MS and tends to increase with the progression of the disease and worsening of the disability. Patterns of abnormality varies with detrusor overactivity being the most common (seen in 50% to 90% of patients) and detrusor areflexia in 20% to 30% of patients [5, 6].
**Spinal Cord Injury (SCI):**

Spinal Cord Injury (SCI) usually affects young adults (median age around 35 years) and mostly males (around 83% of victims). Most common causes include: car crashes, falls from a height, and gun shots. In the USA, the current incidence is 4 per 100,000 people \(^5,17,20\). In the last 100 years, the prognosis after a SCI has dramatically changed. Mortality was almost 90% due to complications from neurogenic bladder. With the advent of antibiotics that could treat urinary infections, and intermittent catheterization to protect renal function, mortality is now less than 5% in 10 years after the injury.

NLUTD is very common in patients with SCI; approximately 81% of patients experience some degree of NLUTD. Epidemiology of NLUTD in spinal cord injury patients can be divided into traumatic and non-traumatic. In traumatic spinal cord injury, NLUTD can be seen in 20%-88% of patients. One Brazilian study of 60 patients with traumatic SCI showed 88.3% of those patients developed symptoms of voiding dysfunction \(^2,10\).

In non-traumatic patients, NLUTD ranged from 5.9% to 90%. \(^2\). Detrusor overactivity was the most frequent urodynamic finding, with different rates reported (11% in a Brazilian study and 85% in another Indian study \(^2,11\)). Detrusor overactivity is more common in patients with injuries proximal to the sacral spinal cord, while around 60% of patients with sacral injury develop detrusor areflexia \(^6\).

**Idiopathic Parkinson’s disease (IPD):**

NLUTD has been present in IPD patients as a manifestation of autonomic failure. Symptoms might also be multifactorial in patients due to mobility impairments, comorbidities like benign prostatic hyperplasia and medication side effects. Symptoms of frequency, urgency or urge incontinence (storage symptoms) are present in 57%-83% of patients with IPD while 17%-27% of patients develop voiding symptoms (weak stream, incomplete emptying or hesitancy) \(^12\). NLUTD was seen in 39.3% of 61 IPD Brazilian patients with a mean disease duration of 4.9 years \(^13\).

Detrusor overactivity was the most commonly documented finding in the urodynamics of IPD patients (either alone or in conjunction with other findings like detrusor-sphincter dyssynergia) \(^12\).

**Spina Bifida:**

This congenital defect of neural tube fusion has an incidence of 0.3-4.5/1000 births, and is one of the main cause of neurogenic bladder in childhood \(^10,13\) \(^14\). At Hospital de Base in Brasilia, Brazil, the most common type was open spina bifida (93,1%), most specifically, myelomeningocele (97.9%) at lumbosacral region (63%), followed by lumbar region (19.2%) and thoracolumbar (11.6%) \(^9\).

It is important to note that almost 4% of patients with spinal cord dysraphism have occult spina bifida \(^7\) \(^15\). All teenagers and young adults that present with urinary symptoms that are not usual for that age range should be examined for occult spina bifida; physical exam of gluteus region may reveal signs of this disease such as asymmetry or low implantation of inter-gluteus fold.

NLUTD is common among patients with Spina Bifida with symptoms ranged from 12% to 94.9%. Detrusor overactivity was reported to range from 25% to 76% while detrusor areflexia varied from 13% to 49.5% \(^2,6,14\).
Stroke:

NLUTD ranged from 11.1% to 76% in published studies. Main symptoms included urgency incontinence, urgency and/or nocturia. Urodynamic detrusor overactivity was reported to be present in up to 90% of stroke patients while detrusor hypo contractility was present in 3% of patients [2, 16].

Other conditions:

Other conditions that might contribute to NLUTD may include Diabetes Mellitus, unintended sequelae following pelvic surgery or conditions related to lumbar spine pathology like cauda equine syndrome, dementia and others (see table 2 with conditions and NLUTD prevalence) [15].

The term “diabetic bladder disease” was proposed by Cai Frimodt-Møller in 1976 to describe the impairment of bladder and sphincters in diabetes (DM) due in special to peripheral and autonomic neuropathy (in 50% of patients with DM type I and 25% with DM type II). Neuropathy affects initially afferent nerves, with lowering of bladder sensitivity, increasing of voiding intervals and increasing distension of detrusor. Hypocontractility is the final result [15]. Women with DM usually have OAB associated with a high residual volume of urine; men with DM and prostate hyperplasia have very intense LUTS, including OAB and incomplete bladder emptying [19, 2]. In all patients with LUTS and DM it must be considered the presence of diabetic bladder as cause of disorder or a major supporting factor.

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<th>TABLE 1: THE MAIN NEUROLOGICAL CONDITIONS THAT CONTRIBUTE TO NLUTD.</th>
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<td>Multiple Sclerosis</td>
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<td>Spinal Cord Injury</td>
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<td>Idiopathic Parkinson’s Disease</td>
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<td>Spina Bifida</td>
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<th>TABLE 2: OTHER NEUROLOGICAL CONDITIONS THAT CONTRIBUTE TO NLUTD.</th>
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<td>Brain tumors</td>
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<td>Dementia</td>
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<td>Mental retardation</td>
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<td>Cerebral palsy</td>
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<td>Spinal stenosis and spine surgery</td>
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<td>Diabetes Mellitus</td>
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<td>Alcohol abuse</td>
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<td>Post pelvic surgery</td>
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References

2) NORMAL PHYSIOLOGY OF THE LOWER URINARY TRACT

Authors: Geraldo Cavalcanti & Naoki Yoshimura

Introduction:

The micturition process is controlled by a complex of neural circuits in the brain and spinal cord that coordinate the activity of smooth muscle in the bladder and smooth and striated muscles in the urethra. These circuits alternate the lower urinary tract (LUT) between two modes of operation: storage and elimination.

Injuries or disease of the nervous system in adults can disrupt the voluntary control of micturition, causing the reemergence of reflex micturition and resulting in detrusor overactivity and urgency incontinence. A variety of neurologic disorders can interfere in the LUT due to the complexity of the central nervous control \(^1\). In addition, intrinsic detrusor myogenic abnormalities can contribute to detrusor overactivity. Urgency incontinence can also be caused by urethral dysfunction, because, in patients with mixed urinary incontinence, stress incontinence can cause urgency incontinence due to leakage of urine into the urethra. Increased bladder outlet urethral resistance in men with benign prostatic hyperplasia or other causes of urethral obstruction cause secondary bladder changes, which evoke bladder remodeling and can result in urgency incontinence \(^1\).

This chapter aims to review the function of the bladder wall, including urothelium and detrusor smooth muscle, contribution of the smooth and skeletal muscle urethral function and the interaction of urethra with bladder function, and the organization of neural pathways controlling the LUT.

Gross anatomy of the lower urinary tract

The bladder can be divided into two parts: a body lying above the ureteral orifices and a base consisting of the trigone and bladder neck (Figure 1). The two areas are different
but homogeneous within themselves with respect to neuromorphology and neuropharmacology. Histologic examination of the bladder body reveals that myofibrils are arranged into fascicles in random directions. This architecture differs from the discrete circular and longitudinal smooth-muscle layers in the ureter or gastrointestinal tract.

The bladder outlet is composed of the bladder base, urethra, and striated urethral sphincter (rhabdosphincter). The bladder base has a laminar architecture with a superficial longitudinal layer lying beneath the trigone. A muscle layer deep to the superficial layer is continuous with the detrusor (2).

![Figure 1: Anatomy of the bladder and its outlet [Reproduced from de Groat et al, 2015 (6)].](image)

The urethra begins at the internal meatus of the bladder and extends to the external meatus. In the male, the preprostatic portion, or the bladder neck, consists of a complete circular collar of smooth-muscle cells that extends distally to surround the proximal portion of the urethra. This smooth muscle is densely innervated by sympathetic nerves which mediate sphincter closure during ejaculation. Although this genital function of the bladder neck is well established, it is not known if the smooth muscle of this region normally plays an active role in maintaining urinary continence. However, it has been reported that the damage to sympathetic nerves or interruption of autonomic reflex pathways to the LUT in patients with multiple system atrophy, produces an open bladder neck at rest.

In women, an anatomic smooth-muscle sphincter at the bladder neck is not obvious and the majority of muscle bundles in this region extend obliquely or longitudinally into the urethra (2). The sympathetic innervation is less dense in this region and the function of the bladder neck in maintenance of continence is uncertain because it is preserved in men and some women after destruction or opening of the bladder neck. A passive mechanism in women involving vascular filling of the urethral lamina propria is also thought to contribute to a urethral seal effect and continence.
Striated muscle, which is present in both genders, forms an rhabdosphincter that is separate from, but connected to, the periurethral skeletal muscle of the pelvic floor (Fig. 1). In the male, the striated muscle extends from the bladder base and the anterior aspect of the prostate to the full length of the membranous urethra. The female has an attenuated striated sphincter mechanism divided into two components: (1) a proximal striated sphincter consisting of circular muscle that forms the outermost layer of the muscle wall and (2) a more distal component comprised of two arch-shaped straps of muscle, the compressor urethrae, that arise laterally near the ischiopubic rami and the urethrovaginal sphincter that closely follows the vaginal wall.

Thus, urinary continence in women is maintained during elevations in intra-abdominal pressure by three processes. First, there is passive transmission of abdominal pressure to the proximal urethra. DeLancey (3) proposes the “hammock hypothesis” that abdominal pressure transmitted through the proximal urethra presses the anterior wall against the posterior wall. The posterior wall remains rigid if there is adequate pelvic support from muscle and connective tissues.

However, urethral pressure rises before cough transmission, implicating an active urethral continence (neural) mechanism in women. A guarding reflex involving contraction of striated muscle of the external urethral sphincter (EUS) in conjunction with contraction of smooth muscle of the proximal urethra and bladder neck can transiently promote continence (2). Thus, urinary continence results from the combination of active muscle tone and passive anatomic coaptation.

Furthermore, understanding voiding and continence requires some working knowledge of the contractile properties of smooth and striated muscle. The contractile properties of bladder smooth muscle cells are well suited for either urine storage or release. Filling the bladder at a slow physiologic rate maintains an intravesical pressure of less than 10 cm H₂O and acute denervation of the bladder does not appreciably alter this low filling pressure. This concept has been used to support the hypothesis that the intrinsic myogenic or viscoelastic properties of cellular and extracellular components are major contributors to low-pressure bladder filling and compliance. Conversely, neural input is required for the rapid and sustained smooth muscle contraction accompanying with voiding.

**Physiology of the lower urinary tract**

Measurements of tissue impedance indicate that the detrusor muscle is less well coupled electrically than other smooth muscles (4). Poor coupling could be a feature of normal detrusor to prevent synchronous activation of smooth muscle cells during bladder filling. Thus, although individual cells may contract spontaneously, contraction of the bladder as a whole generally requires stimulation by parasympathetic nerves (5). In response to acetylcholine released from parasympathetic nerve terminals, muscarinic M3 receptors are thought to induce detrusor muscle contractions by increased polyphosphoinositide hydrolysis resulting in inositol 1,4,5-trisphosphate (IP3) production and release of intracellular calcium stores as well as activation of the Rho-kinase system in addition to initiation of action potentials and calcium entry through nifedipine-sensitive L-type Ca channels (Figure 2) (5). The rise in cytoplasmic calcium concentration brought on by intracellular calcium release and action potentials results in binding of calcium to calmodulin. Calcium-bound calmodulin is then capable of activating myosin light-chain kinase, permitting it to phosphorylate the myosin type II light chain. Phosphorylation of the light chain allows the myosin to interact with actin, leading to force generation (Fig. 2) (6).
Figure 2: Muscarinic M3 receptor-mediated detrusor activation. Calcium influx and activation of the Rho-kinase system are the main pathways mediating activation of the contractile system in the detrusor. Intracellular signaling pathways involved in activation and relaxation of detrusor contractions via M2 and M3 muscarinic and β3-adrenergic receptors, respectively. ACh, acetylcholine; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PKA, protein kinase A; MLC, myosin light chain; IP3, inositol triphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; SR, sarcoplasmatic reticulum; CIC, calcium-induced calcium release. Intracellular Ca release and calcium influx contribute to contractions. Activation of M2 muscarinic receptors inhibits adenylate cyclase and reduces β3-adrenergic receptor-mediated relaxation [Reproduced from de Groat et al, 2015 (6)].

Although the bladder smooth muscle may be spontaneously active (4), another population of cells in the bladder, known as interstitial cells, has an important role in modulating spontaneous activity. In the human bladder, subepithelial interstitial cells stain are linked by gap junctions and make close appositions with C-fiber nerve endings in the submucosal layer of the bladder, suggesting that there is a network of functionally connected interstitial cells immediately below the urothelium that may be modulated by nerves. Purinergic receptors and M3 muscarinic receptors are expressed in suburothelial interstitial cells from guinea pigs, and ATP induces inward currents associated with elevated intracellular Ca in these cells (7). Interstitial cells are also present in the detrusor muscle layer. They generate calcium waves in response to activation of M3 muscarinic cholinergic receptors and are spontaneously active, suggesting that they could act as modulators in transmission of nerve signals to smooth-muscle cells.

While the urothelium has been historically viewed as primarily a “barrier,” there is increasing evidence showing that urothelial cells display a number of properties similar to sensory neurons (nociceptors and mechanoreceptors), and use diverse signal transduction mechanisms to detect physiologic stimuli. The urothelial cells are activated in response to
local mechanical or chemical stimuli, releasing chemical mediators such as nitric oxide (NO), adenosine triphosphate (ATP), acetylcholine, prostaglandins, and substance P. These agents are known to have excitatory and inhibitory actions on afferent nerves, which are located close to or in the urothelium, playing a role in bladder sensation by responding to stimuli and then sends chemical signals to the bladder afferent nerves, which convey information to the central nervous system. It is likely that NO is involved in urothelial sensory signaling mechanisms in the bladder and may have a role in modulating inflammatory and nociceptive pathways. ATP released from urothelial cells during stretch can activate a population of suburothelial bladder afferents expressing purinergic receptors to signal changes in bladder fullness and pain. Prostaglandins are also released from the urothelium. These are assigned two possible functions: (1) regulation of detrusor muscle activity and (2) cytoprotection of the urothelium. In addition, the contribution of muscarinic receptors to bladder function extends beyond detrusor contractility to urothelial-afferent interactions. Muscarinic receptors are expressed in the urothelium at high density and there is a basal release of acetylcholine from the urothelium, which is increased by stretch and aging. Activation of the muscarinic receptors in the urothelium releases substances (e.g., ATP) that modulate afferent nerves and smooth-muscle activity.

The urethral smooth muscle in humans consists of a relatively thick inner layer that is predominantly longitudinally arranged, and an outer thinner layer of circular muscle. Contraction of the longitudinal smooth muscle could play a role in the opening of the bladder neck during micturition or in stabilizing the urethra and allowing force generated by the circular muscle elements to occlude the lumen during urine storage.

Striated muscle in the urethra forms a rhabdosphincter and are characterized as slow- and twitch-type. Twitch-type myofibrils can be further classified as slow and fast on the basis of functional and metabolic characteristics. Slow-twitch fibers seem ideally suited for maintaining the sphincter tone for prolonged periods, whereas fast-twitch fibers may be needed to enhance the sphincter tone rapidly to maintain continence when intra-abdominal pressure is abruptly increased. The striated muscle of the distal sphincter mechanism contains predominantly slow-twitch fibers.

**Neural control of the lower urinary tract:**

In general, the lower urinary tract is innervated by three sets of peripheral nerves involving the parasympathetic, sympathetic and somatic nervous systems. Pelvic parasympathetic nerves arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra. Lumbar sympathetic nerves outflow from the rostral lumbar spinal cord inhibit the bladder body and excite the bladder base and urethra. Pudendal nerves excite the urethral striated sphincter.

1. Peripheral efferent innervation:

Bilateral efferent axons of the autonomic nervous system are carried in the pelvic nerves (sacral parasympathetic), hypogastric nerves and sympathetic chain (thoracolumbar sympathetic). Preganglionic axons carrying information from the spinal cord to the bladder and urethra synapse with autonomic ganglion cells widely distribute throughout the peripheral nervous system in: (1) the pelvic plexus; (2) prevertebral sympathetic ganglia (inferior mesenteric ganglia); (3) paravertebral sympathetic chain ganglia; and (4) ganglia on the serosal surface and in the wall (intramural ganglia) of the organs. The striated muscles of the external urethral sphincter (EUS) and pelvic floor (levator ani) are directly innervated by axons originating from motoneurons in the spinal cord by pudendal nerves and another set of somatic nerves innervating the pelvic floor (levator ani nerves), respectively.
Excitatory parasympathetic neuroeffector transmission in the bladder is mediated by acetylcholine acting on postjunctional muscarinic receptors (Fig. 3B) (5). Both M2 and M3 muscarinic receptor subtypes are expressed in bladder smooth muscle. However, the use of subtype-selective muscarinic receptor antagonists and muscarinic receptor knockout mice revealed that the M3 subtype is the principal receptor involved in excitatory transmission (Figure 3). Activation of M3 receptors triggers intracellular calcium release whereas activation of M2 receptors inhibits adenylate cyclase (5). The latter may contribute to bladder contractions by suppressing adrenergic inhibitory mechanisms which are mediated by beta-3 adrenergic receptors and stimulation of adenylate cyclase (Fig. 2).

In bladders of various animals, stimulation of parasympathetic nerves also produces a non-cholinergic contraction that is resistant to atropine and other muscarinic receptor-blocking agents. ATP is the excitatory transmitter mediating the non-cholinergic contractions (5). ATP excites the bladder smooth muscle by acting on purinergic receptors which are ligand-gated ion channels. Purinergic transmission does not play an important excitatory role in normal human bladder, but it appears to be involved in bladders from patients with pathologic conditions such as detrusor overactivity, chronic urethral outlet obstruction, or interstitial cystitis.

Parasympathetic input to the urethra induces relaxation during voiding (5). In various species the relaxation is not affected by muscarinic antagonists and therefore is not mediated by acetylcholine. However inhibitors of NO synthase block the relaxation in vivo during reflex voiding or block the relaxation of urethral smooth-muscle strips induced in vitro by electric stimulation of intramural nerves, indicating that NO is the inhibitory transmitter involved in urethral relaxation (3).

Sympathetic preganglionic pathways that arise from the T11–L2 spinal segments pass to the sympathetic chain ganglia and then to prevertebral ganglia in the superior hypogastric and pelvic plexus (Fig. 3A) and also to short adrenergic neurons in the bladder and urethra. Sympathetic postganglionic nerves that release norepinephrine provide an excitatory input to smooth muscle of the urethra and bladder base, an inhibitory input to smooth muscle in the body of the bladder, and inhibitory and facilitatory input to vesical parasympathetic ganglia (3, 5). Alpha-adrenergic receptors are concentrated in the bladder base and proximal urethra, whereas beta-adrenergic receptors are most prominent in the bladder body (Fig. 3B) (5). These observations are consistent with pharmacologic studies showing that sympathetic nerve stimulation or exogenous catecholamines produce beta-adrenergic receptor-mediated inhibition of the body and alpha-adrenergic receptor-mediated contraction of the bladder base and urethra. Molecular and physiologic studies have shown that beta-3 adrenergic receptors elicit inhibition and a alpha-1 adrenergic receptors elicit contractions in the human bladder (5). The alpha-1A adrenergic receptor subtype is most prominent in the normal bladder but the alpha-1D subtype is upregulated in bladders from patients with outlet obstruction, raising the possibility that a alpha-1 adrenergic receptor excitatory mechanisms in the bladder might contribute to storage lower urinary tract symptoms in patients with benign prostatic hyperplasia (5).

Somatic efferent pathways to the EUS are carried in the pudendal nerve from anterior horn cells in the third and fourth sacral segments of the human spinal cord (Onuf nucleus).
2. Peripheral afferent innervation:

Afferent axons in the pelvic, hypogastric, pudendal, and levator ani nerves transmit information from the lower urinary tract and pelvic floor to second-order neurons in the lumbosacral spinal cord. Pelvic nerve afferents that innervate the bladder and urethra originate in caudal lumbosacral dorsal root ganglia (DRG) and are divided into two populations: small myelinated Aδ-fibers and unmyelinated C-fibers. The pudendal and levator ani nerves also contain larger-diameter myelinated afferents. Aβ-fiber afferents that terminate in the skin are present in the pudendal nerve and Aα-fiber afferents that innervate muscle spindles are present in the levator ani nerve.

Aδ-fiber mechanoreceptor afferents identified in the pelvic nerve or the sacral dorsal roots of the cat respond to both passive distension as well as active contraction of the bladder, indicating that they are in series tension receptors. These afferents are silent when the bladder is empty but during slow filling of the bladder occur a successive recruitment of mechanoreceptors with different thresholds during bladder filling. The normal micturition reflex is triggered by myelinated Aδ-fiber afferents.

In contrast to the low-threshold mechano-sensitive Aδ-fiber bladder afferents, the C-bladder afferents in cats are generally mechano-insensitive (“silent C-fibers”). Many of these afferents are nociceptive and respond to cold stimuli or chemical/noxious stimuli.
Following exposure to these stimuli silent afferents become mechanoreceptive and the sensitivity of bladder mechanoreceptors to distension also increases. Because capsaicin, the C-fiber afferent neurotoxin, does not block normal micturition reflexes in cats and rats, it is believed that C-fiber afferents are not essential for normal voiding. On the other hand, the efficacy of capsaicin in reducing bladder overactivity induced by noxious stimuli indicates that C-fiber afferents do play an important role in lower urinary tract dysfunction in pathologic conditions (9).

3. Reflex circuitry controlling micturition:

The reflex circuitry controlling micturition consists of four basic components: primary afferent neurons, spinal efferent neurons, spinal interneurons, and neurons in the brain that activate or modulate spinal reflex pathways.

In the spinal cord, afferent nerves terminate on second-order interneurons that relay information to the brain or to other regions of the spinal cord. Because disynaptic or polysynaptic pathways mediate bladder, urethral, and sphincter reflexes, interneuronal mechanisms must play an essential role in the regulation of lower urinary tract function.

Thus spinal interneurons in these locations receiving afferent input from the lower urinary tract have also been identified by firing in response to stimulation of bladder afferents. Some of these interneurons make excitatory and inhibitory synaptic connections with postganglionic neurons and participate in segmental spinal reflexes, whereas others send long projections to supraspinal centers, such as the periaqueductal gray (PAG), pontine micturition center (PMC, Barrington's nucleus), the hypothalamus and thalamus that are involved in the supraspinal control of micturition (6).

Nociceptive and non-nociceptive sensory input from the lower urinary tract is transmitted to the brain via multiple spinal tracts. In humans, these ascending sensory pathways are located in the most lateral part of the spinal cord, about midway between the anterior and posterior horns (spinothalamic tract). However most patients with unilateral lesions of the spinothalamic tract did not notice any change in bladder function and retained normal sensation of a full bladder and desire to micturate. Following damage to the cauda equina or the spinal cord below the mid lumbar level, afferent axons passing through prevertebral sympathetic nerves and the sympathetic chain to the rostral lumbar or caudal thoracic segments (T11-L2) can also initiate sensations from the lower urinary tract. A second spinal ascending pathway from the pelvic viscera that initiates painful sensations is located in the dorsal columns. This pathway originates in spinal neurons in the region of the dorsal commissure and projects along the midline to make synaptic connections with neurons in the nucleus gracilis which then relay information to the ventral posterior lateral nucleus of the thalamus (1).

Many populations of neurons in the brain that are involved in the control of bladder, urethra, and the EUS have also identified, including the PMC, PAG, medullary raphe nuclei, which contain serotonergic neurons; the locus coerules, which contains noradrenergic neurons, and the A5 noradrenergic cell group (Figure 4). More rostral regions in the hypothalamus, dorsal thalamus, the primary and secondary motor cortices and entorhinal and piriform cortices also exhibit virus-infected cells by pseudorabies virus (PRV) in animal studies. In the cat, PRV tracing from the urinary bladder or the EUS identified a cluster of neurons extending from the PMC ventrolaterally into the pontine reticular formation (11).

In humans the descending tracts subserving the conscious control micturition and coordination of bladder function are located within the lateral columns in close association with the ascending sensory pathway at the level of the central canal throughout the length of the spinal cord.
These multiple reflex pathways organized in the brain and spinal cord mediate coordination between the urinary bladder and the urethra. The central pathways controlling lower urinary tract function are organized as simple on-off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet. Some reflexes promote urine storage, whereas others facilitate voiding. Direct activation of these reflexes by electrical stimulation of the sacral spinal roots very likely contributes to therapeutic effects of sacral nerve root neuromodulation.

Figure 4: Connections between the lumbosacral spinal cord and brain areas involved in bladder control. The central pathways involved in controlling the urinary bladder can be visualized in rats using trans-neuronal virus tracing. Injection of pseudorabies virus into the wall of the urinary bladder leads to retrograde transport of the virus and the sequential infection of postganglionic neurons, preganglionic neurons, spinal interneurons and then various supraspinal neural circuits that are synaptically linked to the spinal preganglionic neurons and interneurons. The supraspinal sites labeled by the virus transport include the pontine micturition center (Barrington’s nucleus), the cerebral cortex, the paraventricular nucleus (PVN), the medial preoptic area (MPOA) and periventricular nucleus (PeriVN) of the hypothalamus, the periaqueductal gray (PAG), the locus coeruleus (LC) and subcoeruleus, the red nucleus, the raphe nuclei, and the A5 noradrenergic cell group [Reproduced from Fowler et al., 2008 (15)].

a. The storage phase of the bladder:
- The accommodation of the bladder to increasing volumes of urine is primarily a passive phenomenon dependent on the intrinsic properties of the vesical smooth muscle and stroma, as well as, the quiescence of the parasympathetic efferent pathway. The bladder to sympathetic reflex also contributes as a negative feedback to urine storage mechanism that promotes closure of the urethral outlet and inhibits neurally mediated contractions of the bladder during bladder filling. Sympathetic reflex activity is elicited by a sacralolumbar intersegmental spinal reflex pathway that is triggered by vesical afferent activity in the pelvic nerves (Figure 5). The reflex pathway is inhibited when bladder pressure is raised to the threshold for producing micturition. This inhibitory response during voiding is abolished by transection of the spinal cord at the lower thoracic level, indicating that it originates at a supraspinal site, possibly the PMC. Thus, the vesicosympathetic reflex represents a negative-feedback mechanism that allows the bladder to accommodate larger volumes during bladder filling but is turned off during voiding to allow the bladder to empty completely.
• During bladder filling, the activity of the sphincter electromyogram also increases, reflecting an increase in outlet resistance that contributes to the maintenance of urinary continence. Contraction of the EUS also induces firing in afferent axons in the pudendal nerve, which in turn activate inhibitory interneurons in the spinal cord that suppress reflex bladder activity by inhibiting postganglionic nerve and interneurons on the micturition reflex pathway. Thus the bladder-to-EUS-to-bladder reflex pathway represents a second negative-feedback mechanism in the spinal cord that promotes urinary continence. Activation of afferents in the pudendal nerve, some of which very likely innervate the EUS, also elicits reflex contractions of the EUS and contributes to continence (the guarding reflex). During micturition, the firing of sphincter motoneurons and the negative feedback is inhibited. This inhibition is dependent in part on supraspinal mechanisms.

b. The emptying phase of the bladder:
• The storage phase of the bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. The former is readily demonstrated in the human infant or in patients with neuropathic bladder when the bladder wall tension during increased volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder reverses the pattern of efferent outflow, producing firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the urethral sphincter followed in a few seconds by a contraction of the bladder, an increase in bladder pressure, and the flow of urine. Relaxation of the urethral smooth muscle during micturition is mediated by activation of a parasympathetic pathway to the urethra that triggers the release of NO and by removal of excitatory inputs to the urethra. Secondary reflexes elicited by flow of urine through the urethra facilitate bladder emptying. These reflexes require the integrative action of neuronal populations at various levels of the neuraxis. Barrington identified two components of a facilitatory urethra to bladder reflex that could promote complete bladder emptying. One component was activated by a somatic afferent pathway in the pudendal nerve and produced facilitation by a supraspinal mechanism involving the PMC. Studies in cats using brain-lesioning and electrophysiologic techniques revealed that reflex micturition is mediated by a spinobulbospinal pathway consisting of an ascending sensory limb that passes from the sacral spinal cord to circuitry in the rostral brainstem, leading to activation of neurons in the PMC that send excitatory signals back to the sacral spinal cord to complete the reflex circuit (Fig 5).
• Pharmacologic studies indicate that circuitry in the PMC and periaqueductal gray (PAG) allows the spinobulbospinal micturition reflex pathway to function as a switch that is either in a completely “off” mode (storage) or maximally “on” mode (voiding). Because pharmacologic modulation of the PAG circuitry clearly alters the bladder volume threshold, it seems reasonable to conclude that PAG inputs to the PMC switching circuit also regulate the set point for the micturition switch.
• The other component was activated by a visceral afferent pathway in the pelvic nerve and produced facilitation by a spinal reflex mechanism. This may be an explanation of why stress incontinence and urgency incontinence often occur together in women.
• Human and animal brain imaging studies using various methods have examined the areas of the brain involved in the control of micturition. During urine storage activation
occurs in the PAG, thalamus, insula, prefrontal cortex, anterior cingulate, pons, medulla, and supplementary motor area. These results are consistent with the notion that the PAG receives information about bladder fullness and then relays this information (possibly through the thalamus) to other brain areas involved in the control of urine storage. The insula, where normal visceral sensations such as desire to void are thought to be mapped, is regarded as a key center for processing bladder afferent input. During voiding, activation occurs in the prefrontal cortex, insula, hypothalamus, PAG, and PMC.

Figure 5: Neural circuits that control continence and micturition. (A) Urine storage reflexes. During the storage of urine, distension of the bladder produces low-level vesical afferent firing. This in turn stimulates sympathetic outflow in the hypogastric nerve to the bladder outlet (the bladder base and the urethra) and pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle and modulates neurotransmission in bladder ganglia. A region in the rostral pons (the pontine storage center) might increase striated urethral sphincter activity. (B) Voiding reflexes. During the elimination of urine, intense bladder afferent firing in the pelvic nerve activates spinobulbospinal reflex pathways (shown in blue) that pass through the pontine micturition center. This stimulates parasympathetic outflow to the bladder and to the urethral smooth muscle (shown in green) and inhibits sympathetic and pudendal outflow to the urethral outlet (shown in red). Ascending afferent input from the spinal cord might pass through relay neurons in the periaqueductal gray (PAG) before reaching the pontine micturition center. Note that these diagrams do not address the generation of conscious bladder sensations, nor the mechanisms that underlie the switch from storage to voluntary voiding, both of which presumably involve cerebral circuits above the PAG. R, receptors on afferent nerve terminals. [Reproduced from Fowler et al., 2008 (15)].

Conclusions
The functions of the lower urinary tract to store and periodically eliminate urine are regulated by a complex neural control system that performs like a simple switching circuit to maintain a reciprocal relationship between the bladder and urethral outlet. The switching circuit is modulated by several neurotransmitter systems and is therefore sensitive to a variety of drugs and neurologic diseases. Further research is needed, particularly in humans using brain imaging techniques, to identify the pathways in the forebrain that exert voluntary control over primitive micturition reflex circuitry in the brainstem and spinal cord.
References


3) PATHOPHYSIOLOGY OF NEUROLOGICAL LOWER URINARY TRACT DYSFUNCTION AND TOPOGRAPHIC CORRELATION OF NEUROLOGICAL LESIONS

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Trauma or diseases of the Central Nervous System (CNS) are frequent causes of neurological lower urinary tract dysfunction (NLUTD) that may impose a significant risk for the urinary tract as well as a negative impact on the quality of life. Complications such as urinary incontinence, urinary tract infections, hydronephrosis and even renal failure may be consequences of NLUTD.

The evaluation and treatment of patients with NLUTD demands a good understanding of the neurophysiology of the lower urinary tract as well as the pathophysiological changes that may result from a variety of neurological conditions.

Normal vesico-sphincteric function – Neurophysiology

The lower urinary tract includes different organs and structures that function in association to promote bladder filling at low pressures with adequate urinary continence and periodic complete voluntary emptying of the bladder under low pressure. The micturition cycle may be divided into two phases: bladder filling/urine storage and bladder emptying/voiding. For these phases to occur properly, it is necessary that the bladder smooth muscle (detrusor) relaxes and the urethral sphincter increases its activity during the filling (storage) phase of the micturition cycle and the opposite during the voiding (emptying) phase. The coordination of the bladder and the urethral sphincter activities involves a complex interaction between the central and peripheral nervous systems and local regulatory factors, and is mediated by various neurotransmitters.

The bladder function is coordinated at different levels of the CNS located in the spinal cord, pons and higher brain centers, through excitatory and inhibitory neurologic inputs that
travel to the LUT organs and from sensory afferent nerves originating from these organs. Peripherally, the LUT is innervated by three types of fibers: (1) parasympathetic; (2) sympathetic and (3) somatic nerves. The vesical parasympathetic innervation is originated from neurons located at the intermediolateral spinal cord segments S2 to S4 and courses through the pelvic nerve to the ganglia located in the pelvic plexus. This is located laterally to the rectum and gives an origin to postganglionic parasympathetic fibers that innervate the bladder. The efferent sympathetic innervation originates at the thoraco-lumbar spinal cord level (T10 to L2) and travels through the sympathetic chain to the superior hypogastric plexus (pre-Aortic plexus). Its caudal subdivision forms the hypogastric nerve, which contains postganglionic efferent nerves to the bladder and urethra. The urethral rhabdosphincter innervation is predominantly somatic. It originates from the Onuf’s nucleus, located at the anterior horn of the sacral spinal cord (S2-S4) and travels to the urethra through the pudendal nerves. There is evidence showing that the urethral sphincter receives sympathetic and parasympathetic innervation originating from the branches of the hypogastric and pelvic nerves, respectively. Afferent sensory nerve fibers coursing along the same nerves transmit sensory signals from the bladder wall and the urethra to the dorsal horn of the spinal cord where they connect to secondary neurons directed to structures in the brainstem and the brain.(3, 4)

The neurological activity of the spinal cord centers is controlled by supraspinal centers located at the brainstem and the brain, through ascending and descending cephalospinal tracts. The micturition is coordinated at the brainstem, specifically at the pontomesencephalic regions, known as the pontine micturition center (PMC), which acts as a switching center for the bladder motoneurons. Under normal circumstances, the micturition depends on a spinal-bulbo-spinal reflex enabled by the PMC.(3, 4) The PMC is under control of the higher brain centers, including the periaqueductal grey (PAG), cerebral cortex, cerebellum, basal ganglia, thalamus and hypothalamus, mostly inhibitory. (3-6)

Briefly, the normal micturition cycle can be described as follows: (1) Filling: progressive bladder distension is accompanied by spinal sympathetic reflexes that facilitate bladder filling through the hypogastric nerve, which are mediated by stimulation of alpha-1-adrenergic receptors in the smooth muscle urethral sphincter and bladder neck and by beta-3-adrenergic receptors in the bladder body smooth muscle. Bladder distension also promotes the release of substances from the urothelium that may influence bladder contractility, including acetylcholine, nitric oxide, adenosine triphosphate, prostaglandins and other peptides. The PAG and higher brain centers continuously monitor the bladder filling and maintain an inhibitory influence over the parasympathetic sacral spinal center while gradually increasing activation of the urethral sphincter; (2) Voiding: as bladder distension reaches a critical point and in the presence of voluntary desire to void, the PMC inhibits the efferent activity to the rhabdosphincter and also the sympathetic spinal activity while activating the efferent parasympathetic pathways resulting in massive contraction of the bladder smooth muscle and relaxation of the bladder outlet.(2) The normal micturition cycle displays these two modes and is continuously switching from inhibition of the voiding reflex and activation of storage reflexes to inhibition of the storage reflexes and activation of the voiding reflex.(2, 5)

Pathophysiology of Neurogenic Lower Urinary Tract Dysfunction

Knowledge of the neuroanatomy and neurophysiology involved in the control of the normal micturition cycle may help one to predict which types of lower urinary tract abnormalities may arise from injuries to the nervous system.(1) In this regard, the location of the structures affected by the neurological disease/injury and the physiologic function
of the affected areas are critical. In the schematic classification that follows, the vesico-
sphincteric dysfunction associated with injuries at different neurological levels is assuming
a complete neurological lesion after the initial phase of spinal or brain shock following spinal
cord injuries or cerebrovascular accidents:

(1) Neurological lesions above the brainstem, usually result in involuntary detrusor
contractions with coordinated vesico-sphincteric function (Figure 1). Bladder
sensation is generally preserved. Detrusor areflexia may occur either initially or
as a permanent dysfunction. Lower urinary tract symptoms (LUTS) may include
increased urinary frequency, urgency, urgency incontinence and nocturia. Occasional patients with detrusor areflexia or underactivity may have voiding
symptoms. Deterioration of the upper urinary tract is uncommon. The most
frequent neurological conditions in this category are cerebrovascular accidents,
Parkinson disease, Multiple system atrophy and brain tumors.(1, 7, 8)

(2) Suprasacral spinal cord lesions generally result in involuntary detrusor
contractions with incoordinated (dyssynergic) vesico-sphincteric function and
decreased or abolished bladder sensation. In lesions below the T6 level, smooth
sphincter function is usually synergic, with striated sphincter dyssynergia. In
lesions above this level, both sphincters are dyssynergic (Figure 2). The main
neurological conditions causing injuries at this level of the spinal cord are
traumatic spinal cord injury, Multiple sclerosis, thoraco-lumbar myelodysplasia
(myelomeningocele) and myelitis of different etiologies. (7, 9-11) In these patients,
LUTS usually include both storage and voiding symptoms. Increased bladder
pressures pose a significant threat to the bladder and upper urinary tracts,
especially in association with high postvoid residuals. These conditions
predispose to urinary tract infections and progressive bladder and upper urinary
tract deterioration and may ultimately lead to renal function impairment.

(3) Sacral spinal cord injuries below S2 generally result in detrusor areflexia, since
the parasympathetic micturition center is damaged. Decreased compliance
may ensue as a result of bladder fibrosis. Bladder sensation is usually impaired.
Urethral sphincter function may be affected in different ways. Striated sphincter
retains a residual resting tone but is not under voluntary control. Stress
urinary incontinence may occur due to sphincteric deficiency (Figure 3). LUTS
include voiding symptoms such as decreased urinary flow, Valsalva voiding,
interrupted flow and storage symptoms such as stress urinary incontinence.
Overflow incontinence may also occur. Neurological conditions most commonly
associated with injuries at this level are traumatic spinal cord injuries, lumbosacral
myelodysplasia (myelomeningocele) and sacral malformations. (1, 12, 13)

(4) Injuries to the peripheric nerves usually behave similarly to those affecting the sacral
spinal cord including detrusor areflexia, possible decreased compliance and sphincteric
dysfunction. Common causes are extensive pelvic trauma and radical pelvic surgeries.

It is important to highlight that the abovementioned vesico-sphincteric patterns are
dictated by a number of factors, not only the neurological level of the injury. These include the
severity of the injury (complete vs. incomplete), etiology (destructive vs. irritative/reversible),
previous or concomitant neurological lesions, concomitant urological conditions (benign
prostatic hyperplasia or severe vaginal prolapse) and the progression of the NLUTD. Thus,
it is not possible to accurately predict the pattern of vesico-sphincteric behaviour based
exclusively on the level of the neurological injury. (1, 13, 14)
References

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) (also referred to as neurogenic bladder [NGB]) refers to dysfunction of the urinary bladder and urethra due to lesions of the central nervous system or peripheral neurogenic lesions. So NLUTD can occur in a large population of patients suffering from various neurologic conditions such as spinal cord injury (SCI), stroke, traumatic brain injury, brain tumor, meningomyelocele, cerebral palsy, multiple sclerosis, disk disease, Parkinson's disease, and other diseases with long-term neurologic dysfunction, such as diabetes, pernicious anemia, and tabes dorsalis. The pattern of voiding dysfunction depends on the extent, the evolution and the site of the neurological dysfunction and may require close monitoring for symptomatic control and evaluation for potential upper tract deterioration.

Diagnostic evaluation

The urinary tract is evaluated in detail. Patients can remain asymptomatic until in some cases, lower urinary tract symptoms (LUTS) develop. The clinical symptoms of NLUTD, depends on the levels of lesions. Clinical assessment of these patients includes a detailed history, a systematic physical examination, a bladder diary, laboratory exams and urodynamic tests. Table 1.
**History taking**

History taking should include past and present symptoms and disorders of:

(a) Urinary tract: bladder sensation, initiation of micturition (normal, precipitate, reflex, Credé), interruption of micturition (normal, paradoxical, passive), enuresis, mode and type of voiding (catheterization).

(b) Bowel: Frequency and fecal incontinence, desire to defecate, defecation pattern.

(c) Sexual: Genital or sexual dysfunction symptoms, sensation in genital area. Male (erection, orgasm, ejaculation). Female (dyspareunia, orgasm).

(d) Neurological history. Acquired or congenital, mental status and comprehension, neurological symptoms, spasticity or autonomic dysreflexia, mobility and hand function.

(e) Medication history should be reviewed.

Special attention should be paid to possible warning signs and symptoms (pain, hematuria, infection, fever) requiring further investigation.

Suprapontine neurologic lesions differ from other neurologic insults because they lead to loss of tonic inhibition of the pontine micturition center (PMC). This can lead to involuntary bladder contractions with sphincter synergy and preserved bladder sensation, and neurogenic detrusor overactivity (NDO) is likely to develop, which is different than detrusor overactivity (DO) that occurs after supra-sacral SCI. In the case of SCI, a period of spinal shock occurs, after which a segmental reflex develops at the level of the sacral spinal cord, mediated by C-fiber afferents, which leads to DO. This category is characterized by storage dysfunction. Normal uroflow and normal postvoid residual (PVR) can generally be expected. In some cases detrusor underactivity (DU) has been reported, as well as detrusor overactivity with impaired contraction (DOIC), so it is important to acknowledge that DO is not the only finding in supra-pontine injury. Another common cause of suprapontine neurologic lesion are cerebrovascular accident (CVA), CVA is most commonly associated...
with urge urinary incontinence (UUI) and DO. It is thought to be due to loss of the inhibitory function of the frontal cortex on the PMC. Typically the sphincter is coordinated and only DO results from a suprapontine lesion, keeping the upper tracts more safe than an infra-pontine lesion, such as SCI. DO is not the only finding that is possible in CVA, however. In fact one prospective observational series of consecutive post-CVA patients reported 79% of 106 patients were incontinent, with 56% exhibiting DO on urodynamics, 14% with DOIC, and 15% with DU. Traumatic brain injury (TBI) can be associated with 47% of all SCI’s. Due to the complex cognitive and mobility issues that often accompany these patients, it is best to take a team approach and follow the guidelines for SCI when assessing a patient with TBI.

With cerebral diseases the risk for upper urinary tract (UUT) damage is low. Therefore, e.g. in a stroke patient with overactive bladder symptoms, urodynamic study is not necessary when voiding is without PVR.

Spinal cord lesions can be traumatic, vascular, medical, or congenital. A high correlation exists between the clinical neurological findings and NLUTD in single-level traumatic spinal cord lesions, but not in myelomeningocele and combined traumatic spinal cord lesions. Supra sacral spinal cord injury (SCI) leads to DO via establishment of new C-fiber mediated segmental reflexes as described above with the additional loss of coordination of the smooth urethral sphincter, known as detrusor sphincter dyssynergia (DSD). This category is characterized by storage and emptying dysfunction. Urinary urgency/frequency, UUI, and intermittent stream or hesitancy can be expected. Urinary retention is common during the first 6–8 weeks after a SCI, a period known as spinal shock phase, but not all supra-sacral neurologic disorders are caused by SCI. Urinary retention may persist after spinal shock has resolved. Supra sacral SCI has been associated with upper tract deterioration. Non-relaxing urethral sphincter obstruction or DSD has been associated with elevated voiding pressures and may contribute to damage to the upper urinary tract, and has poor compliance, whether associated with vesicoureteral reflux (VUR) or not.

Sacral SCI leads to weak or absent detrusor contraction (neurogenic detrusor underactivity or neurogenic acontractile detrusor) and a tonic contraction of the smooth urinary sphincter (“non-relaxing urethral sphincter obstruction”). Emptying dysfunction predominates. Uroflow can be expected to be absent or diminished. Urodynamics may reveal abdominal straining to empty and elevated PVR.

In suprasacral SCIs, invasive urodynamic study (UDS), or preferably video urodynamic study (VUDS), should be performed regularly, at least during the first 3–5 years after the injury, as the change in compliance and pressure due to increasing DSD may be present before symptoms occur, and can then be diagnosed in time before possibly irreversible changes in the urinary tract have occurred.

Also sacral and infrasacral lesions deserve regular controls, especially when the bladder is expressed by Valsalva or Credé, as these maneuvers may create unphysiologically high intravesical pressure, causing vesicoureteral reflux. But also a low-compliance bladder may develop over time despite an incompetent sphincter, a condition only detected by UDS.

**Physical examination**

On physical examination assessment of mobility, balance, spasticity, weakness, coordination, and cognition are taken, for example in regard to accessing and using toilet facilities, and potential ability to use specific treatment options. Hand function is a particular consideration, since the ability to hold a catheter and the genitals is a requirement for intermittent catheterization (IC).

The physical examination includes testing sensations and reflexes, mapping out distinct areas of sensory impairment helps to further localize the site of lesion. Figure 1.
• Sensation S2-S5: Presence (increased/normal/reduce/absent), Type (light touch/pin prick), in case affected dermatomes.
• Anal sphincter tone: Presence (increased/normal/reduce/absent). Voluntary contraction of anal sphincter and pelvis muscles.
• Reflex Testing: Can be graded (increased/normal/reduced/absent)
• Bulbocavernosus reflex: Contraction of external anal sphincter or bulbocavernous muscle elicited by briskly squeezing the glans penis.
• Anal reflex: contraction of the anal sphincter on irritation of the anal skin.
• Cremasteric Reflex: contraction of the ipsilateral cremaster muscle, when the upper inner aspect of the thigh is stroked longitudinally.
• Babinski reflex: Plantar responses are normal if the great toe moves in a plantar fashion following a stimulus to the foot, an extensor plantar response results in extension of the great toe following by abduction “fanning” of the rest of the toes.
• Deep Tendon Reflexes.
  • The knee jerk is tested by striking the quadriceps tendon directly with the leg hanging freely off the edge of a chair. The ankle reflex is elicited by holding the relaxed foot with one hand and striking the Achilles tendon with the hammer and noting plantar flexion.
  • Exaggerated reflexes suggest corticospinal tract dysfunction causing disinhibition of the locally-mediated spinal reflex. Absent or suppressed may be sign of an underlying peripheral neuropathy or myopathy. (15)

Figure 1. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum (B), and male external genitalia.
**Bladder Diary**

A bladder diary is valuable, as it identifies polyuria, nocturnal polyuria, daytime and nighttime frequency, pad usage and incontinence episodes. Optimal diary duration is 3 or 4 days in the general population, as a suitable compromise balancing information captured against inconvenience to the patient; studies on optimal duration have not been formally reported in NLUTD.

**Specific Questionnaires**

Three condition specific questionnaires have been developed for the evaluation of neuro-urological patients (7,11).

- Urinary symptoms: Qualiveen for Multiple Sclerosis (MS) and SCI patients. Neurogenic Bladder Symptom Score for MS, SCI, spina bifida patients.
- Bowel dysfunction: Quality of Life scoring tool related to Bowel Management (QoL-BM) for MS and SCI patients.
- Quality of life: Incontinence Quality of Life Instrument (I-QOL), King’s Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12). No evidence was found for which validated questionnaires are the most appropriate for use.

**Laboratory exams**

Patients with NLUTD may be at risk of UTI. In many cases, symptoms may not reflect the presence of UTI and bacterial colonization, potentially contributing to the clinical presentation, so urinalysis is a requirement (12). Measuring of serum creatinine, and calculating the glomerular filtration rate (GFR), yields a reasonable estimation of renal function. Creatinine clearance provides a more accurate assessment. The GFR scintigraphy is recommended when renal function is poor, in individuals with reduced muscle mass and high-risk patients.

Renal function and structure assessment can be made by serum tests and ultrasound scans respectively. The PVR urine volume is measured by ultrasound or alternatively by in-out catheterization. The PVR volume should be measured on different occasions to establish how bladder emptying varies at different times and circumstances. Patients with high risk of upper urinary tract disease, surveillance ultrasonography should be undertaken periodically (at least 6 months) to detect upper urinary tract dilation.

**Urodynamic tests**

The nature and severity of NLUTD can be difficult to appreciate from clinical assessment alone, and urodynamic tests are tools that evaluate bladder and outlet function during bladder filling and emptying, by measuring multiple functional parameters in NLUTD. Relevant investigations include: bladder diary, urodynamic studies (cystometry, electromyography (EMG), uroflowmetry, pressure-flow study), diagnostic imaging with voiding cystourethrography and ultrasonography. The use of multichannel cystometry and pressure flow studies with synchronous imaging (video-urodynamics) offers suitable testing in most patients.

**Initial Study**

Timing of the initial UDS in patients with an acute neurologic injury depends on the return of their bladder reflexive function. The initial 3 months from the injury, are usually the
period of spinal shock phase. Spinal shock was first defined by Whytt in 1750 as a loss of sensation accompanied by motor paralysis with initial loss but gradual recovery of reflexes, following a SCI most often a complete transection, reflexes in the spinal cord below the level of injury are depressed (hyporeflexia) or absent (areflexia). Recovery of bladder function often manifests with incontinence between catheterizations as well as with new onset of lower extremity spasms.

Recommendations for the timing of UDS in children with spinal dysraphism is not well defined (1,14). The International Consultation on Incontinence has the only recommendations about UDS in children, stating that “to help identify children at risk for subsequent urinary tract deterioration or a changing neurologic picture, initial UDS studies early in the neonatal period are recommended for children with myelodysplasia or occult spinal dysraphism.”

**Filling Rate**

The initial filling rates for patients with NLUTD, as indicated by the International Continence Society in their “Good urodynamic practices” document should be slow, a pump should infuse body-warm saline at 10 mL/min, in addition to the natural bladder filling with physiologic urine production. This is to gain a clear appreciation of the pressure change with increasing volume (compliance).

**Electromyography**

EMG is especially important in evaluation of patients with neurologic lesions suggestive DSD or other evidence of impaired bladder emptying. DSD is seen during the voiding phase of the UDS.

**Filling cystometry**

Bladder properties are assessed over the course of filling from empty to maximum capacity, evaluating sensation, detrusor function during filling, leak point pressures.

During filling cystometry, various urodynamic observations may be made:

1. Reduced or absent bladder sensation, bladder oversensitivity, abnormal sensations, bladder pain and non-specific bladder awareness.
2. Detrusor function during filling cystometry: Neurogenic detrusor over activity and incontinence.
3. Urodynamic stress incontinence: the patient is asked to do a series of strong coughs, to see whether the resulting rise in abdominal pressure causes urinary leakage.
4. Poor bladder compliance, signifying a rise in pressure with ongoing bladder filling, which can be particularly exaggerated if filling rate is accelerated. Compliance can be highly problematic for renal function, due to implications for ability of urine emptying from the renal pelvis. The recognition that bladder storage pressure is related to upper tract damage was first published in 1978 by Light and colleagues, who reported upper tract deterioration in children with myelodysplasia. This was followed by the landmark work of McGuire and colleagues, in 1981, who described more definitively that myelodysplastic children with elevated detrusor leak point pressure (DLPP) are at risk to
develop upper tract disease, there was close relationship between UUT deterioration and intravesical pressure on urethral leakage of >40 cmH2O. The compliance could be affected by functional mechanism, like when a disease affects the sacral part of spinal cord, for example, or by structural one when connective scarring tissue of the bladder wall decrease its viscoelastic properties.

**Conclusion**

Preservation of renal function is the main goal of management of a patient with NLUTD. The Urodynamic Study is the study of choice to identify patients at risk for upper tract deterioration as evidenced by high DLPP. This patient population presents a unique set of challenges because they often lack symptoms, and/or the severity of symptoms does not correlate with the extent of potential risk for the renal function. Patients with acute neurologic injury should have initial evaluation delayed until recovery of the initial period of spinal or cerebral shock, once bladder function returns, which often occurs around 3 months after injury. Children with spinal dysraphism should have initial studies performed early in life to identify those at higher risk. Follow-up UDS are performed in patients with change in symptoms, impairment of renal function, or concerning imaging studies.
References


5) (VIDEO-) URODYNAMICS

Introduction

Urodynamic investigation (UDI) is the gold standard to evaluate lower urinary tract function in patients with neurological diseases, especially when there is evidence or history of spinal cord injury (SCI) (1, 2). Indeed, complete neuro-urological assessment including UDI is strongly recommended in all acute SCI patients, regardless of the ability to walk (3). Urodynamic parameters, in combination with the bladder diary and the medical history, allow for diagnosis and treatment. Special attention should be given to appropriate standardization of the urodynamic technique since this is the prerequisite for reproducible and reliable results. Hence, UDI has to be performed and reported in accordance with the standards of the International Continence Society (ICS) (4). Any technical source of artefacts must be critically considered, and all urodynamic findings have to be reported in detail (table 1).
**Urodynamic observations**
- Intravesical pressure (cmH₂O)
- Abdominal pressure (cmH₂O)
- Detrusor pressure (cmH₂O)
- Filling rate (mL/min)
- Bladder sensation (First sensation of bladder filling, first desire to void, strong desire to void; normal, increased, reduced, absent, non-specific bladder sensation, bladder pain or urgency)

**Storage**
- Maximum cystometric capacity (mL)
- Bladder compliance (volume change divided by the change in detrusor pressure) (mL/cmH₂O)
- Abdominal leak point pressure (cmH₂O)
- Detrusor leak point pressure (cmH₂O)
- Maximum detrusor pressure during storage phase (cmH₂O)

**Voiding**
- Voided volume (mL)
- Voiding time (s)
- Maximum flow rate (mL/s)
- Average flow rate (mL/s)
- Maximum detrusor pressure during voiding phase (cmH₂O)
- Maximum detrusor pressure at maximum flow rate (cmH₂O)
- Post void residual (mL)

**Urodynamic diagnosis**
- Detrusor function
- Normal detrusor function
- Detrusor overactivity
- Phasic detrusor overactivity
- Terminal detrusor overactivity
- Detrusor overactivity incontinence
- Acontractile / hypocontractile (underactive) detrusor
- Bladder compliance: normal, low
- Bladder capacity: normal, low, high
- Stress urinary incontinence

**Outlet / urethral function**
- Normal urethral function
- Abnormal urethral function
- Bladder outlet obstruction
- Detrusor sphincter dyssynergia
- Non-relaxing urethral sphincter obstruction

*Table 1. Urodynamic characteristics / findings (5)*
**Filling cystometry**

Filling cystometry is performed to assess the storage (filling) phase. A double-lumen transurethral or suprapubic (6–10 French) catheter (the catheter lubricant should be without anesthetic additive to avoid an impact on bladder sensation) is used. The bladder has to be emptied with intermittent catheterization before each UDI. A physiological filling rate (ideally, should not exceed body weight in kilograms divided by four) should be used. The fill medium can be physiological saline, or a mixture of a contrast medium and saline at body temperature. A fast fill rate, nonphysiological ion concentrations, and low temperature of the filling fluid may all negatively affect urodynamic results. During filling, provocation tests, including coughing, change of position from supine or sitting to standing, or hand washing, can be used to demonstrate inducible detrusor overactivity, urgency or stress urinary incontinence.

Bladder sensation during UDI is assessed on the basis of the volume in the bladder at the patient’s first sensation of bladder filling, first desire to void, and strong desire to void. Urgency is defined as the sudden, compelling desire to void.

The “ice water test” can be used to test for temperature-sensitive reflex detrusor contraction mediated by afferent C fibres. Detrusor overactivity may be demonstrated, even if there is no detrusor activity in the standard UDI, thereby helping to unmask a putatively acontractile detrusor. Since the “ice water test” is a nonphysiological investigation that may relevantly bias subsequent UDIs, it should be performed at the end of (and not precede) more physiological standard UDIs.

**Pressure-flow study**

A pressure-flow study is performed to assess the voiding (emptying) phase, and reflects the coordination between the detrusor and urethra/pelvic floor during micturition. Possible pathological findings include detrusor acontractility/underactivity and bladder outlet obstruction, including detrusor sphincter dyssynergia (DSD) and postvoid residual. It has to be considered that many patients with SCI will not be able to void spontaneously; that is, maximum cystometric capacity and postvoid residual will be identical.

**Electromyography**

Electromyography (EMG) of the pelvic floor, including urethral and anal sphincter activity, is an established method for the diagnosis of bladder sphincter dysfunction. The pelvic floor EMG is usually simultaneously measured with cystometry. Surface electrodes should be placed ventral and close to the anus. The EMG amplitude is measured in millivolts (mV) and provides a simple semi-quantitative tracing of the muscle activity over time. Surface electrodes are therefore highly vulnerable to artefacts, and the signal should be monitored throughout the measurements (e.g., by zoom tracing on the tracking software, oscilloscope, or audio signal). Urine leakage (especially in the supine position) can lead to misinterpretation of EMG findings, as fluid contact with the surface electrodes may mimic DSD (defined by the ICS as a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscles).

**Video-urodynamics**

Urodynamic evaluation (or “urodynamics”) is aimed at defining the pattern of (dys)function of the lower urinary tract and should reproduce the patient’s urinary complaints. However, potential discrepancies between the findings of conventional urodynamics and
clinical presentation are not unusual. For this reason, the idea of combining simultaneous fluoroscopy to urodynamics, with the objective of providing additional information about the anatomy and function of the lower urinary tract, has arisen (8).

After more complicated descriptions, such as ‘synchronous cine-pressure-flow-cysto-urethrography’ (8), the term “video-urodynamics” was introduced in 1980 to describe fluoroscopy coordinated with concurrent cystometry (9). Video-urodynamics can be defined as a diagnostic technique based on simultaneous recording of the various urodynamic parameters with visualization of the urinary tract using fluoroscopy or ultrasound techniques (10).

Video-urodynamics requires a more complex structure, availability of expensive equipment and specialized staff. Exposure to radiation is also a limiting factor. Thus, before referring patients to video-urodynamics, it is essential to have two fundamental questions in mind: 1. Which additional information can this examination provide? 2. Which patient benefits the most from this diagnostic modality?

With broader utilization of video-urodynamics in the 1970s, it proved to be of special value in neurogenic lower urinary tract dysfunction (NLUTD) (11, 12). According to the guidelines of the European Association of Urology (EAU), video-urodynamics are the gold standard for urodynamic investigation in neuro-urological disorders (2). It provides information on the anatomy of the urinary tract that can be analysed in conjunction with the urodynamic parameters of interest in real time. In this way, artefacts and errors of interpretation could be minimized. On the other hand, improved understanding of anatomy and function would yield more accurate diagnoses and thereby improve therapeutic decision making (13). Video-urodynamics allow a comprehensive assessment of many parameters of interest, such as (12, 13):

- the position of the bladder neck in relation to the pubic symphysis;
- bladder neck closure during rest and with stress;
- identification of divertica of the bladder and urethra;
- urethral opening before observed urinary leakage;
- visualization of vesico-vaginal and urethro-vaginal fistulas and vesico-ureteral and vesico-uretero-renal reflux;
- distinguishing bladder neck vs. rhabdosphincter dyssynergia (i.e. detrusor internal sphincter dyssynergia versus detrusor external sphincter dyssynergia), and accurate localization of urethral obstruction.

The principles that guide the realization of video-urodynamics are the same as those recommended by the International Continence Society (ICS) for conventional urodynamics (4). A double lumen (6-10 Fr) catheter is usually recommended for assessment of intravesical pressures and for infusion of sterile radiographic contrast medium. Nevertheless, there is no standardization for the fluoroscopy time during video-urodynamics. Most reports do not state dosage or exposure time and do not report the imaging protocol (12, 14-17).

Anding et al. suggested that when using video, every attempt should be made to minimize exposure based on the ALARA (as low as reasonably achievable) principal (12). These authors indicate that recommendations on the use of video with urodynamics in neurogenic and non-neurogenic lower urinary tract dysfunction rely primarily on expert opinion and come from single centre and uncontrolled series.
Potential indications of video-urodynamics

Video-urodynamics are usually indicated in clinical practice for patients with multifactorial aetiology of urinary incontinence, especially for those individuals with suspected anatomical abnormalities of the lower urinary tract. Adding video to urodynamics may also provide useful information for patients with NLUTD (18), as there are some risk factors for upper urinary tract deterioration that can only be detected by this technique.

Neurogenic lower urinary tract dysfunction (NLUTD)

Video-urodynamics allow the accurate diagnosis of detrusor sphincter dysfunction (including detrusor internal or external sphincter dyssynergia, anatomical causes of infravesical obstruction, etc.) (Figure 1). In addition, this technique provides important information on morphological changes of the bladder and upper urinary tract secondary to NLUTD, such as (pseudo-) diverticula, neurogenic bladder conformation, vesico-uretero-renal reflux, hydronephrosis, reflux into the seminal vesicles and prostate. Video-urodynamic follow-up is often indicated for patients with spinal cord injury and allows early detection of risk factors that precede renal deterioration (17).

Bladder outlet obstruction

Video-urodynamics are considered the technique of choice for evaluation of women with suspected bladder outlet obstruction (19-21), especially when there is suspected anatomical cause (e.g. after mid-urethral sling surgery). Combining pelvic floor electromyography may also be of great value for differential diagnosis (e.g. dysfunctional voiding).
It is important to remember that video-urodynamics provide a topographic diagnosis of the bladder outlet obstruction. Thus, it provides accurate information for young men with suspected primary bladder neck obstruction (“Marion's disease”), and for patients with suspected urethral stenosis or bladder neck sclerosis after radical prostatectomy.

**Lower urinary tract dysfunction in children**

Video-urodynamics represent an important diagnostic tool in children with suspected vesico-uretero-renal reflux, especially when there is NLUTD (e.g. meningomyelocele) and other congenital abnormalities (such as posterior urethral valve).

The occurrence of high-grade vesico-uretero-renal reflux (VUR) in patients with neurogenic detrusor overactivity and detrusor sphincter dyssynergia may overestimate bladder compliance and cystometric capacity during the conventional urodynamic study (Figure 2).

![Figure 2. High-grade vesico-uretero-renal reflux](image)

**Evaluation of artificial urinary sphincter function**

Video-urodynamics may also aid in the evaluation of patients with implanted devices in the lower urinary tract, such as the artificial urinary sphincter (AUS). This is true for centres that use contrast medium to fill up the system. Malfunctioning of AUS may be related to mechanical failure of implanted components (reservoir, control pump, cuff), urethral erosion, leak of fluid from the system.
TAKE HOME MESSAGES: VIDEO-URODYNAMICS

- There is expert consensus on the additional value of video-urodynamics, which is regarded as the gold standard for assessing the lower urinary tract function in neuro-urological patients.

- Video-urodynamics can detect vesico-uretero-renal reflux, bladder trabeculation, (pseudo-)diverticula, reflux into the seminal vesicles and prostate and also differentiate between bladder neck vs. rhabdosphincter dyssynergia (detrusor internal sphincter dyssynergia versus detrusor external sphincter dyssynergia).

- There is not standardization for the imaging protocol. Radiation dosage and exposure time represent limitations to be taken into consideration before indicating video-urodynamics. Ionizing radiation should be kept to a minimum according to the as low as reasonably achievable (ALARA) principle.

Safety

The main risks of UDI are associated with urethral catheterization. If the patient’s sensation is preserved, dysuria is quite common in the first days following UDI. Patients with impaired bladder and urethral sensation are at risk for more severe complications since catheterization problems may not be recognized promptly due to impaired urogenital sensation.

Prophylactic antibiotics reduce the risk of bacteriuria, but not of urinary tract infection after UDI (22). Thus, antibiotic prophylaxis is not generally recommended, especially when taking into account the alarming prevalence of antibiotic resistance worldwide.

A relevant issue in SCI patients, particularly in those with a lesion at or above T6, is UDI-induced AD (23, 24); overall incidence is up to 73%. Thus, if available, continuous cardiovascular monitoring during UDI is strongly recommended. In the case of AD during examination, stopping UDI and immediate emptying of the bladder is mandatory to avoid a life-threatening situation, and further treatment (e.g., with nifedipine) may be necessary (23).

A history of potential allergies is important, especially considering the allergic potential of latex gloves, catheters, and contrast media.

Conclusions

Video-urodynamics represent an important diagnostic tool for selected patients and are regarded as the gold standard for assessing neuro-urological patients. However, there is an urgent need for standardization of the imaging protocol and ionizing radiation should be kept to a minimum according to the as low as reasonably achievable (ALARA) principle.
References


Introduction

The bladder, in concert with the urethra and the pelvic floor, is responsible for storage and periodic expulsion of urine. The integrated function of these components of the lower urinary tract (LUT) is dependent on a complex control system in the brain, spinal cord and peripheral ganglia, and on local regulatory factors (1-3) (de Groat and Yoshimura, 2001; 2006; 2015). Dysfunction of the central nervous control systems or of the components of the LUT can produce voiding difficulties and retention of urine, or different types of urinary incontinence (mainly urgency and stress incontinence), or the symptom complex of the “overactive bladder” (OAB), characterized by urgency, frequency with or without urgency incontinence, often with nocturia (4) (Abrams et al, 2002).

Pharmacologic treatment of urinary incontinence and LUT symptoms (LUTSs) including OAB is a main option, and several drugs with different modes and sites of action have been tried (5-9) (Andersson, 2016; Andersson et al, 2013; Andersson and Wein, 2004; Bechis et al. 2015; Sacco and Bientinesi, 2015). However, to be able to optimize treatment, knowledge about the mechanisms of micturition and of the targets for treatment is necessary. Theoretically, failure to store urine can be improved by agents that decrease detrusor activity and increase bladder capacity, and/or increase outlet resistance.

In this chapter, a brief review is given of the normal nervous control of the LUT and of some therapeutic principles used in the treatment of urinary incontinence.
Targets for pharmacologic intervention

Central nervous system targets

Anatomically, several CNS regions may be involved in micturition control: supraspinal structures, such as the cortex and diencephalon, midbrain, and medulla, and also spinal structures (10-15) (Fowler et al., 2008; Fowler and Griffiths, 2010; Griffiths, 2004; Griffiths et al., 2005; Holstege, 2005; Sugaya et al., 2005). Several transmitters are involved in the micturition reflex pathways and may be targets for drugs aimed for control of micturition (1) (de Groat and Yoshimura, 2001). However, few drugs with a CNS site of action have been developed (16) (Andersson and Pehrson, 2003; Yoshimura et al., 2014).

Opioid Receptors

Endogenous opioid peptides and corresponding receptors are widely distributed in many regions in the CNS of importance for micturition control (1) (de Groat and Yoshimura, 2001).

Morphine given intrathecally was effective in patients with DO due to spinal cord lesions, but it was associated with side effects, such as nausea and pruritus. Further side effects of opioid receptor agonists comprise respiratory depression, constipation, and abuse (4) (Andersson and Wein, 2004). Attempts have been made to reduce these side effects by increasing selectivity toward one of the different opioid receptor types. At least three different opioid receptors - µ, δ, and κ - bind stereospecifically with morphine have been shown to interfere with voiding mechanisms. Theoretically, selective receptor actions, or modifications of effects mediated by specific opioid receptors, may have useful therapeutic effects for micturition control.

Tramadol is a well-known analgesic drug. By itself, it is a weak µ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the µ-receptor. However, the drug also inhibits serotonin (5-HT) and noradrenaline reuptake (17) (Raffa and Friderichs, 1996). This profile is of particular interest, since both µ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of DO/OAB.

Safarinejad and Hosseini (2006) evaluated in a double-blind, placebo-controlled, randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol sustained release every 12 h for 12 weeks. Clinical evaluation was performed at baseline and every two weeks during treatment. Tramadol significantly (p<001) reduced the number of incontinence periods per 24 hours from 3.2+/− 3.3 to 1.6+/−2.8) and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. However, the study was later retracted due to unacceptable statistical errors (18) (Safarinejad and Hosseini, 2006; retracted 2014).

Serotonin (5-HT) Mechanisms

Lumbosacral autonomic, as well as somatic, motor nuclei (Onuf’s nuclei) receive a dense serotonergic input from the raphe nuclei, and multiple 5-HT receptors have been found at sites where afferent and efferent impulses from and to the LUT are processed (Ramage, 2006). The main receptors shown to be implicated in the control of micturition are the 5-HT1A, 5-HT2, and 5-HT3 receptors (19) (Ramage, 2006). There is some evidence in the rats for serotonergic facilitation of voiding; however, the descending pathway is essentially an inhibitory circuit, with 5-HT as a key neurotransmitter.
It has been speculated that selective serotonin reuptake inhibitors (SSRIs) may be useful for treatment of DO/OAB. On the other hand, there are reports suggesting that the SSRIs in patients without incontinence actually can cause incontinence, particularly in the elderly, and one of the drugs (sertraline) seemed to be more prone to produce urinary incontinence than the others (20) (Movig et al, 2002). Patients exposed to serotonin uptake inhibitors had an increased risk (15 out of 1000 patients) for developing urinary incontinence. So far, there are no RCTs demonstrating the value of SSRIs in the treatment of DO/OAB.

Duloxetine is a combined noradrenaline and serotonin reuptake inhibitor. The effects of duloxetine was studied in a placebo-controlled study comprising women with OAB (21) (Steers et al, 2007) and was, compared with placebo, shown to cause significant improvements or decreases in voiding and incontinence episodes, for increases in the daytime voiding intervals, and for improvements in quality-of-life (I-QoL) scores. Urodynamic studies showed no significant increases in maximum cystometric capacity or in the volume threshold for DO.

GABA Mechanisms

Both in the brain and in the spinal cord, GABA has been identified as a main inhibitory transmitter (1) (de Groat and Yoshimura, 2001). GABA functions appear to be triggered by binding of GABA to its inotropic receptors, GABA_A and GABA_B, which are ligand-gated chloride channels, and its metabotropic receptor, GABA_B (22) (Chebib and Johnston, 1999). Since blockade of GABA_A and GABA_B receptors in the spinal cord and brain (23) (Pehrson and Andersson, 2002) stimulated rat micturition, an endogenous activation of GABA_A and GABA_B receptors may be responsible for continuous inhibition of the micturition reflex within the CNS. In the spinal cord, GABA_A receptors are more numerous than GABA_B receptors, except for the dorsal horn where GABA_B receptors predominate. Normal relaxation of the striated urethral sphincter is probably mediated via GABA_A receptors (23-24) (Pehrson et al, 2002; Pehrson and Andersson, 2002), GABA_B receptors having a minor influence on motoneuron excitability (25) (Rekling et al, 2000).

Gabapentin was originally designed as an anticonvulsant GABA mimetic capable of crossing the blood–brain barrier (26) (Maneuf et al, 2003). The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial (Maneuf et al, 2003), even if it has been suggested that it acts by binding to a subunit of the α_2δ unit of voltage-dependent calcium channels. Gabapentin is also widely used not only for seizures and neuropathic pain but also for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

In a pilot study, Carbone et al (2003) reported on the effect of gabapentin on neurogenic DO (27). These investigators found a positive effect on symptoms and significant improvement in urodynamic parameters after treatment with gabapentin, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and nonneurogenic DO. Kim et al (2004) studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. It is possible that gabapentin and other α_2δ ligands (eg, pregabalin and analogs) will offer new therapeutic alternatives (28).

Noradrenaline Mechanisms

Noradrenergic neurons in the brainstem project to the sympathetic, parasympathetic, and somatic nuclei in the lumbosacral spinal. Bladder activation through these bulbospinal noradrenergic pathways may involve excitatory α-ARs, which can be blocked by α-AR antagonists (29) (Yoshiyama et al, 2000). Doxazosin given intrathecally normalized bladder
activity in animal models of DO (30) (Persson et al, 1998). It was suggested that doxazosin has a site of action at the level of the spinal cord and ganglia.

A central site of action for α1-AR antagonists has been discussed as an explanation for the beneficial effects of these drugs in LUTS (especially storage symptoms) associated with benign prostatic hyperplasia (BPH) (4-31) (Andersson and Gratzke, 2007; Andersson and Wein, 2004).

**Dopamine Mechanisms**

Patients with Parkinson's disease may have neurogenic DO, possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory D1 receptors (32) (Andersson, 2004). However, other dopaminergic systems may activate D2 receptors, facilitating the micturition reflex. Apomorphine, which activates both D1 and D2 receptors, induced bladder overactivity in anesthetized rats via stimulation of central dopaminergic receptors. The effects were abolished by infracollicular transection of the brain and by prior intraperitoneal administration of the centrally acting dopamine receptor blocker, spiroperidol. It has been shown that the DO induced by apomorphine in anesthetized rats resulted from synchronous stimulation of the micturition centers in the brainstem and spinal cord, and that the response was elicited by stimulation of both dopamine D1 and D2 receptors. Blockade of central dopamine receptors may be expected to influence voiding; however, the therapeutic potential of drugs having this action has not been established (4) (Andersson and Wein, 2004).

**NK-1 Receptor Mechanisms**

The main endogenous tachykinins, substance P, neurokinin A (NKA), and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control (33-35) (Covenas et al, 2003; Lecci and Maggi, 2001; Saffroy et al, 2003).

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting (36) (Massaro and Lenz, 2005), significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence, as shown in a well-designed pilot RCT (Green et al, 2006). Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. Another NK-1 receptor antagonist, serlopitant, significantly decreased daily micturitions but did not offer advantages in efficacy compared with tolterodine (38) (Frenkl et al, 2010). The results of these studies suggest that NK-1 receptor antagonism holds promise as a potential treatment approach for OAB, but so far, the drugs available have not been very effective.

**Peripheral Targets**

There are many possible peripheral targets for pharmacologic control of bladder function (39) (Andersson and Arner, 2004). Although many effective drugs are available targeting these systems, most of them are less useful in the clinical situation due to the lack of selectivity for LUT, which may result in intolerable side effects.

**Muscarinic Receptors**

Muscarinic receptors comprise five subtypes, M1 – M5, encoded by five distinct genes,
and in both animal and human bladders, the mRNAs for all muscarinic receptor subtypes have been demonstrated, with a predominance of mRNAs encoding \( M_2 \) and \( M_3 \) receptors. These receptors are also functionally coupled to G proteins, but the signal transduction systems vary\(^{39-40}\) (Andersson, 2011; Andersson and Arner, 2004).

Detrusor smooth muscle contains muscarinic receptors mainly of the \( M_2 \) and \( M_3 \) subtypes. The \( M_3 \) receptors in the human bladder are the most important for detrusor contraction\(^{4}\) (Andersson and Wein, 2004). Carbachol-induced contraction of human detrusor is mediated via \( M_3 \) receptors, and furthermore, largely depends on transmembrane \( Ca^{2+}\)-flux through nifedipine-sensitive calcium channels as well as activation of the Rho-kinase pathway\(^{41}\) (Schneider et al, 2004).

It has been suggested that \( M_2 \) receptors may oppose sympathetically mediated smooth muscle relaxation, mediated by \( \beta\)-ARs\(^{42}\) (Hegde, 1997). \( M_2 \) receptor stimulation may also activate nonspecific cation channels and inhibit \( K_{ATP} \) channels through activation of protein kinase C. However, the functional role for the \( M_2 \) receptors in the normal bladder has not been clarified, but in certain disease states, \( M_2 \) receptors may contribute to contraction of the bladder. Pontari et al (2004) analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from \( M_3 \) to the \( M_2 \) receptor subtype. They concluded that although normal detrusor contractions are mediated by the \( M_3 \) receptor subtype, in patients with neurogenic bladder dysfunction, contractions could be mediated by the \( M_2 \) receptors\(^{43}\).

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as \( M_2 \) in the rabbit and rat, and \( M_4 \) in the guinea pig, rat, and human bladder\(^{39}\). Prejunctional facilitatory muscarinic receptors appear to be of the \( M_1 \) subtype in the rat and rabbit urinary bladder (Andersson and Arner, 2004). Prejunctional muscarinic facilitation has also been detected in human bladders. The muscarinic facilitatory mechanism seems to be upregulated in DO from chronic spinal cord–transected rats. The facilitation in these preparations is primarily mediated by \( M_3 \) muscarinic receptors\(^{44}\) (Somogyi et al, 2003).

Muscarinic receptors have also been demonstrated in the urothelium and in the suburothelium\(^{45-46}\) (Bschleipfer et al, 2007; Chess-Williams, 2002; Mansfield et al, 2005), but their functional importance has not been clarified. It has been suggested that they may be involved in the release of an unknown inhibitory factor (Chess-Williams, 2002), or they may be directly involved in afferent signaling, and thus a target for antimuscarinic agents, explaining part of the efficacy of these drugs in DO/OAB\(^ {4, 47, 48}\) (Andersson, 2004; Andersson and Yoshida, 2003; Kim et al, 2005; Yokoyama et al, 2005).

**Antimuscarinics**

In general, antimuscarinics can be divided into tertiary and quaternary amines\(^{49, 50}\) (Abrams and Andersson, 2007; Guay, 2003). They differ with regard to lipophilicity, molecular charge, and even molecular size, tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood–brain barrier, but for some of the drugs, this counteracted by active transport out of the CNS. Quaternary ammonium compounds, like propantheline and trospium, are not
well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side
effects (50) (Guay, 2003). They still produce well-known peripheral antimuscarinic side effects,
such as accommodation paralysis, constipation, tachycardia, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or
inactive metabolites (50) (Guay, 2003). The most commonly involved P450 enzymes are
CYP2D6 and CYP3A4. The metabolic conversion creates a risk for drug–drug interactions,
resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate
competition) plasma concentration/effect of the antimuscarinic and/or interacting drug.
Antimuscarinics secreted by the renal tubules (e.g., trospium) may theoretically be able to
interfere with the elimination of other drugs using this mechanism.

Antimuscarinics are still the most widely used treatment for urgency and urgency
incontinence (Andersson et al, 2013). However, currently used drugs lack selectivity for the
bladder, and effects on other organ systems may result in side effects, which limit their usefulness.
For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained, if the subtype(s)
mediating bladder contraction, and those producing the main side effects of antimuscarinic
drugs, were different. Unfortunately, this does not seem to be the case. One way of avoiding
many of the antimuscarinic side effects is to administer the drugs intravesically. However,
this is practical only in a limited number of patients.

Adrenergic Receptors

A. α-ARs

Most investigators agree that there is a low expression of α-ARs in the human detrusor
(51) (Michel, 2006). Malloy et al (1998) found that two-thirds of the α-AR mRNA expressed
was α₁D, and one-third was α₁A (there was no α₁B) (52). The role of α₁D-ARs in the detrusor
muscle on DO or OAB is unclear.

Sugaya et al (2002) investigated the effects of intrathecal tamsulosin (blocking α₁A/D-ARs)
and naftopidil (blocking preferably on α₁D-ARs) on isovolumetric bladder contractions in rats
(53). Intrathecal injection of tamsulosin or naftopidil transiently abolished these contractions.
The amplitude of contraction was decreased by naftopidil but not by tamsulosin. It was
speculated that in addition to the antagonistic action of these agents on the 1A-ARs of prostatic
smooth muscle, both agents (especially naftopidil) may also act on the lumbosacral cord (α
₁D-ARs). This observation is of particular interest considering the findings that in the human
spinal cord, α₁D-AR mRNA predominated overall (Smith et al, 1999).

B. β-ARs

It has been known for a long time that isoprenaline, a non–subtype selective β-AR
agonist, can relax bladder smooth muscle (55) (Andersson, 1993). All three subtypes of β
-ARs (β₁, β₂, and β₃) can be found in the detrusor muscle of most species, including humans
(51) (Michel and Vrydag, 2006), and also in the human urothelium (56) (Otsuka et al, 2008).
However, the expression of β₃-AR mRNA (Nomiya and Yamaguchi, 2003; Michel and Vrydag,
2006) and functional evidence indicate a predominant role for this receptor in both normal
and neurogenic bladders (51) (Michel and Vrydag, 2006). The human detrusor also contains
β₂-ARs, and most probably both receptors are involved in the physiological effects (relaxation)
of noradrenaline in the bladder (39,51) (Andersson and Arner, 2004; Michel and Vrydag, 2006).
The generally accepted mechanism by which β-ARs induce detrusor relaxation in
most species, is activation of adenylyl cyclase with the subsequent formation of cAMP.
However, there is evidence suggesting that in the bladder K+ channels, particularly $B_{K_{Ca}}$ channels, may be more important in $\beta$-AR mediated relaxation than cAMP (58) (Frazier et al., 2008). $\beta$-AR agonists have generally been considered to relieve OAB symptoms by relaxing detrusor muscle, inhibiting spontaneous contractile activity in the detrusor (in vitro: microcontractions; in vivo: non-voiding contractions), and reducing bladder afferent activity (59) (Igawa and Michel, 2013). However, Gillespie and colleagues have questioned the accepted view on the mode and site of action of $\beta_3$-AR agonists (Gillespie et al., 2015a; 2015b), and suggested that effects on neither spontaneous micro-contractions, nor on non-voiding contractions in e.g., obstructed rats, can fully explain the effects of mirabegron (60,61). Assuming that acetylcholine (ACh) release from cholinergic terminals during bladder filling contributes to OAB symptoms, the finding that activation of pre-junctional $\beta_3$-ARs may down-regulate ACh release resulting in an inhibitory control of parasympathetic activity, may be of importance (62,63) (Rouget et al., 2014; D’Agostino et al., 2015).

The in vivo effects of $\beta_3$-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), $\beta_3$-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume (64) (Igawa et al., 2010). A number of $\beta_3$-AR selective agonists are currently being evaluated as potential treatment for OAB, but so far the only drug approved for treatment in humans is mirabegron. The effects of mirabegron in men and women with OAB have been summarized in several recent reviews (65-69) (Chapple et al., 2014; Cui et al., 2014; Rossanese et al., 2015; Samuelsson et al., 2015; Warren et al., 2016), and also in men with both voiding and OAB symptoms (70,71) (Suarez et al. 2013; Otsuki et al, 2013).

**Ion Channels**

**A. Calcium Channels**

There is no doubt that an increase in $[Ca^{2+}]$ is a key process required for the activation of contraction in the detrusor myocyte. However, it is still uncertain whether this increase is due to influx from the extracellular space and/or release from intracellular stores. Furthermore, the importance of each mechanism in different species, and also with respect to the particular transmitter studied, has not been firmly established (72) (Kajioka et al, 2002).

Theoretically, inhibition of calcium influx by means of calcium antagonists would be an attractive way of inhibiting DO/OAB. However, there have been few clinical studies of the effects of calcium antagonists in patients with DO. Naglie et al (2002) evaluated the efficacy of nimodipine for geriatric urgency incontinence in a randomized, double-blind, placebo-controlled crossover trial, and concluded that this treatment was unsuccessful.

Thus, available information does not suggest that systemic therapy with calcium antagonists is an effective way to treat DO/OAB (4) (Andersson et al, 2013; Andersson and Wein, 2004).

**B. Potassium Channels**

Potassium channels represent another mechanism to modulate the excitability of the smooth muscle cells. There are several different types of K+ channels and at least two subtypes have been found in the human detrusor: ATP-sensitive K+ channels ($K_{ATP}$) and large conductance calcium-activated K+ channels ($B_{K_{Ca}}$). Studies on isolated human detrusor muscle and on bladder tissue from several animal species have demonstrated that K+ channel openers reduce spontaneous contractions as well as contractions induced by carbachol and electrical
stimulate. However, the lack of selectivity of presently available K⁺-channel blockers for the bladder versus the vasculature has thus far limited the use of these drugs. The first generation of K-channel openers, such as cromakalim and pinacidil, were found to be more potent as inhibitors of vascular smooth muscle than of detrusor muscle (Andersson and Arner, 2004). No effects of cromakalim or pinacidil on the bladder were found in studies on patients with spinal cord lesions or detrusor instability secondary to outflow obstruction. Also with more recently developed K<sub>ATP</sub>-channel openers, claimed to have selectivity toward the bladder, negative results have been obtained in an RTC on patients with idiopathic DO (Chapple et al, 2006)

Thus, at present, there is no clinical evidence to suggest that K⁺-channel openers represent a treatment alternative for DO/OAB (Andersson et al, 2013; Andersson and Wein, 2004).

P2X3-receptors and P2X3 receptor antagonists
During bladder filling the urothelium is stretched and ATP is released from the umbrella cells, thereby activating mechanotransduction pathways via stimulation of purinergic receptors on suburothelial sensory nerves to initiate the voiding reflex and to mediate the sensation of bladder filling and urgency (Burnstock, 2013; 2014). P2X receptors are ligand-gated ion channels, and seven P2X receptor subunits have been identified from molecular studies and characterized functionally and pharmacologically (North and Surprenant, 2000; Gever et al., 2006; Ford and Cockayne, 2011). Sensory nerve fibers expressing P2X3 immunoreactivity have been found projecting into the lamina propria, urothelium and detrusor smooth muscle (Ford and Cockayne, 2011), where this and several other P2X receptors are functionally expressed (Ford and Cockayne 2011; Shabir et al., 2013). P2X3 and P2X2/3 receptors may be important in sensing volume changes during normal bladder filling, and may participate in lowering the threshold for C-fiber activation under pathophysiological conditions.

An increased density of P2X3 and TRPV1-expressing nerve fibers has been observed in the bladders of patients with neurogenic detrusor overactivity, and following treatment with resiniferatoxin, patients responding to treatment showed diminished levels of both TRPV1 and P2X3 immunoreactivity (Brady et al., 2004).

It has been suggested that ATP can be released and act on spinal P2X3 and P2X2/3 receptors to affect afferent signals originating from the bladder (Ford, 2013). Spinal ATP may then constitute an endogenous central presynaptic purinergic mechanism to regulate visceral sensory transmission. Further characterization of this spinal purinergic control in visceral activities may help the development of P2X3 and P2X2/3 antagonists to treat urological dysfunction, such as DO/OAB (Ford, 2012).

TRP channels and TRP channel antagonists
The transient receptor potential (TRP) channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder, and may act as sensors of stretch and/or chemical irritation (Araki et al., 2008; Everaerts et al., 2008; Andersson et al., 2010; Skryma et al., 2011; Avelino et al., 2013; Deruyver et al., 2015; Franken et al., 2014). TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder (Tominaga et al., 1998; Birder et al., 2001; Gevaert et al., 2007). TRPV1 is present and active both in the urothelium and in the nerve fibers of several species including humans (Ji et al., 2002; Charrua et al., 2009). TRPV4 was initially described in the urothelium...
of rodents and humans (95) (Janssen et al., 2011). Co-expression of the two receptors was observed in 20% of rat urothelial cells (96) (Kullmann et al., 2009). Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30% of L6 dorsal root ganglia neurons that project to the urinary bladder co-express TRPV1 and TRPV4 (97, 98) (Cao et al., 2009; Charrua et al., 2012). The physiological meaning of this observation is unclear.

It is known for long that TRPV1 is involved in the emergence of neurogenic detrusor overactivity following spinal cord transaction (99) (Avelino & Cruz, 2006). A TRPV1 antagonist GRC 6211 has been shown to decrease reflex detrusor overactivity in rats after chronic spinal cord transaction. With increasing doses, it was possible to obtain a total suppression of bladder activity (100, 101) (Santos-Silva et al., 2012). Kitagawa et al. (2013) evaluated the effects of the selective TRPV1 antagonist JTS-653 on the increased pelvic nerve discharge and intravesical pressure induced by intravesical infusion of capsaicin, in anesthetized rats. The drug significantly suppressed both parameters. The clinical relevance of this finding will be certainly further investigated in the future. Interestingly, Uvin et al. (2015) found evidence for involvement of TRPM8 in rat and mouse models of acute cold-induced urinary urgency (102).

There seem to be several links between activation of different members of the TRP superfamily and LUTS/DO/OAB, and further exploration of the involvement these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof of concept studies in humans are still lacking.

**Botulinum Toxin-Sensitive Mechanisms**

Botulinum toxin (BoNT), the neurotoxin produced by Clostridium botulinum, comprises seven subtypes, of which sub-type A (BoNT-A), which has the longest duration of action, is clinically the most relevant. BoNT/A is available in three different commercial forms, which differ in their relative potency: onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A. Although there are differences in potency between the forms, there are no reasons to believe that their basic mechanisms of action is different. Most of the information available preclinically and clinically derives from the use of onabotulinum toxin A.

The mechanisms of action of BoNT in the nerve terminal have been discussed by several investigators (103, 104) (Humeau et al. 2000; Chancellor et al. 2008). Briefly, it involves cleavage of the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment proteins (the SNARE complex) include synaptosome-associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein) and syntaxin. BonT/A cleaves SNAP 25 rendering the SNARE complex inactive (103-104) (Humeau et al. 2000; Chancellor et al., 2008). In striated muscle, paralysis occurs by inhibition of acetylcholine (ACh) release from cholinergic motor nerve endings (103) (Humeau et al. 2000).

In the human bladder, SNAP-25 expression has been demonstrated in parasympathetic, sympathetic and sensory fibers (105) (Coelho et al, 2012). Blockade of ACh release is believed to play an essential role in the detrusor hypo- or acontractility that follows BoNT/A injection in the bladder. However, BoNT/A may also have effects on sensory fibers, since about half of the peptidergic sensory fibers express SNAP25 (105) (Coelho et al, 2012). It has been well documented that BoNT/A can inhibit release from sensory nerves both in the CNS and peripherally (106-110) (Aoki, 2005; Ikeda et al, 2012; Lucioni et al., 2008; Meng et al., 2007; Rapp et al, 2006). BoNT/A was found to reduce afferent firing from sensory nerves.

In addition to its effect on neurotransmitter release, BoNT/A, injected into the bladder wall, seems to influence the receptor profile of important neurotransmitters. Apostolidis et
al. (2005) found that the mucosal levels of P2X3 and TRPV1 were decreased 4 weeks after BoNT/A injection, and even more so after 16 weeks (111). The decrease in the levels of these receptors seemed to correlate with those patients who experienced decreased urgency after the injection. Datta et al. (2010) found that patients with OAB had decreased levels of muscarinic receptors in the urothelium/suburothelium and that the levels of muscarinic receptors 1 and 3 were normalized after treatment with BoNT/A (112). Furthermore, they found

an inverse association with receptor level and patient reported symptoms. The relationship between mucosal receptor profile and patient symptoms indicates that this may be an important effect mechanism of BoNT/A.

References


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A. MANAGEMENT STRATEGIES FOR THE NEUROGENIC OVERACTIVE DETRUSOR IN COMBINATION WITH THE NORMAL, OVERACTIVE AND UNDERACTIVE SPHINCTER

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Introduction
The most important goals of treatment in neuro-urological patients are1,2:

- protection of the upper urinary tract
- improvement of patients’ quality of life
- achievement / maintenance of urinary continence

Other relevant causes than the neurological disorder leading to detrusor overactivity have to be excluded and appropriately treated such as urinary infection, anatomical / mechanical bladder outlet obstruction, distal ureteric stone, bladder stones, bladder tumors including carcinoma in situ.

Treatment outcome assessment is based on lower urinary tract symptoms (history taking, validated questionnaires), bladder diary and other assessment tools as appropriate (such as urinalysis / urine culture, post void residual measurement, ultrasonography, uroflowmetry, blood chemistry, physical examination, urethro-cystoscopy, bladder washing cytology, urodynamics (in patients with risk factor for upper urinary tract damage), pelvic neurophysiology and renal scintigraphy).

1. Neurogenic overactive detrusor in combination with normal sphincter

Non-pharmacological measures

Lifestyle modification: Including reduction of fluid intake as appropriate (especially during the evening and night) as well as bladder training and pelvic floor muscle training / biofeedback can influence clinical outcomes. In patients with neurogenic detrusor overactivity, non-medical treatment is mostly associated with medical therapy.
**Non invasive and minimally invasive neuromodulation:** Tibial nerve stimulation \[3\] and transcutaneous electrical nerve stimulation \[4\] may be effective and safe for treating neurogenic detrusor overactivity with the advantage that bladder emptying is not impaired and that also neurogenic bowel dysfunction can be successfully treated. However, more reliable evidence is required warranting well-designed randomized controlled trials \[3, 4\].

**First-line treatment: antimuscarinics**

a) **Mechanism of action:** Antimuscarinic agents inhibit competitively the action of acetylcholine at muscarinic receptors of the bladder wall (M2 and M3), leading to detrusor relaxation, lower intravesical pressure and increased bladder capacity. The reduced storage symptoms may also be influenced by the effect on afferents of the parasympathetic pathways.

b) **Choice of antimuscarinic agent:** Systematic reviews and meta-analyses suggests that the main difference between the different antimuscarinics is their safety profile \[5-7\]. In neurological patients, central nervous side effects by antimuscarinics such as alterations in cognition and consciousness have to be considered carefully, especially also taking into account that the cumulative use of agents with anticholinergic properties is associated with increased risk of cognitive impairment. Thus, drugs already being used by the patients should be reviewed before prescribing antimuscarinics. Moreover, agents not readily crossing the blood-brain barrier or having high affinity for the bladder muscarinic receptors such as trospium chloride or darifenacin, respectively, should be preferred in susceptible neurological patients.

c) **How to proceed:** Patients’ response varies widely. If no appropriate effect is achieved with the regular doses of antimuscarinics during a minimum treatment duration of 1 month, titration of the dosage to the optimal balance of therapeutic and adverse effects is recommended (table). In case of intolerance or lack of therapeutic result, at least one other antimuscarinic should be tried before moving to second-line treatments \[1, 2, 8\]. Combination of antimuscarinic agents may also be an option to maximise outcome.

d) **Side effects:** The high incidence of anticholinergic adverse events is the main contributor to treatment discontinuation. Hence, it is important to discuss the most common side-effects with patients such as dry mouth, constipation, blurred vision, tachycardia and drowsiness. Post void residual may also increase and should be monitored.

e) **Contraindication:** Narrow angle glaucoma, pregnancy, obstructive bowel disorders and myasthenia gravis.

**Other drugs**

**Beta-3 agonists:** A treatment alternative recently introduced for overactive bladder with the advantage of not causing the typical antimuscarinergic side effects. Moreover, combination of a beta-3 agonist with an antimuscarinic agent may be an attractive option. However, there are no high-level evidence studies available in patients with an underlying neurological disorder \[1\] and especially cardiovascular adverse events have to be considered.

**Desmopressin:** Temporarily reduces urine production and volume-determined detrusor overactivity being useful for the treatment of urinary frequency, nocturia or nocturnal polyuria, providing symptom relief for up to 6 hours. However, desmopressin should be prescribed with caution in patients older than 65 years and/or in those with leg oedema. Importantly, desmopressin should not be used more than once in 24 hours because of the risk of hyponatremia and/or congestive heart failure \[2\].
Second line treatment: OnabotulinumtoxinA injections into the detrusor

Patients with refractory neurogenic detrusor overactivity (i.e. failed behavioral and pharmacological treatment with at least 2 antimuscarinics) are candidates for intradetrusor onabotulinumtoxinA injections [9, 10].

**a) Mechanism of action:** Inhibition of presynaptic acetylcholine release from efferent nerves leading to temporary chemodenervation of the detrusor. In addition, it seems highly probable that onabotulinumtoxinA also modulates afferent pathways.

**b) How to proceed:** OnabotulinumtoxinA is currently the only botulinum toxin preparation approved for urological indications. The standard dose for neurogenic detrusor overactivity is 200 units [1, 2], although the doses are tailored according to patients response between 100-300 units. Using cystoscopy, 10 to 30 injections into the detrusor are performed. Remarkably, suburothelial (forms a bubble) injections show similar efficacy compared to intradetrusor injections and there is no evidence that trigonal injections would cause vesico-uretero-renal reflux [9].

**c) Outcomes:** OnabotulinumtoxinA causes a long-lasting but reversible effect for about 9 months and can be repeated in the long-term with good therapeutic effects [1, 2, 10].

**d) Side effects:** Manifest within hours to weeks after onabotulinumtoxinA treatment. Most frequent side effects are urinary infection and urinary retention. Vision problems, difficulty to swallow and speak, as well as dizziness may also occur and very rare, but potentially life-threatening adverse events include autonomic dysreflexia, respiratory problems and generalised muscular weakness.

**e) Pre-and postoperative considerations:** Prior to treatment, urinary tract infection should be excluded and the patients informed about the risk of onabotulinumtoxinA-induced urinary retention and potential need of intermittent self-catheterisation. Antibiotic prophylaxis seems not to be mandatory and needs to be critically reconsidered, especially taking into account the alarming antibiotic resistance worldwide [10]. The effect of onabotulinumtoxinA becomes obvious 5-10 days after treatment. In patients voiding spontaneously, a follow-up visit 2 weeks after treatment with measurement of post void residual, and a urodynamic outcome assessment 4-12 weeks after treatment in patients at risk for upper urinary tract damage is recommended. Although there are no generally accepted criteria to initiate intermittent self-catheterisation, post void residual >150 mL combined with lower urinary tract symptoms seem reasonable.

**f) Factors which may affect treatment results:**

Patients with low-compliance bladder often not dot appropriately respond to onabotulinumtoxinA treatment due to the underlying anatomical changes (bladder fibrosis). Inadequate preparation and/or surgical technique: onabotulinumtoxinA should be stored at low temperatures until the injection; the preparation should not be shaken, because the molecular structure is very fragile and can easily lose its properties; the injections should be performed in a uniform pattern and not too fast, otherwise part of the preparation may reflow through the injection hole and be lost. The onabotulinumtoxinA effect may be potentiated by neuromuscular blockers and aminoglycoside antibiotics so that caution is advised if such substances are used in combination [9].
Other second-line treatments

Sacral neuromodulation (SNM): May be effective and safe for treating neuro-urological patients, but there is a lack of randomized controlled trials and it is unclear which neurological patients are most suitable [11]. Thus, well-designed prospective and adequately powered studies are urgently needed before more widespread use of sacral neuromodulation for neuro-urological patients can be recommended [12].

Sacral deafferentation (dorsal rhizotomy) with or without sacral anterior root stimulation (SARS): Sacral deafferentation reduces detrusor overactivity and is nowadays mostly used adjuvant to SARS, which has been developed by Brindley and leads to detrusor contraction but which is only applicable to highly selected patients with complete lesion above the implant location due to the fact that stimulation amplitude is over the pain threshold [1].

Third line treatment: surgery

Bladder augmentation

Bladder augmentation is a valid option to decrease detrusor pressure and improve low bladder compliance, whenever more conservative approaches have failed. Several different techniques have been published, with comparable and satisfactory results. Complications associated include recurrent urinary tract infection, stone formation, perforation or diverticula, possible malignant changes and metabolic abnormality [1].

Urinary diversion

In the case no other treatment is successful, urinary diversion has to be considered as an ultima ratio to protect the upper urinary tract and to improve the patient’s quality of life.

Continent diversion: There are various techniques to create a continent catheterizable reservoir (pouch) and the stoma is often placed in the umbilicus because of cosmetic reason. The catheterizable channel can be formed using the appendix vermiformis (Mitrofanoff procedure), a bowel segment (Monti and Casale procedure) or the salpinx in female patients. Frequent complications include leakage or stenosis. Outcomes show good protection of the upper urinary tract and a short-term continence rates >80% [1].

Incontinent diversion: In patients with limited dexterity and/or renal failure an incontinent diversion, usually an ileum conduit, may become necessary. To avoid stoma and peristomal skin complications choosing the right stoma location and instructing the patient about stoma care routines is essential.

2. Neurogenic overactive detrusor in combination with overactive sphincter (detrusor sphincter dyssynergia)

Patient with detrusor sphincter dyssynergia have an increased risk for upper urinary tract damage (mostly in patients with suprasacral spinal cord injury or spina bifida).

Treatment options

Alpha-blockers: May improve bladder storage and voiding but data for neuro-urological patients are very limited.

Indwelling catheter / intermittent catheterisation: Intermittent self-catheterisation is the first choice but the type of catheterisation depends upon several factors such as
General recommendations

- The frequency for bladder emptying should be decided individually, generally it is between 4-6 times per day with maximal bladder emptying volume of 400–500 mL [1]
- For intermittent catheterization, the catheter size most often used is 12-16 French [1]
- Indwelling catheters should be changed regularly every 4-6 weeks to prevent catheter obstruction, encrustation, and urinary tract infection
- Consider the use of antimuscarinics in individuals with suprasacral lesions with detrusor overactivity despite using indwelling catheters [8]

Sphincterotomy: Sphincter incision can reduce bladder outlet resistance without completely losing the closure function of the urethra. The procedure needs to be repeated at regular intervals in many patients. If secondary bladder neck fibrosis occur, combined bladder neck incision may be considered [1]

Others: Neuromodulation procedures (transcutaneous electrical nerve stimulation, tibial nerve stimulation, sacral neuromodulation), onabotulinumtoxinA sphincter injections, balloon dilatation, urethral stents.

3. Neurogenic overactive detrusor in combination with underactive sphincter

In combination with the specific treatment for overactive detrusor, the increase of bladder outlet resistance can improve continence.

Nevertheless, these procedures can cause high intravesical pressure and urinary retention, being indicated only when bladder activity can be controlled and no significant reflux exists. Otherwise, simultaneous bladder augmentation and intermittent catheterisation may become necessary [1].

Treatment options

- Urethral sling: Autologous material is preferred over the synthetic material
- Artificial sphincter: An option for both female and male patients
- Others: Bulking agents (but have only short term effects), drugs are not indicated

If surgery is not an option or has been unsatisfactory, men can be fitted with external drainage systems if needed [1].
<table>
<thead>
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<th>Antimuscarinic</th>
<th>Release</th>
<th>Prescription</th>
<th>Ability to Cross Blood-Brain Barrier</th>
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<tr>
<td>Darifenacin</td>
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<td>7.5mg-15mg 1x/d</td>
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<td>CR</td>
<td>4mg-8mg 1x/d</td>
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<tr>
<td></td>
<td>CR</td>
<td>5mg-20mg 1x/d</td>
<td>moderate/high</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>One patch every 3-4 days</td>
<td>moderate/high</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>CR</td>
<td>5mg-10mg 1x/d</td>
<td>moderate</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>IR</td>
<td>2mg-4mg 1-2x/d</td>
<td>low</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>4mg 1x/d</td>
<td>low</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>IR</td>
<td>15-20mg 2x/d</td>
<td>almost none</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>60mg 1x/d</td>
<td>almost none</td>
</tr>
</tbody>
</table>

Table: Most commonly used antimuscarinic drugs (adapted from Panicker JN et al. [2])
IR: immediate release; CR: controlled release; x/d: times x per day
References


B. DETERUSOR UNDERACTIVITY

Authors: José Carlos Truzzi, Rizwan Hamid

Introduction

Voiding, is a result of the relationship between detrusor contraction on one hand and the urethral resistance on the other. A detrusor contraction of sufficient magnitude that can overcome the resistance offered by urethra will result in a normal urinary flow. Failure to obtain this bladder contraction corresponds to the biological condition detrusor deficit contractility. The urodynamic finding of this “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” corresponds to the definition of the detrusor underactivity adopted by the ICS (Abrams et al, 2002). Symptoms due to inefficient contraction are grouped as underactive bladder. The main reason to propose the concept of underactive bladder was to establish parameters that allow one to initially identify and treat patients with this bladder dysfunction without the need of complex or invasive exams and to differentiate it from bladder outlet obstruction (Chapple et al, 2015). The II International Congress on Underactive Bladder (CURE-UAB 2) defined underactive bladder as a “symptom complex suggestive of detrusor underactivity and is usually characterized by prolonged urination time, with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling and a slow stream, palpable bladder, always straining to void, enuresis and/or stress incontinence” (Dewulf et al, 2017).

According to the aspects described above, it is fundamental to recognize the existence of terms related to physiology (detrusor contractile deficit), urodynamics (detrusor hypocontractility), and symptoms (underactive bladder) that correspond to a functional transient or established poor bladder emptying. In general, the terms detrusor hypocontractility and underactive bladder are the most used in literature and research.

Detrusor underactivity (DU) is defined by a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span.

Underactive bladder: (symptom) Underactive bladder is characterized by a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms (footnote).
**Epidemiology**

There are no population data that allow the correct estimation of the prevalence of detrusor hypocontractility and underactive bladder. The lack of specificity of urinary symptoms and the usual need of invasive evaluation (urodynamic study) for diagnosis impair the estimation of the correct real number of cases. Estimates have been obtained from investigational studies on LUTS (lower urinary tract symptoms), in specific groups submitted to urodynamic evaluation that identified no other cause for the voiding dysfunction but detrusor hypocontractility. Jeong et al, evaluated 1179 patients with LUTS undergoing urodynamic evaluation, 40 men and 13 women without any neurological disease or anatomic bladder neck obstruction were diagnosed with detrusor hypocontractility (non-neurogenic and non-obstructive) (4) (Jeong et al, 2012).

Bladder aging is one of the factors that most contributes to the increase of patients with detrusor hypocontraility. Many studies observed a prevalence of detrusor hypocontractility of 9% to 28% in non-neurological patients with up to 50 years old; that number raised to 48% among men and up to 45% in women older than 70 years old. Despite this high prevalence, detrusor hypocontractility is a disease and not consequence of natural process of aging (5, 6) (Osman et al, 2014; Resnik et al, 1989).

Detrusor hypocontractility may still be a bladder manifestation of several neurological diseases. In multiple sclerosis, 75% to 90% of patients will complain some form of voiding dysfunction along life. Approximately 20% of patients with multiple sclerosis will present detrusor hypocontractility with poor bladder emptying (Figure 1). In Parkinson disease, bladder dysfunction is the most frequent autonomic disturbance. Although the most common observed aspect is detrusor overactivity during bladder filling, around 16% of patients present detrusor hypocontractility contributing to the incomplete bladder emptying process due the bladder neck obstruction, caused by bradykinesia of urethral sphincter. In males with Parkinson disease, this is worsened by eventual enlargement of prostatic volume. In stroke, one of the most prevalent neurological diseases, urinary retention is observed in almost 50% of patients during the initial phase. Three quarters of them with detrusor hypocontractility. This bladder pattern usually reverses, and most patients evolve to detrusor overactivity during bladder filling after this first moment. In diabetes mellitus, 50% to 80% of patients report bladder dysfunction not only due to neurological disorder but also due to alterations of bladder muscle, causing detrusor hypocontractility (2, 7) (Daneshgari et al, 2009; Chapple et al 2015).

**Figure 1**

Male, 49 years old, multiple sclerosis for 15 years – detrusor overactivity (bladder filling phase) and detrusor hypocontractility with partial resistant sphincter
Classification and Etiopathology

Adequate bladder function depends on the neurologic and muscular integrity of lower urinary tract. Voiding physiology is not yet totally understood in all its details; many steps of bladder contraction may be related to detrusor hypocontractility. In the physiological voiding process, during bladder filling, afferent nerves continuously send impulses from urothelium and myovesical plexus through pelvic nerves to spinal cord. These nerve impulses ascend by spinal-thalamic tract to periaqueductal gray substance (PAG) that, in turn, sends impulses to pontine center of continence and limbic system, base nuclei and pre-frontal cortex; at the same time, PAG inhibits the pontine center of voiding. Once bladder filling reaches an adequate volume, at cortical level, in order to begin emptying, cerebral centers send information to PAG that in turn unblock pontine center of voiding and send sequential stimuli via spinal cord and subsequently to hypogastric nerves, pelvic plexus and pudendal nerve, in order to achieve synchronous urethral sphincter relaxation and detrusor contraction. During the voiding phase intensity and duration of bladder contraction are generally controlled by efferent nerves. Integrity and integration of afferent nervous system, brainstem, basal nuclei, cerebral cortex, limbic system and efferent nervous system are fundamental to achieve adequate voiding pressure, in order to achieve complete bladder emptying. Also, detrusor muscle needs an adequate cellular structure, quantity and distribution of muscular fibers integrated to collagen framework, to work adequately.

As described in the beginning of this chapter, underactive bladder is a definition based only on symptoms assuming the presence of detrusor hypocontractility. According to urodynamic point of view evaluation and the adopted concepts of CURE-UAB 2, detrusor hypocontractility is an urodynamic diagnosis defined as an impaired voiding efficiency (VE) – lower than 90% - in men and women, characterized by reduced contraction of detrusor and reduced or absent urinary flow at urodynamic evaluation. In this context, detrusor hypocontractility can be classified as:

1. **Neurogenic**: the primary cause of detrusor hypocontractility is neurological, located at the neuro-axis (multiple sclerosis, herniated disc, Parkinson disease, spinal cord injury, neuro-syphilis), or at peripheral nerves (lesions due radical surgeries, pelvic trauma, diabetes mellitus and herpes virus infection).

2. **Myogenic**: due to contractile failure of detrusor, consequent to structural or functional disorders observed in diabetes mellitus, bladder aging, or secondary to urodynamic disorders, such as chronic bladder outlet obstruction

3. **Idiopathic**: when not classified as neurogenic or myogenic disorders.

Neurogenic detrusor hypocontractility may be caused by functional disorder of any segment of central nervous system, as well as by peripheral neural diseases related to voiding phase. Lesions of the sacral spinal cord (particularly S2-4 segments) and peripheral nerves represent the classical bladder-sphincter underactivity with detrusor hypocontractility (Figure 2). In these situations, aside from detrusor contraction failure, it is observed disorders of urethral sphincter (insufficiency or fixed position that partially or totally obstruct urinary flow). However, diseases of cerebral and supra-sacral spinal cord structures may also cause detrusor hypocontractility. Failures of an integrated system due to neurological disease can lead to altered transmission of information from cerebral areas down the spinal cord and to the detrusor may lead to inefficient detrusor function. At the cerebral shock phase of stroke, 50% of patients present urinary retention, mostly caused by detrusor hypocontractility. In turn, cervical spinal cord lesions show detrusor hypocontractility in up to 17% of patients (Kaplan et al, 1991).
Myogenic theory assumes that there is no failure of muscle stimulation or alteration of nerve supply. The myogenic hypothesis suggests a disorder of activation of cholinergic system, ATP mitochondrial conversion, until release of calcium by the sarcoplasmatic reticulum and activation of actin-myosin complex (Smith et al, 2016). Integration of millions of muscular cells, intercellular transmission, coordination of contraction of interstitial cells, and interaction of myocytes and elastic and viscoelastic fibers are fundamental for the production of expulsive strength of urinary flow.

Along with the lack of correct information about natural history, incidence, prevalence and related factors, the heterogeneity of situations where hypocontractile bladder is observed leads to conclude that it is of multifactorial etiopathogenic origin. One example is the higher frequency in older people. In that age group, potentially there is more neurological involvement, with lowering of axonal content, reduction of parasympathetic activity (recognized by lowering of number of positive acetylcholinesterase fibers), increase of bladder filling sensation threshold, proportional reduction of muscle-collagen relation and consequent disorder of bladder cyto-architecture (Chapple et al, 2015). In women, estrogenic deficiency and genital prolapses may be related to failure of contraction of bladder muscle. In aging males, the increase of prostate volume may potentially obstruct urinary flow (Figure 3). Long-term bladder outlet obstruction is classically related to a failure of detrusor contractile capacity. Experimental models of acute obstruction showed bladder distension and muscular hypertrophy followed by contractile failure. There is a cyclic ischemic process with loss of more than 50% of normal blood flow followed by reperfusion and release of oxygen reactive species, infiltration of collagen tissue, immunologic cells and reduction of the expression of proteins of cellular junction (Greenland et al, 1996). Although those aspects supposedly occur in human bladder, there is not enough evidence in literature.

Diabetic cystopathy is another example of mixed pathophysiology. It is related to glucose level, time of evolution and severity of the disease. Neurologically, it presents as segment demyelination, axonal degeneration and ischemia, affecting functionally the autonomic innervation. There is impairment of detrusor contractile capacity and bladder filling sensation. Muscle cells lose their contractile capacity and impair bladder emptying. At molecular level, there is an increase of expression of fine protein filaments, and alteration of the intracellular signaling and receptor distribution. In diabetic detrusor hypocontractility release of oxygen reactive species, ultra-structural disorders of detrusor muscle cells and reduction of their density in relation to extracellular matrix and infiltration of connective tissue (Daneshgari et al, 2009; Chapple et al., 2015; Smith et al, 2016) are prominent features.

Figure 2

Male, 49 years old, post-operatory of pelvic sarcoma exeresis – detrusor hypocontractility
Diagnosis of hypoactive/hypocontractile bladder

Underactive bladder is a clinical concept defined by symptoms and physical exam. The aim is to facilitate diagnosis and start initial treatment without the need of invasive investigations. The problem is that men and women with bladder outlet obstruction share the same symptoms of underactive bladder. Some retrospective studies have tried to identify a higher prevalence of some lower urinary tract symptoms in underactive bladder (11, 12) (Gammie et al, 2016; Stav et al, 2013). Urgency, urinary hesitancy, urinary straining, nocturia, increase of number of voiding, and necessity to compress the suprapubic region to complete bladder emptying, are the most common reported symptoms. But these symptoms are also observed in patients with bladder outlet obstruction. In a study by Gamie et al (11) (2016), the symptoms of men and women with detrusor hypocontractility without bladder outlet obstruction, bladder outlet obstruction without detrusor hypocontractility, and normal patients (without obstruction or hypocontractility) were compared using urodynamic evaluation. Men with hypocontractility showed more frequently palpable bladder sensation, absence or lowering of bladder filling sensation, straining to void, enuresis and stress urinary incontinence, compared to those with bladder outlet obstruction. Women with detrusor hypocontractility showed the same symptoms of men and also, reduction of urinary flow. The study has a limitation: patients with concomitant hypocontractility and bladder outlet obstruction, as well as, those with detrusor overactivity, were not included. Another study that compared women with detrusor overactivity and hypocontractility or with normal voiding contraction, showed that hesitancy, reduced urinary flow, intermittence, straining in the end of voiding, terminal drip and incomplete emptying sensation, are more frequent when there are both detrusor overactivity, with hypocontractility in the emptying phase (12) (Stav et al, 2013).

Although not necessary to evaluate underactive bladder, urodynamic study is the only objective method to evaluate detrusor contractile function to differentiate hypocontractility and bladder outlet obstruction. Voiding dynamics is the product of generated strength of detrusor contraction and urethral resistance (sphincter action). With the increase of detrusor pressure and urinary flow, urethral resistance is lowered, reaching its minimum when maximum urinary flow is achieved. In many instances, in the same scenario, symptoms of poor bladder emptying may represent the association of bladder outlet obstruction and hypocontractility. This is observed in prostatic benign hypertrophy, with bladder outlet obstruction and detrusor hypocontractility, which symptoms are indistinguishable (Figure 3). Free uroflowmetry, a very used non-invasive exam, cannot distinguish obstructive disease and hypocontractility. The same is valid to post-voided residual urine volume.

The International Congress on Underactive Bladder in 2015 defined detrusor hypocontractility as reduced voiding efficiency, characterized by lowered detrusor contraction and lowered or absent urinary flow (3) (Dewulf et al, 2017). This consensus stated that there are not enough data to support a specific definition in women, young people and children. Functionally, bladder hypocontractility corresponds to detrusor contraction failure evaluated by intravesical pressure in the presence of normal urethral resistance. In general, detrusor contraction strength is the most used parameter evaluated at urodynamic studies through pressure records.

In the voiding phase of urodynamic evaluation, during pressure-flow study, detrusor pressure at maximum flow can classify detrusor contractility of adult men as normal (>40 cm H2O), slight hypocontractility (30-40 cm H2O), moderate hypocontractility (20 to 30 cm H2O) and severe hypocontractility (<20 cm H2O). For women, there are no clear parameters to differentiate normal contractility and hypocontractility. One of the causes is the capacity that most women present to void normally with good sphincter relaxation, with minimum...
rise of intravesical pressure (Figure 4). In females, efficiency of bladder emptying (post-void residual urine volume) is relevant in the evaluation of detrusor hypocontractility.

Detrusor pressure recorded at the moment when voiding is interrupted (isovolumetric pressure) may estimate the strength of detrusor contraction. Projected isovolumetric pressure (PIP) may be calculated by the formula: \( P_{\text{det}} + K \times Q_{\text{max}} \), being \( K \) a fixed constant representing the slope of the bladder outlet resistance. This \( K \) constant in old men is 5 cmH2O/ml/s and in women 1 cmH2O/mL/s. PIP value categorizes detrusor contractility as strong (>150), normal (100-150), weak (50-100) and very weak (<50) \(^{(2)}\) (Chapple et al, 2015).

**Figure 3**

![Graph showing detrusor pressure and other parameters over time for a male patient with bladder neck obstruction (PBH) and detrusor hypocontractility.](image)

Male, 61 years old, bladder neck obstruction (PBH) with detrusor hypocontractility

**Figure 4**

![Graph showing detrusor pressure and other parameters over time for a female patient with stress urinary incontinence due to sphincter deficiency and detrusor hypocontractility with reduced urinary flow and incomplete bladder emptying.](image)

Female, 64 years old, stress urinary incontinence due to sphincter deficiency and detrusor hypocontractility with reduced urinary flow and incomplete bladder emptying

Other methods that can diagnose hypocontractility are Schaffer Nomogram (linear passive urethral resistance relation – Lin PURR), Watts Factor and Bladder Contractility Index (BCI).

Schaffer nomogram classifies bladder outlet obstruction grades in seven areas. To each of these areas is assigned the detrusor contraction strength, to help differentiate
detrusor hypocontractility and bladder outlet obstruction (Figure 1). The line of urethral resistance characterizes the relation of detrusor pressure and flow.

Watts Factor (WF) is obtained by the mathematic formula: \( WF = \frac{[(P_{\text{det}} + a)(V_{\text{det}} + b) - ab]}{2\pi} \), where \( V_{\text{det}} \) is the velocity of shortening of detrusor and \( a \) and \( b \) are constants (\( a = 25 \text{ cmH}_2\text{O}, b = 6 \text{ mm/s} \)). It measures detrusor potency by bladder surface unit, and the value 7W/m\(^2\) corresponds to hypocontractility.

BCI, easy to calculate, is the most used, where \( \text{BCI} = P_{\text{det}}@Q_{\text{max}} + 5Q_{\text{max}} \). BCI >150 is considered strong, BCI 100–150 - normal, and BCI < 100 - weak.

The three evaluation methods described above are highly correspondents. Watts factor and BCI do not evaluate the grade of bladder outlet obstruction and do not distinguish both situations (obstruction and hypocontractility) and their coexistence. When other urodynamic parameters in men are analyzed, comparing individuals from the extremes of the pressure-flow studies (in percentile 10 - supposedly hypocontractile, and in percentile 90 - compatible to bladder outlet obstruction), hypocontractile patients show higher medium cystometric capacity and higher post-void residual volume, lower voiding efficiency, lower voiding volume, lower maximum and medium urinary flow, and reduced bladder contractility index and detrusor pressure at maximum flow (13) (Oelke et al, 2015). These findings are in accordance to those of Gammie et al study (11) (2016) that observed higher volume when bladder filling was perceived, higher cystometric capacity and higher abdominal pressure during maximum flow and lower voiding volume in men and women with hypocontractility, when compared to patients with bladder outlet obstruction.

**Treatment of Underactive detrusor**

The treatment of neuropathic underactive detrusor (nUAD) is not well defined as the natural history is not well known. It should be tailored to the patient's expectations with the aim of facilitating bladder emptying and to prevent the complications like urinary tract infections, frequency, nocturia, and/or overflow incontinence and to improve the quality of life.

**The treatment can be aimed at:**
1. Detrusor – underactive
2. Sphincter – that could be underactive, overactive or normoactive

**Management strategies**

The treatment strategies could be divided into:

**Conservative Methods**

As there is a risk of progression to an acontractile detrusor and almost no risk of upper tract deterioration, watchful waiting could be offered as a treatment of choice for asymptomatic patients or those not wanting any active treatment.

Pelvic floor physicaltherapy (PFPT) has been suggested with some anecdotal experience and extrapolation from pediatric literature on dysfunctional voiding. Although nUAD cannot be equated to dysfunctional voiding, PFPT may be helpful to relax the pelvic floor decreasing outlet resistance and facilitating bladder emptying (14) (Van Koeveringe et al, 2011).

One the other hand patients with increased residuals should be encouraged to perform timed voiding and to double voiding to decrease incomplete emptying.

There is paucity of data on upper tract changes in these patients, however, these large and capacious bladders do not have high pressure and don’t demonstrate.
Pharmacologic Management
A number of medications have been used to treat underactive detrusor.

Parasympathomimetics
These aim to provide direct stimulation of muscarinic receptors by muscarinic receptor agonists like bethanechol and carbachol. Anticholinesterase inhibitors like distigmine, pyridostigmine, and neostigmine can potentially increase endogenous acetylcholine at the muscarinic receptors, thus increasing detrusor contractility.

In actual practice a meta-analysis of six randomized trials using bethanechol and carbachol revealed no significant improvement in voided volumes, post-void residuals, or flow rates compared to placebo or no treatment \(^\text{(15)}\) (Barendrecht et al, 2007). Distigmine was compared to placebo in a randomized trial and not found to be significantly better than placebo while another study found that patients on distigmine did worse than those on placebo \(^\text{(15)}\). Additionally, the parasympathomimetics have significant side effects like flushing, nausea, vomiting, diarrhea, gastrointestinal cramps, bronchospasm, headache, salivation, sweating, visual disturbances and rarely cardiac arrest \(^\text{(15)}\) (Barendrecht et al, 2007).

Currently, there is little evidence to suggest that there is a role for parasympathomimetics in management of nUAD.

Alpha-Blockers
An alpha-blocker could be used in men to reduce bladder outlet resistance through smooth muscle relaxation, thus allowing a more effective Valsalva voiding. The role of alpha-blockers in women is debated as there is not a significant evidence of their in the bladder neck region.

Clean Intermittent Catheterization
This is the mainstay of bladder emptying in cases where there is evidence of incomplete emptying and symptoms of recurrent urinary tract infections or overflow urinary incontinence. It is recommended to undertake self catheterization every 4 to 6 hours to keep volumes drained <500 ml.

Surgical Management
There are various surgical techniques that could be employed to facilitate bladder emptying.

Catheterizable Stoma/Indwelling Catheters
In cases where a patient is unable to catheterize through the urethra due to body habitus or other physical/personal limitations, a continent catheterizable stoma may be constructed.

On the other hand in situations where there are significant co-morbidities or patient unwillingness to undergo a major surgery, an indwelling catheter could be used a means of bladder drainage. In this situation a suprapubic catheter is preferable in the longer term to avoid the risk of urethral strictures in men and urethral erosion in both sexes. \(^\text{(20)}\)
Sacral Neuromodulation
Sacral neuromodulation (SNM) may be offered to a select group of urological patients. It is thought to restore voiding in patients with DU by modulating pelvic/perineal afferent pathways. It is postulated to alter afferent pathways by increasing parasympathetic activity in the bladder while suppressing the sympathetic urethral and somatic sphincter components of the guarding reflex leading to outlet relaxation and improved bladder emptying. (21)

Transurethral Resection of the Prostate
The evidence for transurethral resection of the prostate (TURP) for benign prostatic enlargement in men with DU and BOO is not strong. There are some studies demonstrating a significant improvement in mean IPSS score and quality of life after TURP in patients with DU on urodynamics. (22)

Reduction Cystoplasty
It has been reported that reduction cystoplasty in men with acontractile bladders and large bladder capacity improves detrusor contractility. Though, this has only been shown in 1 study and currently there is no evidence to support this management strategy. (23)

Latissimus Dorsi Detrusor Myoplasty
It has been reported that free transfer of autologous latissimus dorsi muscle to the bladder restores detrusor function and was first reported about 20 years ago. However, long term results are not known, hence, at present this is not recommended as a treatment option.

Treatment of concomitant sphincteric abnormalities
In infra sacral lesions the underactive detrusor can be associated with any of the sphincteric conditions including overactive, underactive or normoactive.

The treatment strategies for managing sphincteric abnormalities are:

Treatment for underactive sphincter

Bulking Agents
Success rates vary between 20-50% with collagen and polydimethylsiloxane and hence are used sparingly but do have a role in complicated patient. (24)

Slings and Tapes
The bladder neck slings have been used but mainly in paediatric population with success around 70%. The main problems are failure and difficulty in catheterization due to the angulation of the urethra. Lately, transvaginal tape has been successfully used in the female neuropathic incontinence with about 60% success at 10 years. (24)
Artificial Urinary Sphincter (AUS)

The most successful treatment of stress related urinary incontinence in a neuropathic patient is the use of an AUS. There are 3 components: peri-urethral cuff, pump in the scrotum and balloon in the retropubic space. Recent reports in the adult neuropathic population indicate long-term success rates of around 70%, but almost half require additional procedures (25).

Bladder Neck Closure

This is used as a last resort and is combined with either a catheterisable stoma or a suprapubic catheter with success rates of around 75%. The main disadvantage is irreversibility and loss of secondary access to bladder (26) in case of failure to catheterise. In females this is performed vaginally and Martius fat pad is interposed between bladder neck and anterior vaginal wall to prevent fistulisation.

Treatment for overactive sphincter

External Sphincterotomy

If left untreated DSD leads to a complication rate of 50% including urosepsis, hydronephrosis, stones and reflux, which can all lead to deterioration of renal function. External sphincterotomy is the gold standard for treating DSD, although often needs to be repeated. The complications include sepsis, bleeding and erectile dysfunction. A bladder neck incision might be necessary later on to overcome bladder neck dysnergia.

Urethral Stents (8)

There are 2 main types of urethral stent; Memookath (temporary) and Urolume (permanent). They are both potentially reversible and require a shorter hospital stay than sphincterotomy. The potential complications are migration, encrustation, blockage, bladder neck dyssynergia and incomplete emptying with development of AD. A memokath stent can be inserted through a Urolume to overcome bladder neck dyssynergia.

Botulinum toxin A

Injection of Botulinum toxin A into the urethral sphincter can relax the urinary sphincter, reduce bladder outlet resistance, and facilitate bladder emptying for patients with nUAB. Botox injections have been used to treat detrusor sphincter dyssynergia, however the effects are temporary and hence need to be repeated. It has been reported that Botulinum toxin A injections can improve voiding in 76% of patients with detrusor areflexia (Liao & Kuo, 2007). It can be a viable treatment option in this patient group (16).

Future Direction

A recent review by Van Koveringe et al, (17) 2014 suggested new research strategies in animal models. A number of new therapies have been considered including prostaglandin E2 (PGE2) which can enhance detrusor contraction and relax the urethra. It may also increase afferent activity by stimulating the urothelial and myogenic pathways.

Capsaicin and resiniferatoxin can stimulate bladder activity via activation of transient receptor potential (TRP) channel V1. According to animal data, TRPV1 agonists may stimulate activity in the urothelial and myogenic pathways and have direct effects on the detrusor (18) (Andersson 2010).
The use of insulin like growth factor and nerve growth factor is under investigation as well to improve muscle and nerve function in the lower urinary tract. Stem cells and gene therapy may be considered to improve detrusor contractility.

Recently, an international CURE-UAB support foundation was established to increase awareness of this condition amongst healthcare professionals and allow for public-private partnerships to advance UAB research (Chancellor 2014). This includes an online portal for physicians and patients understand this condition and to promote research on UAB. It includes professional material and videos (www.underactivebladder.org).

**Conclusion**

UAB is a complex disease with a multifactorial etiology. It is probably underreported and no much advancement has been made in the past decade. However, this is changing and there is a renewed interest in this condition. It is envisaged that would be more research and collaboration between healthcare physicians to support patients with this condition.
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C. INTERMITTENT CATHETERIZATION

Authors: Marcio Augusto Averbeck & Helmut Madersbacher

Introduction

Intermittent catheterization is nowadays the therapy of choice for patients who cannot or not completely empty their urinary bladder and in whom this condition cannot be treated otherwise. In this case, a catheter is introduced several times daily either via the urethra or via a surgically created stoma in the lower abdomen for emptying the bladder. If possible, catheterization should be carried out by the patient him-/herself (self-catheterization) or by the carer (third-party catheterization) (1). With intermittent catheterization other concomitant complications caused by the bladder dysfunction, e.g. urinary incontinence, can be abolished or improved, if necessary supported by pharmacotherapy. The most common complication of intermittent catheterization is urinary tract infection (UTI). However, the UTI rate is significantly lower with intermittent catheterization than in any form of permanent urinary diversion, whether transurethral or suprapubic.

Intermittent catheterization (IC) is usually indicated for assisted bladder emptying in neuro-urological patients, providing benefits, such as preservation of the upper urinary tract function and improvement of urinary incontinence. In addition, IC provides higher independence to the patient and consequently a better quality of life (2). Nevertheless, IC may be associated with specific complications.

History and development of intermittent catheterization

The technique of intermittent catheterization was introduced for the first time in 1947 by the neurosurgeon Sir Ludwig Guttmann, then head of the Stoke-Mandeville Rehabilitation Center (UK), in order to routinely empty the bladder in spinal cord injured patients during the spinal shock phase. The sterile technique implied the use of sterile materials, handled with sterile gloves. At that time, sterile technique was complex and costly, with limited indication outside the hospital environment (3).

On the other side of the Atlantic, in the USA, the urologist Jack Lapides (1972) also started intermittent catheterization to empty a non-functioning bladder, but as “clean intermittent catheterization” (CIC), with multi-use PVC catheters. For this purpose a reusable catheter is used, which is rinsed, cleaned and disinfected after catheterization (4). For catheterization no gloves are worn, but the catheterizing person washes the hands carefully with soap and water before. Lapides stressed, “Much more important is the frequency of CIC in 24h than a sterile technique.” He recommended the catheterization every 3-4 hours, in order to quickly remove the bacteria thus introduced into the bladder.

The catheterization under sterile conditions, as introduced by Sir Ludwig Guttmann, was subsequently only applied in intensive care units and in the operating room. But the principle of catheterization under sterile conditions has been implemented in daily practice as “aseptic catheterization,” especially in Europe. For this purpose sterile packaged disposable catheters are used which are discarded afterwards. The special packaging of the catheters with tear lines in the inner packaging envelope allows the catheter to be inserted “from out of the sheath” without touching the catheter itself (“no-touch technique”).
In the last two decades the catheters have been further developed in terms of materials, design and packaging. Initially, prior to introducing the catheter, the urethra was made slippery by instilling a lubricant to avoid mucous membrane lesions as far as possible. In 1983 Jan Utas developed the “Urotonic Surface Technology” which was the basis for the development of the hydrophilic catheter: A special coating of the catheter surface with salt caused the surface to become particularly slippery by contact with water, thus facilitating insertion of the catheter without or with minimal pain (5).

Hydrophilic catheters have a polymer layer, which coats the surface of the catheter and has high affinity for water. These characteristics form a slippery surface, which facilitates the catheter’s entrance into the urethra. The development of such catheters facilitated the “no touch” technique, providing benefits in terms of less external contamination (6).

The water needed to activate the coating had to be added initially, but consequently products were developed in which sterile water was already prepacked to the catheter, known nowadays as a “ready-to-use catheter.” Such ready-to-use catheters are coated catheters, either hydrophilic or prelubricated with a sterile gel. Thus the armamentarium to perform aseptic catheterization was extended by coated catheters and ultimately by the ready-to-use products.

European Association of Urology (EAU), the International Consultation on Incontinence (ICI), the American Urological Association (AUA) and the National Institute for Health Care Excellence (NICE) intermittent catheterization is consistently addressed as the safest method of bladder emptying in patients with acute and chronic urinary retention with regard to urological complications, quality of life and costs for society (7). However, the evidence for this clinical experience is weak. The reason is that in studies on catheterization, especially in comparative studies, the method, the materials and the technique used as well as the design of the catheter are not exactly described, with the consequence that even simple questions cannot be answered with evidence. Therefore an exact terminology is the prerequisite to improve the situation.

There is conflicting evidence suggesting that the use of prelubricated or hydrophilic catheters is associated with lesser risk of symptomatic urinary infections in neuro-urological patients (8). On the other hand, the costs of the hydrophilic catheters can still limit their broad use in different communities.

### TABLE 1. INTERMITTENT CATHETERIZATION TECHNIQUES (7)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean intermittent catheterization:</td>
<td>A mostly reusable catheter is inserted with the help of the washed hands, gloves are not necessary for self-catheterization.</td>
</tr>
<tr>
<td>Aseptic catheterization:</td>
<td>For this purpose a sterile packaged catheter is used. For insertion the “no-touch technique” should be applied. Either “uncoated” or “coated” catheters can be used. The ready-to-use catheters have the advantage that they can be used without additional manipulation.</td>
</tr>
<tr>
<td>Sterile catheterization:</td>
<td>This technique is nowadays only used in the hospital setting, in particular in intensive care units or operating rooms for diagnostic and therapeutic procedures. In daily practice sterile catheterization has been replaced by aseptic catheterization.</td>
</tr>
</tbody>
</table>

### Complications of Intermittent Catheterization

One of the main drivers of the success of IC is the reduction of symptomatic urinary tract infections (UTIs) and preservation of renal function compared to indwelling catheters. However, this management method is lifelong and all long term complications need to be considered since there are possible delayed complications.

The more common complications of IC are recurrent symptomatic UTIs, lesions of the urethral mucosa, urethral stricture and false passages (8, 10). Other possible complications are listed in table 2.
TABLE 2. COMPLICATIONS ASSOCIATED WITH IC \(^{(11, 12)}\) AND INDWELLING CATHETERS

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
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<tbody>
<tr>
<td>Recurrent or persistent urinary tract infections</td>
</tr>
<tr>
<td>Urethral mucosa lesions</td>
</tr>
<tr>
<td>Urethral strictures</td>
</tr>
<tr>
<td>Falsa passages</td>
</tr>
<tr>
<td>Pain/discomfort</td>
</tr>
<tr>
<td>Bladder stone</td>
</tr>
<tr>
<td>Urethral meatus stenosis</td>
</tr>
<tr>
<td>Bladder perforation</td>
</tr>
<tr>
<td>“Knotting” (catheter retention)</td>
</tr>
<tr>
<td>Epididymitis</td>
</tr>
<tr>
<td>Loss of bladder compliance</td>
</tr>
<tr>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Vesicoureteric reflux</td>
</tr>
</tbody>
</table>

Wyndaele & Maes conducted a retrospective study with a mean follow-up of 7 years, demonstrating that 20% of the patients who perform clean IC with conventional non-coated PVC catheters with lubricant had some sort of complication. Urethral lesions in males were the most frequent of these including urethral stricture or false passage. \(^{(9)}\).

Perrouin-Verbe et al also assessed the incidence of long-term clean IC complications. Twenty-eight percent of the patients developed UTIs. At a 5-year follow-up, the rate of epididymitis was 28.5% and the rate of any urethral stricture was 19% \(^{(10)}\).

Adequate frequency of catheterization, good education on hygiene and the avoidance of bladder overfilling and maintenance of a low pressure bladder are amongst the most important to prevent UTI \(^{(13)}\).

Complications of Intermittent Catheterization Compared to Indwelling Catheters

Chronic Indwelling catheterization has similar types of complications as IC, however the frequency of many of these complications has been reported to be much higher as is the case with cystitis, pyelonephritis, hydronephrosis secondary to bladder wall thickening and fibrosis, urethral trauma and bleeding, urethritis and bladder stones (consort 2006). Complications unique to indwelling urethral catheters (as opposed to suprapubic) include urethral fistula formation, bladder neck incompetence, sphincter erosion. Other potential morbidities include a higher risk of pressure ulcers as well as more frequent and longer hospitalizations among those treated with indwelling catheters \(^{(14)}\).

Several studies have directly compared the two bladder management methods. In terms of infections Shekelle et al. performed a systematic review of risk factors for UTI in adults with spinal cord lesions and evaluated 22 studies\(^{(15)}\). These authors found increased bladder residual volume as a risk factor that was supported by evidence from two studies. They also found that patients on IC had fewer UTI episodes than those with Indwelling. Fortunately, urinary sepsis was rare, but management with indwelling catheter represented a risk for developing sepsis. Several authors have also reported similar findings of up to six fold rate of UTI in patients with indwelling catheters compared to IC \(^{(1, 16, 17)}\). In a Cochrane Review \(^{(18)}\), fourteen trials were reviewed comparing the evidence for urinary tract infection in indwelling urethral catheterization with intermittent catheterization. Due to clinical and statistical heterogeneity the results were inconclusive with a very low quality of evidence.
Ku et al. (19) retrospectively studied the influence of bladder management on epididymo-orchitis in 140 patients with spinal cord injury (SCI) and found that IC was an independent risk factor for the development of epididymo-orchitis compared to indwelling catheters (19). IC men had a rate of 67% compared to 25% in the indwelling group over the 17 years of the study. Urethral strictures were more common in the men on IC but these were not an independent contributing factor for the development of epididymo-orchitis. In contrast another long term study of 316 men post SCI (1) indwelling urethral catheterization had a far greater risk of urethral stricture, epididymitis and periurethral abscess than those performing IC. Of note the patients with suprapubic tubes had a very low rate of urethral complications.

Kidney stones are more common in patients with SCI compared to the general population. The rate of kidney stones based on bladder management has been variable in the literature. Chen et al (20) found that approximately 7% of SCI patients experienced the first kidney stone within 10 years of injury, and any form of bladder instrumentation (indwelling catheterization, IC, or condom catheterization) resulted in more kidney stones compared with spontaneous voiding. Ku et al. (21) retrospectively studied the risk factors for urinary stone formation in 140 men with SCI over 17 years’ follow up and found that renal stones were more common in patients managed with indwelling catheters compared to those with spontaneous voiding or IC. Complete injury was also an independent risk for renal stone formation. Several other long-term follow-up studies (1, 22, 23) have also found an increased risk for upper-tract stones with indwelling catheter management compared with IC, but others (24) have found the opposite result.

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A very high incidence (up to 30%) of bladder stones have been reported in patients managed with long-term indwelling catheters (1). In a group of 457 SCI patients (25) the absolute annual risk of bladder stone formation with an indwelling urethral or suprapubic tube was 4% compared to 0.2% on IC and having formed a stone in the past year quadrupled the risk of stone formation in the indwelling catheter group to 16%. There was no difference in the stone formation rate between suprapubic and urethral catheters. Other studies have shown a threefold increase in bladder stones with an indwelling catheter (17) or even higher (1). Hydronephrosis and vesicoureteric reflux have also been shown to be more common in patients with indwelling catheters with rates as high as 30-38% for upper tract changes and 22-28% reflux for indwelling urethral and suprapubic tubes respectively compared to IC with rates closer to 18% and 8% (1). These changes are likely due to bladder wall thickening and the resulting loss of bladder compliance associated with indwelling foreign bodies (26).

Igawa et al. (12) found that iatrogenic hypospadias can be caused by downward pressure of the indwelling urethral catheter on the urethra. In women with neurogenic lower urinary tract dysfunction (NLUTD), one major complication seen is urine leakage around the catheter, which may be due to urethral and sphincter erosion with large catheters and large balloons. A pressure sore of the urethra associated with large sized catheters and improper fixation of the catheter can develop an abscess, a fistula, a diverticulum or iatrogenic hypospadias. In a small study of 35 women with SCI followed for 2-12 years, among 13 patients treated with indwelling catheters, 92% developed incontinence around the catheter between two and four years after placement due to urethral erosion, sphincter incompetence or bladder dysfunction. Among the 22 women treated with IC, none became incontinent (27).

**Studies Comparing Hydrophilic versus Conventional Catheters**

Ridder et al conducted a prospective, randomized study, including 123 SCI patients, comparing the intermittent bladder catheterization with hydrophilic catheters versus conventional catheters with lubricant. In this study, UTI was defined as a clinical infection with symptoms of
UTI and for which treatment was prescribed. The symptoms suggestive of UTI were not reported. There was no statistically significant difference between the groups regarding the occurrence of bacteriuria or leucocytes. However, after 1-year follow-up, there were more symptomatic urinary infections in the group using a conventional catheter with lubricant (82% versus 64%, respectively; \( p = 0.02 \)) \(^{(8)}\). Only 57 out of 123 patients completed the 12-month study (46%).

Bjerklund Johansen et al. \(^{(28)}\) assessed patient openness to changing and satisfaction with catheters used in IC for urinary retention due to NLUTD, and compared patients’ response to conventional catheters and to hydrophilic catheters. Of 409 patients recruited, 378 (283 males, 95 females; mean age: 43.5 years) completed a 12-day trial of the hydrophilic catheter. Patients evaluated their current catheter at recruitment and the hydrophilic catheter after the 2-week trial by questionnaire. Patient satisfaction was expressed on a Visual Analogue Scale for seven topics covering use and general satisfaction. The main finding of this study was that more than 50% of the patients wished to continue with the novel catheter and reported increased satisfaction regarding introduction of the catheter, handling, time spent, perception of IC, general satisfaction, and ability to cope with daily life \(^{(28)}\).

Vapnek et al compared the incidence of hematuria, pyuria and symptomatic urinary tract infections in patients who performed self IC using hydrophilic catheters versus standard plastic catheters \(^{(29)}\). Sixty-two male patients mostly with SCI who performed self IC to manage NLUTD were randomized into 2 treatment groups at 3 study sites. Urinary tract infection was defined as a bacterial colony count of 100,000 CFU or greater and at least 1 clinical symptom, such as fever, chills, malodorous urine, increased spasticity or malaise. A positive urine culture in the absence of clinical symptoms was not regarded as a urinary tract infection. Forty-nine patients (79%) completed the 12-month study. The withdrawal rate was not different in the 2 groups. At the end of the study there was statistically less hematuria in the hydrophilic coated catheter group compared with controls. In addition, there was a significant decrease in the urinary tract infection rate from baseline in the hydrophilic coated catheter group but not in controls \((p=0.027)\).

Diokno et al conducted a pilot study to determine patient satisfaction with a new hydrophilic catheter, which included 16 new patients and 25 experienced with clean IC \(^{(30)}\). Patients were asked questions regarding convenience, ease of handling, comfort, and general opinion about the catheters. Four new and eight experienced patients dropped out of the study. Of the new patients who completed the study 75% found clean IC less troublesome than expected and all wanted to continue using the catheter. Among the experienced patients, 81% had a more favorable general opinion about the disposable when compared to the previous catheter, 81% found the disposable catheter to be more convenient, and 88% thought it was easier to handle.

More recently, Chartier-Kastler et al evaluated whether the discreet design of a compact hydrophilic catheter could improve quality of life in IC users compared with standard catheters \(^{(31)}\). A non-blinded, randomized, multicenter, 2-way crossover study with 2 treatment periods of 6 weeks ± 3 days has been carried out. A total of 125 patients with NLUTD were included in the study from 17 study sites. Seven patients who discontinued the study after only documentation of baseline data were not included in analysis of the 118 intention-to-treat patients. Quality of life was evaluated by the intermittent self-catheterization questionnaire (ISC-Q). The ISC-Q score increased significantly due to compact catheter use. An estimated mean difference of 17.0 points between the compact and standard intermittent catheters \((p <0.001)\) was observed, corresponding to a 28% increase. Sixty-three percent of patients preferred the compact catheter, although they were experienced catheter users and satisfied with the previous catheter.

Clark et al. \(^{(32)}\) studied the cost-effectiveness of IC for SCI patients, from a lifetime perspective, for the usage of two different single-use catheter designs: hydrophilic-coated and un-
coated. A probabilistic Markov decision model was constructed, to compare lifetime costs and quality-adjusted life years, taking renal and UTI health states into consideration, as well as other catheter-related events. UTI event rates for the primary data set were based on data from hospital settings to ensure controlled and accurate reporting. The model predicted that a 36-year-old SCI patient with chronic urinary retention would live additional 1.4 years if using hydrophilic catheters compared with uncoated catheters, at an incremental cost of £2100. However, much more important than the mere price of the catheter are indirect costs caused by complications. Therefore further studies should focus on this issue as an important factor for decision making based in costs. Moreover, the lifetime number of UTI events would be reduced by 16%.

Prieto et al. (33) reviewed the evidence on strategies to reduce UTI, other complications or improve satisfaction in IC users by comparing: (1) one catheter design, material or technique versus another; (2) sterile technique versus clean; or (3) single-use (sterile) or multiple-use (clean) catheters (33). Thirty-one trials (13 RCTs and 18 randomized crossover trials), addressed the inclusion criteria comparing method or design and UTI/bacteriuria, other complications or participant assessed outcomes. Studies varied widely in follow-up, UTI definition and attrition; in some, data could not be combined. Where there were data, confidence intervals were wide and hence clinically important differences could neither be reliably identified nor ruled out. Authors concluded that current research evidence is weak and design issues are significant. It has not yet been established whether incidence of UTI, other complications such as hematuria, or user satisfaction are affected by sterile or clean technique, coated or uncoated catheters, single or multiple-use catheters or by any other strategy. However, this review has been withdrawn following the feedback from several neuro-urologists who identified several possible errors in the analysis of data (34). It is important to emphasize that this systematic review included not only spinal cord injured adults, but also children with neurogenic bladders due to myelomeningocele, men with prostatic obstruction and women with multiple sclerosis. Studies varied in setting, length of follow up, definitions of outcomes, and participants. There were a variety of settings—acute care neurology units, community, long-term care.

Li et al. (35) conducted a systematic review and meta-analysis of randomized controlled trials comparing the use of hydrophilic and non-hydrophilic catheters for IC in patients with SCI. Five studies involving 508 subjects; 462 subjects completed the study and were included in this meta-analysis. There was a significantly lower incidence (OR=.36; 95% CI, 24%-54%; P<.0001) of reported UTIs in the hydrophilic-treated group compared with the non-hydrophilic-treated group. Hematuria was also reported significantly less in the hydrophilic catheter group than in the non-hydrophilic catheter group (OR=.57; 95% CI, 35%-92%; P=.001). This meta-analysis supports the benefit of hydrophilic catheters over non-hydrophilic ones in patients with spinal cord injury. The odds reduction of urinary tract infection was cited at 64%, and 43% for hematuria. Most of the evidence came from men, and so it does not seem that these data can generalized to women with spinal cord injury without further evidence.

IC Techniques and Strategies to Avoid Complications

Clean IC patients shall be instructed to wash their hand well, use non-contaminated catheters and lubricants, in addition to cleaning the region of the urethral meatus before introducing the catheter. The cleaning of the hands and the urethral meatus can be done with water and soap (36).

The patient may adopt different positions to perform the catheterization (sitting, lying or standing), depending on his/her physical limitations and the place where the procedure is carried out (11). Women may use a projected mirror for better visualization of the urethral
meatus, which is especially important in the phase of the patient's rehabilitation. Care provided by multidisciplinary team is recommended to check technique and educate the family members and/or care takers about the importance of avoiding external contamination. Printed information leaflets and educational videos can help for adequate comprehension of the technique. In cases of motor deficit, which makes auto-catheterization impossible, family members or a care taker can undertake responsibility to perform the procedure. The number of catheterizations indicated per day mostly depends on oral liquid intake, but it is usually 4 to 6 times within 24 hours. A lower number of IC in 24 hours may result in urinary infections, while very frequent catheterizations may increase the risk of urethral complications. IC frequency may vary according to urodynamic parameters (bladder complacency and detrusor pressure). Bladder distension shall be avoided (> 400 ml), in order to prevent against urinary infections.

Asymptomatic bacteriuria is a frequent finding in neuro-urological patients on IC. There is no indication to perform routine urine culture exam in these patients. Asymptomatic bacteriuria shall not be treated, except in cases, when the patient must undergo surgical or endoscopic manipulations which is also the recommendation of the Infectious Disease Society of America.

Routine antibiotic prophylaxis is not justified. Although it reduces the incidence of asymptomatic bacteriuria, there is no evidence that it reduces symptomatic UTIs. On the other hand, non-specific symptoms, such as exacerbation of spasticity (and difficulty to insert the catheter in the urethra due to the spasms of the pelvic floor), worsening of incontinence, fever, abdominal and back pain may suggest occurrence of urinary infection in SCI patients. In these cases, urine culture may be useful to guide antimicrobial treatment. Whenever a SCI patient presents episodes of symptomatic UTI, IC technique must be reinforced. Hydrophilic catheters and no-touch technique may also be offered for patients on IC and recurrent complications.

### Table 3. Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians must not treat asymptomatic bacteriuria except in cases when the patient must undergo surgical or endoscopic manipulations (GR A).</td>
<td></td>
</tr>
<tr>
<td>Clinicians should/must reinforce proper IC technique whenever a neuro-urological patient presents with episodes of symptomatic UTI (GR B). Hydrophilic catheters and no-touch technique may also be offered for patients on IC presenting recurrent complications.</td>
<td></td>
</tr>
<tr>
<td>Clinicians should not ignore non-specific signs and symptoms of UTI in SCI patients, such as exacerbation of spasticity, difficulty to insert the catheter into the urethra due to the spasms of the pelvic floor, worsening of incontinence, fever, abdominal and back pain, which may suggest presence of urinary infections in SCI patients (GR B).</td>
<td></td>
</tr>
<tr>
<td>When recommending IC make sure that patient does not overdistend the bladder. Therefore a controlled fluid intake and an adequate frequency of IC is mandatory.</td>
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</table>

**Conclusions**

The introduction of IC represented a milestone in the urological management of neuro-urological patients. Currently the most used technique in Latin and North America is “clean” IC, which provides evident benefits in terms of preservation of the renal function. Recent advances include prelubricated catheters, hydrophilic catheters and the no-touch technique, which could potentially minimize the risk of complications, such as UTIs and urethral injuries. However, the costs of hydrophilic catheters can still be a limiting factor for the dis-
semination of this technique. A national survey carried in Canada (2008) reported that only 26% of spinal cord injured patients who rely on IC do use hydrophilic catheters either exclusively or sometimes (42). Although policy changed in the USA in 2008 resulting in an increased provision of single-use catheters, a 2013 survey indicates that 56% reuse their catheter a median of 20 times (43). So far, it is not possible to make evidence-based recommendations on the most appropriate method to clean and store the reusable catheters.

Asymptomatic bacteriuria is a frequent finding in patients, who perform IC. Routine urinalysis and culture exam is not recommended. Attention shall be paid to non-specific signs and symptoms, which may suggest presence of urinary infections in neuro-urological patients, especially those with spinal cord injuries.

Factors that may help in the prevention against recurrent urinary infections include education strategies (reinforcement of IC technique), prevention of bladder over distension, and the use of aseptic technique (no-touch technique). For neuro-urological patients, choice of catheter will depend on personal preference, cost, portability, and ease of use (33).

References


D. PHARMACOLOGICAL TREATMENT OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTIONS

Authors: Luis Augusto Seabra Rios, Francisco Cruz

Introduction

The lower urinary tract is susceptible to secondary dysfunctions related to virtually any neurological pathology. Its complex physiology consists of two stages, storage and elimination, through antagonistic mechanisms that alternate in a harmonious and coordinated way. The bladder storage phase, results from the relaxation of the detrusor muscles associated with activation of a sphincter mechanism that promotes urethral closure. The elimination phase, involves the inversion of these mechanisms with sphincter relaxation, detrusor contraction, emergence of urinary flow and complete elimination of the bladder contents. Neurophysiology, distribution of receptors of the vegetative nervous system and the concepts of basic pharmacology of the lower urinary tract are described in chapters 2 and 6 of the first section of this manual.

Neurogenic lower urinary tract dysfunctions (NLUTD) are separated into two categories: storage dysfunctions and bladder elimination dysfunctions. Storage disorders may be due to changes in bladder function, especially detrusor overactivity, or may result from altered sphincter mechanisms. Elimination disorders are secondary to anatomical obstruction or functional processes of the bladder outlet (bladder neck and urethra) or detrusor contractility deficit.

It is important to emphasize that, in the case of neurological diseases, the dysfunctional disorders discussed here are not mutually exclusive and may occur simultaneously or associated. The possibility of associations of these disorders in several degrees and intensity makes it fundamental to having an individualized approach of these patients in order to make a specific pharmacological option for each situation. (See Chapter 6).

1. Drugs used for the treatment of bladder dysfunctions

Detrusor overactivity can be treated with a large number of drugs that include antimuscarinics, antidepressants, calcium channel blockers, mixed drugs, beta-adrenergic agonists and toxins, among others.
**Antimuscarinics**

Antimuscarinics are the drugs most commonly used both in neurogenic and non-neurogenic disorders. The antimuscarinics are tertiary or quaternary amines with a capacity to block competitively cholinergic receptors on the detrusor muscle or urothelium. Its effect is attributed on the reduction of contractile capacity of the bladder and can be obtained by several compounds and molecules with greater or less “selectivity” of the bladder. The ubiquity of the distribution of cholinergic receptors in the body implies in possible side effects that should be discussed in advance with patients. These adverse effects may be due to the blockage of cholinergic receptors in several organs and systems, with the most frequent being decreased oral secretions, visual difficulty and increased intraocular pressure, intestinal constipation, palpitation and arrhythmias in addition to the effects on the central nervous system, especially cognitive dysfunctions such as impairment of memory and attention. Antimuscarinic compounds with specificity for M2 and M3 receptors, predominant in detrusor and urothelium, are effective in improving voiding symptoms and produce lower indices of adverse effects. The clinical benefits of this class of drugs are irrefutable and involve the reduction of urinary frequency, nocturia, voiding urgency and episodes of urge incontinence. Although there is ample evidence, based on basic science, supporting the use of antimuscarinics in NLUTD, most of the good methodological clinical studies involving these drugs have been performed on overactive bladder / non-neurogenic detrusor overactivity. Evidence of increased M2 receptor density and antimuscarinic responsiveness to denervated bladders reinforces its use in NLUTD (1).

Recent systematic reviews to evaluate antimuscarinic studies in NLUTD revealed that, although many of them lack adequate methodological quality, the patients studied had an increase in cystometric capacity (+ 50 ml, on average), a higher volume of involuntary detrusor contractions (+ 50 ml on average) and detrusor pressure drop (-38 cmH2O on average) when compared with placebo (2,3).

Of the various antimuscarinics available, and already used in the treatment of NLUTD, we only have oxybutynin, darifenacin, tolterodine and solifenacin in our market. Trospium and propiverine offer some advantages, especially for neurologic related adverse events and reduced oral secretions, but are not commercialized in Brazil.

The use of prolonged release antimuscarinics are critical in avoiding plasma drug spikes, significantly reducing the potential for adverse effects. Meta-analyzes of antimuscarinic therapies for non-neurogenic micturition dysfunctions have demonstrated that long-acting formulations are more effective and have a lower rate of side effects. Regarding the effectiveness of each of the antimuscarinics in particular, no advantage was shown of any of these drugs when compared to each other. The transdermal and intravesical routes of administration may be useful as they also prevent the onset of undesirable systemic effects and are clinically effective, although their use is only well studied in non-neurogenic disorders. Intravesical use of oxybutynin is generally done by dilution of the tablet into saline solution and instillation of the solution into the bladder in patients under intermittent catheterization. This form of use is possible both in adults and in children with NLUTD (4,5). The presentation in the form of gel of transcutaneous application, that is equally effective, is not available in our practice.

The rationale for the use of antimuscarinics in overactive bladder is clear but the blockade of bladder cholinergic receptors carries with it the risk of impairment to detrusor contractility and eventual urinary retention. Studies evaluating the effects of antimuscarinics on NLUTD found no significant differences in efficacy among the various drugs used but suggest that the therapeutic benefit is obtained at the expense of
doses higher than those used in non-neurogenic hyperactivity. In spite of this, there was no increase in the incidence of side effects in this group (6,7). In any case, it is essential that the use of antimuscarinics in bladder dysfunctions should be done with the therapeutic window of these drugs in mind.

a) Oxybutynin
Oxybutynin hydrochloride is a tertiary amine compost with myorelaxant and antimuscarinic action. Clinical studies with its use in NLUTD are limited but the drug is effective and safe for the treatment of dysfunctions in adults and children. It is contraindicated in patients with angle-closure glaucoma, myasthenia gravis and obstructive intestinal cases. The doses applied in the studies varied between 10 to 30 mg / day, in adults needing to be adjusted according to clinical response and adverse effects. It was observed increased bladder capacity, reduction in the number of micturitions in 24 hours, reduction of episodes of incontinence and nocturia. In a clinical study of patients with multiple sclerosis, spinal cord injury (SCI) and Parkinson ‘s disease, patients were not accompanied by elevation of post-voiding residual (8). Urodynamic findings in the pediatric population revealed an increase in pressure reduction and reduction capacity. In the group of children studied the clinical and urodynamic benefits occurred equally with the three formulations (tablets, syrup or prolonged-release tablets) (9).

b) Tolterodine
Tolterodine tartrate is an antimuscarinic with vesical selectivity and low affinity for the receptors of the salivary glands. Comparative studies between tolterodine and oxybutynin demonstrated similar clinical efficacy but with advantage for tolterodine in relation to side effects, especially dry mouth. The doses needed to improve NLUTD are higher than in the non-neurogenic population (10).

In an open study in which 46 patients with NLUTD with the usual dose of tolterodine (4 mg / day) were observed, in addition to the usual clinical and urodynamic benefits, a significant decrease in detrusor pressure in patients with compliance deficit (11). Doses used in patients with NLUTD range from 2 to 8 mg / day. Elevation of the QT interval on the electrocardiogram of patients taking tolterodine limits the safety dose to 8 mg / day. The use of tolterodine in children with NLUTD was recently tested and found to be effective and safe in this population (12).

c) Darifenacin
Darifenacin hydrobromide is a tertiary amine with moderate lipophilicity and selectivity for M3 receptors. These physicochemical characteristics, associated with the active transport of darifenacin out of neurons, give this molecule a degree of protection over effects on the central nervous system. Although darifenacin has been extensively studied in idiopathic overactive bladders, there are no adequate studies that evidenced its role in NLUTD.

d) Solifenacin
Solifenacin succinate, similar to darifenacin, has been poorly studied in the neurogenic population. Recently, however, Amarenco et al. published a study on the urodynamic effects of treatment of patients with NLUTD secondary to multiple sclerosis and SCI with solifenacin. It’s a multicenter, randomized study evaluating the efficacy and safety of solifenacin in two dosages (5 and 10 mg) compared to oxybutynin (15 mg) and placebo. Both solifenacin and oxybutynin promoted improvement of the maximum cys-
tometric capacity, as well as the perception of improvement of the bladder condition. The benefits obtained with solifenacin were similar to those offered by oxybutynin in the comparison against placebo (13). In another recent study, the rate of adherence to solifenacin treatment was higher in the NLUTD population (58%) than in the idiopathic overactive bladder group (32%) at one-year follow-up. It is important to emphasize that adherence to the use of antimuscarinics is low over time and this finding may reflect on the clinical benefit of the drug. (14)

Antidepressives
Imipramine
Imipramine is a tricyclic antidepressant currently underutilized for the treatment of depression because of the emergence of more modern drugs with a better safety profile and effectiveness. Because of its anticholinergic and alpha-adrenergic action, it was widely used for the treatment of urinary incontinence in patients with neurogenic, non-neurogenic bladder dysfunction and in children with nocturnal enuresis. Despite demonstrating clinical improvement in some of these patients, there are no randomized controlled trials that allow its routine use. It also has cardio toxic potential that limits its use especially in the elderly and children.

Beta-adrenergic agonists
Mirabegron
The first drug representative of this pharmacological class available in the market and already approved for clinical use in Europe, USA and Brazil is mirabegron. This drug has selective agonist action on beta-3 adrenergic receptors. These receptors represent 97% of the beta receptors present in the bladder and are responsible for the main mechanism of detrusor relaxation in humans. The mechanism of action of mirabegron allows it to have no interference with the physiology of detrusor contraction and bladder emptying and its specificity causes it to have a low rate of side effects. These, when they occur, usually resume to a small increase in blood pressure or heart rate. Unlike antimuscarinics, mirabegron does not cause dry mouth, constipation or cognitive changes.

Its use in idiopathic overactive bladders has been extensively studied but its role in NLUTD is still unclear. The therapeutic effects of mirabegron include reduction of urinary frequency and voiding urgency and, even in men with infravesical obstruction, there was no increase of post-voiding residue or episodes of urinary retention (15). A recent study evaluated the clinical and urodynamic effects of mirabegron in patients with NLUTD secondary to spinal cord trauma treated for a period of at least 6 weeks. After a retrospective analysis of 15 charts, it was concluded that there was a significant improvement in urinary frequency, episodes of urinary incontinence, increased bladder capacity, and improved detrusor compliance (16). In 13 patients with multiple sclerosis, mirabegron significantly improved urinary symptoms without causing adverse effects, such as hypertension, increased voiding residual, or cognitive impairment.

Drug Combinations
Many drug combinations have already been used in order to broaden the clinical response of patients with NLUTD.
The combination of two antimuscarinics appears to be effective and safe in patients with NLUTD, both in adults and in the child population.

In patients already on intermittent bladder catheterization (IC), in whom urinary retention is no longer a problem, both the increase in dose and combinations of antimuscarinics may be used more freely and with greater symptomatic effectiveness.\(^{(17,18)}\)

The association of antimuscarinics with alpha blockers is successfully performed in men with LUTS irresponsible to the use of the alpha-blocker alone. In patients with NLUTD the synergistic action of the two drugs seems to be useful, reducing the occurrence of side effects of each of them and promoting clinical and urodynamic improvement, especially detrusor compliance.\(^{(19)}\)

Other combinations such as imipramine, antimuscarinic and even triple combinations with the addition of alpha blockers have been used with some success in small series of cases.

The combination of antimuscarinic and beta-3 agonist was evaluated in 7 patients with NLUTD, little responsive to isolated cholinergic blockade. It was found that the association of mirabegron promoted improvement of continence and bladder compliance in all patients.\(^{(20)}\) For a small number of cases, these findings should, of course, be evaluated with caution until more methodological studies are carried out.

**Toxins**

\(\text{a) Vanyloids}\)

Some toxins have therapeutic effects in patients with bladder dysfunction. Vanyloids, especially capsaicin and resiniferatoxin, act by desensitizing nerve afferent fibers type C vesicles that are hyperactivated in patients with NLUTD. They are used through bladder instillation and the initial results showed reduction of detrusor overactivity, voiding frequency and episodes of urinary incontinence. Its use started in the recent past has, however, been interrupted after the appearance of botulinum toxin that has superior effectiveness and is universally proven.\(^{(21)}\)

\(\text{b) Botulinum toxin}\)

It is a neurotoxin produced by Clostridium botulinum that interferes in the protein system responsible for the formation of cytoplasmic vesicles of neurotransmitters, including acetylcholine, and its release in the synaptic cleft. The blockade of this system called SNARE (soluble N-ethylmaleimidesensitive fusion attachment protein receptor) occurs in parasympathetic, sympathetic and sensory synapses, and ultimately will produce detrusor paralysis. It is believed that in addition to parasympathetic blockade the interference in sensitive (afferent) vesical fibers contributes to the therapeutic effects of ToxBot in urinary dysfunctions. Of the seven types of ToxBot, Type A is the one with the longest lasting effects and therefore the most studied and used clinically. ToxBot A is available in some commercial preparations that differ by the protein that surrounds the complex molecule of the toxin. These medicinal products have different clinical efficacy and their respective therapeutic doses are not numerically interchangeable. According to the different protein coatings used by the laboratories that produce them, they were given the following generic names: Onobotulinum toxin (Botox®), Abobotulinum toxin (Dysport®) and Incobotulinum toxin (Xeomin®). A fourth medicine produced in China under the trade name Prosine has not yet received a generic name. ToxBot type B, or Rimabotulinum, toxin B (Miobloc® and Neurobloc®), has been used in a few studies of NLUTD carriers.
Since the pioneering work of Schurch in patients with NLUTD undergoing intradetrusor injection of ToxBot in 1999, this drug has assumed a role of immense importance in the management of patients with neurogenic and non-neurogenic voiding dysfunctions \(^{22}\). ToxBot detrusor injection is indicated in patients with NLUTD inadequate response to traditional oral pharmacological treatments. Doses between 200 and 300 U (Onabot A) or 500 and 1000 U (Abobot A) are used after dilution in 10 to 20 ml of physiological solution and applied at 20 to 30 points of the retro-trigonal detrusor (0.5 to 1 ml /Score). It should be noted, however, that no studies have compared the relative potency of the toxins so the conversion is empirical.

Phase 3 studies including patients with MRT and multiple sclerosis have shown that positive effects occur in at least \(\frac{3}{4}\) of patients and include increased cystometric capacity, reduction in detrusor pressure, reduction in the frequency of involuntary detrusor contractions, decreased urination and / or episodes of urinary leakage, reduction in the number of auto-catheterisms (in IC patients) and improvement in quality of life. Two randomized, multicenter studies compared the effects of onobotulinum toxin A (Botox®) at doses of 200 and 300 units with placebo in patients with NLUTD. Both found significant clinical and urodynamic differences with the two doses of ToxBot compared to the placebo group. There were, however, no differences in results observed between doses of 200 or 300 units. In both studies the chance of complete disappearance of urinary incontinence ranged from 36 to 41% and clinical, urodynamic and quality of life improvement were homogeneous and consistent in patients receiving ToxBot \(^{23,24}\).

Most of the patients included in the classic clinical trials were carriers of SCI and multiple sclerosis; between these two populations no differences in effectiveness were found. The treatment effect lasts an average of 9 months, a fact that requires a program of repeated injections in the long term. Comparisons of the effects of ToxBot on different neurological diseases were made in smaller, non-randomized studies. Patients with Parkinson's disease, stroke and other neuropathies may have different results than those obtained in MRT and MS. The average duration of the effect of ToxBot ranges from 6 to 16 months for onobotulinum A toxin and from 5 to 12 months for abobotulinum B toxin \(^{25}\).

Adverse effects may occur and include increased pos-voiding residue or urinary retention, hematuria, and urinary tract infection. Systemic effects of the drug with generalized muscle fatigue and fatigue are very uncommon, with a risk of 0.005% for onabotulinum toxin A and 0.026% for abobotulinum toxin B \(^{25}\).

In order to reduce the risk of urinary retention in patients with multiple sclerosis who maintains spontaneous urination, a randomized study of Botox 100 U vs placebo has shown that that dose achieves a reduction or cure of urinary incontinence similar to that seen in studies using 200 or 300 U, but with much lower incidence of urinary retention or urinary infections \(^{25}\).

The positive results obtained in the clinical, urodynamic and quality of life domains have been observed systematically in different populations and studies performed internationally. This effectiveness caused ToxBot to fill a large therapeutic gap that previously existed between pharmacological treatment and major surgical procedures such as denervatory surgeries with neurostimulators (Brindley) and enterocystoplasty.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>ADVERSE EFFECTS *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin (antimuscarinic)</td>
<td>10 a 30 mg/day</td>
<td>*</td>
</tr>
<tr>
<td>Tolterodine (antimuscarinic)</td>
<td>2 a 8 mg/day</td>
<td>*</td>
</tr>
<tr>
<td>Solifenacin (antimuscarinic)</td>
<td>5 a 10 mg/day</td>
<td>* Causes more constipation than other antimuscarinics</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7.5 a 15 mg/day</td>
<td>* Lower potential for effects on the CNS (attention and memory disorders)</td>
</tr>
<tr>
<td>Mirabegron (beta 3-agonist)</td>
<td>25 a 50 mg/day</td>
<td>Discrete elevation of heart rate and blood pressure (1-2 mm Hg)</td>
</tr>
<tr>
<td>Imipramine (tricyclic antidepressant)</td>
<td>10 a 45 mg/day</td>
<td>Dizziness, dry mouth, constipation, visual turbidity, dyspepsia, cardiac arrhythmia (high doses)</td>
</tr>
<tr>
<td>Botulinum toxin (endoscopic injection in the detrusor)</td>
<td>200 a 300 units (onabotulinumtoxin) 500 a 1000 units (abobotulinumtoxin)</td>
<td>Urinary infection, hematuria, increased urine retention, urinary retention. Generalized muscle fatigue and paresis (rare)</td>
</tr>
</tbody>
</table>

Table 1 - Drugs for treatment of bladder dysfunctions

* All antimuscarinics may cause dry mouth, constipation, visual turbidity, increased post-void residue, dyspepsia, and cognitive impairment. The preference for slow release products is reasonable because of fewer adverse effects in comparison to immediate release drugs.

2. Polyuria Treatment

Desmopressin (DDAVP)
Desmopressin is a synthetic analogue of arginine vasopressin (Anti-Diuretic Hormone or ADH), a substance responsible for the circadian cycle of urinary production in humans. It is an effective drug in the treatment of polyuria, a relatively common condition in patients with neurological diseases, especially in people with spinal cord injury and in the elderly. Nocturnal polyuria frequently interferes with sleep quality and may become disabling and responsible for significant changes in quality of life. It has a multifactorial etiology that includes diurnal water retention, physical immobility and inappropriate ADH secretion. Desmopressin, widely used for the treatment of nocturnal enuresis in children, has been more widely used in adults, neuropaths and elderly patients with nocturnal polyuria. Other causes of secondary polyuria such as diabetes mellitus, congestive heart failure, chronic renal failure, use of diuretics, and sleep apnea should be identified and treated. The diagnosis of polyuria is made through the careful preparation of a diary of water intake and urination for at least 48 to 72 hours. From the voiding diary one can extract ingested water volume, diurnal
and nocturnal urine volume, number of micturitions, episodes of diurnal urine losses, episodes of nocturia and enuresis. Urinary nocturnal volumes exceeding 30% of the total volume (24 hours) are considered high and establish the diagnosis of nocturnal polyuria. The use of desmopressin is effective in polyuria patients with NLUTD and has been studied in individuals with SCI and multiple sclerosis with good results. In two patient series of MRT and polyuria patients, 11 of 15 patients treated with desmopressin eliminated the need for nocturnal IC and the remaining 4 patients reduced the number of nocturnal catheterizations to only once at night (26,27).

The effects of desmopressin in patients with multiple sclerosis were well studied and helped produce a meta-analysis including 5 randomized, double-blind, placebo-controlled studies. This meta-analysis showed a significant reduction in urine volume within six hours after the drug intake, with benefits that justified the desire of 82% of the patients in one study to continue treatment (28).

The recommended starting dose of desmopressin in adults is 0.05 mg and may be adjusted to 0.2 mg. There is a risk of hyponatremia and water retention which should be carefully evaluated before and after starting treatment. Monitoring of long-term plasma sodium levels is recommended.

3. Drugs with actions in the detrusor and the sphincter mechanism

**Alpha-Blockers**

The blockade of the alpha-adrenergic receptors localized in the proximal urethra and bladder neck is pharmacologically obtained with the use of compounds including terazosin, doxazosin, alfuzosin and tamsulosin among others unavailable in our country. The selectivity for alpha1-adrenergic receptors confers to these drugs a profile of safety and effectiveness quite adequate for their clinical use. The most common side effects are rhinitis, dizziness, postural hypotension and ejaculatory dysfunction, and the less selective medicinal products (terazosin and doxazosin) should be adjusted at the beginning of treatment.

For these reasons, alpha blockers have been used with great frequency and occupy a prominent role in the treatment of men with LUTS. Relaxation of the smooth muscle of the bladder neck and prostatic urethra promoted by these compounds brings symptomatic relief in at least 70% of men with symptomatic BPH. It has been shown that this population when treated with alpha blockers shows symptomatic improvement and, contrary to what might be expected, these effects are not restricted to urinary emptying symptoms. Parallel to the benefits related to bladder emptying, there is often an improvement in storage symptoms such as polaciuria, urinary urgency and nocturia.

In patients with NLUTD, terazosin and urapadil alpha blockers have been shown to be effective in improving detrusor overactivity and complacency (19,29).

Patients with NLUTD with preserved urination may also benefit from the use of alpha blockers. Improvement of voiding symptoms, urinary flowchart, maximum cystometric capacity, urethral closure pressure and post-void urinary residue score have been verified in clinical studies (30,31).

It is known, however, that alpha blockers rarely reestablish the spontaneous urination of patients with NLUTD who are in chronic urinary retention. Patients with MRT who suffer from autonomic dysreflexia may also benefit from the use of alpha blockers (32).
The most commonly used drugs, doses, and most common side effects are listed in Table 2.

<table>
<thead>
<tr>
<th>ALFA-BLOCKERS</th>
<th>DOSAGE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>5 a 10 mg/day</td>
<td>Few ejaculatory problems and less dizziness and hypotension</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>2 a 8 mg/day</td>
<td>Dizziness and postural hypotension; needs titulation</td>
</tr>
<tr>
<td>Terazosin</td>
<td>2 a 10 mg/day</td>
<td>Dizziness and postural hypotension; needs titulation</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>0,4 a 0,8 mg/day</td>
<td>High levels of ejaculatory dysfunction; less dizziness and postural hypotension</td>
</tr>
</tbody>
</table>

Table 2 - Drugs with alpha-blocking effect

4. Drugs with action in the sphincter mechanism

Botulinum Toxin
The application of ToxBot to the sphincter is possible and results in a reduction of the sphincter resistance especially in patients with detrusor-sphincteric dissinergia. The recommended doses are 100 U of onabotulinum toxin or 150 U of abobotulinum toxin. Some studies published in the literature suggest better effects in patients with SCI than in patients with multiple sclerosis, in relation to the reduction of the detrusor pressure and the post-void residue (33, 34). More studies are needed to define the role of the use of ToxBot on the sphincter. The duration of effect of ToxBot injected into the sphincter is about 3 months, as is typical of the duration of the toxin effect on skeletal muscles. Some pharmacological principles with alpha-stimulating action (phenylpropanol-amine) have been used in the past to treat urinary incontinence due to sphincter dysfunction. The results can be considered anecdotal and to date there are no drugs with proven effects for the treatment of neurogenic sphincter deficiency.
References


Introduction
Tanagho and Schmidt developed sacral neuromodulation (SNM) via stimulation of the S3 sacral root in 1988. However, these authors focused on patients with neurogenic bladder. In 1997, SNM was approved by the US Food and Drug Administration (FDA) to treat idiopathic refractory OAB and in 1999 to treat chronic non-obstructive urinary retention [1]. Since then, a growing number of patients have been treated with this modality and the list of indications has expanded to include various bowel applications.

Another kind of device using an electrical input was developed by McGuire in 1980 and consisted of tibial nerve stimulation with a percutaneous needle [2]. It was further developed by Stoller and approved for OAB patients in 2000.

Both SNM and percutaneous tibial nerve stimulation (PTNS) are considered third line treatments for refractory OAB [3]. SNM can also be used in patients with chronic non-obstructive retention (especially in patients with Fowler’s syndrome – idiopathic retention thought to be due to subtle striated sphincter contraction during voiding leading to bladder inhibition) [4]. SNM is also utilized for patients with neurogenic bladder and those with bladder pain. Although it’s not officially approved in the United States, some European countries (as well as some centers in the US) also have experience using SNM in neurogenic patients and in those with bladder pain syndrome (the latter with considerable controversy) [4,5].

Mechanism of action
Electrical stimulation of the efferent fibers to the striated urethral sphincter can inhibit detrusor contractions as shown by Shafik et al. [6]. This inhibitory effect can be induced by pudendal nerve stimulation, but also by tibial nerve stimulation as described by McGuire [7]. The posterior tibial nerve is a sensory and motor nerve, containing axons passing through L4 – S3 spinal roots. Electrical stimulation therefore inhibits bladder activity by stimulating somatic afferent fibers and inducing central inhibition of voiding reflex pathway in the spinal cord and in the brain [7].

SNM probably has a more complex mechanism of action in OAB patients. Inhibition of C-fibers, inhibition of voiding reflex through pudendal nerve stimulation and changes in brain response seem to occur [8]. Alternative theories suggest that neurostimulation blocks aberrant information originating from the bladder/pelvic floor that causes OAB and thus allows restoration of a normal voiding balance. Blok et al. [8] showed that SNM changes the focus of brain activation from the areas related to sensorimotor learning to areas involved in voiding initiation and sense of bladder filling.

In the treatment of pain, the mechanism of action is believed to follow the gate-control
theory (pain perception would depend more on peripheral nerves input rather than sensory receptor information). Pain is more related to C-fiber activity and results in increased synaptic signaling. A-fibers inhibit synaptic transmission and close the gate. SNM seems to inhibit C-fibers.

In neurogenic bladder the mechanism of action is less clear, since it depends on the location and extension of the lesions.

**Assessment and indications**

As noted previously, SNM can be used in a number of indications. However, the majority of available data concerns patients with refractory OAB. PTNS is only indicated for OAB. The initial evaluation begins with medical history, physical examination, voiding diary and urinalysis. Urodynamics are not mandatory in patients with OAB, but may be helpful in select patients with concomitant disturbances (for example, bladder outlet obstruction (BOO) or detrusor hypocontractility). The American Urological Association defines refractory OAB as the failure of appropriate behavioral therapy and the failure or inability to tolerate at least one OAB (antimuscarinic or beta-3 agonist) medication for a 4 to 8 week period. Figure 1 shows the AUA/SUFU guidelines for OAB treatment.

In patients with chronic non-obstructive urinary retention (UR), SNM can be an alternative to intermittent catheterization. Fowler’s syndrome responds well to SNM. The initial evaluation of the patients with UR includes medical history, physical examination, post-void residual urine (PVR), urinalysis and ultrasound. Urodynamics can be helpful in UR.

SNM in neurogenic bladder is controversial, however, it is often used for patients with neurogenic OAB or retention due to a variety of neurological disorders. Patients with sacral
nerve lesions may not be candidates, since the S3 root must be preserved. The evaluation of these patients is the same as that typically used to evaluate those with a neurogenic bladder. One area of caution involves the need for future MRI. Most centers will not perform non-head MRI on patients with an implanted SNS device and this group of patients may require future MRIs – which may limit the availability of SNS for those with a neurogenic etiology.

In bladder pain syndrome (BPS), SNS may be used only after traditional and conservative treatment failure and there is no general acceptance among physicians that SNM has a role in this patient group [13]. However, of note, the AUA Interstitial Cystitis/Bladder Pain Syndrome Guideline recommends the use of SNS as a fourth line treatment. Evaluation of these patients should focus on excluding other diseases and includes urinalysis, ultrasound and cystoscopy.

Technical considerations

SNM is usually a two-stage procedure.

1) A testing phase with the introduction of the quadripolar tined-lead into the S3 root.
2) The implantation of the definitive device. Some physicians prefer to perform the initial test using a temporary lead that can be placed in the office, with local anesthesia and with or without radiological guidance. This is called percutaneous nerve evaluation (PNE) and the electrode is left in for up to a week. If the patient has a positive response, the quadripolar electrode and the definitive stimulation device are implanted in the same surgery (“full-implantation”). However, depending on the country, urologists can adopt the two-stage procedure with the placement of the permanent tined-lead, in the operating room, with radiological guidance and then the definitive device with the patient shows more than 50% improvement. The S3 foramen is located approximately 9 cm cephalad to the coccyx, 2 cm lateral to the midline. The needle is inserted 2 cm above this point (figures 2 and 3)
Results

A number of important randomized control trials (RCTs) utilizing PTNS have been published [7]. SultiT compared PTNS to a sham device. In the SultiT trial, patients treated with PTNS reported a significantly higher rate of moderate to marked improvement than those who had the sham treatment (54.5% PTNS versus 20.9% sham). Patients described a reduction in number of voids in 24 hours and fewer episodes of urgency and incontinence with PTNS. The OrBIT trial compared PTNS to extended-released tolterodine for 12 weeks. Considering subjective evaluation, 79.5% women reported improvement with PTNS and 60.5% with tolterodine. However, the voided volume was similar and modest in both groups. The European Association of Urology considers PTNS as a reliable treatment for OAB patients (level of evidence 2b).

There are more studies concerning the use of SNM for various indications. Most of these studies evaluated patients with OAB and urgency-frequency syndrome. Kessler et al. [4] described a significant reduction in number of voids, episodes of incontinence and a high subjective symptom improvement rate (median: 80%) in patients with OAB. The recently published InSite Study [14] described an 85% success rate. Positive studies describing the use of SNM for UR have been published as well. Kessler et al. [4] showed an improvement in voiding and a reduction in self-catheterization rates in patients treated with the device. Peeters et al. [15] also showed a 73% success rate in idiopathic UR. The device is approved by the FDA for both of these in the United States. Of note, a number of newer types of SNS devices are currently under study.

SNM for neurogenic bladder and chronic pain remains controversial. Although, there is some data supporting its use in selected situations [4,5,12,13], these patients need to be evaluated on a case by case basis. The data for its use in those with neurogenic bladder is more robust than that for those with bladder pain.
References


CLINICAL SECTION II

UROLOGICAL TREATMENT OF DNTUI IN NEUROLOGICAL DISEASES
1. CONGENITAL CAUSES FOR NEUROGENIC LUT DYSFUNCTION

Introduction
The etiologies of neurogenic in the pediatric population are listed in the following table.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Myelodysplasia</td>
<td>85%</td>
</tr>
<tr>
<td>Closed/Occult Myelodysplasia (lipoma, lipomeningocele, split cord syndrome, anterior meningocele)</td>
<td>8%</td>
</tr>
<tr>
<td>Sacral Agenesis</td>
<td>1%</td>
</tr>
<tr>
<td>Associated syndromes (Imperforate Anus 40%)</td>
<td>1%</td>
</tr>
<tr>
<td>Injury to Central Nervous System (cerebral palsy, primary or metastatic tumors to the brain/spinal cord)</td>
<td>4%</td>
</tr>
</tbody>
</table>

As is evident from the table, approximately 96% of children with neurogenic bladder have a congenital cause and approximately 93% of cases are due to spinal dysraphism. In patients with obvious outward signs of congenital defects, as with open spinal dysraphism or imperforate anus, the urologist is often consulted after a diagnosis has already been made by the primary pediatricians, pediatric surgeons or neurosurgeons. In communities where prenatal ultrasounds are routine, these diagnoses are most commonly made prior to the birth of the child. When associated anatomic defects are more subtle as with occult spinal dysraphism or sacral agenesis; the patient may often present with difficulty toilet training at an appropriate age. It is incumbent upon the urologist to be suspicious of underlying neurogenic disorders in children presenting with complaints of lower urinary tract symptoms. These children will not likely improve with conservative measures of therapy that are helpful in the non-neurogenic population. Further, children with neurogenic bladder disorders are at great risk for progression to renal failure if not properly managed. A special note is to caution about the risk of spinal cord tethering in children since that condition can be reversible if treated early but will progress to an irreversible, life-long state if cord de-tethering is delayed.

Both the diagnostic and management strategies in this chapter are based on the terminology and recommendations of the International Children's Incontinence Society[1].

Initial Evaluation[2]
The form of the initial evaluation varies on whether the patient is a newborn with a known congenital defect or a child of toilet training age presenting with LUTD. Both will be discussed below.
History:

Newborns
1. Obtain information regarding all prenatal ultrasounds. Was a spinal defect observed? Was there evidence of hydronephrosis or distended bladder? Were amniotic fluid levels normal?
2. Ascertain if there were any problems associated with the pregnancy to determine if any other problems should be suspected. Presence of diabetes in the mother is associated with sacral agenesis. Mothers who are not routinely taking folic acid from conception onward are at greater risk of having children with spina bifida.
3. Is the child hemodynamically stable? If not, then urologic investigation may be delayed.
4. Is there an immediate need to surgically close the spine? This may also delay urologic investigation.
5. Has the child been voiding? Have post void residuals been measured via ultrasonographic bladder scanner or catheterization and if so, what have the residuals been?

Children of Toilet Training Age
1. What are the presenting lower urinary tract complaints and how long have they been going on? This would be included as a typical work up for all children presenting with lower urinary tract symptoms (LUTS). If the problems have been persistent since birth, there is more concern for a congenital cause.
2. Is incontinence present during the day, night or both? Children with neurogenic problems typically have both.
3. Has the child experienced one or more urinary tract infections (bladder or kidney)?
4. Has conservative therapy (timed voiding, bowel regimen with laxatives) been tried? Failure at conservative therapy strongly suggests further investigation as children with neurogenic bladders are typically refractory to such intervention.
5. Have the children undergone prior investigations such as renal ultrasounds, uroflowmetry, voiding cistourethrogram, or urodynamics? Also inquire about prenatal ultrasounds. Any abnormalities should be followed up as they could suggest a neurogenic diagnosis.
6. Assess bowel function such as constipation, hard stools, fecal incontinence, etc.. However, these are typically present in all children with LUTS.
7. Does the child have any neurological signs or symptoms such as lower extremity weakness, paralysis, decreased sensation, or seizures? Presence of any of these should raise suspicion of neurologic etiology.
8. Any child who complains of new onset bladder or bowel dysfunction with or without associated lower extremity weakness or decreased sensation should raise concern for a tethered spinal cord.
9. Voiding diaries that detail frequency and volume of daily voids, including fluid intake and episodes of incontinence can provide significant information at the initial evaluation. They should be done for a minimum of 2, not necessarily consecutive days. Bowel diaries covering 1-2 weeks are also helpful.
Physical Examination:
1. Examination of the spine is critical in all children presenting with LUTS. Newborns with an open spinal dysraphism will have an obvious lesion. Any newborn, even in the absence of urological concerns, who has a hair bearing patch or dimple over the lower spine warrants a spinal ultrasound and MRI to look for occult dysraphism. Older children (>3 months) require an MRI but no ultrasound. Approximately 95% of children with occult dysraphism are diagnosed in the newborn period based on these signs or an abnormal gluteal cleft. Flattened buttocks and a shortened gluteal cleft are pathognomonic for sacral agenesis.
2. Abdominal examination should focus on palpable kidneys suggestive of hydronephrosis, suprapubic mass consistent with urinary retention and full bladder, and full bowels indicative of constipation.
3. Complete neurological examination with emphasis on the lower extremities and also on anal sphincter tone. Abnormalities suggest further work up for neurological issues.
4. Muscle atrophy, change in gait and lower extremity weakness are signs of underlying neurological defects.

Imaging:
1. Renal/bladder ultrasounds should be performed on all newborns with a new neurological diagnosis, children with histories/physical exams suggestive of a neurological diagnosis as outlined above, or in older children with LUTD that is refractory to conservative therapy. Hydronephrosis, hydroureter, abnormally thick bladder wall, or discrepancy in renal size/contour should prompt further workup with voiding cystourethrogram and urodynamics which are often performed concurrently.
2. Spinal ultrasound and spinal MRI are warranted in newborns suspected of occult dysraphism. Spinal ultrasound is not useful in children >3 months and so the spinal MRI is performed exclusively. In children of toilet training age who have clinical signs/symptoms of a tethered cord, prompt spinal MRI is warranted and if found to confirm the diagnosis, immediate referral to a neurosurgeon.
3. Abdominal X-ray or KUB is often done in children of toilet training age to assess bowel function. The morphology of the spine should always be carefully assessed as well for possible occult dysraphism or sacral agenesis.
4. Voiding cystourethrogram can be done in isolation or in combination with urodynamics. It should be performed in all children with open dysraphism, patients with neurological disorders with LUTS and abnormal renal/bladder ultrasound or children who present with a history of febrile urinary tract infection.

Urodynamics (UDS)[3]:
Ideally, urodynamics is performed concurrently with the VCUG and is thusly called “video-urodynamics.” All children born with open spinal dysraphism should undergo this study at approximately 2-3 months of life and when they have recovered from spinal surgery. Any child who presents with LUTS and is subsequently found to have occult dysraphism should also undergo UDS. Patients who are refractory to conservative therapy for LUTS but who do not have any evidence of an underlying neurological defect may benefit from UDS but it is up to the patient/family and provider as to how aggressively they should pursue this invasive test. Frequently, patients who are suspected by neurosurgical colleagues of having tethered cord will be referred for urodynamics. In many cases, the sensitivity of urodynamics to find even subclinical changes in bladder function will drive the decision towards surgical de-tethering. This can be of extraordinary benefit in expediting proper surgical management and preventing the development of urinary dysfunction.
Special Consideration of UDS in Pediatrics:
Urodynamics is covered as a topic in a separate chapter and so this section will focus on some of the challenges in performing the study in the pediatric population.

1. Invasive urodynamics can be anxiety provoking which introduces significant artifact into the study. Child life specialists can be invaluable in preparing and calming children and their parents for the examination. Babies may benefit from blowing soap bubbles or using attention focusing toys. Older children may benefit from videos, videogames or other distracting diversions. General anesthesia can greatly affect voiding physiology and should be avoided during the study period. However, placing catheters under anesthesia may be necessary for some patients. Intranasal midazolam, 0.5mg/kg, can be effective in reducing anxiety, has minimal risk, and does not appear to affect study results.

2. Patients are ideally seated during the voiding phase but may not be possible for children with neurological deficits. In these cases, and for all infants, only the storage phase may be observed as the flow studies may not be reliable. However, information on the detrusor contractility, a visible urinary stream and the post-void residual urine quantification will give us some important information regarding the emptying phase.

3. As with adults, filling must be done at 5-10% of bladder capacity/minute or a maximum of 10mL/minute. Infants typically have bladder volumes in the range of 20-30mL but no accepted formula for estimating the bladder capacity exists. Performing 2-3 cycles may aid in adjusting to a proper instillation rate. For children age 4-12 years, the estimated bladder capacity in mL, EBC=(age in years+1)x+30 up to a maximum of 390mL in 12 year olds.

4. A 6 Fr dual lumen catheter in the bladder and an 8 Fr rectal balloon are suggested for children.

5. Measuring sensation can be difficult in young children and impossible in infants where "first desire to void" and "strong desire to void" will not be meaningful. For pediatric patients, sensation can be based on physical observation and noted as normal, increased or hypersensitive, decreased or hyposensitive, or absent.

6. Normal children, without urologic pathology, can have variable post void residuals. Children 4-6 years old with a single PVR measurement of >30mL or >21% of EBC, or repeated PVR>20mL or >10% EBC is considered significant. In children 7 to 12 years old the cutoffs are >20mL or >15% of EBC in a single measurement or repeated measurements of >10mL or >6% of EBC.

Follow-up Evaluation:

1. Newborn to toddler
If the initial UDS demonstrates detrusor overactivity, the patient should be placed on anticholinergics and CIC. UDS should be repeated 2-3 months afterward to insure that therapy is effective in reducing pressures and overactivity. These children should be followed with renal ultrasound every 6 months for the first two years of life and suspicion should be high for these patients to develop tethered cord. VCUG should be repeated if there are increased hydronephrosis, appearance of kidney damage, or febrile uti. For children with hostile bladders on UDS and reflux, a DMSA scan to assess baseline renal scarring may be useful.
2. **Toddler to adolescent**

   Yearly renal ultrasounds are warranted along with a physical exam to check for any progression of neurological symptoms. UDS should be done if there are progressive changes on the ultrasound, if neurological function worsens, or if there are functional changes in bladder and bowel. Investigation for tethered cord may be initiated if UDS suggest bladder deterioration.

3. **Adolescent to adulthood**

   Yearly physical examination and renal ultrasound should be performed with high index of suspicion for cord tethering during growth spurts. Hormonal and anatomic changes during puberty may improve continence in up to half of patients. Significant changes in urinary function should prompt repeat UDS. After Tanner V is reached, renal ultrasounds and examinations can be spaced out to every 2 years.

**Management**

Intervention for children with neurogenic LUTD has two distinct goals: 1) protecting the kidneys from damage and 2) achieving social continence. The first goal should be pursued aggressively as children with neurogenic bladder have historically high rates of early renal failure and mortality when not appropriately managed. The second goal should be pursued with the needs of the patient and family kept firmly in focus. Many of these patients and their families will not share the same level of concern regarding continence as their medical providers. Since patient/family participation is critical in successful continence regimens, a high level of motivation is required.

**Intermittent catheterization (IC):**

Arguably the most important advance in managing children with neurogenic bladder since the 1970s has been the introduction of intermittent catheterization. In the newborn period, IC can be done as a diagnostic tool to ascertain whether the child is capable of emptying the bladder on their own volitionally or via low pressure leakage. The most important factor in initiating IC in children is based on the bladder function as assessed by UDS. Children with detrusor sphincter dyssynergia, poorly compliant bladders, DLPP >40cm H2O, multiple uti or worsening hydronephrosis should be started on IC. For children who have good outlet resistance but are unable to effectively empty their bladder, IC can be useful in achieving social continence. It can be started at the discretion of the provider, patient and the parents or caregivers.

The European Association for Urology recommends in its guidelines for management of neurogenic bladder that single use catheters be used with an aseptic technique. The International Children's Continence Society does not make this recommendation, citing lack of clear evidence, and suggest that the decision to employ single vs. multi-use catheters and clean vs. aseptic technique be made on an individual basis.

Catheter size should be chosen based on the size and anatomy of the child. Babies are typically started with a 6 or 8 Fr catheter. Coude catheters can be easier to use in boys. As the child grows, the catheter size should be increased appropriately as more efficient emptying can benefit patient compliance. Many school age children can tolerate a 10 Fr catheter and this can be increased to 12 Fr as they get closer to puberty. Adolescents and adults should use the smallest catheter possible that allows efficient emptying.
Pharmacotherapy:
Level 1 evidence supports the use of anticholinergic medication for children with detrusor overactivity and/or high storage pressures to prevent progressive damage to the upper and lower urinary tracts. These medications can also help children with overactivity to achieve continence. Due to regulatory issues, the most common medications used in the pediatric population include oxybutynin and tolterodine. The dose of oxybutynin is 0.2-0.4mg/kg and is usually given q8/12hr. A solution of 1mg/mL is typically administered until the child is capable of swallowing pills and is on at least a 5mg dose. As with adults, slow release formulations, transdermal applications, and infrequently intravesical approaches can be used to decrease side effects and increase patient compliance. Few of these have been formally studied in children but they are commonly used in practice.

The most common side effects of anticholinergics in children include constipation, dry mouth and heat intolerance. Patients and parents should be asked about these issues at every clinic visit and adjustments may be required with respect to dose and route of administration. There is now controversy regarding the long term effects of anticholinergics on the cognitive function in young and growing children. Studies are not definitive at this time but it is likely that there will be a shift to more selective anticholinergics or to bladder relaxants with alternative mechanisms such as β3 agonists. For now, oxybutynin and tolterodine in short and long acting forms remain the most commonly used medications.

Intravesical injection of botulinum toxin:
Intravesical botulinum toxin injections, approved for adults with neurogenic bladder; is currently undergoing regulatory testing in children. Botox is useful in treating detrusor overactivity and decreasing bladder storage pressures in patients who do not have a successful response to anticholinergic therapy. In pediatrics, Botox may be very useful in children who have indications for bladder augmentation but who are too young for this major operation. It also provides a choice for patients of any age who either need to protect their kidneys or achieve continence but who would like to avoid surgery. Patients undergoing Botox injections should be counselled that an effective response may take several weeks after injection and that the procedure, if effective, will need to be repeated every 3 to 8 months.

Antibiotics:
Patients presenting with signs/symptoms of a UTI should always have cultures sent and antibiotic treatment should be based on the sensitivity report using the most narrow spectrum agent. Since patients who perform IC routinely have colonized urinary tract, it is imperative that treatment only be offered for symptomatic UTI and not for asymptomatic bacteriuria. This is critical as overtreatment leads to emergence of greater virulence and antibiotic resistance with no clinical benefit. Further, there is level 1 evidence against routine antibiotic prophylaxis in this patient population. In select patients, however, limited periods of prophylaxis may be warranted. In these cases, trimethoprim/sulfamethoxazole, nitrofurantoin, or intravesical gentamicin can be useful to break cycles of infections but should not be used indefinitely.

Neuromodulation:
Studies using sacral nerve stimulation or transcutaneous neuromodulation, while promising in neurologically intact children, have yielded disappointing results in patients with neurogenic bladder. They should be considered investigational at this time.
**Biofeedback:**

Biofeedback has not been sufficiently studied in children with neurogenic bladder. Given the relatively low risk and non-invasiveness of the intervention, its use may be entertained in children with a relatively normal neurological physical exam, intact sensation and some control over the urinary sphincter.

**Surgery:**

Surgical intervention may be required in a minority of children with neurogenic bladder where IC and anticholinergic therapy are inadequate to protect the kidneys and/or achieve continence. The approach must be individually tailored based on the clinical picture and evaluation with imaging and UDS.

1. **Vesicostomy**

Vesicostomy is typically done in children with hostile bladders, worsening hydronephrosis and/or recurrent infections who either cannot or will not utilize IC. Usually they are temporizing measures until the child is capable of tolerating IC, either as a result of maturation or creation of a conduit, such as a Mitrofanoff. Drainage from a vesicostomy can be problematic in older children where protective undergarments are difficult to find in an appropriate size.

2. **Bladder augmentation**

Augmenting the bladder with a portion of small or large intestine can be very effective in increasing bladder size and decreasing storage pressure and overactivity. Use of gastric patches has fallen out of favor, and strongly discouraged, due to hematuria/dysuria syndrome. While enterocystoplasty can be invaluable for some patients, children may experience severe complications. Mucous production, usually worse in the first 6 to 12 months, must be irrigated daily to prevent infection and stone formation. Metabolic acidosis can lead to bone demineralization and stunted linear growth. Most importantly, there is a significant risk of malignancy as these children age and therefore, annual surveillance with cytology and cystoscopy should be performed starting 5-10 years after surgery.

3. **Bladder neck reconstruction (BNR)**

BNR is the most effective way to achieve continence in children with poor outlet resistance. Particularly in children, a goal should be to limit the decrease in bladder capacity that occurs with these procedures. Flap based BNR, such as the Pippe-Salle procedure, work very well and allows the urethra to be catheterized with a 12 Fr or smaller catheter. The Young-Dees-Leadbetter procedure, while very effective in the exstrophy population, can be very difficult to catheterize and should be avoided in this patient population. Although a high continence rate is achieved with BNR the rate of reoperation should not be underestimated.

4. **Fascial slings**

Suspension of the bladder neck to the rectus muscle or pubic bone should be done with autologous fascia, and not synthetic materials, in children. They may be done as the sole procedure in children with mild sphincteric defects or concurrently with BNR for children with little to no outlet resistance. Better results with slings are achieved in girls in comparison with boys.
5. **Artificial urinary sphincters**
   As these devices have improved, revision rates have fallen but still remain an issue for patients who may live for many more decades. In children who have reached full growth, artificial sphincters are a reasonable option that can achieve continence while allowing for urethral IC. Patients must be counselled that they will likely require several revisions for malfunction or erosion over the course of their lives.

6. **Mitrofanoff/Monti-Yang conduits**
   Creation of a continent conduit from the bladder to the abdominal wall, ideally hidden in the umbilicus, with either the appendix (Mitrofanoff) or segment of small intestine (Monti-Yang) provides an alternative to catheterization via the urethra. These are particularly helpful in children with limited manual dexterity, sensate urethra or bladder necks, obstruction of the urethra or bladder neck, and wheelchair bound children. Wheelchair dependent females gain considerable independence when they do not have to rely on caregivers to assist with catheterization. Stoma stenosis requiring revision is the most common complication with these followed by development of false passages and leakage due to faulty continence mechanism.

**Bowel management[5]:**
Most children with neurogenic bladder also have an associated neurogenic bowel that requires management. Laxatives are routinely necessary and stool softeners, such as Miralax, are the first line of therapy. Stimulating laxatives, such as bisacodyl, may be needed as well. Suppositories and manual dis-impaction serve as adjuncts to routine laxative use. To achieve fecal continence, cone tipped enemas may be performed daily and are the most frequently used therapy for this purpose. Peristeen is a new device for trans-anal irrigation that can more effectively wash out the bowel to prevent soiling. When these measures are not successful, antegrade colonic enemas can be very effective but require either placement of a Chait cecostomy tube or using the appendix as a conduit that is brought up as a percutaneous stoma (Malone Antegrade Continence Enema or MACE procedure). Infections, leakage around the tube or from the conduit, and stenosis of the stoma are frequent complications.

**Transition to Adult Care**
In centers where patients are transferred from the care of the pediatric urologist to an adult urologist, good communication between the referring and receiving physicians is paramount for these complex patients. Once growth is complete, changes in urinary function are unusual and so surveillance with renal ultrasounds can be spread out to every three years. UDS only needs to be repeated if there is a clinical change in urinary function. One of the leading prognostic factors for the well-being of these patients is adherence to a CIC regimen. Therefore, they should be followed closely and strongly encouraged to maintain this practice. UTI and stones are common complications for adult patients with congenital neurogenic bladders and should be dealt with promptly to avoid long term negative consequences.
References


1. Introduction
After acquiring urinary control, children may present with lower urinary tract symptoms (LUTS) and lower urinary tract dysfunction (LUTD). These symptoms do not necessarily represent pathology and may disappear with time along with neurophysiologic maturation. When they persist after 5 years of age, they are considered to be dysfunctional (1).

Main symptoms include:
- Urgency, frequency, daily incontinence, enuresis, hesitancy, delayed voiding, nocturia, weak and interrupted stream
- Children frequently perform maneuvers to postpone voiding and to avoid urine leakage, such as squeezing the genitals, crossing the legs, or crouching. When LUTD is associated with constipation, it is called bladder bowel dysfunction (BBD).

For several reasons, LUTD must be recognized and treated:
1. Symptoms are unpleasant to children;
2. It may suggest current or future bladder alterations such as detrusor hypertrophy, reduction of capacity and compliance and detrusor failure.
3. It may be associated with psychological disorders, vesico-ureteral reflux and/or urinary infection. On many occasions, it is only necessary to provide behavioral guidance to improve symptoms, but sometimes it is necessary to use more specific treatments. In this Chapter, we will discuss the main aspects of LUTD.

2. Epidemiology
Approximately 10% of children older than 5 years suffer from urinary urgency or daily incontinence (2). At 7 years of age, it is estimated that 6% of girls and 4% of boys have daily urinary incontinence (3).
3. Associated conditions

LUTD is frequently associated with vesicoureteral reflux, psychological disorders, urinary infection, obesity and intestinal constipation.

3.1. Vesicoureteral reflux

• Vesicoureteral reflux is found in up to 46% of patients who present with LUTD (4). Usually, reflux is secondary to increase of intravesical pressure and resolves spontaneously following treatment of LUTD. More commonly, the reflux is low grade.

3.2. Psychological disorders

• Around one third of children with LUTD present with behavioral or psychological issues such as social withdrawal, shyness, irritability, anxiety, aggressiveness and depression.
• They are more prone to anxiety, sadness, social isolation, aggressive behavior, transgression, deficit of attention and hyperactivity, oppositionally defiant behavior, and low self-esteem (5). Children with associated stool incontinence seem to be more affected.
• It was believed that psychological disorders cause LUTD. At the present, it appears that this is due to altered activity of neurological supra-spinal centers related to emotion control and executive function that also control lower urinary tract (6).

3.3. Defecation disorders (BBD)

• Around half of the children with LUTD also present with intestinal constipation (7). There are several theories to explain the association of both conditions:
  1. The same supra-spinal centers that regulate lower urinary function also regulate bowel function, and both have the same embryological origin.
  2. The presence of a big fecal mass at the rectum could alter lower urinary tract function due to mechanical compression.
  3. Contraction of anal sphincter to prevent defecatory urgency simultaneously contracts the urethral sphincter, inhibiting voiding.
  4. Conversely, the contraction of urethral sphincter would also contract anal sphincter, relaxing the rectum and worsening rectal emptying.

Interestingly, not all LUT symptoms are associated with bowel dysfunction. A recent study showed that constipation was associated only with symptoms related to urinary retention, decreased frequency of daily voiding and delayed voiding (8).

4. Physiopathology

Time is necessary for urinary tract function maturation. Normal function means adequate filling of bladder at rest, with correct capacity, low pressure during storage, and adequate contraction to obtain complete emptying. In the first months of life, infants urinate interruptedly, since they do not relax completely the external urethral sphincter. With maturation, they learn to initiate voiding and to relax urethral sphincter.

LUTD is a constellation of symptoms that arise from abnormalities during the filling and/ or voiding phases. Micturition sensations may be increased or decreased, and there may be a reduced ability to voluntarily inhibit the voiding reflex. Sometimes, the urethral sphincter or bladder neck don't relax during voiding and this is formally defined as voiding dysfunction.

It was classically thought that peripheral disorders (bladder and spinal reflex) were responsible for LUTD. Functional magnetic resonance and PET CT studies have shown cerebral activities disorders in patients with LUTD. Disorders of the girus cingulus, insula,
periaqueduct gray zone and pre-frontal cortex contribute to LUTS and to constipation and associated pathologies. Cerebral activity alterations may cease spontaneously as the child grows and the brain matures, which results in resolution of symptoms. However, symptoms persist in many children. Involuntary contraction, bladder overdistension, and bladder-sphincter incoordination, may cause detrusor hypertrophy, nitric oxide release, type C neuronal fibers stimulation, that would abnormally stimulate the cerebrum, maintaining a vicious cycle.

7. Diagnosis

LUT symptoms are detected from the history and are not well identified in children less than 5 years old. Some children receive toilet training later in life and maintain an immature pattern of voiding. After 5 years old these symptoms are considered to be pathological.

Symptoms may be quantified by specific question forms such as the Dysfunctional Voiding Score System (9). Scores may evaluate the evolution of symptoms following treatment and are important to standardization in publications. Constipation may be evaluated by questionnaires such as Roma III or IV or the Bristol scale.

Voiding diary is an important instrument to clarify patients’ symptoms. During two days (not necessarily consecutive), voiding is written down, including amount and kind of ingested liquid, time of voiding and urine volume. Also, episodes of urgency and leakage are recorded.

Some imaging and laboratory tests are important for LUTD evaluation:

Pelvic ultrasound including post-void urine volume. Bladder wall thickness is evaluated (ideally lower than 3 mm, but is inaccurate, since it depends on the degree to which the bladder is distended at the time of the study). Also, bladder capacity (BC) is estimated: total voided urine + post-void residual urine volume. Rectal diameter is also measured, and it is abnormal if > 3 cm. Normal post-void urine volume varies according to age. When increased, evaluation must be repeated. Post-void urinary volume must be registered in the first 5 minutes after voiding. In order to increase reliability, bladder volume before voiding must be > 50% of EBC (age+1)x30 or lower than 115% of EBC, to avoid bladder under or overdistention.

For children with 4 to 6 years old, > 30 ml or 20% of BC in a single sample or 10% of BC in a repeated exam (10). For children with 7 to 12 years old, > 20 ml or 15% of BC in a single sample or > 10 ml or 6% of BC in a repeated exam.

Uroflowmetry: ideally, to evaluate Qmax (maximal flow), we should use nomograms that consider the voiding volume, since they correlate proportionally and linearly (11). According to ICCS (2016), if Qmax squared is equal or superior to voided volume, urinary stream probably is normal (1). A minimum of 50 ml of voided urine is necessary to analyze uroflow.
• An important aspect of uroflow is the shape of the curve (figure). In general, it is a sinusoidal curve. A tower shape is characteristic of overactive bladder, a sign of bladder “explosion.” A flat stream may represent dysfunctional voiding, bladder neck obstruction or a variant of normality. Stacatto flow is typical of dysfunctional voiding, and interrupted is characteristic of hypoactive bladder. There is often a considerable overlap of sinusoidal and tower and flat curves that complicates interpretation (12).
• Electromyography is useful when performed along with uroflowmetry; it may help diagnose dysfunctional voiding or bladder neck dysfunction. However, interpretation is difficult and the exam is influenced by artifacts.
• Urodynamic exam: it is unnecessary for most patients presenting with LUTD who do not have a neurological diagnosis. The presence of detrusor overactivity on urodynamics is not mandatory for the diagnosis of overactive bladder, an imminently clinical condition. Also, bladder compliance is normal in most cases. Since conservative treatment of LUTD is inexpensive, has very low morbidity, and is highly effective for most children, urodynamic exam is reserved for patients with failed treatment. Children with hypoactive bladder or bilateral ureteral dilation are also more likely to benefit from urodynamic studies.

• Videourodynamic exam may help identify vesico-ureteral reflux and define voiding dysfunction or primary dysfunction of the bladder neck.

6. Classification
According to ICCS standardization, some conditions are included in LUTD, singly or combined:

• Overactive bladder: presence of urgency, usually associated with daily urine leakage and pollakiuria. Children that postpone voiding may also present with urgency. Maneuvers to avoid urinary leakage may be present. It is pure or isolated when bladder emptying is adequate and there is only alteration of bladder filling phase. Post-void residual urine volume is not increased and urinary flow has a shape of bell or tower (figure).

• Dysfunctional voiding: incoordination of bladder contraction and relaxation of external urethral sphincter. During voiding, urethral sphincter doesn't relax or contracts. Post-void residual urine may be increased. During uroflowmetry, it is observed that the stream is staccato or flat curve, or rarely, interrupted.

• Delayed voiding: children voluntarily delay voiding, often performing holding maneuvers. Usually, they void less than 4 times per day. Bladder emptying is adequate.

• Hypoactive bladder: The number of micturitions per day is reduced (3 or less) and there is a great volume of post-void residual urine. Uroflowmetry shows an interrupted curve (figure). Detrusor hypocontractility is demonstrated on urodynamics. There is evidence that this condition can be caused by untreated dysfunctional voiding.

• Primary dysfunction of bladder neck: symptoms are similar to those of dysfunctional voiding and urinary flow may be similar. However, with a dysfunctional bladder neck there is no electromyography activity at ultrasound. It may be diagnosed by videourodynamic exam.

• Extraordinary daytime only urinary frequency: presence of severe pollakiuria with sudden onset. There may be associated urgency, but usually with low intensity. Usually, there is no nocturia and the frequency normalizes or diminishes when the child is engaged in activity that requires attention and focus. It is associated with stressful situations experienced by children with an anxious disposition.

• Giggle incontinence: presence of urinary incontinence only when the child laughs.

• Vaginal dribbling: girls may assume an inadequate position to void, by joining the legs together (as opposed to having the legs spread apart) and bending over at the waist. By doing that, urine is collected inside the vagina. When the child leaves the toilet and stands upright, urine drips from the vagina. It is usually observed in more obese children.
7. Treatment

Initial treatment of LUTD is based on several guidelines to improve voiding habits, called standard urotherapy. Main actions include: voiding at least every 3 hours, voiding when desire is present or when holding maneuvers are initiated, double voiding, avoidance of caffeine, good hydration during the day, but these have low impact on pure overactive bladder.

Usually, standard urotherapy may be used for two months, and, in case of failure, more specific measures must be adopted. Constipation has to be treated first usually with Miralax.

Overactive bladder

Initial treatment must include antimuscarinic drugs or neuromodulation (transcutaneous or percutaneous parasacral electrostimulation of posterior tibial nerve).

Most used antimuscarinic drug is oxybutynin, in a short or long acting formulation. Short action drug (1 mg/ml or 5 mg tablets) may be used at a dose of 0.3 to 0.6 mg/kg/day (maximum dose 15 mg/day) but dose may be increase until side effects are present. Extended release formulations may be used at the dose of 5 mg to 10 mg and must be swallowed intact. These have the advantage of lower side effects. Total efficacy is around 20-40% and 30-40% present partial response [13,14]. Transdermal oxybutynin patches are an option, but there is only one paper in literature describing their use in children [15]. The main inconvenience is that they must be applied two times per week and 35% children in the sole study had complaints of skin irritation. Drug dose that is released is 3.9 mg/day. Oxybutinin gel has not been studied formally in children but regulatory testing has been initiated. The main side effects of antimuscarinic drugs are intestinal constipation, dry mouth, heat intolerance and, rarely, disorientation. In the presence of side effects, it may be used 1 mg every 12 hours or once a day (long action tablets of 2 or 4 mg). Solifenacin, 5 mg/day has shown some benefits in initial studies with few children. Mirabegron, a Beta 3 agonist with few of the aforementioned side effects, may be tried off-label when the other drugs don’t show any results.

Also, in refractory overactive bladder, imipramine may be used before more invasive measures. Another option is the combination of drugs, but the costs are increased.

Neuromodulation

- Parasacral TENS (transcutaneous parasacral electrical neurostimulation) seems to be effective in randomized long term studies [16,17]. Fifty to 65% of patients show complete resolution of symptoms and 20-30% have a partial response. The main advantage of neuromodulation over antimuscarinic drugs is that parasacral TENS also improves intestinal function, unlike antimuscarinic drugs [18]. Posterior tibial nerve percutaneous electrical stimulation may also be used, but the results are inferior to parasacral TENS [18]. Parasacral TENS is used in two different regimens: daily 10HZ current frequencies for 20 minutes, or sessions of 20 minutes three times a week at an ambulatory clinic. Percutaneous electrical stimulation of posterior tibial nerve uses 20 HZ current, 30 minutes once a week.

Refractory patients

- An option is to use botulin toxin injection 5-10 UI/kg (lethal dose is 40 UI/kg), in general a total of 50 to 100 UI. Higher doses are usually used in neurogenic bladder. The main inconvenience is the possibility of temporary urinary retention which may require the use of intermittent catheterization [19].
- Another option is the implantation of sacral neuromodulators with good response, but lead migration has been reported in up to 55% of patients and surgical revision is frequently necessary [20].
Dysfunctional voiding
The standard treatment of perineal-bladder incoordination is biofeedback; if available, it can be more effective in children when used along with interactive games. Success rate is 80%, considering emptying symptoms and improvement of uroflowmetry (21). Some children persist with overactive bladder symptoms and may be treated as mentioned above. When the presence of bladder neck dysfunction is suspected, alpha-blockers (such as doxazosin, 1-2 mg/day) may be used.

Hypoactive bladder
Patients are treated with intermittent catheterisation, alpha-blockers and neuromodulation. Implantation of sacral neuromodulators may be an option.

Giggle incontinence
Very hard to treat. Usually, there are no responses to common treatments. Methylphenidate may be an effective therapeutic option.

Vaginal incontinence
Change of posture. It is recommended to spread legs during voiding, with the back straight.

Extraordinary daytime only urinary frequency
Typically self-limiting and so initially observation is warranted. If symptoms persistent for months, they must be treated as overactive bladder. A psychological consultation may be warranted.

Figure- shape of the curves: A) Bell, B) Tower, C) Staccato, D) Intermittent, E) Flat.
ICCS Standardization (1)
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Introduction

Spinal cord injury (SCI) is a sudden devastating life-changing event. This may be a consequence of trauma, infection, vascular or iatrogenic injury. Once the acute phase is over, neurological consequences are usually stable and persist lifelong. The severity of SCI is reflected in the degree of paralysis and sensation loss as well as the (in)ability to perform activities of daily living.

Epidemiology

The epidemiologic characteristics have changed over time and there are regional differences (1). The life expectancy of patients with SCI continues to increase. Those who sustain an injury between the ages of 25 and 34 can expect to live on average 38 years after injury, with 43% surviving at least 40 years (2). The most common cause of death in contemporary series is diseases of the circulatory (40%), and of the respiratory system (24%), in contrast to primarily renal mortality in earlier series (3).

Over the longer term, there are both clinical and social implications. The management of urologic complications is to be balanced with fertility issues as both carry great importance in the socioeconomic re-integration of these patients (Table 1).

<table>
<thead>
<tr>
<th>MANAGEMENT OF UROLOGIC COMPLICATIONS</th>
<th>SEXUAL AND REPRODUCTIVE MANAGEMENT GOALS</th>
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<tbody>
<tr>
<td>Urinary tract infections</td>
<td>Quality of life</td>
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<tr>
<td>Secondary reflux</td>
<td>Well being</td>
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<tr>
<td>Bladder calculi</td>
<td>Sexual intercourse</td>
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<tr>
<td>Autonomic Dysreflexia</td>
<td>Social integration</td>
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<td>Chronic renal disease</td>
<td>Family constitution</td>
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<tr>
<td>Urinary incontinence</td>
<td>Pregnancy</td>
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Table 1: Different aspects and goals on spinal cord injury patients management.
Assessment
The aim of the therapeutic measures are to prevent bladder and renal deterioration, protect upper tract, achieve continence and improve quality of life. Initial assessment of the patient should be holistic, not only focusing on lower urinary tract symptoms, but also on bowel and sexual function impairment. It is also important to assess mental status and comprehension along with visual and hand function as these all will have a bearing on future treatment options.

Clinical history
A detailed history of onset and duration of symptoms is required. The storage and voiding dysfunction are separately documented. Special attention is required for evaluation of urinary incontinence in a neuropathic patient. This is especially true if the patient has mixed incontinence or a suggestion of overflow incontinence. A carefully description of neurologic symptoms with duration and treatment is considered with attention to mental status, medications and importantly mobility and hand function. It is helpful to assess for family support. Particular attention is given to evaluate possible “red flags” including recurrent infections, pain and haematuria. It is not uncommon to ignore the bowel and sexual function whilst taking urological history. However, in neurological diseases all 3 systems are generally affected and direct questioning would lead to unmasking of dysfunction in these areas.

Physical Examination
A general physical examination followed by detailed urologic examination and a focused neurologic evaluation is performed. The overall mobility and hand function is assessed in general examination. A urologic examination includes evaluation for bladder emptying, external genitalia and rectal examination.

The reflexes and sensations in the genital area are carefully assessed. The dermatomes and reflexes are evaluated as figure 1 below. (4)

![Fig 1: lower limb and perineal dermatomes – adapted from ICS SSC (4)](image-url)
Special considerations

a) **Autonomic Dysreflexia (AD):** a medical emergency caused by disruption of normal autonomic response in spinal cord injuries (5) commonly seen in above T6 lesions. It may be elicited by visceral stimuli (UTI, constipation, pressure ulcers, sphincteric dyssinergia, during urodynamic studies or cystoscopy. It is characterised by arterial hypertension and bradycardia, with the symptom constellation of headache, anxiety, profuse sweating flushing and piloerection above the injury and dry/pale skin below the injury. The best way to reduce the risks associated with AD is in prevention. If the patient does develop AD during a urological procedure, the patient should be sat up (to minimise the chance of hypertensive brain injury), and the cause must be quickly identified and removed (usually by bladder emptying). In the majority of cases this should resolve the AD. The guidelines of the consortium for spinal cord medicine recommend further treatment if systolic blood pressure continues to be above 150mmHg in an adult. A short acting rapid onset antihypertensive should then be administered (such as sublingual nifedipine).

b) **Spinal Shock:** This is characterised by flacid paralysis below the neurologic level seen after the acute SCI. After this state of transitory muscle weakness, which can take from weeks to months there is a gradually return of muscular excitability and spasticity, below the lesion level (6). This is manifested by return of bulbo cavernous reflex. During this period bladder is generally managed by an indwelling cateter.

Baseline and follow up investigations

The basic investigations include urinalysis, estimation of urea and creatinine and ultrasound scan of the kidneys with uroflowmetry and estimation of post void residual (7). A bladder diary is kept for 3-5 days (7).

Quality of Life assessment (Qualiveen)

A number of assessment tools are available for able bodied patients but they are not suitable for SCI patients. A specific questionnaire has been developed for SCI patients, Qualiveen (8). This can distinguish between SCI patients with varying degree of disability and reference scores are available. However, it is more suited to be used for research rather than routine clinical practice.

Video-Urodynamics (VCMG)

One of the few areas of agreement between experts is the need for Urodynamic studies for assessment of SCI patient and is recommended that VCMG gives best evaluation.

The safety of the patient should be paramount during the study. There should be careful assessment of the patient’s ability to sit and stand safely and this should be documented in the report.

Filling Phase

It is recommended to start filling at 20 ml/min with body warm fluid. It is possible to evaluate for NDO (Figure 2), loss of compliance, incontinence abnormal (fir tree) bladder morphology (Figure 3). Additionally, loss of sensations, reflux and DSD can be detected.
Voiding Phase

This can only be performed in patients who can stand safely. The abnormal findings detected in this phase include detrusor acontractility, incontinence, DSD (figure 4), reflux and incomplete emptying.

Specific complementary investigations like CT scans, urethrograms and nuclear medicine scans may be individualized, as necessary.

Treatment

The management plan should be formulated in a holistic manner after consultation with the multidisciplinary team. The most important consideration in decision making is the patient's wishes. It is very important to acknowledge that although achieving a normal urinary tract is the aim, the prognosis can be very different in tetraplegics as compared to paraplegics.

This can be divided into conservative and surgical management.
**Conservative therapies**

These include drugs, use of catheters and external collection devices.

**Drugs to decrease NDO**

Neuropathic patients usually require higher doses of oral antimuscarinics to control NDO, albeit with increased side effects. Oxybutynin has also been used intravesically with fewer side effects but has not been widely accepted due to the need for catheter instillation.

**Drugs to decrease outlet resistance**

There are no drugs available to relax the external sphincter. However, selective and non-selective alpha blockers can be used to relax bladder neck and have been employed to facilitate bladder emptying and decrease the incidence of autonomic dysreflexia.

**Intermittent Catheterisation (IC)**

Popularised by Lapides, IC is performed by the patient (self) or by carers, 4-6 times per day. The patient should be motivated with good hand function and adequate mental capacity. Complications include urethral trauma with bleeding, false passages and urine infections.

**Indwelling Catheters**

These should be avoided long-term. Occasionally, however this maybe the only practical method of bladder management. There is controversy in the literature regarding the adverse outcome with long term catheterisation but overall this does not appear to lead to significant renal deterioration. The advantage of the suprapubic catheter is that the urethra is protected from cleavage and it is hygienically superior. Indwelling catheters increase the risk of bladder cancer as a result of chronic irritation and recurrent infection but there is no consensus as to the best method of screening these patients. Cystoscopy failed to detect any cancers in a 12 year follow-up study.

**Assisted Emptying**

Reflex voiding is generally not recommended especially in an upper motor neurone type bladder. Bladder contraction against a closed external sphincter secondary to detrusor external sphincter dysynergy can lead to high bladder pressures resulting in obstruction to upper tract drainage or incomplete emptying causing recurrent infections and incontinence. However, in suitable patients this can be employed after external sphincterotomy or stenting of the sphincter. Similarly, bladder emptying by abdominal straining (Valsalva emptying) in a lower motor neurone type injury is not encouraged as this can lead to incomplete emptying and infections along with prolapse of the pelvic organs.

**External Devices**

Various collecting devices such as condom catheters can be used in males. However, as a significant number of patients can have altered sensations this has to be monitored carefully to avoid skin lacerations. In both sexes pads are an option if all other measures fail.
Surgical treatment
The surgical options for treatment of a NBD are summarised in table 2

<table>
<thead>
<tr>
<th><strong>FAILURE TO STORE</strong></th>
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<tr>
<td>• Decrease detrusor contractility</td>
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<tr>
<td>• Botulinum toxin A</td>
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<tr>
<td>• Cystoplasty</td>
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<tr>
<td>• Auto-augmentation</td>
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<tr>
<td>• Increase outlet resistance</td>
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<tr>
<td>• Artificial urinary sphincter</td>
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<tr>
<td>• Slings</td>
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<td>• Bulking agents</td>
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<tr>
<th><strong>FAILURE TO EMPTY</strong></th>
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<tr>
<td>• Enhance detrusor contractility</td>
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<tr>
<td>• Sacral anterior root stimulator</td>
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<tr>
<td>• Sacral neuromodulation</td>
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<tr>
<td>• Decrease outlet resistance</td>
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<tr>
<td>• External sphincterotomy</td>
</tr>
<tr>
<td>• Stents (temporary &amp; permanent)</td>
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<td>• Botulinum toxin – A</td>
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<tr>
<th><strong>PROCEDURES TO CIRCUMVENT BLADDER</strong></th>
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<tr>
<td>• Ileal conduit</td>
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<td>• Orthotopic bladder</td>
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Table 2: Surgical treatments for managing neuropathic bladder after SCI

Treatments to decrease detrusor contractility

**Botulinum toxin A**

Botulinum toxin A has been very successfully used to control NDO since been popularised by Schurch (12). This has now become the mainstay of controlling NDO. It is a temporary treatment with effects lasting an average of 9 months. Repeat injections have been successful and no ultrastructural changes have been detected to date. There have been reports of generalised muscle weaknesses especially with English Botulinum Toxin A (Dysport). The approved dose is 200U Botox mixed with 30 mls of normal saline injected intradetrusor at 30 sites sparing trigone (13).

**Clam Cystoplasty**

In patients with uncontrolled NDO refractory to other treatment, clam cystoplasty is successful in expert hands. The bladder is bivalved and bowel, preferably terminal ileum is used to increase the bladder capacity and decrease NDO. The 5-year success rate for continence and increasing bladder capacity is in excess of 90% (40). However, there can be a number of short and long term complications (14).

Treatments to increase outlet resistance

**Bulking Agents**

Success rates vary between 20-50% with collagen and polydimethylsiloxane and hence are used sparingly but do have a role in the infirm patient.
Slings and Tapes
The bladder neck slings have been used but mainly in paediatric population with success around 70%. The main problems are failure and difficulty in catheterization due to the angulation of the urethra. Lately, transvaginal tape has been successfully used in the female neuropathic incontinence with about 60% success at 10 years.

Artificial Urinary Sphincter (AUS)
The most successful treatment of stress related urinary incontinence in a neuropathic patient is the use of an AUS. There are 3 components: peri-urethral cuff, pump in the scrotum and balloon in the retropubic space (Figure 9). Recent reports in the adult neuropathic population indicate long-term success rates of around 70%, but almost half require additional procedures.

Bladder Neck Closure
This is used as a last resort and is combined with either a catheterisable stoma or a suprapubic catheter with high success rates. The main disadvantage is irreversibility and loss of secondary access to bladder in case of failure to catheterise. In females this is performed vaginally and Martius fat pad is interposed between bladder neck and anterior vaginal wall to prevent fistulisation.

Treatments to enhance detrusor contractility
A variety of techniques have been described to enhance detrusor contractility but only Sacral anterior root stimulation (SARS) has stood the test of time. This can only be performed for complete lesions as the stimulation is very painful. It will also stimulate the urethral sphincter but micturition occurs as the striated muscle relaxes faster than the smooth muscle. Although there is no need to CISC, posterior rhizotomy means loss of reflex erections. However by changing the parameters this technique can be used to induce erection and defecation.

Sacral neuromodulation (SNM)
Neuromodulation is the process in which the influence of activity in one neural pathway modulates the pre-existing activity in another pathway through synaptic interactions. A stimulator is surgically implanted in the buttocks. This stimulates the appropriate nerves by using mild or moderate electrical impulses. This can help restore coordination between brain, pelvic floor, bladder or bowel and sphincter muscles, with increasing evidence in the literature that SNM suppresses NDO, increases capacity and is reversible.

Treatments to decrease outlet resistance
External Sphincterotomy
If left untreated DSD leads to a complication rate of 50% including urosepsis, hydronephrosis, stones and reflux, which can all lead to deterioration of renal function. External sphincterotomy is the gold standard for treating DSD, although often needs to be repeated. The complications include sepsis, bleeding and erectile dysfunction. A bladder neck incision might be necessary later on to overcome bladder neck dysnergia.

Urethral Stents
There are 2 main types of urethral stent; Memookath (temporary) and Urolume (permanent). They are both potentially reversible and require a shorter hospital stay than sphincterotomy. The potential complications are migration, encrustation, blockage, bladder neck dyssynergia and incomplete emptying with development of AD. A memokath stent can be inserted through a Urolume to overcome bladder neck dyssynergia.
Botulinum toxin A
Lately, Botox injections have been used to treat DSD, however the effects are temporary and hence need to be repeated.

Treatments to circumvent bladder

Continent diversion
This should be the first choice for diversion if the patient cannot (limited dexterity)/ will not use their urethra. A mitrofanoff tube is fashioned from appendix, ileum or fallopian tube and is tunnelled into the ileocystoplasty augment, resulting in continence. The umbilicus is a cosmetically excellent exit site but has a high stenosis rate. Short-term continence rates are over 80%.

Incontinent diversion
An ileal segment is usually used and patients require life-long follow-up to detect complications including infections, anastomotic stenosis, deterioration of renal function and metabolic disturbances. Importantly, if the bladder has been left behind there is 30% chance of developing pyocystitis.

Sexual dysfunction

Males
Sexual dysfunction in both males and females with SCI is common. Around 40% of males are unable to attain an erection spontaneously, and over a third report anejaculation. Patients with lesions above L2 typically can attain erections in response to reflex and psychogenic stimuli. First line treatment of erectile dysfunction (ED) in SCI patients is based on phosphodiesterase inhibitors (PDE-5). The reported ED improvement rate with sildenafil is more than 75%. Should initial treatment with PDE5 inhibitors fail, then second line therapies are effective. Vacuum erection devices tend to have modest patient satisfaction rates, but intracavernosal injections are well tolerated with response rates in excess of 90%. A penile prosthesis can be considered in refractory cases which have excellent patient satisfaction rates, but a significant complication rate of up to 10%.

As the majority of SCI patients have difficulty ejaculating, the most commonly employed technique to obtain semen is vibro-ejaculation, performed with a specially designed vibrator applied to the underside of the glans penis. In those with infrasacral lesions, vibro-ejaculation may not be successful and electroejaculation may then need to be considered. This is performed by using a transrectal electrical stimulation probe that directly stimulate the seminal vesicles. Electroejaculation is however an invasive therapy and there is a risk of rectal injury. It may require a general anaesthetic for those with incomplete lesions as it is painful. Semen parameters are often impaired even when erection and ejaculation are not impaired with the presence of retrograde ejaculation making sperm harvest more difficult (15). Overall pregnancy rates however using combinations of the above techniques are 51% with a live birth rate of 40% (15).

Conclusion
SCI is a multisystem disease and clinical presentation depends on the level and completeness of the lesion. The aim is to complete a thorough holistic assessment of a newly injured patient with SCI and tailor patient expectations and aims to ensure upper urinary tract protection is coupled with acceptable continence and low risk of urological complications. Regular follow up is of paramount importance, and any deterioration in parameters should trigger an alteration in bladder management. Furthermore as part of the holistic assessment and treatment of individuals with SCI, one should enquire about bowel and sexual function, and instigate changes in management to improve patient’s quality of life.
References

4. NON-TRAUMATIC SPINAL CORD LESIONS

Authors: Silvio Almeida, Blayne Welk

Introduction
While traumatic spinal cord injuries are common, there are other infectious, degenerative, vascular and malignant conditions which can also result in spinal cord dysfunction and lead to neurogenic lower urinary tract dysfunction.

Vascular lesions and tumors of spinal cord
Vascular diseases of the spinal cord are rare and clinical symptoms depend on which vessel is affected. An anterior arterial infarction will evolve with tetra or paraplegia with loss of heat and pain sensitivity, and preservation of proprioception. Posterior arterial infarction syndrome will present with the loss of proprioception and vibration sensitivity. An infarction of central groove artery will evolve into a Brown-Sequard syndrome. Spinal cord infarction symptoms arise very rapidly, and when associated with pain can mimic angina or myocardium infarct. Arterial-venous fistula or venous diseases present as slow progressive myelopathy, that is worsened by a Valsalva maneuver.

Spinal tumors are classified in three categories: extra-dural, extra-medullary intra-dural and intra-medullary intra-dural tumors. Localized pain is the most common symptom as a result of epidural tumor compression, followed by motor weakness. The treatment of these tumors depends on the stability of the column, neurologic status and pain, and may include surgery, radiotherapy and/or chemotherapy. Rehabilitation guidelines used in patients with spinal cord trauma are appropriated to patients with spinal tumors.

Chronic cervical Myelopathies
Cervical degenerative myelopathies result from several diseases, such as osteoarthritis, spondylolisthesis, ossification of longitudinal posterior ligament, and are the main cause of spinal cord dysfunction. However, most patients will never develop symptoms, and even fewer will need surgery. The literature highlights the importance of clinical and electromyographic follow-up to predict myelopathy progression. Older patients usually have a worse prognosis compared to young people and older patients with other types of myelopathies.

Lumbar disc disease
Lumbar disc disease is very common, and affects an estimated 1-2% of the general population. In order to appreciate the potential effects of this condition on bladder function,
a brief review of the anatomy is necessary. The cauda equina starts at the L2 vertebral body, and contains all the nerve roots that exit below this level. Therefore, the sacral nerve roots (which carry somatic innervation to pelvic floor and exit via S3 and S4 roots), and the parasympathetic system (which controls storage of urine and exit via S2, S3, and S4 roots) are contained in the cauda, and may be potentially affected by lumbar disc disease below the L2 vertebrae. The sympathetic nerves (which control voiding) are contained in the L1, L2, L3 nerve roots. As the most frequently herniated discs are L4/L5 or L5/S1, these sympathetic nerve roots are not common affected.

In the case of lumbar disc disease that results in herniation of the disc, the direction of the herniation will impact the potential severity of the neurologic symptoms. A posterolateral disc herniation is the most common type of herniation, and is usually directed to one side of the spinal cord. It tends to cause unilateral radicular pain down the leg due to pressure on one of the nerve roots as it exits the vertebral column. A medial disc herniation is less common, however it is more likely to cause the compression of actual nerves within the spinal canal, and potentially lead to cauda equina syndrome. Cauda equina syndrome is a medical emergency characterized by saddle anesthesia, and urinary/anal sphincter dysfunction, often associated with acute back pain/sciatica and sensory and/or motor dysfunction of the lower limbs. It is rare, and occurs with only approximately 1/1000 patients with lumbar disc herniation. Recovery of normal bladder function is less likely among patients with complete cauda equina syndrome at presentation (defined as painless urinary retention with overflow incontinence and complete saddle anesthesia), and in those with delayed surgical intervention.

The mechanism by which posterolateral disc herniation can affect the nerve roots include both direct compression which can induce overstimulation of the nerve fibers, or demyelination due to ischemia or atrophy as a result of chronic or progressive herniation. The urologic manifestations associated with these neurologic injuries as a result of lumbar disc herniation are most commonly detrusor areflexia, detrusor overactivity, and decreased bladder sensation; most often these patients will have associated radicular symptoms. The coexistence of urinary symptoms with a lumbar radiculopathy (in the absence of cauda equina syndrome) does not change the approach of the urologist and spine surgeon: the urinary symptoms are treated as they would be in the absence of a disc herniation, and the radiculopathy symptoms are initially treated with conservative management (such as physiotherapy, pain management, lumbar supports, and transcutaneous electrical nerve stimulation). In cases where the radiculopathy requires surgical management, there are only a few studies reporting the outcome from a urinary symptom perspective. Some suggest that urinary symptoms and urodynamics normalize, while others suggest that this happens infrequently. In addition, the surgery itself carries the risk of de novo bladder dysfunction, which complicates the interpretation of these studies.

Transverse myelitis

Transverse myelitis is an inflammatory disorder that interrupts the neurologic pathways in the transverse plane of the spinal cord, which leads to a specific abnormal sensory level. Potential etiologies include autoimmune disease, infection, demyelinating diseases or idiopathic. It is quite rare (1-10 per million people), and usually affects people less than 40 years of age. Over half of patients have a partial or complete recovery afterwards. Most of the recovery happens in the first 3 months, and generally continues for a year afterwards. It is therefore important not to perform any permanent urologic interventions in the initial recovery period, until bladder function has stabilized.
Evaluation and Prognosis

There is little written on the treatment of these patients, due to a low incidence of these diseases. Unlike traumatic lesions, these patients are often treated outside of large centers. However, the guidelines on the treatment of patients with a spinal cord trauma are generally used to treat these patients with similar results. There is often an initial period of urinary retention which can be managed with an indwelling catheter or intermittent catheterization. After this, the patient may develop detrusor overactivity (with urgency incontinence), or detrusor-sphincter-dyssynergia/detrusor areflexia (with urinary retention). Even with complete recovery of motor function, a large number of patients may have residual urinary frequency, urgency or hesitancy, and associated urodynamic abnormalities. Similar to spinal cord injured patients, there are no good predictors of high risk urodynamic features, which underscores the importance of a careful neuro-urologic evaluation of these patients.

For patients with a myelopathy, there are a few differences that may influence evaluation and prognosis for these patients including a lower incidence of deep venous thrombosis, autonomic dysreflexia and orthostatic hypotension. There are also data showing a higher incidence of incomplete spinal cord lesions, with better recovery in the presence of preservation of bladder sensitivity and in young patients. Patients with an American Spinal Injury Association score of 'A' after one month have a worse prognosis for recovery of spontaneous voiding.

History

A detailed history should review previous and present intestinal, urinary and sexual symptoms. Specifically:

1. Neurologic exam must include reflexes and evaluation of the sensitivity of the urogenital region.
2. Urinalysis is important, since urinary infection is a common complication.
3. Uroflowmetry if possible.
4. Ultrasonography for urinary upper tract follow-up and for measurement of the residual urine volume

Suggested Treatment

After resolution of the spinal shock phase (6-8 weeks), it is important to do a urodynamic study. The use of Madersbacher classification is adequate to estimate the risk to the upper urinary tract. Neurologic tests, such as improvement of the bulbocavernous reflex and sensitivity to pain may indicate neurological recovery and consequently improvement of detrusor function. Compared to patients with traumatic spinal cord lesions, those with non-traumatic diseases usually have a higher cystometric capacity during urodynamic studies, a lower detrusor pressure, higher voided volume and lower residual volumes. This is explained by the fact that an incomplete lesion is more frequent in this group of patients, with preservation of more neuronal pathways, and therefore a higher likelihood of normal bladder function.

Recommendations

Safe management of these patients must include reduction of detrusor pressure, treatment of neurogenic detrusor overactivity, and safe emptying in the presence of detrusor-sphincter dyssynergia. Abdominal straining to empty the bladder must be avoided, especially in the presence of detrusor-sphincter dyssynergia. The use of intermittent catheterization is the preferred method of bladder emptying when necessary.
References


Introduction
Parkinson disease (PD) is included in the group of neurodegenerative diseases characterized by progressive loss of structure or function of neurons, including neuron apoptosis. Neurodegeneration may be observed in different levels of neural circuits, from molecular level to systemic aspects, and therefore is capable to cause low urinary tract symptoms (LUTS).

PD physiopathology begins at the dorsal motor nucleus of vagus nerve. From there, it progresses cranially through inferior portion of cerebral stem and basal forebrain to reach the cerebral cortex.

Initial symptoms include non-motor alterations, as demonstrated by Khoo et al (213) in a comparative study of patients with initial PD and normal controls. The frequency of non-motor symptoms was 8.4% at PD and 2.8% at normal controls. More frequent non-motor symptoms include sialorrhea (56% vs 6%), urinary urgency (46% vs 19%), hyposmia (44% vs 10%), constipation (42% vs 7%), and anxiety (42% vs 10%) (1).

LUTS and PD
LUTS are frequent autonomic symptoms in PD (2) and significantly affect quality of life. Pathophysiology of PD includes degeneration of dopaminergic neurons at Substantia nigra-Substantia nigra, although several cerebral regions and neurotransmitters may be involved. The fact that PD LUTS are only partly responsive to levodopa treatment suggests complex pathophysiology (Uchiyama, Sakakibara, Hattori, & Yamanishi, 2003). The improvement of LUTS and quality of life related to PD demands for additional therapy.

At the Substantia nigra, there are D1 receptors that inhibit voiding reflex, and D2 receptors that stimulate this reflex. In simple terms, voiding dysfunctions of PD patients (in special detrusor hyperactivity) are caused by low inhibition of D1 receptors or excessive stimulation of D2 receptors.

Cerebral dopamine influences voiding control by dopaminergic receptors and GABA, that also has an inhibitory function of voiding reflex.

Cerebral Dopamine and Voiding
Main influence of Basal ganglia over voiding is inhibition. Functional images of the brain during bladder filling show activation of Globus pallidus in normal subjects, and of the Putamen in patients with PD. Images that evaluate dopamine transport showed a reduced activity in patients with PD and LUTS in comparison to patients with no voiding symptoms. Electrical stimulation of Substantia nigra, and of the Striatum, pars compacta, inhibits voiding reflex. Levels of striatal dopamine raise significantly during bladder filling in experimental studies (3)(Sakakibara, Panicker, Finazzi-Agro, Iacovelli, & Bruschini, 2016).
Urinary symptoms and PD
Uchiyama and cols. (2011) showed that urinary symptoms are present during initial stages of PD but mostly are sub-clinical and do not affect quality of life (4). Those authors studied 50 untreated consecutive patients with PD with a median duration of the disease of 23.6 months (Hoehn&Yahr scale: 1.9). During urodynamic studies, detrusor overactivity was observed in 82%, although urinary symptoms rarely affected quality of life of this group of patients with PD. Clinical significant urinary symptoms correlate to severity, and therefore to PD duration. Time from PD start and beginning of LUTS in most studies is 5 years.

Clinical evaluation
The objective of clinical evaluation of LUTS in PD is based on the identification of relationship and eventual co-morbidities that may be involved in the genesis of those symptoms. Mixed LUTS etiology may occur and the clinician must establish the real role of causal factors (PD, prostatic hyperplasia, urinary infection, etc) and how they are related and worsen the symptoms.

History
Anamnesis is fundamental to clinical evaluation of patients with PD and must include the following questions and measures:

1. Bladder
Filling and emptying urinary symptoms may be observed in PD. Most frequent urinary symptoms include filling symptoms, especially nocturia in 86%, frequency in 71% and urgency in 68% of patients. Emptying symptoms are less prevalent (17 to 27%), in special hesitance, weak stream and two-time voiding (5) (Sakakibara, Tateno, Kishi, Tsuyuzaki, Uchiyama, & Yamamoto, 2012). It is important to evaluate nocturia, since it may be caused by several factors that include detrusor overactivity (and consequently reduction of functional bladder capacity), impairment of detrusor compliance, incomplete bladder emptying or nocturnal polyuria. Nocturnal polyuria by itself is a complex diagnosis, that demands specific investigation to identify its cause (ADH secretion alteration, cardiovascular imbalance, sleep disturbances, etc). It is important to stress that nocturnal polyuria is only identified by micturition diaries and may be associated to other low urinary tract dysfunctions that may provoke LUTS.

Important questions:
- Since when are LUTS present (already present before PD diagnosis?)
- How long has PD been diagnosed?
- In patients with significant LUTS before PD diagnosis, other co-morbidities such as prostatic hyperplasia may be the initial cause of symptoms, and not the recent diagnosed PD.
- The use of voiding diary (of at least 48 hours) is mandatory to clinical evaluation of patients with LUTS and neurological diseases, since it provides more precious information than simple voiding history.
- Drugs – in special those for PD
- At present, dopaminergic agonists are the first line of treatment of PD for patients with less than 65 years old. Those drugs present low influence on low urinary tract
function but affect sexuality. In patients with over 65 years of age, L-DOPA is still the drug of choice with alpha-blocker and anti-muscarinic effects. Apomorphin is a third line drug which depresses enormously detrusor function and may cause increase of post-voiding residual urine volume.

- L-DOPA and other drugs for PD may present an on-off phenomena in relation to their effect on the disease. The benefits usually lower along time and with the progress of the degenerative disease. This means that anti-parkinsonian drugs effects on urinary symptoms may be different in the beginning of therapy in relation to the final useful period of the drug. This fact must be observed during clinical evaluation of those patients.

**Anti-parkinsonian drugs and LUTS**

The effects of levodopa on LUTS of patients with PD are still unknown (Seki, Igawa, Kaidoh, Ishizuka, Nishizawa, & Andersson, 2001) (Yoshimura, Mizuta, Yoshida, & Kuno, 1998). Dopaminergic agonists showed facilitating effects on bladder storage. A questionnaire-based study showed that emptying symptoms (intermittence and incomplete bladder filling sensation) were more common in patients using levodopa and bromocriptine (D2-selective agonist) than in those using levodopa singly (Sakakibara & Fowler, Brain diseases, 2001).

Another study showed that apomorphin caused increase of bladder filling capacity (Aran-da & Cramer, 1993). This drug may alter detrusor function, decreasing detrusor contractile capacity and may cause increase of post-voiding urinary residual volume or chronic urinary retention.

Monoamino-oxidase inhibitors (MAO) type B block dopamine effect but show no effect on voiding until recently (Gulur, Mevcha, & Drake, 2011). Cholinesterase inhibitors (for patients with PD and cognitive deficit/dementia): see Dementia chapter.

2. Intestine

Physiopathology of intestinal dysfunctions in patients with PD is quite different than that of patients with medullary trauma or multiple sclerosis. Striated muscle dystonia of pelvic floor and external sphincter explain bowel movement dysfunctions. This etiology is proved by the observation that pelvic floor dysfunction improves with the use of L-Dopa. Bowel transit is normally prolonged in PD and is considered one of the first signals of the disease along with alterations of inferior cerebral stem. Patients must be questioned regarding intestinal rhythm and constipation.

3. Sexuality

Sexual dysfunctions are common in patients with PD. Most frequently, loss of libido, erectile dysfunction, difficulty to reach orgasm and sexual dissatisfaction are observed. Hypersexuality is possible, among several disturbances of sexual impulse control related to patients with PD, and is related to anti-parkinsonian drugs (in particular, dopaminergic agonists).

**Clinical Exam**

Rectal exam is extremely important. It is necessary to evaluate anal tonus (present, weak, absent?), capacity to voluntarily contract pelvic floor muscles and anal sphincter, presence of impacted feces, and obviously, prostate evaluation. The importance to evaluate the capacity of the patient to voluntarily contract anal sphincter is discussed below at the section of indications of prostatic surgery in PD.
Urine exams: to identify and treat urinary infections before specific evaluation.
Urofluxometry: desirable when possible.
Post-voiding urinary residual volume: measured by ultrasound exam and, when increased, it may be related to a) prostatic obstruction, b) sphincter bradykinesia due to PD, c) drugs (apomorphin) and, d) a combination of the above factors.

**Suggested Treatment**
Typical patient attended by the urologists for LUTS treatment is aged, with motor symptoms for more than 10 years and several years of treatment with L-Dopa and other drugs that provoke on-off phenomena. Many patients present cognitive deficit that may be worsened by drugs. Some are highly compromised, immobile, bedridden, with speech deficiency, and the most frequent urinary symptoms are nocturia with or without urgency, and urge-incontinence.

**Recommendations**
Initially, treat urological/gynecologic co-morbidities. Level of investigation is determined by the ability of the patient to receive specific treatment.

The use of drugs must be careful regarding the already anti-parkinsonian drugs been used. Patients with overactive bladder must receive anti-muscarinic drugs that do not induce CNS side-effects, therefore those that do not cross the blood-brain-barrier and/or those without active eflux. Drugs with higher M1-receptors affinity may provoke more cognitive effects (Figure 1).

**High risk for CNS side effects**
- Oxybutynin
- Oxybutynin transdermal patch?
- Tolterodine
- Propiverine
- Trospium
- Darifenacin
- Solifenacin
- Fesoterodine

**Less risk for CNS side effects**

*Figure 1: Risk of side-effects on CNS of different anti-muscarinic drugs*
An alternative to anti-muscarinics is mirabegron, an adrenergic beta-3 agonist; however, there are still very few studies in patients with neurogenic overactive bladder.

Intra-detrusorial injections of botulinum toxin A may be more adequate than anti-muscarinic drugs since it does not induce general side effects. Four studies at present showed benefic effects, using 100 UI dose of onabotulinic A toxin \(^{(11-13)}\) (Botox\(^{®}\) (Giannantoni, Rossi, Mearini, Del Zingaro, Porena, & Berardelli, 2009) (Kulaksizoglu & Parman, 2010) (Anderson, Orenberg, & Glowe P, 2014).

Electrical stimulation or deep brain stimulation (DBS) of sub-talamic nuclei is considered a succesfull surgical option for the treatment of motor symptoms of PD in patients that do not respond to conventional drugs. Urodynamic studies in animal and human models showed improvement of urinary symptoms after electrical stimulation of subthalamic nuclei. Seif et al. presented a series of 16 patients that showed normalization of urodynamic parameters during filling phase, with delay of first sensation of voiding desire and increase of bladder capacity \(^{(14)}\) using DBS (Seif, 2004). The same results were presented by Herzog et al. (2008). Those authors concluded that the positive results with DBS are related to neuromodulation of bladder reflex, particular of bladder afferent impulses to cortical and sub-cortical areas \(^{(15)}\) (Herzog, 2008).

Although DBS is a promising therapy for LUTS in most studies, a few patients presented worsening of voiding dysfunction. Specifically, thalamic DBS may worsen voiding frequency and may reduce bladder capacity \(^{(16)}\) (Kessler et al., 2008). Whichever teraphy is choosed, it is important to share the results with the consultant neurologist.

**Special Situations**

Patients with PD and urinary symptoms – is the prostate of PD patient that cause symptoms? Flow-pressure studies associated to electromyography or video-urodynamics may evaluate sphincter function. Lack of sphincter relaxation or increase of sphincter activity during voiding in PD patients may be related to bradykinesia (delay of lack of sphincter relaxation in parkinsonian patients). These patients do not show classic detrusor-sphincter dyssynergia and the term bradykinesia describes more precisely the specific dysfunction in PD patients. Another possible characteristic is pseudo- dyssynergia, or lack of relaxation of sphincter as an attempt to block urinary leakage, due to involuntary detrusor contraction, by voluntary contraction of pelvic floor.

Prostate endoscopic resection in PD patients may cause or increase urinary urge-incontinence?

Before any surgery in PD patients it is mandatory to perform urodynamic evaluation or video-urodynamic study. This evaluation will verify bladder neck obstruction and will determined more precisely detrusor function (detrusor overactivity, reflex volume, detrusor compliance).

Cold water test may be performed to differentiate neurogenic and non-neurogenic detrusor overactivity. It is positive in patients with detrusor neurogenic overactivity.

The risk of post-surgical urinary incontinence is much higher in patients without the ability to voluntarily contract the anal sphincter. On the other hand, urinary incontinence after prostate TUR is lower in patients who cannot contract the anal sphincter. \(^{(17)}\) (Staskin, Vardi, & Siroky, 1988).

**Parkinson Disease vs Multi System Atrophy (MSA)**

MSA is a progressive neurodegenerative disease with a bad prognosis (median life expectancy of 4 to 9 years). Initially, it presents with PD symptoms, but do not respond
to L-dopa treatment. Patients rapidly present cerebral ataxia, autonomic failure and early voiding dysfunction during the evolution of the disease.

Urinary symptoms are caused by the following sequential events: brain stem lesion causes detrusor over or underactivity, spinal cord intermedial-lateral degeneration causes parasympathetic failure and loss of contractile detrusor capacity with incomplete bladder emptying; sympathetic failure causes loss of bladder neck function verified by video-urodynamics that shows an open bladder neck.

Also, Onuf nucleus atrophy causes weakness of striated sphincter, and, in particular in the cerebral sub-type (MAS-C) early erectile dysfunction associated with urinary incontinence, constipation and occasionally urinary retention are observed (Ciolli, Krismer, Nicoletti, & Wenning, 2014).

<table>
<thead>
<tr>
<th><strong>Beginning of urogenital symptoms</strong></th>
<th><strong>MSA</strong></th>
<th><strong>DP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Precede neurological deficits/ cardiovascular imbalance</td>
<td>Usually is secondary and late to neurological deficit</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bladder dysfunction</strong></th>
<th><strong>MSA</strong></th>
<th><strong>DP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Early severe incontinence Overactive bladder symptoms → progress to chronic urinary retention</td>
<td>Less severe incontinence Overactive bladder symptoms, nocturia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bladder ultrasound</strong></th>
<th><strong>MSA</strong></th>
<th><strong>DP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Early post-voiding urinary volume increase during the evolution of the disease</td>
<td>Usually normal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Video-urodynamic study</strong></th>
<th><strong>MSA</strong></th>
<th><strong>DP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor over- or underactivity Open bladder neck may be observed</td>
<td>Detrusor over- or underactivity Brady-/Pseudo-dyssynergia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sexual dysfunction</strong></th>
<th><strong>MSA</strong></th>
<th><strong>DP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ED (usually first symptom)</td>
<td>ED (eventual compulsive sexual behavior)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Differences between PD and MSA in relation to beginning of symptoms, urinary dysfunction, urodynammic parameters and sexual function

Urinary incontinence in patients with MSA may be caused by: 1) detrusor overactivity; 2) bladder emptying difficulty (check post-voiding urinary residual volume and overflowing leakage) or 3) intrinsic sphincter dysfunction (check urodynamic study) and anal external sphincter failure (check anal tonus).

**Treatment of LUTS in patients with MSA**

Detrusor overactivity is initially treated with behavioural measures (toilet training) to improve bladder emptying. It is recommend double or triple voiding; anti-muscarinic drugs may be used but without evidence of efficacy.

Intermittent catheterism is indicated to patients with high post-residual urine volume (in particular those above 50% of bladder capacity). In advanced cases, the only alternative may be prolonged urethral catheterism or cystostomy.

Avoid desobstructive surgeries in men with BPH, since the results are usually unsatisfactory or disastrous.
Summary

Urinary symptoms in PD are more common in the late phases of the disease, and may be observed 5 to 10 years after the beginning. Severity is related to neurologic limitations. It is important to stress that LUTS in PD may have a neurogenic, urologic or mixed source. It is highly recommended that any urological condition must be treated initially.

Patients with overactive bladder may use anti-muscarinic drugs, particularly those with lower cerebral side effects. Mirabegron is a new alternative with good response. Botulinic A toxin or electrical neuromodulation may be options to be used after trials with less invasive treatments.

In male patients with PD and bladder neck obstruction, prostate TUR may be used, and it is not expected worsening of urinary urgency and urge-incontinence, in particular in men with good voluntary control of pelvic floor muscle and of anal and urinary sphincters.

In MAS, urinary symptoms, particularly overactive bladder and urgency, are observed early and may precede neurological symptoms. Bladder emptying and filling symptoms may be present. Autonomic symptoms such as erectile dysfunction, may occur early in the disease, and may be the first expression. Treatment of urinary symptoms is conservative, initially with behavioural therapy and, when necessary, intermittent catheterism. Desobstructive surgeries must be avoided since usually fail.
References

6. DEMENTIAS

Authors: Marcio Augusto Averbeck, Jalesh Panicker

Introduction
Dementia is a pathological, neurodegenerative process leading to progressive decline in cognitive and functional abilities. It has multiple causes, diverse manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes (1).

<table>
<thead>
<tr>
<th>Neurodegenerative</th>
<th>Alzheimer’s Dementia, Dementia with Lewy Bodies, Frontotemporal dementia, Parkinson’s disease with dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Multi-infarct dementia, strategic infarct</td>
</tr>
<tr>
<td>Infections</td>
<td>Creutzfeld Jakob disease, Syphillis, Whipple’s disease, Herpes encephalitis and other viral encephalitides, Chronic meningitis, Progressive multifocal leukoencephalopathy, Subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Toxins</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Structural pathology</td>
<td>Tumour</td>
</tr>
<tr>
<td>Inflammatory disorders</td>
<td>Multiple sclerosis, Vasculitis, Non-vasculitic autoimmune encephalopathies</td>
</tr>
<tr>
<td>Metabolic-related dementias</td>
<td>B12 deficiency, thyroid disease, parathyroid disease</td>
</tr>
</tbody>
</table>

Table 1. Causes for Dementias
The dementias can be classified according into four major groups, (I) Alzheimer's disease; (II) vascular dementia (post stroke dementia); (III) the Parkinson's group (including Lewy Body disease, dementia of Parkinson's and Alzheimer's dementia with Parkinson's); (IV) the frontotemporal group (2).

Alzheimer disease (AD) is the most common form of dementia, comprising up to 80% of cases; however, not all studies distinguish AD from all-cause dementia. The estimated prevalence of all-cause dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, with North America falling between at 6.4%. Currently, over 46 million individuals live with dementia worldwide and this number is projected to increase to 131.5 million by 2050 (1).

Vascular dementia is regarded as the second most type of dementia (2). The cardinal features of vascular dementia include history of stroke, fluctuating course, focal neurological symptoms, wide-based gait, and the presence of arteriosclerotic risk factors such as hypertension (3). Of these features, Kotsoris et al. found that LUTS, reported in 50% of patients, frequently preceded the development of dementia by 5 years or more. Similarly, gait disturbance, noted in 24%, preceded the development of dementia by 2 years or more (4). Post-stroke dementia (PSD) or post-stroke cognitive impairment (PSCI) may affect up to one-third of stroke survivors. PSD has been proposed as a label for any dementia following stroke in temporal relation (5). Stroke is a leading cause of disability (6). Research and interventions have historically focused on physical disabilities, while cognitive impairment – an important aspect for stroke survivors – has been rather neglected (7, 8). Even minor stroke affects daily functioning, executive functions, and cognition, consequently affecting participation, quality of life, and return to work (8). Stroke survivors are at increased risk of developing cognitive impairment. Obviously, the acute tissue damage may affect cognition. Nevertheless, despite prospective data being available, results are conflicting and the direct cognitive effect of a stroke event beyond the cognitive decline associated with age and vascular risk factors remains poorly understood. Physical impairments tend to improve, to a greater or lesser degree, following stroke; however, for reasons which remain unknown, cognitive impairments progressively worsen.

The pathognomonic pathology in Lewy body dementia (LBD) is an abnormal aggregation of the protein α-synuclein, referred to as a Lewy body, within the cytoplasm of neurons. Besides cognitive decline, common symptoms of LBD are visual hallucinations, sleep disturbance, autonomic dysregulation, fluctuating attention, depression, and Parkinson like symptoms of bradykinesia, rigidity, and tremor (1). Clinically, LBD is distinguished from PDD by onset of dementia before or within the first year of onset of parkinsonism. Autopsy studies suggest that LBD accounts for 15% to 25% of dementia cases, making it the third most common type of dementia (9).

Unlike previously discussed dementias, frontotemporal dementia (FTD) is most prevalent among individuals aged 60 to 69 years, with roughly 13% having onset when younger than age 50 (10). Younger onset may be due in part to heavy genetic loading for FTD, with up to 50% of cases being familial and up to 40% autosomal-dominant in nature (10). Clinical presentation of frontotemporal dementia is usually heterogeneous. Progressive behavioural impairment and decline in executive functions are not uncommon (1).

Lobo et al. compared the age- and sex-specific prevalence of dementia, AD, and vascular dementia (VaD) across European population-based studies of persons 65 years and older (11). Data from these studies were also pooled to obtain stable estimates of age- and sex-specific prevalence. A total of 2346 cases of mild to severe dementia were identified in 11 cohorts. Age-standardized prevalence was 6.4% for dementia (all causes), 4.4% for AD, and 1.6% for VaD. The prevalence of dementia increased continu-
ously with age and was 0.8% in the group age 65 to 69 years and 28.5% at age 90 years and older. The corresponding figures for AD (53.7% of cases) were 0.6% and 22.2%, and for VaD (15.8% of cases), 0.3% and 5.2%. Variation of AD prevalence across studies was greatest for men. In the VaD subtype, a large variation across studies was observed, as well as a difference in prevalence between men and women that was age dependent. Dementia is more prevalent in women, and AD is the main contributor to the steep increase of prevalence with age.

More recently, de Pedro-Cuesta et al. (12) studied the prevalence of dementia in Spain (people aged 70 years and above). The survey included Central and North-Eastern Spanish sub-populations obtained from 9 surveys and totalled 12,232 persons and 1,194 cases of dementia (707 of Alzheimer’s disease, 238 of vascular dementia). Prevalence of dementia and Alzheimer’s disease in Central and North-Eastern Spain is higher in females, increases with age, and displays considerable geographic variation that may be method-related. People suffering from dementia and Alzheimer’s disease in Spain may approach 600,000 and 400,000 respectively (12).

Prevalence of LUTS in patients with dementia

Urinary incontinence (UI) and Alzheimer’s disease (AD) are common in the elderly population and have increased rapidly in recent decades (13). It is difficult to distinguish LUT problems caused by bladder aging from those due to other concomitant diseases (14). It has been shown that in geriatric patients with dementia, incontinence is much more frequent than in non-demented patients (15, 16). Grant et al. (17) extracted data on 54,816 people aged 60–89 with dementia and an age-gender stratified sample of 205,795 people without dementia from 2001 to 2010 from The Health Improvement Network (THIN), a United Kingdom primary care database demonstrated that, compared to individuals without a dementia diagnosis, those with dementia were approximately three times more likely to report urinary incontinence (17).

Urinary incontinence and its prevalence have been the focus of most studies on LUTS in dementia, and have relied on both patient and caregiver reports. Possibly, due to differences in patient selection among these studies, incontinence prevalence rates have varied considerably (2). Overall, urinary incontinence affects around 50% of men and 60% of women with dementia, inevitably occurring in advanced stages of disease (18-20).

Alzheimer’s disease (ALD) is the most common type of dementia in clinical and autopsies surveys. In patients with ALD, the prevalence of UI ranges from 23% to 48% (21, 22). The onset of incontinence usually correlates with the disease progression (23). Male to female ratio of dementia related incontinence was found to be 1:15.

However, symptoms of an overactive bladder (OAB) occur more commonly in dementia with Lewy bodies (DLB) and vascular dementia (48%), than in patients with Alzheimer’s disease (AD) (40%) (18, 20). In addition, the association of severe cognitive decline and urinary incontinence may be useful in differentiating Alzheimer’s disease versus Lewy Bodies Disease. Urinary incontinence is associated with severe cognitive decline in pure Alzheimer’s disease, but usually precedes significant cognitive impairment in Diffuse Lewy Bodies disease. This temporal pattern of cognitive decline and incontinence could be useful in differentiating these two subtypes of dementia (24).

LUTS have been reported in 93% of the patients with Idiopathic Normal Pressure Hydrocephalus (NPH). In this group, storage symptoms were more common than voiding symptoms (93 versus 71%). The most frequent LUTS were urgency (64%), frequency (64%) and incontinence (57%) (25).
Prognosis of lower urinary tract dysfunction in patients with dementia

Plateauing in Alzheimer’s Disease
In Alzheimer’s Disease (AD), a plateau refers to a patient’s remaining on a mild level of cognitive decline for more than two years. Survival curves (Kaplan-Meier method) showed that patients with plateauing reached several end-points such as very severe functional or cognitive impairment, urinary incontinence, and death significantly later than patients with progressive illness (p < 0.04). Patients with plateauing showed a smaller cognitive loss (p < 0.01) in terms of the mean annual rate of progression of mental decline. Patients who were plateauing in an early stage of Alzheimer’s Disease have been reported to have a more favourable course (26).

Lumbar puncture and shunt operation for the treatment of Normal Pressure Hydrocephalus (NPH)
Lumbar puncture and removal of 50 ml CSF has been shown to improve detrusor overactivity temporarily in NPH, and abolished by shunt operation. Urodynamic testing after lumbar puncture may predict the outcome of a shunt operation in cases of normal pressure hydrocephalus (27).

Urodynamic testing after lumbar puncture may predict the outcome of a shunt operation in these cases (2). According to Sakakibara et al., a positive spinal tap test may predict successful outcome of shunt surgery, and the recovery rate of bladder function after shunt surgery ranges 30–70% of patients (28).

Management of LUTS in patients with dementia
LUTS in dementia patients can be caused by the dementia itself, by the neurological and urological pharmacotherapy, and by the ageing bladder or comorbidities (2).

Conservative management
Urinary incontinence in Alzheimer’s disease patients is frequently associated with cognitive impairment, suggesting its central nervous system origin. Therefore behavioural therapy, toilet training and prompted voiding would be most useful treatment modalities for this type of incontinence (2).

Hutchinson et al. suggested that caregivers of patients with Alzheimer’s disease should study toileting behaviours. This would permit them to provide physical and cognitive assistance while attempting to avoid accidents and catastrophic events (29). The conservative treatment should be tailored to individual patient needs and disease status, taking into account factors like mobility, cognitive function and general medical condition (30). It has been demonstrated that prompted voiding decreases incontinence episodes in the short-term (31).

Medical treatment
First-line treatment for symptoms of the overactive bladder comprises behavioural therapy and antimuscarinics (2). The ability of antimuscarinics to cross the blood–brain barrier and to be bound to the M1-receptors in the brain varies, for example, permeates the blood–brain barrier with relative ease and also binds to the M1-receptors. A
placebo-controlled study documented the deterioration of short-term memory, in an amount that corresponds to brain ageing over 10 years, when 10mg of oxybutynin ER was taken during 3 weeks (32). Tropium chloride, however, is relatively impermeable to the healthy blood–brain barrier, as demonstrated by Staskin et al. in a group of healthy people above the age of 70 (33). Darifenacin and solifenacin do cross the blood–brain barrier, but are less bound to M1-receptors, and therefore is associated with fewer CNS side effects than could be expected (2). Propiverine crosses the blood–brain barrier only to a minor extent (34). However it must be remembered that evidence supporting these considerations in clinical practice is limited (35) and caution is advised when using an antimuscarinic agent in the susceptible neurological patient.

In general, antimuscarinic-induced cognitive impairment is considered reversible on discontinuation of antimuscarinic therapy. However, a few studies suggest that use of medications with anticholinergic properties, such as antimuscarinics for the bladder, may be associated with an increased risk for dementia (36).

CNS side effects of antimuscarinics become crucial when they are prescribed to dementia patients already on acetylcholinesterase-inhibitors (AChEI). These medications are usually prescribed as first-line treatment to arrest cognitive impairment in conditions such as Alzheimer’s disease, vascular dementia and dementia with Lewy Bodies. There is evidence to suggest that AChEIs may influence LUT functions, and Starr et al. reported that rivastigmine and donepezil (cholinesterase inhibitors) may worsen urinary incontinence in Alzheimer’s disease (37).

Conclusions
Different types of dementia cause LUTS at differing time points of the disease and need different therapeutic approaches. The degree of incontinence is strongly associated with patient’s general status and ambulation. Although LUTS are highly prevalent in dementia patients, high-quality data to guide the choice of treatment strategies in this population are lacking. The extensive and aggressive therapy of LUTS should be reserved for those with good general status and ambulation. Behavioural therapy, including toilet training and prompted voiding, may be especially useful in patients with unawareness UI. The use of antimuscarinics that do not easily cross the blood–brain barrier or are more M2/M3 selective seems to be a rationale approach. On the other hand, current evidence suggests that antimuscarinics, especially oxybutynin, can be associated with cognitive worsening, due to antagonist effects at the M1 receptors of the brain. There are no studies on the use of beta-3 agonists for dementia patients so far. The extensive and aggressive therapy of incontinence in dementia patients should be reserved for patients with good general status and ambulation.
References


Introduction

Multiple sclerosis (MS) is a progressive, demyelinating disease of the central nervous system. Primarily, the disease affects adults aged between 20 to 50 years with a twofold higher incidence in women than men. The demyelinating process most commonly involves the lateral corticospinal (pyramidal) and reticulospinal columns of the cervical spinal cord, and it is thus not surprising that lower urinary tract dysfunction and sphincter dysfunction are so common. MS causes lower urinary tract symptoms (LUTS) in 34-99% of the patients in the course of the disease [1-3]. This incidence is related to the disability status and has a major impact on quality of life [3, 4].

Assessment

LUTS in MS patients may constitute the sole initial complaint or may be part of the presenting symptom complex in up to 15% of patients. Patients presenting acute urinary retention of unknown cause or an acute onset of urgency and frequency, MS diagnosis should be suspected [5].

As the neurological condition progresses, the bladder dysfunction can become more
difficult to treat. This may be attributed to worsening of detrusor overactivity, inefficient emptying of the bladder in the context of worsening paraparesis, recurrent urinary tract infections, spasticity, reduction in general mobility, and sometimes cognitive impairment. In contrast to neurogenic lower urinary tract dysfunction following traumatic spinal cord injury, multiple sclerosis less frequently causes upper urinary tract damage [6]. However, this also may change with disease progression [7].

Generally, the following aspects should be considered in the assessment of LUTS and their underlying dysfunction in MS patients:

- The most frequent LUTS caused by MS are:
- Storage symptoms – frequency/urgency (32% to 99%) and incontinence (19% to 80%) [1]
- Voiding symptoms – incomplete bladder emptying / urinary retention in 8% to 74% [1]
- LUTS may be present before MS diagnosis
- LUTS severity often correlate with the degree of spinal cord involvement and, hence, the patient’s general level of disability
- LUTS may worsen, since a relapsing and remitting, or more commonly progressive, clinical course is a characteristic of MS

Clinical and work-up evaluation

Besides LUTS, clinical history should include bowel symptoms, sexual function, comorbidities and use of prescription and other medication and therapies.

Factors such as mobility, hand function, cognitive function, social support and lifestyle should be evaluated since they will affect how LUTS can be managed.

1. Physical examination:
- Abdominal and external genitalia examinations should be performed routinely.
- Light touch and pinprick sensibility test of the S2-S5 dermatomes provides information on the integrity of pelvic afferents travelling through the posterior columns and spinothalamic tract, respectively.
- The digital rectal examination provides next to information on prostate size and texture in men also important information on anal sphincter tone, voluntary anal sphincter contractility, and integrity of the bulbocavernosus reflex (anal sphincter contraction in response to squeezing the glans penis or clitoris). Spasticity of the pelvic floor was present in all patients with striated sphincter dyssynergia but in none with detrusor overactivity alone. Although sphincteric flaccidity is relatively rare and occurs in fewer than 15% of patients [8], it could contribute to and predispose patients to stress urinary incontinence.
- A vaginal examination if clinically indicated (for example, to look for evidence of pelvic floor prolapse).

2. Urine analysis:
- If the result and patient’s symptoms suggest an infection, antibiotic treatment is recommended. Be aware about bacterial colonization. Do not treat asymptomatic bacteriuria!

3. Bladder diary
- It is an important assessment and follow-up tool particularly for patients with predominance of storage symptoms
4. **Post-void residual urine evaluation (sonography)**
   - Consider taking several measurements on different occasions to establish how bladder emptying varies at different times and in different circumstances.

5. **Urinary flowmetry (incl. post-void residual volume measurement)**
   - It is an easy and useful screening and follow-up tool of flow rate, flow pattern, and completeness of micturition in patients who are able to void voluntarily.

6. **Renal ultrasound scan:**
   - Renal ultrasound is a non-invasive examination that provides useful information regarding the integrity of the upper urinary tract. It must be carried out periodically (annually).

7. **Filling cystometry:**
   - Filling cystometry is the most comprehensive neuro-urological examination to assess and describe LUT (dys)function. It requires a specialized education and training to provide qualitative and reliable measurements and analysis.
   - Most patients with MS may have a low risk for upper urinary tract complications and therefore evaluation using filling cystometry is not routinely recommended. However, abnormal urodynamic findings are common (table 1) even in asymptomatic patients. Hence, based on the principle that adequate diagnosis should precede treatment, filling cystometry should be indicated at least for patients with LUTS refractory to clinical treatment approach, for those with urinary tract complications and also before performing surgical treatments for lower urinary tract dysfunction.
   - The most common cystometrical finding in patients with MS is detrusor overactivity (Table 1). This is commonly complicated by striated sphincter dyssynergia, with varying sequelae based on the patient’s ability to empty completely at acceptable voiding pressures.
   - The most important parameters predisposing patients with MS to significant urologic complications are striated sphincter dyssynergia in men, high detrusor storage pressure and an indwelling catheter.

<table>
<thead>
<tr>
<th>CYSTOMETRIC FINDING</th>
<th>INCIDENCE IN PATIENTS WITH MS [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor overactivity</td>
<td>43 - 99</td>
</tr>
<tr>
<td>Detrusor sphincter dyssynergia</td>
<td>5 - 83</td>
</tr>
<tr>
<td>Detrusor underactivity</td>
<td>0 - 40</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
</tr>
</tbody>
</table>

*MS (multiple sclerosis)*

**Management**

There are some useful national consensus statements available. However, they differ in some aspects, especially regarding diagnosis and follow-up.

Since the underlying neurological disease is not yet curable, the current management of lower urinary tract dysfunction is most commonly predicated on symptomatic and urodynamic findings.
First-line treatments

The treatment regimens used are: behavioral therapy, medications alone, antimuscarinic agents to decrease detrusor overactivity plus intermittent self-catheterization (ISC), ISC alone.

1. Behavioral / Physiotherapeutical approach

Bladder reeducation and pelvic floor exercises can demonstrate benefit with substantial improvements in quality-of-life [9, 10].

2. Antimuscarinics

- Despite the low evidence for the use in MS patients [11], antimuscarinic drugs have been generally demonstrated effective in neurogenic detrusor overactivity [12].
- Offer antimuscarinic drugs to patients with symptoms of an overactive bladder such as increased frequency, urgency, urge incontinence and for those with cystometric evaluation showing detrusor overactivity.
- Consider to measure postvoid residual urine (PVR) volume in people who are not using ISC before and after starting antimuscarinic treatment. This is particularly important if the patient’s symptoms indicate that there is a component of incomplete voiding (Figure 1).
- Antimuscarinics known to cross the blood-brain barrier (for example oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion).
- Antimuscarinic drugs can induce or worsen constipation.
- Fatigue syndrome is a common in MS patients and may become aggravated with antimuscarinic drugs.
- The licensed antimuscarinic agents in Brazil are oxybutynin, tolterodine, solifenacin and darifenacine.

3. Desmopressin

- Desmopressin suppresses diuresis and may be an option to treat nocturia in MS patients with normal or high bladder capacity [13].

4. Intermittent self-catheterization

- ISC is advocated for patients who have a post voided residual volume of over 100 ml. The frequency of ISC may be adapted to the extent of post void residual volume. Sometimes ISC alone may eliminate all symptoms due to retrieval of the full bladder capacity. If symptoms such as frequency or urgency persists, and/or cystometry reveals detrusor overactivity, antimuscarinic agents should be added (Figure 1).
- The effective measure to improve bladder emptying is trough ISC. There have been claims that α-blockers can reduce PVR volumes [14]. However, the clinical impression that α-blockers are effective in individual patients is not strong, possibly because incomplete bladder emptying in patients with MS is thought to be the result of a combination of poorly sustained and ill-coordinated detrusor contractions, or of an inappropriate contraction of the striated urethral sphincter, a dysfunction on which α-blockers are thought to be ineffective [15].

Second-line treatments

For patients refractory to first-line treatment, second-line treatments become necessary (Figure 2):
1. **Botulinum toxin type A**
   - There is a significant improvement of LUTS in MS patients after intradetrusor injections of botulinum toxin A [16, 17]. The dose of botulinum toxin A commonly used to treat neurogenic detrusor overactivity in patients with multiple sclerosis is 200 units [18]. Lower doses can be preferred in selected patients [19]. To be considered eligible for treatment, all patients should accept and be instructed to perform ISC, since the risk of increased post-void residual volume and/or urinary retention after botulinum toxin A injection is high, especially with 200 units. There are insufficient data on the risk of symptomatic urinary tract infections after botulinum toxin A intradetrusor injections with or without prior antibiotic prophylaxis. One study reported in 7% of patients without prior antibiotic prophylaxis a post-interventional symptomatic urinary tract infection [20]. The according conclusion that this result favours antibiotic prophylaxis is highly questionable as 93% of patients would have been unnecessarily treated with an antibiotic.

2. **Percutaneous / transcutaneous tibial nerve stimulation (PTNS / TTNS)**
   - It is a form of neuromodulation at which electrical current is intermittently applied to the tibial nerve near the ankle either by using an acupuncture needle (PTNS) or an surface electrode (TTNS). The tibial nerve derives inter alia from S3 roots that also contain the nerves controlling the detrusor and perineal floor.
   - This technique has the advantage, versus traditional sacral root neuromodulation, to be less invasive.
   - The results of PTNS are obtained only after several stimulation sessions.
   - Protocol with 12 consecutive weekly sessions seems to be effective and leads to a persistent improvement [21-23].

3. **Sacral neuromodulation**
   - Sacral neuromodulation (SNM) is well established in the treatment of refractory, non-neurogenic lower urinary tract dysfunction, and has been explored also for lower urinary tract dysfunction of neurological etiology during recent years. However, the evidence is still limited as the first randomized controlled trial is still pending [24, 25]. So far, the results of recent cohort studies suggest that SNM is an effective and safe treatment option for LUTS in MS patients [26-28]. Further and larger studies as well as randomized controlled trials are needed to confirm its clinical role in patients with MS.

**Tertiary treatments**

**Urinary diversion**

As a last resort, if all treatments failed to adequately treat symptoms and/or prevent upper urinary tract deterioration, surgical options such as augmentation cystoplasty, catheterisable pouch, and ileal conduit may be necessary [29, 30]. Catheterizable, continent solutions make sense only if ISC can be reliably performed within the next years.
**Follow-up**

Irrespective of the selected treatment or management of LUTS in MS patients, regular follow-up is mandatory because the underlying LUT dysfunction can deteriorate, particularly in chronic progressive diseases such as MS. Certainly, follow-up is indicated when symptoms become worse or the treatment/management needed to be changed. Patients with treatments aiming at the reduction of detrusor storage pressures should not only be followed-up clinically but also urodynamically to effectively evaluate the effect of the treatment on the detrusor pressure. A fixed follow-up interval is not defined but should be adjusted to the risk profile of the individual patient. That means, that patients with a high risk profile for further deterioration of lower and upper urinary tract function (e.g. detrusor overactivity +/- detrusor-sphincter-dyssynergia, LUTS refractory to treatment, recurrent symptomatic urinary tract infection, known vesicoureteral reflux, renal impairment) should be followed-up more regularly and intensively, i.e. at least once per year using (video-)urodynamics.

*Figure 1*


*PVR (postvoid residual urine); CISC (clean intermittent self-catheterization)*
Secondary and tertiary interventions for the MS patient with refractory urinary symptoms

- Botulinum toxin
  - 200-unit detrusor
  - 100-unit external sphincter
- Suprapubic tube
  - Changed monthly
- Bladder neck closure
  - Chronically debilitated
  - 100-mL bladder capacity
- Urinary diversion

Interventions for selected MS patients
- Ileovesicostomy
- Enterocystoplasty

Secondary and tertiary treatments for multiple sclerosis patients with urinary symptoms.
Tracey JMT, Stoffel JT1.
References


8. BRAIN STROKE

Authors: Luis Augusto Seabra Rios, Jalesh Panicker

Epidemiological Data

Stroke is the third leading cause for death in the Western world, after myocardial infarction and cancer. They occur more frequently in people older than 65 years, and the survival rate after 5 years is 56% in men and 64% in women.

Lower urinary tract symptoms are common following stroke. Twenty to 50% of stroke patients present with urinary symptoms including urinary incontinence. The symptoms are more common in the early phase of stroke. In an epidemiological study, Nagayama and colleagues reported that more than 50% of stroke patients presented with urinary symptoms three months after the beginning of the disease, and urinary incontinence persisted in 20 to 30% after six months (1).

At the time of maximum symptoms from stroke, 46% of women and 37.3% of men present with urinary incontinence (2). The presence of symptoms seems to be a powerful prognostic factor and those with urinary incontinence seven days following stroke have lower survival and lower recovery of functional independence in mid-term and late follow up (3,4).

Loss of bladder sensitivity is also a prognostic factor of severity, since patients with urinary incontinence and absence of bladder sensations fare worse than those with incontinence and maintenance of bladder perception of feeling and voiding desire (5).

Physiopathology and Topographic Correlation of Urinary Symptoms

Based on the knowledge of urinary neurophysiology and clinical studies that evaluated urodynamic findings in patients with stroke, the main cause of urinary symptoms is detrusor overactivity. These same studies showed that voiding reflex in these patients, although dysfunctional and premature, is coordinated; detrusor-sphincteric dyssynergia (DSD) is rare. DSD is common in suprasacral spinal cord lesions due to interruption of fibers that connect
the spinal cord center (S2-S4) to mesencephalic and pontine centers that control voiding and urinary continence. Therefore, supra-pontine ischemic lesions do not cause severe DSD as in spinal trauma and patients with spinal diseases.

Topography of cerebral lesion is relevant, though there is no consensus of severity of urinary symptoms and side of affected hemisphere. It was speculated that lesions of right cerebral hemisphere or dominant hemisphere has higher incidence of urinary incontinence; however, Sakakibara and colleagues could not confirm this finding in a study that evaluated patients with stroke using computer tomography and magnetic resonance imaging. They concluded that regardless of the side of cerebral lesion, those that affect anterior regions (antero-medial frontal lobe), their descending pathways and base ganglia, are the main sites responsible for urinary dysfunction in stroke patients (6-8).

Ischemic lesions of cerebral brainstem in general are associated with more voiding symptoms and urinary retention than lesions of frontal and temporal lobes. A study evaluated urinary symptoms of 39 patients with brainstem stroke showed that 50% presented urinary symptoms: nocturia and voiding symptoms in 20%, urinary retention in 21% and urinary incontinence in only 8% of patients (9).

Urinary incontinence following acute stroke is caused by failure of central inhibitory mechanisms that affect urinary control centers located at the brainstem and spinal cord. The main lesions responsible for bladder dysfunction following cerebral ischemia are lesions of the antero-medial portion of frontal lobe, their descending pathways and basal ganglia. However, alteration of bladder sensitivity and perception of bladder filling may cause urinary symptoms and urinary incontinence in patients with cerebral ischemia. Those who lost bladder sensitivity in general show more lesions of the parietal lobe compared to frontal lobe.

**Clinical Evaluation**

After acute stroke, the most common urinary symptoms are nocturia and urinary incontinence. Sakakibara observed a 53% rate of urinary complaints after three months of stroke in 72 patients followed up since the beginning of the disease. Nocturia was the most common symptom in this group of patients (36%), and urgency-incontinence occurred in 29% and voiding symptoms in 25%. Urinary retention was observed in 6% of patients in the acute phase (8).

Due to the occurrence of the above symptoms, it is important to perform a detailed urinary history as well as physical and neuro-urologic exams. Presence of palpable bladder suggests urinary retention. Rectal exam must be performed to verify prostate volume and stool impaction. Neuro-urological exam must evaluate anal tone, voluntary contraction of anal sphincter and bulbo-cavernous reflex.

Urinary sediment exam, urinary culture and post-voiding residual urine measurement are fundamental exams to be performed before treatment.

**Treatment**

Treatment must be adapted according to the phase of stroke. During the acute phase, the management plan must be formulated according to the clinical status of patient. In general, it is recommended to introduce a bladder catheter or cystotomy in the intensive unit care until the general and neurological status has stabilized to deviate urinary flow and to control diuresis and fluid balance; after this phase, patients with incomplete bladder emptying or high post-void residuals should undergo intermittent bladder catheterization. Those who become incontinent after catheter removal without high post-void residual urine...
should use containment appliances such as diapers or penile sheath until clinical status allows for hospital discharge.

Once neurological and clinical conditions have stabilized, specific urological diagnosis can be established. Clinical and physical exam findings, voiding diary and urodynamic study will characterize the urological disease.

Patients with persistent urinary retention, those with high post-void residual urine volume and with urine loss due to overflow must maintain intermittent bladder catheterization. Urodynamic evaluation is fundamental in this group of patients, since it will allow differentiation of neurogenic detrusor underactivity and bladder neck obstruction. In the last group, treatment of obstruction should be considered.

Patients with symptoms mainly of bladder filling (frequency, urgency, urgency-incontinence, nocturia), that usually at urodynamic evaluation show detrusor overactivity, must be treated with voiding reeducation techniques, physiotherapy (electro-stimulation and biofeedback) and anti-muscarinic drugs. It is important to observe that antimuscarinic drugs are potentially harmful for cognition, in particular of elderly, fragile patients with cognitive impairment; they must be used cautiously and preferably drugs with lower permeability of blood-brain barrier should be used (trospium, propiverin and darifenacin).

Recently, the use of beta-3-adrenergics (mirabegron) has become available among to treat detrusor overactivity. Although the effect on patients with neurogenic urinary symptoms is not well studied, this drug may be an attractive therapeutic option due to its low side-effects.

Nocturia, the most frequent symptom in patients with stroke, must be carefully evaluated by voiding diaries, to verify the presence of nocturnal polyuria. Patients with that disorder may benefit with the use of vasopressin analogues (DDAVP) to reestablish the circadian cycle of urinary production.

In patients with detrusor overactivity that do not respond to anti-muscarinic drugs, a safe and effective alternative is bladder injections of botulinum toxin. Several studies and systematic reviews have been published in the last years confirming the efficacy of botulinum toxin in the treatment of neurogenic detrusor overactivity. A high percentage of patients show clinical and urodynamic benefits with this treatment. The effect lasts variably and there are reports in literature ranging from 6 to 16 months, depending on the dose. In general, recommended doses to treat neurogenic bladder dysfunction are 200 to 300 units. In a study of patients with neurogenic bladder, those due to stroke had inferior results than those with spinal trauma. However, botulinum toxin may increase post-void residual urine or cause urinary retention, in particular obstructed patients. For this reason, patients must be informed about side effects and the eventual need of intermittent bladder catheterization.

Sacral neuromodulation has been used in patients with non-neurogenic overactive bladder that do not respond to clinical treatment. In patients with neurological disease, scientific evidence is scarce and its use is off-label in well-selected patients.

Males with prostatic obstruction that suffer acute stroke must be carefully evaluated. It is known that patients with low bladder capacity and inability to contract the pelvic floor voluntarily have higher risk for developing urinary incontinence following procedures to overcome obstruction. In this group of patients, neuro-urological exam and urodynamic exam will decisively evaluate detrusor function and confirm and quantify infra-vesical obstruction.
References


Peripheral neuropathies (PN) is a medical condition that affects peripheral nerves therefore distal to the spinal cord. Motor, sensitive, or both nerves could be affected. There are several causes PN with different natural history and prognosis. PN disorders can result in voiding, bowel, and sexual impairment. Processes that affect or interrupt the peripheral reflex arc (coordination among spine, bladder, and urethra) may cause storage or emptying dysfunctions that resemble those seen after distal spinal cord or nerve root injury. Detrusor acontractility often develops, and low compliance may result. The smooth sphincter may be relatively incompetent, and the striated sphincter may exhibit fixed residual tone that does not voluntarily relax.

To become more didactic this chapter, we will discuss in section the most common causes of PN related to voiding dysfunction.

**Diabetes Cystopathy**

As soon as the reader think in an association of voiding dysfunction and peripheral neuropathies immediately emerge in your mind diabetic cystopathy (DC). Indeed, there is a high prevalence of lower urinary tract symptoms (LUTS) in patients with diabetes mellitus (DM). DM is the most common cause of peripheral neuropathy in Americas and Europe. DC is considered as a part of spectrum of autonomic disturbances associated with DM together with gastroesophageal hypotonia, hyperhidrosis, erectile dysfunction, and autonomous cardiac abnormalities (1). Presence of peripheral neuropathy in patients with DM has a high prevalence of abnormalities in the lower urinary tract (LUT) during a urodynamic study, even in absence of LUTS.

Classically voiding dysfunction associated to DC first affects sensorial afferent pathways, which result in impaired bladder sensation (2). There are several factors that could contribute to sensorial impact including ischemia, altered glucose metabolism, and/or free radical formation. Therefore, the classic described urodynamic findings were impaired blad-
sensation, increased cystometric bladder capacity, and increased residual urine. Currently, there are evidences that both sensorial and motor neuropathies are involved in the pathogenesis of LUT dysfunction in those patients with DM. A great numbers of animal studies have been done to evaluate the impact of DM in the LUT. Based on these studies, the pathophysiology of DM can be attributed to overexpression of muscarinic receptor (M₂), direct neural damage, microvascular disease which inducing endothelial dysfunction and nitric oxide release, increased reactive oxygen species, production of diacylglycerol causing activation of protein kinase C, and decreased in neuronal growth factor (NGF). All the factor can contribute to neuronal and muscular impairment observed in DC. Because different animal's models showed different partners, translational research are still necessary.

Some authors have reported that urodynamic findings seen in classic DC not represent the prevalent form of voiding disorders seen in patients with DM. The classic DC described as a sensory deficit occurs in only 35% of patients in a series of cases. The main key point that reader should know at this moment is that DC is not a stable disease at timeline. Indeed, early DM affect sensory afferent pathways of the bladder compromising sensation. As the injury continues, a gradual increase in the time interval between micturition results. If the process does not stop, overdetrusor distension occur resulting finally in detrusor smooth muscle (DSM) impairment at end point in the timeline. More recently, detrusor overactivity (DO) has been cited as the more frequent urodynamic finding. It has been hypothesized that initially osmotic diuresis induced by hyperglycemia causes bladder wall stretching, which with increased intravesical pressure results in compensatory bladder hypertrophy. This stage would correspond clinically to storage symptoms early in the disease time course.

In one study 182 patients with DM were evaluated with urodynamic study (UDS). Of the 182 patients 100 (55%) had DO, 42 (23%) had impaired detrusor contractility, 20 (11%) had indeterminate findings, 19 (10%) had detrusor underactivity and 1 (1%) was normal. Bladder outlet obstruction (BOO) occurred in 66 patients (36%), all men (57%) (3). Besides proper consequences of DM, presence of comorbidities such BOO or cerebrovascular disease could also result in DO that has been shown in UDS.

**Lumbar disk**

Voiding dysfunction is a well known complication of lumbar disk disease. The true incidence of voiding dysfunction is not known. In a review of the literature the incidence ranged from 27% to 92%.

Before address the pathophysiology, it is very important understand neuroanatomy of distal end of spinal cord and your nerves roots. In the adult, the sacral segments of the spinal cord are at the level of the first and second lumber vertebral bodies. This distal end of the spinal cord is commonly called the conus medullaris. The spinal cord segments are named for the vertebral body at which the nerve roots exit the spinal canal. Thus, although the first sacral segment of the spinal cord is located at L1, its nerve roots run in the subarachnoid space posterior to the vertebral bodies L2–L5 until they reach the first sacral vertebral body, at which point they exit the canal. Therefore, all the sacral nerves which originate at the L1 and L2 levels run posterior to the lumbar vertebral bodies until they reach their appropriate site of exit from the spinal canal. This group of nerves running at the distal end of the spinal cord is commonly referred to as the cauda equine. The most frequent sites of lumbar disc prolapse are the L4/5 and L5/S1. As only in 1-15% of lumbar disc prolapse are central, just in few cases compression of spinal roots may occur. Most frequently prolapses of lumbar disc are posterolateral and did not cause compression of cauda equine. Exceptionally a large
posterolateral prolapse may migrate medially also causing compression of spinal roots. Besides direct compression, a prolapsing disc can also affect the sacral nerves by interfering with blood flow to and from the cauda equina.

Compression of lumbar nerves branches involved in parasympathetic excitatory input of detrusor, sympathetic somatic input to striated muscular sphincter and pelvic floor afferent sensitive nerves, and sensorial nerves result in detrusor acontractility with impaired sensation. Therefore, the most common presentation of voiding dysfunction in patients with lumbar disc prolapse is detrusor acontractility with impaired sensation. Although, urinary symptoms are only one aspect of cauda equina syndrome. Classically, saddle anesthesia, bilateral sciatica, lower back pain and, in men, erectile dysfunction are also present in cauda equina syndrome. DO is observed in some patients with lumbar disc prolapse. DO has been attributed to progressive compression with consequent irritation of the nerve roots.

Therefore, the clinical presentation depends on the extent of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract. Clinically, the patient describes pain in the lower back, radiating in a girdle-like fashion along the lumbar dermatome involved; physical examination may reveal reflex and sensory changes consistent with nerve root compression. LUTS, when present, are emptying in nature and include compromised urinary flow rate, interrupted stream due to abnormal straining to void, residual urine, and incontinence. The voiding symptoms are secondary to the degree of injury to the autonomic parasympathetic nervous input to the lower urinary tract.

The most characteristic findings on physical examination are sensory loss in the perineum or perianal area (associated with the S2–4 dermatomes), sensory loss on the lateral foot (S1–2 dermatomes), or both. The bulbocavernosus reflex (BCR) should be checked because it reflects pudendal (somatic) nerve function. This reflex is absent in all patients with complete lower motor neuron lesions of the sacral cord. To evaluate patients a cystometrogram (CMG) with simultaneous pelvic floor electromyography (EMG) is sufficient for urodynamic investigation, and the predominant finding is usually detrusor acontractility with or without sphincter neuropathy. In cases of incomplete injury, the somatic innervation remains intact and the external urethral sphincter may be unable to relax when the patient force to void. Suspicion of lumbar disc disease should be evaluated with magnetic resonance.

Primary treatment evolve correction of underlying cause (disk disease) and usually require a laminectomy. Although, in some instances LUTS may not improve after laminectomy. In author opinion, it is strong recommended that every patient with lumbar disc prolapse should be evaluated with UDS prior to submitted to laminectomy. It may be difficult postoperatively to separate causation of voiding dysfunction resulting from the disk sequelae from changes secondary to the surgery. The medicolegal implications of a PR surgical and postsurgical
urodynamic evaluation are obvious. Additionally, the sequelae of laminectomy, such as spinal stenosis or orchiditis, can also affect bladder function. In one study two UDS test was done. The authors find that 68.4% of 143 patients preoperatively already had abnormal test been sensorial impairment and detrusor underactivity the most common findings. It was concluded by the authors due to high prevalence of abnormal UDS preoperatively documentation of voiding function to compare with postoperative findings is recommended (6).

Urologic approach depends of bladder compliance, urethral sphincters, and upper urinary condition. If bladder compliance is adequate, a trial of cholinergic stimulation with bethanechol chloride alone (50 mg up to four times daily) or in combination with metaclopramide (5–10 mg up to four times daily) may be given, but should not be continued if no significant response is achieved by the time medication has been prescribed for a month. decreased compliance with a concomitant fixed outlet resistance can impair ureteral function and place the upper tracts at risk. In these patients, a regimen of anticholinergic medications, usually combined with self-catheterization, should be utilized. When this is unsuccessful bladder augmentation may be necessary to lower detrusor pressure and protect the upper urinary tracts. Emptying, again, is by self-catheterization. When incontinence results from poor sphincter function, the options are similar to those for any woman with intrinsic sphincter dysfunction: anti-incontinence treatment.

**Radical Pelvic Surgery**

The inferior hypogastric plexus (pelvic plexus) which innervates the viscera of the pelvic cavity is a paired structure located on the side of the rectum in males and at the sides of the rectum and vagina in females. LUT dysfunction after pelvic plexus injury occurs most commonly after abdominoperineal resection (APR) and radical hysterectomy.

APR to treat colorectal neoplasias has the higher incidence of voiding dysfunction 50% compared to low anterior resection (LAN) 15-25%. Over the years, technical modifications have allowed surgeons to achieve oncologic control while preserving the autonomic nerves that innervate the bladder and genitalia. Colorectal surgeons performing a total mesorectal excision with autonomic nerve preservation enables both local tumor control and preservation of autonomic nerves involved in urinary and sexual function. As result, the new trends in treatment of rectal carcinoma is decrease number of APR with consequent increase in number of LAN nerve sparing surgery. Although locally advanced tumors and neoadjuvant chemotherapy and radiation can make identification of the autonomic nerves and plexus more difficult. The most common sequela from autonomic nerve damage during surgery of the colon and rectum is detrusor denervation (parasympathetic), resulting in impaired contractility of the bladder. Although the initial presentation is likely as a failure to empty, the most serious complications are abnormalities in urinary storage, which may lead to small capacity, poorly compliant, high-pressure bladders. In some patients with denervation injury, return of normal bladder function may not occur, and patients may persist with decentralized, non-compliant bladders with high storage pressures. Left unmanaged, these storage alterations can lead to deleterious changes in upper urinary tract function. This may predispose to hydronephrosis, urinary reflux, pyelonephritis, and declining renal function. Thus, all patients with abnormal bladder function should undergo a UDS to rule out the development of a non-compliant, high-pressure storage bladder. Patients with urinary retention after colorectal surgery are encouraged to perform clean intermittent catheterization (CIC). As patients remain unable to void with high residual volume, they are evaluated with UDS at approximately 2 to 3 months postoperatively. Patients with poor bladder compliance can be treated with a combination of medications and surgery. In the postoperative setting,
these patients may present after extensive, partial bladder resection from their extirpative procedure or because of neurogenic impairment. The use of anticholinergic medications can decrease the pressures within the bladder during storage as well as marginally increase bladder volumes. In that cases which anticholinergics do not improve bladder compliance, botulinum toxin injection into detrusor may be a second line option. If previous therapies fail a major bladder reconstructive procedures like bladder augmentation. The principal aim of all modalities of treatment is preserve upper urinary tract function.

Voiding dysfunction represents the most common complication after radical pelvic surgery for gynecologic cancers. However, the true incidence is not known because of lack of standardization of definitions and because of different techniques of surgeries which are not comparable. So, the incidence varies among different studies from 8 to 80%. Pre-operative and postoperative complete urodynamic explorations are necessary to evaluate the incidence of voiding dysfunction related to surgery because up to 80% of patients already complains about LUTS before the surgery. It is important discuss the mechanism of neurological injury that may occur during the treatment of gynecology cancer. The injury could be a temporary blockade of signal transmission without axon lesion (neurapraxia) with functional disorders resolving hours to weeks following surgery, transection of the axon with intact nerve sheets (axonotmesis) allowing regeneration at the site of the injury and distal to the injury with a nerve growth velocity varying from 0.25 mm/day to 4 mm/day or a complete transection of the nerves including their sheets is also possible with no potential to regenerate. However, injury to vascular supply of the pelvic never may be more important that the injury of themselves. e combination of stretch and ischemia makes the nerve more vulnerable to injury. Voiding dysfunction could also be result from direct surgical injury to the bladder wall, lymph stasis, interruption of the blood supply, and fibrosis of the urethra. Stress urinary incontinence (SUI) and storage and/or empty LUTS increased significantly following radical pelvic surgery. Early voiding dysfunction is characterized by decreased bladder capacity, detrusor underactivity, and diminished bladder sensation which may require urethral catheterization. Late voiding dysfunction usually reveals hesitation with abdominal straining, decreased bladder compliance, detrusor overactivity, and urinary incontinence. In one literature review it was observed that the overall incidence of urodynamic voiding dysfunction after radical hysterectomy was 72%. In the early postoperative period, low compliance is found in 24.4% (range: 18%–73%) of cases, mixed urinary incontinence in 24.5% (range: 11%–50%), and SUI in 40% (range: 11%–81%). However, following the patients for a period superior than 12 months, the above mentioned rates are reduced to 35%, 17%, and 38%, respectively, and ≥16% of women experience voiding dysfunction severe enough to seek medical care. Bladder dysfunction may be due to the unmasking of intrinsic detrusor activity, characterized by loss of β-adrenergic innervations with subsequent α-adrenergic hyperinnervation, or due to the impact of residual sympathetic innervations. In fact, the significant decrease of the maximal urethral closure pressure encountered in the early postoperative period could be attributed to the damage of the pelvic plexus and pudendal nerves with loss of perirethral tone. The loss of sympathetic adrenergic stimulation may have an excitatory effect on parasympathetic transmission to the detrusor muscle during urine storage and may lead to permanent relaxation of the bladder neck and the proximal urethra. These alterations could contribute to the characterization of urinary stress incontinence and detrusor overactivity and incontinence after radical pelvic surgery. Spontaneous recovery of bladder function is generally to be expected within 6–12 months after surgery. The mechanisms of spontaneous recovery are complicated. It could be attributed to plasticity reorganization which occurs at multiple levels in the central and peripheral nervous system in response to peripheral injuries.
Referências


Introduction

The reduction in overall birth and mortality rates as well as the increase in life expectancy has led to the rapid aging of the population in developed countries contributing to increased number of people with age-related diseases.

Urinary incontinence (UI) is one of the most common urologic conditions in the elderly population and should not be considered as normal or an inevitable part of the aging process. It is commonly associated with underlying medical conditions or other factors rather than chronologic age itself.

The prevalence of UI increases with age. In women; moderate to severe UI affects 7% between 20 to 39yr of age, 17% between 40 to 59yr of age, 23% between 60 to 79yr of age, and 32% above 80yr of age. The prevalence in men is approximately one third of that in women until it gets equalized in the ninth decade. Nursing home residents have especially high rates of UI, ranging from 60 to 78% in women and 45 to 72% in men [1].

UI has a substantial negative impact on the healthcare of the elderly population. The primary impact is on quality of life, including self-concept and self-esteem, besides negative effect on daily activities such as work, travel, social interaction, physical activity, sexual function, and sleep [2]. Chronic incontinence can also be associated with skin irritation, development or worsening of pressure ulcers, urinary tract infections, falls and fractures and impairment of mental health, including increased rates of depression [3]. Furthermore, UI may result in increased dependence on caregiver assistance and a need for nursing home placement [4].

Urinary incontinence as a geriatric syndrome

The understanding and treatment of UI in the frail elderly population require a broader consideration of the “disease” concept that focuses on patient-level factors and should not be considered as an isolated bladder, bowel and/or neurogenic dysfunction. From a clinical perspective, UI can be considered both a specific diagnosis and a geriatric syndrome, as many of its risk factors are not directly related to the genitourinary tract [5-7]. Geriatric syndromes have been defined as “multifactorial health conditions that occur when accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges” [5]. Examples of geriatric syndromes include, besides UI, frailty, falls, pressure ulcers, polypharmacy and delirium.
Different syndromes can interact and influence one another. For example, frailty is linked to falls and both conditions are closely associated with UI. Each of these syndromes can have direct and indirect effects on urologic health in older adults [8].

Therefore, assessment of frail people requires a wide scope. Failure to address the multifactorial nature of disease and treatment limits not only clinical care but also important opportunities to improve function and quality of life [9]. Successful prevention or treatment often requires a multidisciplinary approach, and must address many associated factors and impairments shared with other geriatric syndromes.

### Age-related changes and lower urinary tract

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<td>Increase night-time urine production</td>
<td>Nocturia and night-time UI</td>
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</tbody>
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Table 1: Age-related changes in the urinary tract and the associated consequences that may affect urinary continence.
Other factors causing or contributing to urinary incontinence [10]

### a. Medications / Polypharmacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential effects on continence</th>
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<td>Alpha-adrenergic agonists</td>
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<td>Alpha-adrenergic antagonists</td>
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<tr>
<td>Anticholinergics</td>
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</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Impaired bladder emptying, urinary retention and constipation all of which can contribute to UI&lt;br&gt;Dependent edema which can contribute to nocturnal polyuria</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Increased bladder contractility&lt;br&gt;Precipitate urgency UI</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Increased diuresis&lt;br&gt;Precipitate UI</td>
</tr>
<tr>
<td>Lithium</td>
<td>Polyuria as a result of nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Urinary retention, constipation, confusion and immobility all of which can contribute to UI</td>
</tr>
<tr>
<td><strong>Psychotropic drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>Confusion and impaired mobility&lt;br&gt;Precipitate UI&lt;br&gt;Anticholinergic effects</td>
</tr>
<tr>
<td>Hypnotics</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Histamine-1 receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin re-uptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>Increased cholinergic transmission&lt;br&gt;Precipitate UI</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Edema which can lead to nocturnal polyuria, nocturia and UI</td>
</tr>
<tr>
<td>Glitazones</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory agents</td>
<td></td>
</tr>
<tr>
<td>Comorbid medical illness</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Poor glycemic control can cause polyuria and precipitate or exacerbate UI; also associated with increased likelihood of urgency UI and diabetic cystopathy.</td>
</tr>
<tr>
<td>Degenerative joint disease</td>
<td>Can impair mobility and precipitate urgency UI.</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>Associated cough can worsen stress UI.</td>
</tr>
<tr>
<td>Congestive heart failure Lower extremity venous insufficiency</td>
<td>Increased night-time urine production can contribute to nocturia and UI.</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>May elevate nocturnal urine volume via increased production of atrial natriuretic peptide.</td>
</tr>
<tr>
<td>Severe constipation and fecal impaction</td>
<td>Association with “dual” incontinence (urine and faecal)</td>
</tr>
</tbody>
</table>

Table 3: Systemic comorbidities that are commonly encountered in the elderly population and their potential effects on urinary incontinence.
b. Neurological and psychiatric conditions

<table>
<thead>
<tr>
<th>Neurological and psychiatric condition</th>
<th>Comments</th>
<th>Implications for management</th>
</tr>
</thead>
</table>
| **Stroke**                           | Can precipitate urgency UI and less often urinary retention, may also impair mobility. | UI after an acute stroke often resolves with rehabilitation; persistent UI should be further evaluated.  
Regular toileting assistance is essential for those with mobility and/or cognitive impairment.  
Optimizing management may improve mobility and improve UI. |
| **Parkinson's disease**               | Associated with urgency UI, also causes impaired mobility and cognition in late stages. | Regular toileting assistance is essential for those with mobility and/or cognitive impairment. |
| **Normal pressure hydrocephalus**    | Presents with UI, along with gait and cognitive impairments. | Patients presenting with all three symptoms should be further evaluated with brain imaging to rule out this condition, as symptoms may improve with ventriculoperitoneal shunt placement. |
| **Dementia (Alzheimer's, multi-infarct, others)** | Associated with urgency UI; impaired cognition and apraxia interferes with toileting and hygiene. | Regular toileting assistance is essential for those with mobility and/or cognitive impairment. |
| **Depression**                        | May impair the motivation to be continent; may also be a consequence of incontinence. | Optimizing pharmacological and non-pharmacologic management of depression may improve UI. |

Table 4: The neuropsychiatric conditions that are commonly encountered in the elderly population and their potential effects on urinary incontinence.
c. Functional impairments

<table>
<thead>
<tr>
<th>Functional impairments</th>
<th>Comments</th>
<th>Implications for management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired mobility</td>
<td>Impaired cognition and/or mobility due to a variety of conditions listed above and others can interfere with the ability to toilet independently and precipitate UI</td>
<td>Regular toileting assistance is essential for those with mobility and/or cognitive impairment.</td>
</tr>
</tbody>
</table>

Table 5: The functional impairments that are commonly seen in the elderly population and their potential effects on urinary incontinence.

d. Environmental factors

<table>
<thead>
<tr>
<th>Environmental factors</th>
<th>Comments</th>
<th>Implications for management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inaccessible toilets</td>
<td>Frail, functionally impaired elderly people require accessible, safe toilet facilities, and in many cases human (caregiver) assistance is needed in order to be continent.</td>
<td>Environmental alterations may be helpful; supportive measures such as pads may be necessary if caregiver assistance is not regularly available.</td>
</tr>
</tbody>
</table>

Table 6: The environmental factors that may be surrounding the elderly population and their potential effects on urinary incontinence.

Bladder Outlet Obstruction (BOO); Underactive Bladder and Urinary Retention - Detrusor Hyperactivity with Impaired Contractility (DHIC) (The title is too crowded, could not understand if this is the continuation of “LUTD in Geriatric Patients” section or a separate heading)

Introduction

Lower urinary tract symptoms (LUTS) are highly prevalent in the aging population. The prevalence and incidence of benign prostatic hyperplasia and associated LUTS (BPH/LUTS) increase with increasing age and vary by symptom severity. The relationship between BPH and LUTS is a complex one and involves several factors. Traditionally, enlarged prostate was considered as the main reason for developing LUTS. However, the actual condition is not that simple. Aging is responsible for many changes within the bladder wall which often lead to problems in the emptying and storage phases of the micturition cycle. (These changes are
compromising the ability of detrusor to contract efficiently. The poor contractility of detrusor muscle leads to the condition known as “Underactive Bladder” or “Underactive Detrusor”.

Normal voiding requires a well-functioning detrusor and an intact afferent and efferent neural control mechanism that is centrally coordinated. In the majority of the patients with DUA, more than one of these components have been affected. Diabetes mellitus with or without neurological sequale and coexistent bladder outlet obstruction is a good example for this multifactorial etiology.

Clinical Assessment

Based on ICS definition; UAB is characterized by a contraction of reduced strength and/or prolonged duration, resulting in failure to achieve complete bladder emptying within a usual time span \(^{(11)}\). Underactive bladder is a symptom complex, characterized by prolonged urination time with or without sensation of incomplete bladder emptying, hesitancy, reduced sensation on filling, slow urinary stream. Typically, patients with UAB presents with more than one lower urinary tract symptom \(^{(10)}\).

The complexity of this condition is also due to the fact that bladder wall changes secondary to aging and BPH-associated bladder outlet obstruction (BOO) often coexist. In their Doppler study involving a BOO model, Greenland et al. have shown that ischemia and reperfusion alternate in a cyclic manner during bladder filling and emptying. \(^{(12)}\) This continuum eventually leads to the release of intracellular calcium that activates protease and phospholipase which in turn activates lipid peroxidation and induces damage to the subcellular membrane of myocytes and neuronal cells within the detrusor wall. In a normal bladder, there are larger increases in blood flow during the filling and emptying phases when compared to the condition in UAB.

The above-mentioned complex changes in the bladder wall can also include partial denervation and afferent activation that induces overactive detrusor contractions. The vascular and neural damage, when combined, is the main reason why a patient with poor detrusor contractility during bladder emptying can have a paradoxical, exaggerated detrusor contractility in the filling phase. \(^{(13)}\)

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS OF UAB AND/OR BOO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased or interrupted stream</td>
</tr>
<tr>
<td>Hesitancy</td>
</tr>
<tr>
<td>Feeling of incomplete bladder emptying</td>
</tr>
<tr>
<td>Palpable bladder</td>
</tr>
<tr>
<td>Decreased sensation of bladder filling</td>
</tr>
<tr>
<td>Lower number of total voids/day</td>
</tr>
<tr>
<td>Prolonged interval between voiding episodes</td>
</tr>
</tbody>
</table>

Table 1: Signs and symptoms which could be seen in patients with UAB and/or BOO

Diagnosis

The coexistence of different disorders that might influence lower urinary tract function can make the differential diagnosis between LUTS due to BOO and UAB challenging. Conventional urodynamic measurements might not be enough to predict which patient would benefit from obstruction-relieving procedures such as transurethral resection of the prostate (TURP), laser photo-vaporization or enucleation of the prostate or lifting the prostatic lobes with endoscopically placed anchors (Urolift\textsuperscript{TM}). Bladder contractility index, which is an advanced urodynamic calculation, and the nomogram that incorporates bladder outlet resistance together with bladder contractility might be helpful to unreveal the exact cause of emptying failure.
Detrusor contractility is determined and quantified by the Watts factor (Figure 1, reference 14) (This calculation may be explained in more detail)

<table>
<thead>
<tr>
<th>DIAGNOSTIC WORK-UP:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine analysis and urine culture</td>
</tr>
<tr>
<td>Measurement of post-void residual urine volume</td>
</tr>
<tr>
<td>Uroflowmetry</td>
</tr>
<tr>
<td>Voiding diary</td>
</tr>
<tr>
<td>Cystometrogram and pressure-flow study</td>
</tr>
</tbody>
</table>

Table 7: Diagnostic tools that can be used to differentiate UAB vs. BOO-LUTS

Management

Assessing the presence of BOO and the extent to which it contributes to the clinical presentation is of utmost importance while planning the management. Medical treatment alone with alpha-blockers and/or 5-alpha reductase inhibitors may not be sufficient. Based on the patient’s dexterity, mental status and socio-economic situation, bladder may need to be drained with clean intermittent self-catheterization (the preferred way) or an indwelling catheter. When BOO is clinically significant and/or medical treatment has failed, a surgical intervention should be considered and discussed with the patient. The surgical options are all minimally invasive in nature and include TURP, laser photo-vaporization or enucleation of the prostate or Urolift™.

Nocturia

Nocturnal polyuria, is the medical term that defines excessive urine production at night. Under normal circumstances, the body produces less amount of and more concentrated urine during sleep time. This means that most people don't need to wake up during the night to urinate and can sleep uninterrupted for 6 to 8 hours. Nocturia in elderly population has a significant effect on the quality of life and carries a risk of morbidity and even mortality typically because of the predilection to frequent falls. This symptom must be elicited during the physician-patient interaction. Understanding its underlying causes, risk factors, and consequences is essential in formulating the most suitable management strategy. The key point in the management of nocturia is to identify if the patient needs to urinate at night because of an elevated amount of urine production or because of the failure of the bladder to hold urine. For this reason, concomitant conditions such as diabetes mellitus, diabetes insipidus, urinary tract infections, hypercalcemia, and hypokalemia must be identified and treated.

Base on the underlying cause, the treatment options include desmopressin (DDAVP), antimuscarinic agents, alpha-blockers, and 5-alpha reductase inhibitors. When nocturia is secondary to BOO and medical treatment has failed, surgical treatment alternatives, which are the same as for BOO, should be considered. (15)
References:
