Lower urinary tract dysfunction in the neurological patient: clinical assessment and management

Jalesh N Panicker, Clare J Fowler, Thomas M Kessler

Lower urinary tract (LUT) dysfunction is a common sequela of neurological disease, resulting in symptoms that have a pronounced effect on quality of life. The site and nature of the neurological lesion affect the pattern of dysfunction. The risk of developing upper urinary tract damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida; this difference in morbidity is taken into account in the development of appropriate management algorithms. Clinical assessment might include tests such as uroflowmetry, post-void residual volume measurement, renal ultrasound, (video-)urodynamics, neurophysiology, and urethrocystoscopy, depending on the indication. Incomplete bladder emptying is most often managed by intermittent catheterisation, and storage dysfunction by antimuscarinic drugs. Intradetrusor injections of onabotulinumtoxinA have transformed the management of neurogenic detrusor overactivity. Neuromodulation offers promise for managing both storage and voiding dysfunction. An individualised, patient-tailored approach is required for the management of LUT dysfunction associated with neurological disorders.

Introduction

Lower urinary tract (LUT) dysfunction can result from a wide range of neurological disorders. The “neurogenic bladder” is not a homogeneous entity, but rather a broadly used term to denote LUT dysfunction as a sequela of neurological disease. The high prevalence of LUT dysfunction in neurological diseases reflects the complexity of the neural control of the LUT in health. The site of the lesion in the neurological axis determines the general pattern of LUT dysfunction, which is reflected in the patient’s symptoms.

The importance of LUT dysfunction to patients’ health and quality of life is now being recognised and is rightly attracting interest in neurological practice. Pelvic organ dysfunction in neurological disease encompasses LUT, sexual, and bowel dysfunction, and the complex inter-relationship between these is now much better understood, with the recognition that a holistic approach is required for management. In this Review we aim to describe the principles that underpin the management of LUT dysfunction in the neurological patient, and to familiarise the clinician with the several recent advances that have transformed treatment.

Neurological control of LUT functions

In health, the coordinated activity of the urinary bladder and its outlet results in low-pressure filling and periodic voluntary emptying. A complex neural network distributed across parasympathetic, sympathetic, and somatic pathways acts as a switching circuit to maintain a reciprocal relation between the reservoir function of the bladder and sphincter function of the urethra. The frequency of micturition in a person with a bladder capacity of 400–600 mL will be once every 3–4 h. Voiding lasts only 2–3 min per 24 h and therefore the bladder is in the storage phase for more than 99% of continent life.13 Switching to the voiding phase is initiated by a conscious decision, determined by the perceived state of bladder fullness and an assessment of the social appropriateness of doing so. This bimodal, or phasic, pattern of activity, and degree of voluntary control and dependence on learned behaviour, sets the neural control of the LUT apart from that of other autonomically innervated structures, such as the cardiovascular system.1

To achieve both storage and voiding, connections between the pons and the sacral spinal cord must be intact, as must the peripheral innervation that originates from the most caudal segments of the cord. During bladder filling, sympathetic and pudendal nerves mediate contraction of the smooth (internal) and striated (external) muscles, respectively, of the urethral sphincter. Their contraction maintains continence, whereas sympathetic-mediated inhibition of the detrusor prevents contractions and ensures a low pressure.1 When it is deemed appropriate to void, the pontine micturition centre (PMC) is released from the tonic inhibition of cortical and subcortical centres of the brain, and the reciprocal activation–inhibition of the sphincter–detrusor is reversed.14 Detrusor contraction in response to parasympathetic stimulation, accompanied by relaxation of the pelvic floor and external and internal urethral sphincters, results in effective bladder emptying. Functional imaging experiments during bladder filling have shown that the periaqueductal grey (PAG) of the midbrain, the insula, and the anterior cingulate gyrus are important regions for awareness of visceral sensations.15–17 The prefrontal cortex is thought to be the centre of planning of complex cognitive behaviours and expression of appropriate social behaviour. It has multiple connections with the anterior cingulate gyrus and both regions have connections with the PAG.

LUT dysfunction after nervous system damage

Lesions of the nervous system, central or peripheral, can result in patterns of LUT dysfunction that are influenced by the level of the lesion (figure I).8 Lesions of the relevant suprapontine or spinal pathways regulating LUT functions affect the storage phase, resulting in reduced bladder capacity and detrusor overactivity, expressed as
spontaneous involuntary contractions of the detrusor. The patient might report varying degrees of urinary urgency, frequency, nocturia, and incontinence (collectively known as overactive bladder symptoms). Incontinence in patients with neurological disorders is most commonly caused by detrusor overactivity, identified by urodynamic studies. A sensation of urinary urgency is experienced as the detrusor begins to contract, and if the pressure rise continues, the patient senses impending micturition.

The mechanisms of detrusor overactivity after suprapontine damage are different from those after spinal cord injury (SCI). Damage to the suprapontine neural circuitry results in removal of the tonic inhibition of the PMC so that spontaneous involuntary detrusor contractions occur. By contrast, the detrusor overactivity that results from spinal cord lesions is due to the emergence of a segmental reflex at the level of the sacral cord, mediated by capsaicin-sensitive C-fibre afferents, which drive involuntary detrusor contractions. After an acute SCI there is initially a phase of spinal shock, during which the detrusor is hypocontractile or acontractile and associated with poor bladder emptying, before spontaneous contractions occur. The duration of this phase varies, although it is usually said to be about 6 weeks. However, during the evolution of an insidious spinal disease, the onset of detrusor overactivity can be the first observed event. The mechanism of sensitisation of “silent” C-fibres after SCI is uncertain; however, it is probably mediated by alterations in central synaptic connections and properties of the peripheral afferent receptors.

Injury to the suprasacral spinal pathways also results in loss of coordinated activation of the detrusor and inhibition of the urethral sphincter during voiding. Instead, there is a simultaneous contraction of the detrusor and urethral sphincter, known as detrusor–sphinicter dyssynergia (DSD). This condition can result in voiding difficulties and incomplete bladder emptying and also dangerously high pressures in the bladder. Incomplete bladder emptying can also result from impaired parasympathetic drive caused by damage of descending bulbospinal pathways. Lesions of the sacral cord or infrasacral pathways result in voiding dysfunction associated with poorly sustained or absent detrusor contractions and/or non-relaxing sphincter. Variations from these expected patterns of symptoms and findings should warrant a search for additional urological pathologies that could be occurring concomitantly.

**Risk of upper urinary tract complications**

Detrusor overactivity in combination with DSD can result in high intravesical pressures, which in turn can lead to morphological changes in the bladder wall such as trabeculations and (pseudo-)diverticula, and increase the risk of upper urinary tract complications such as vesico-uretero-renal reflux, hydronephrosis, renal impairment, and eventually end-stage renal disease. One study assessing urodynamic changes in patients with spina bifida suggested that urethral leakage at detrusor pressures greater than 40 cm H₂O indicated increased risk; however, it is unlikely that this is generalisable across neurological disorders. Patients with SCI or spina bifida have a substantially higher risk of developing renal failure compared with the general adult population. By contrast, the prevalence of upper urinary tract damage and renal failure is low in patients with slowly progressive non-traumatic neurological disorders, such as multiple sclerosis and Parkinson’s disease. The reasons for these findings are still unclear, but duration of multiple sclerosis and severity of disability are risk factors for upper urinary tract complications. The differences in urinary tract complications between the two groups of diseases has not been clearly acknowledged so far, but has inevitably resulted in a lack of agreement about management of neurogenic LUT dysfunction: recommendations for the high-risk group are often inappropriate for the low-risk group.

Clearly, patients at high risk of upper urinary tract damage require lifelong close urological supervision, but the low-risk group (ie, those with progressive neurological disease) is much more troubled by poor LUT control than by dangerously high upper urinary tract pressures. Neurologists, aware of the risk associated with neurogenic LUT dysfunction, might therefore have been reluctant to engage with their patients’ troublesome bladder

---

**Figure 1: Patterns of lower urinary tract dysfunction following neurological disease**

The pattern of lower urinary tract dysfunction following neurological disease is determined by the site and nature of the lesion. The blue box denotes the region above the pons and that in green denotes the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. PVR=post-void residual.
symptoms. This reluctance to engage might have led them to overlook potentially treatable symptoms that have a highly adverse effect on patients’ quality of life. This Review attempts to redress that situation.

LUT dysfunction in specific neurological disorders

Dementia
Incontinence is often a prominent symptom in the late stages of dementia, but the timing of its occurrence seems to vary according to the nature of the brain disease. Incontinence tends to occur early in normal pressure hydrocephalus, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia, whereas generally it occurs late in the course of Alzheimer’s disease or Parkinson’s disease with dementia. In patients with dementia and incontinence, pharmacological treatment of one disorder can exacerbate the other. Incontinence can result not only from detrusor overactivity, but also from cognitive and behavioural problems, urological causes, and immobility.

Cerebrovascular accident
More than 50% of stroke patients have urinary incontinence during the acute phase of stroke. Risk factors for incontinence include large lesion size, presence of comorbid illnesses, such as diabetes, and older age. Lesions in the anteromedial frontal lobe, paraventricular white matter, and putamen are most often associated with LUT symptoms. Most commonly, urodynamics provides evidence of detrusor overactivity. Urinary retention has been reported after haemorrhagic and ischaemic stroke, and urodynamics shows evidence of detrusor underactivity. There is evidence to suggest that incontinence is independently associated with subsequent severity of neurological disability, institutionalisation, and mortality. Small-vessel disease of the white matter, leukoaraiosis, is associated with urgency incontinence, and it is becoming increasingly apparent that this is an important cause of incontinence in functionally independent people older than 60 years.

Parkinson’s disease and multiple system atrophy
Severity of LUT dysfunction in Parkinson’s disease has been shown to be correlated with degree of neurological disability, suggesting an association between dopaminergic neurodegeneration and LUT dysfunction. However, LUT symptoms in multiple system atrophy (MSA) can precede other neurological manifestations. In the early stages of MSA, incontinence usually arises from detrusor overactivity and external sphincter weakness, whereas incomplete emptying worsens as the disease progresses. An open bladder neck on video-urodynamics is a sign highly suggestive of MSA in men.

Multiple sclerosis and other demyelinating disorders
Symptoms of LUT dysfunction are common in multiple sclerosis and prevalence increases with duration of disease and extent of spinal cord involvement. Symptoms occur around 6 years into the illness and almost all patients report LUT symptoms 10 years or more after symptom onset. Most commonly, both storage and voiding dysfunction occur. LUT dysfunction is common in acute disseminated encephalomyelitis and can persist after other neurological deficits have resolved.

Spinal cord injury
Patients might initially be in urinary retention during the spinal shock phase that follows SCI, and develop the typical pattern of DSD and detrusor overactivity subsequently as spinal reflexes return. Sustained high intravesical pressures can ensue, increasing the risk of upper urinary tract damage. Autonomic dysreflexia can occur after lesions at or above the T6 spinal cord level, triggered by urinary tract infections (UTIs), interventions of the LUT and bowel, or sexual activity. This is a potentially life-threatening disorder and is characterised by an increase in systolic blood pressure (>20 mm Hg above baseline), headache, flushing, piloerection, stuffy nose, sweating above the level of the lesion, vasoconstriction below the level of the lesion, and dysrhythmias.

Spina bifida
More than 90% of children with spina bifida have LUT dysfunction. Symptoms usually start in infancy or childhood, although occasionally they are delayed until adulthood. Video-urodynamic studies can identify a variety of features, such as detrusor overactivity, detrusor underactivity, or low compliance with ineffective contractions. Findings at the bladder outlet include DSD, or a static or fixed external urethral sphincter. Young patients with apparently normal LUT function initially can develop LUT dysfunction later on in life because of spinal cord tethering. They should therefore be monitored regularly by urologists, because they could be at risk of developing upper urinary tract complications.

Cauda equina syndrome and peripheral neuropathy
Lower motor neuron disturbance in patients with polyradiculopathy or peripheral neuropathy results in reduced or absent detrusor contractions. Patients report reduced sensation of bladder fullness, inability to initiate micturition voluntarily, and bladder distension, to the point of overflow incontinence. However, in a subset of patients, there might be detrusor overactivity, which could be a result of bladder decentralisation due to preserved peripherally sited post-ganglionic neurons.

Fowler’s syndrome
If a young woman in complete urinary retention has no underlying urological or neurological disease, a diagnosis of Fowler’s syndrome should be considered. This syndrome is characterised by a primary disorder of urethral sphincter relaxation, which results in an inhibition of
detrusor contractions. Investigation with urethral sphincter electromyography (EMG) shows a characteristic pattern of activity and the urethral pressures are usually raised. Opiates seem to compound incomplete emptying or retention in women who have fairly mild sphincter abnormalities.29,30 The only treatment modality shown to be effective in restoring voiding is sacral neuromodulation.36,37

### Clinical assessment

The assessment and management of the neurological patient reporting LUT symptoms requires a close collaboration between neurologists and urologists. Table 1 provides an overview of the assessment, which should include evaluation of additional urological and gynaecological comorbidities such as prostate enlargement, stress incontinence, and pelvic organ prolapse.

#### History taking and physical examination

History taking is the preliminary step in neurogenic LUT dysfunction assessment, gathering information on LUT symptoms, congenital and neurological abnormalities, previous urogenital complications and treatments, and urinary tract, sexual, bowel, gynaecological, and neurological function.29 Medication history should be reviewed. For example, an association between opiate use and voiding dysfunction is often overlooked, despite the fact that voiding dysfunction is listed as an adverse effect.34

Other drugs that can cause voiding difficulties are those with anticholinergic properties (e.g., antipsychotic drugs, antidepressant and anticholinergic respiratory agents) and α-adrenoceptor agonists. Patients with neurological disease might report becoming incontinent because of inability to reach the toilet in a timely manner due to their neurological deficits or to poor toilet accessibility (functional incontinence). Evaluation of lifestyle factors such as smoking, alcohol, or addictive drugs as well as quality of life is also important, and attention should be paid to physical and mental disabilities.

The bladder diary is useful because it provides a real-time objective patient-reported measure of LUT symptoms, which might not be obtained through history taking or questionnaires.16 To be of value, however, the patient must be motivated to complete it faithfully.

Physical examination consists of examining the abdomen, loins, and pelvic and genital organs, and when appropriate, assessing urogenital sensations, sacral cord-mediated reflexes (bulbocavernosus reflex, anal reflex), and anal sphincter tone and squeeze response (figure 2).29

#### Investigations

Urinalysis and urine culture (if appropriate) and blood chemistry, if not already done by the referring physician, form part of a basic neuro-urological assessment.

**Ultrasonography**

The post-void residual (PVR) urine volume is measured by ultrasound or alternatively by so-called in–out catheterisation. The PVR volume should be measured on different occasions to establish how bladder emptying varies at different times and in different circumstances.29,32 A raised PVR volume suggests that there is voiding dysfunction; however, it cannot be used to discern whether this is caused by poor detrusor contractility or by obstruction, for which urodynamics would be required.

In patients known to be at high risk of upper urinary tract disease, surveillance ultrasonography should be undertaken periodically (at least every 6 months) to detect upper urinary tract dilatation or renal scar.29 Ultrasound can also be used to demonstrate urinary tract stones, which might develop in patients with neurogenic LUT dysfunction.

Bladder/detrusor wall thickness and ultrasound-estimated bladder weight are being investigated as non-invasive alternatives to assess neurogenic LUT dysfunction, but are not yet established diagnostic options.

#### Urodynamic investigations

Uroflowmetry is a valuable non-invasive investigation, especially when combined with a measurement of the PVR volume, to detect voiding dysfunction. It should be done before any treatment and can be used to monitor treatment outcomes. However, flow rate and PVR volume depend on both detrusor function and bladder outlet resistance. Thus, uroflowmetry is unable to discriminate between the underlying mechanisms, which would require the use of invasive urodynamics.

Invasive urodynamics, generally a combination of cystometry and pressure-flow study in those who are able to void, with or without simultaneous fluoroscopic monitoring (i.e., video-urodynamics), assesses detrusor and bladder outlet function and provides information about detrusor pressure and compliance, and thus the risk factors for upper urinary tract damage. Urodynamics is not only prognostic but also valuable for guidance of appropriate treatment, especially if initial symptom-based therapy has failed. The place of urodynamics in the evaluation of LUT symptoms in patients with neurological disease is a topic of ongoing debate.29 For instance, French guidelines recommend urodynamics for assessment of bladder function in patients with early multiple sclerosis, whereas in the UK, first-line management of multiple sclerosis-related LUT symptoms follows a simple
algorithm using reagent sticks to test for UTIs and PVR volume measurement without invasive urodynamics.\textsuperscript{42} The Madersbacher classification system characterises neurogenic LUT dysfunction on the basis of detrusor and urethral sphincter functions and provides a framework for management but does not consider sensory dysfunction.\textsuperscript{13,14,29}

**Other urological tests**

Since neurogenic LUT symptoms can be mimicked by urethral and bladder pathologies, urethrocystoscopy (combined with bladder washing cytology if appropriate) is used to detect urethral stricture, urethral and bladder stones, and bladder tumours including carcinoma in situ, and this test is mandatory in the case of gross haematuria.\textsuperscript{29}

Measuring serum creatinine, and calculating the glomerular filtration rate (GFR), yields a reasonable estimation of renal function with little cost or inconvenience. Creatinine clearance provides a more accurate assessment, but involves a 24-h urine collection to estimate creatinine excretion and incomplete collection can result in an underestimate of renal function. The GFR is most accurately measured using renal scintigraphy, which is recommended when renal function is poor, in individuals with reduced muscle mass, if function for each renal unit has to be assessed separately, and in high-risk patients.\textsuperscript{29}

**Pelvic neurophysiology**

The role of pelvic EMG in the assessment of the neurological patient with LUT dysfunction is limited. Pelvic floor EMG was first introduced as part of urodynamic studies with the aim of recognising DSD. However, it is now less commonly used since the advent of video-urodynamics. Sphincter muscle EMG is useful for investigating innervation of the sacral second, third, and fourth nerve roots where a cauda equina syndrome is suspected,\textsuperscript{43} or sometimes in patients presenting with a parkinsonian syndrome to aid in the differential diagnosis between idiopathic Parkinson’s disease and

---

**Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes**

The physical examination includes testing sensations and reflexes mediated through the lower spinal cord, and abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of lesion. 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 (C). (D) Root values of lower spinal cord reflexes. Parts A–C adapted from Standring,\textsuperscript{41} by permission of Elsevier.
biofeedback was found to be a safe and effective treatment for urgency, frequency, with or without incontinence.49 Electrical stimulation and pelvic floor training and EMG in women with multiple sclerosis.49

There are a few situations in which an early referral to a specialist urology service is warranted (panel 3).14 There is no agreement on the appropriate incontinence assessment and treatment in young women without complications. There is a lack of evidence base supporting these techniques is limited.45–47

MSA. Urethral sphincter EMG has proved to be useful in the assessment of young women in urinary retention.15

**Principles of management**

The goals of management are to achieve urinary continence, improve quality of life, prevent UTIs, and preserve upper urinary tract function.29 The management of neurogenic LUT dysfunction should address both voiding and storage dysfunction (table 2) and is determined by the severity of symptoms and risk of developing upper urinary tract damage (panels 1 and 2). LUT dysfunction should be seen in the context of the wider overall dysfunctions resulting from neurological disorders, and a multidisciplinary approach between neurology, urology, and primary care is therefore essential. There are a few situations in which an early referral to a specialist urology service is warranted (panel 3).14

**Management of storage dysfunction**

**Physical treatments**

The aim of behavioural interventions is to re-establish control of LUT function by correcting faulty habits such as frequent voiding, which are sometimes seen in individuals with urinary urgency. Behavioural therapies are considered appropriate in individuals whose incontinence is associated with cognitive deficits, and possibly also in patients with motor deficits. However, such treatments require support from caregivers and health-care professionals to be successful. Timed voiding involves separating toilet visits by fixed intervals of time. Habit retraining involves identifying the natural voiding pattern of a patient with incontinence and the development of an individualised toileting schedule that pre-empts involuntary bladder emptying. Verbal prompts and positive reinforcement might help to improve bladder control. However, the evidence base supporting these techniques is limited.29–31

Pelvic floor exercises can enhance the inhibitory effect of pelvic floor contraction on the detrusor, and a prospective study in women with multiple sclerosis showed that this technique resulted in substantial improvements in urinary frequency and number of daily incontinence episodes, and increases in mean cystometric capacity after 1 month.32 The combination of intravaginal electrical stimulation and pelvic floor training and EMG biofeedback was found to be a safe and effective treatment in women with multiple sclerosis.33

**Antimuscarinic drugs**

Antimuscarinic drugs competitively antagonise muscarinic acetylcholine receptors, resulting in detrusor relaxation, lower intravesical pressures, and reduced storage symptoms. The M3 muscarinic receptor is widely distributed throughout the detrusor, urothelium, and suburothelium, whereas the M2 receptor is functionally the most relevant subtype in the bladder. Since the introduction of oxybutynin, several newer antimuscarinic agents have appeared on the market (table 3).34–38 Systematic reviews have not concluded superiority of one agent over others and suggest that the only difference between drugs is their side-effect profiles.39–42 Prescribing patterns of these agents are determined by local guidance.

<table>
<thead>
<tr>
<th>Storage dysfunction</th>
<th>Voiding dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency, frequency, with or without incontinence</td>
<td>Stress incontinence</td>
</tr>
<tr>
<td>Pelvic floor muscle exercises</td>
<td>Intermittent catheterisation; indwelling catheterisation; triggered voiding; α-adrenoceptor blockers*; onabotulinumtoxinA into the external sphincter*</td>
</tr>
<tr>
<td>Sacral neuromodulation*; bladder augmentation; sacral deafferentation/anterior root stimulation; continent/ incontinent urinary diversion</td>
<td>Bulking agents*; autologous/synthetic slings; balloons*; artificial sphincter; continent/incontinent urinary diversion</td>
</tr>
<tr>
<td>Bulking agents*; autologous/synthetic slings; balloons*; artificial sphincter; continent/incontinent urinary diversion</td>
<td>Sacral neuromodulation*; intraurethral stents*; external sphincter/bladder neck incision; transurethral resection of prostate; continent/incontinent urinary diversion</td>
</tr>
</tbody>
</table>

Table 2: Management of lower urinary tract dysfunction in the neurological patient

**Panel 1: Case study—patient with low risk of developing upper urinary tract damage**

A 38-year-old woman with relapsing-remitting multiple sclerosis of 12 years’ duration with a mild neurological disability (score of 3.0 on the Expanded Disability Status Scale) reported urinary urgency, increased daytime frequency (8–10 visits to the toilet), and nocturia (2–3 visits) of 9 years’ duration. In the past 5 years, she had begun to have twice-weekly episodes of incontinence associated with urinary urgency. She had urinary hesitancy and an interrupted urinary stream. She also reported constipation and abdominal bloating and cramps, which she was managing by using senna. She had had two uncomplicated deliveries.

The patient kept a 72-h bladder diary and the findings were consistent with an overactive bladder. It was noted that she consumed four cups of tea and two cans of fizzy drink a day. Her urine was clear of infection and an ultrasound scan of her kidneys and bladder was normal but showed a post-void residual urine volume of 160 mL. After a week, her post-void residual volume was 180 mL. Urea and creatinine concentrations were normal.

The patient had overactive bladder symptoms and incomplete bladder emptying. The risk of upper urinary tract damage was deemed to be low and she therefore did not undergo urodynamics at this stage. She met the nursing team and was advised to reduce tea and fizzy drink consumption and was taught intermittent self-catherisation. The patient was reviewed after 3 months. She was performing intermittent self-catheterisation reasonably well and had not had any UTIs. However, she continued to have episodes of urgency incontinence and was therefore started on an antimuscarinic agent, solifenacin 5 mg. After 6 weeks, she was tolerating the medication, which was increased to 10 mg.

The patient was reviewed again after 3 months and her incontinence had improved markedly. However, she was still reporting nocturia, even though she was using the catheter just before going to bed. She was started on desmopressin 0.2 mg with a plan of periodic monitoring of serum sodium concentrations by her family doctor. At review after 6 months she was doing well.
Panel 2: Case study—patient with high risk of developing upper urinary tract damage

A 24-year-old woman had a snowboarding accident with fracture of the thoracic vertebra 9, which was conservatively managed. She was able to walk and diagnosed with incomplete spinal cord injury (American Spinal Injury Association Impairment Scale D) at neurological level L1 with neurogenic lower urinary tract (LUT) and bowel dysfunction. Spontaneous voiding was no longer possible and she had to rely on intermittent self-catheterisation. Her quality of life was impaired by urinary urgency incontinence. A 72-h bladder diary showed four to six urinary urgency incontinence episodes requiring four to six incontinence pads per 24 h and the pads were often drenched; intermittent catheterisation was documented six times every 24 h with catheterisation volumes of 150–260 mL. After exclusion of a UTI, an antimuscarinic agent, fesoterodine 4 mg daily, was started and the dose was increased to 8 mg daily after 2 weeks. The bladder capacity markedly increased and incontinence episodes decreased, but she was still incontinent and constipation became worse. A switch to other antimuscarinic drugs such as solifenacin 10 mg daily and darifenacin 15 mg daily did not improve the situation. Additionally, the patient developed recurrent pyelonephritis on the left side, which had been treated with antibiotics twice within the past 3 months by her family doctor. Video-urodynamics showed detrusor overactivity incontinence, detrusor–sphincter dyssynergia, and vesico-uretero-renal reflux grade II. Further treatment options were discussed and the patient underwent onabotulinumtoxinA injections (200 units Botox, Allergan, USA) into the detrusor using a rigid cystoscope under local anaesthesia. After 10 days, the patient became completely dry and the antimuscarinic drug was stopped. Video-urodynamics 6 weeks after onabotulinumtoxinA treatment showed a normal cystometric bladder capacity of 475 mL; the detrusor overactivity and vesico-uretero-renal reflux had disappeared. The patient was doing well for 10 months before the urinary urgency incontinence recurred. Urodynamics confirmed detrusor overactivity incontinence and onabotulinumtoxinA injections (200 units Botox) into the detrusor were repeated, which alleviated the urinary incontinence again, leaving the patient completely dry.

Panel 3: Situations warranting early referral to a specialist urology service

- Symptoms refractory to first-line treatments
- Recurrent urinary tract infections
- Suspicion of concomitant pathologies such as bladder outlet obstruction due to prostate enlargement, stress incontinence
- Renal impairment
- Demonstrated hydronephrosis
- Presence of haematuria
- Pain suspected to be originating from the urinary tract

Adverse effects arise as a result of the drugs' non-specific anticholinergic action and include dry mouth, blurred vision for near objects, constipation, and occasionally tachycardia. Some of these symptoms might already be reported by the neurological patient and must therefore be considered before the start of treatment. The effect that these drugs might have on central muscarinic receptors, resulting in alterations in cognition and consciousness in susceptible individuals, has attracted much interest in recent years. Drugs already being used by the patient should be reviewed before prescribing an antimuscarinic agent, especially in older people, because there is evidence to suggest that cumulative use of agents with anticholinergic properties is associated with increased risk of cognitive impairment. Agents that do not readily cross the blood–brain barrier or have relatively high affinity for the muscarinic receptors of the bladder would theoretically have less effect on cognition (table 3). However, evidence supporting these considerations in clinical practice is limited, and caution is advised when using an antimuscarinic agent in the susceptible neurological patient.

Measurement of the PVR volume should be done preferably before antimuscarinic treatment is started. Furthermore, if there is reason to suspect that a patient already established on treatment has developed incomplete bladder emptying (eg, poor response to antimuscarinic drugs), or is reporting recurrent UTIs, the PVR volume should be measured again. In many patients, the judicious combination of antimuscarinic treatment plus intermittent self-catheterisation provides the most effective management for neurogenic LUT dysfunction.

Desmopressin

Desmopressin, a synthetic analogue of arginine vasopressin, temporarily reduces urine production and volume-determined detrusor overactivity, by promoting water reabsorption at the distal and collecting tubules of the kidney. It is useful for the treatment of urinary frequency or nocturia in patients with multiple sclerosis, providing symptom relief for up to 6 h. Desmopressin is also helpful in managing nocturnal polyuria, characterised by increased production of urine in the night, a disorder seen in patients with Parkinson’s disease and various neurological disorders associated with orthostatic hypotension. However, desmopressin should be prescribed with caution in patients older than 65 years or with dependent leg oedema, and should not be used more than once in 24 h because of the risk of hyponatraemia or congestive heart failure.

β3-Adrenoceptor agonists

The recent licensing of the oral β3-adrenoceptor agonist mirabegron for overactive LUT symptoms opens up an additional therapeutic strategy. Although mirabegron does not cause the adverse effects reported with antimuscarinic drugs, such as dry mouth, constipation, and cognitive impairment, side-effects do occur in the cardiovascular system, such as palpitations, raised blood pressure, and rarely atrial fibrillation. There is, however, no high-level evidence of effectiveness in the neurological population.

Neuromodulation

Electrical stimulation of peripheral nerves such as the sacral nerve roots, tibial nerve, pudendal nerve, and...
Review

dorsal genital nerves, has proved to be effective in managing the idiopathic overactive bladder. In patients with an underlying neurological disorder, however, the situation is less clear. Studies have been small with a substantial risk of bias and confounding, such that the overall quality of the evidence is low. Additionally, the mechanism of action is uncertain, although it seems that modulation of sacral afferent nerves and spinal cord-mediated reflexes through inhibitory interneurons is key. Thus, well-designed, and adequately sampled and powered randomised trials are needed to make definitive conclusions about the effectiveness and underlying mechanism of neuromodulation.

Tibial neuromodulation

Electrical stimulation of the tibial nerve is a safe and effective minimally invasive treatment for urgency incontinence caused by detrusor overactivity. Percutaneous tibial nerve stimulation (PTNS) has been shown to improve overactive bladder symptoms and urodynamic parameters in patients with multiple sclerosis and Parkinson’s disease. A typical treatment course consists of stimulating the nerve through a fine gauge stainless steel needle using a fixed frequency electrical signal, once weekly for 30 minutes, over an 8–12-week period. PTNS is a minimally invasive option for managing patients with mild or moderate overactive bladder symptoms and is associated with few adverse effects. Moreover, it is one of the few options for the overactive bladder not associated with increasing PVR volume. However, the effect is fairly short lived and the need to return for treatments can be particularly difficult for neurological patients. Transcutaneous tibial nerve stimulation (TTNS) is an alternative that can be done at home and has proved to be safe and effective in treating urgency incontinence in patients with multiple sclerosis or after stroke.

<table>
<thead>
<tr>
<th>Antimuscarinic drugs</th>
<th>Theoretical ability to cross blood–brain barrier</th>
<th>Active extrusion across blood–brain barrier</th>
<th>Selective receptor binding (M3:M1 affinity ratio)</th>
<th>Dose (mg)</th>
<th>Frequency</th>
<th>Level of evidence for use in neurogenic LUT dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Controlled release High</td>
<td>Yes</td>
<td>Mainly M3 (9·3:1)</td>
<td>7·5–15</td>
<td>Once daily</td>
<td>NA</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Controlled release Very low</td>
<td>Yes</td>
<td>Not subtype selective</td>
<td>4–8</td>
<td>Once daily</td>
<td>NA</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Immediate release Moderate/high</td>
<td>No</td>
<td>Not subtype selective</td>
<td>2·5–5</td>
<td>Two or three times a day</td>
<td>Level 1: Gajewski et al</td>
</tr>
<tr>
<td></td>
<td>Controlled release Moderate/high</td>
<td>No</td>
<td>Not subtype selective</td>
<td>5–20</td>
<td>Once daily</td>
<td>Level 1: Gajewski et al</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch Moderate/high</td>
<td>No</td>
<td>Not subtype selective</td>
<td>36 (releasing ~3·9 mg oxybutynin per 24h)</td>
<td>Replace once every 3–4 days</td>
<td>Level 1: Gajewski et al</td>
</tr>
<tr>
<td>Propiverine</td>
<td>Immediate release NA</td>
<td>NA</td>
<td>Not subtype selective</td>
<td>15</td>
<td>1–3 times daily</td>
<td>Level 1: Stohrer et al</td>
</tr>
<tr>
<td></td>
<td>Controlled release NA</td>
<td>NA</td>
<td>Not subtype selective</td>
<td>30</td>
<td>Once daily</td>
<td>Level 1: Stohrer et al</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Controlled release Moderate</td>
<td>No</td>
<td>Mainly M3 (2·5:1)</td>
<td>5–10</td>
<td>Once daily</td>
<td>Level 2: van Rey and Heesakkers</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Immediate release Low</td>
<td>No</td>
<td>Not subtype selective</td>
<td>2–4</td>
<td>Once or twice daily</td>
<td>Level 3: Ethans et al</td>
</tr>
<tr>
<td></td>
<td>Controlled release Low</td>
<td>No</td>
<td>Not subtype selective</td>
<td>4</td>
<td>Once daily</td>
<td>Level 3: Ethans et al</td>
</tr>
<tr>
<td>Trospondiamine</td>
<td>Immediate release Almost none</td>
<td>Yes</td>
<td>Not subtype selective</td>
<td>20</td>
<td>Twice daily (before food)</td>
<td>Level 1: Mazo and Babanina</td>
</tr>
<tr>
<td></td>
<td>Controlled release Almost none</td>
<td>Yes</td>
<td>Not subtype selective</td>
<td>60</td>
<td>Once daily</td>
<td>Level 1: Mazo and Babanina</td>
</tr>
</tbody>
</table>

Antimuscarinic drugs are presented in alphabetical order. In susceptible individuals, use of drugs that are less likely to result in central side-effects is desirable. The following factors should be considered (1) theoretical ability to cross the blood–brain barrier: physicochemical properties of a drug can affect its passive permeability across the blood–brain barrier (eg, trospondiamine is a poorly lipophilic, positively charged quaternary ammonium compound that does not readily cross the blood–brain barrier); (2) active extrusion across the blood–brain barrier: active transport efflux proteins at the barrier might extrude a drug and thereby lower concentrations (eg, trospondiamine, darifenacin, and fesoterodine are substrates for the permeability-glycoprotein ATP-dependent efflux pump, which actively extrudes these drugs across the blood-brain barrier from the brain); (3) selective receptor binding: differential binding to muscarinic receptors might minimise central effects (eg, darifenacin has a greater affinity for the M3 receptor, the functionally important muscarinic acetylcholine receptor subtype of the bladder, than it does for the M3 subtype, which is prevalent in the brain). LUT=lower urinary tract. NA=not available.

Table 3: Commonly used antimuscarinic drugs for management of overactive bladder, by preparation
The benefits of PTNS and TTNS are that they are minimally invasive or non-invasive and are associated with few adverse events. Also, the absence of a metallic implant means that the possibility of future MRI scans is not compromised.

**Sacral neuromodulation**

Sacral neuromodulation (SNM) was initially deemed to be unsuitable in neurological patients because of the impaired peripheral neuronal innervation, but it has since become a promising treatment option for neurogenic LUT dysfunction. SNM is not only an effective treatment for LUT dysfunction, but also for bowel dysfunction. It does not increase the PVR volume and its effect is not temporally limited, as is the case with intradetrusor onabotulinumtoxinA injections. Although a multicentre randomised controlled trial is in progress, it is still unclear which neurological patients are most suitable for this intervention. Nevertheless, it is generally agreed that patients with a progressive neurological disease are not candidates for SNM.

Remarkably, early bilateral SNM during the phase of spinal shock seems to prevent the subsequent development of neurogenic detrusor overactivity and urinary incontinence in patients with complete SCI, although long-term results are awaited. SNM seems to involve modulation of spinal cord reflexes and brain networks by peripheral afferents rather than direct stimulation of the motor response of the detrusor or urethral sphincter, and presumably mediates an inhibitory effect. Indeed, the importance of afferent pathways is supported by several neurophysiological studies. Even the anal sphincter contraction (bellows response) during SNM testing is not a direct stimulation effect but rather an afferent-mediated response.

**Botulinum toxin**

Although antimuscarinic drugs are the pharmacological treatment of choice for neurogenic overactive bladder, their effectiveness is limited and many patients discontinue treatment because of side-effects. In 2000, Schuch and colleagues reported on the successful use of botulinum toxin injections into the detrusor for treatment of neurogenic detrusor overactivity in patients with SCI. This treatment has since revolutionised the management of neurogenic overactive bladder.

There are seven serotypes of botulinum toxin, but it is type A that is generally used for urological indications. Botulinum toxin A is available as several different preparations (ie, onabotulinumtoxinA [Botox; Allergan, USA], abobotulinumtoxinA [Dysport; Ipsen, USA], incobotulinumtoxinA [Xeomin; Merz, USA]). All these agents have different physicochemical properties and there has been no adequate comparative trial, but only onabotulinumtoxinA is licensed for treatment of detrusor overactivity incontinence. OnabotulinumtoxinA received US Food and Drug Administration and European Union approvals in August, 2011, on the basis of the results of two pivotal phase 3 studies in patients with multiple sclerosis and SCI suffering from neurogenic detrusor overactivity incontinence. Intradetrusor onabotulinumtoxinA injections have been shown to be highly effective, safe, and well tolerated. These effects seem to occur irrespective of the underlying neurological disorder, but data for conditions other than SCI and multiple sclerosis are scarce. Twenty to 30 injections are made into the bladder wall, requiring a cystoscopy (rigid or flexible), an intervention that can be done under local anaesthesia in most neurological patients. Long-term data confirm the efficacy of repeat onabotulinumtoxinA injections, and cost-effectiveness seems to be superior to best supportive care. However, a de-novo self-catheterisation rate of up to 42% has been reported, highlighting the importance of providing patient information before starting onabotulinumtoxinA treatment.

**Management of voiding dysfunction**

There is little consensus about the best time to begin intermittent catheterisation; however, several factors such as the PVR volume and risk of upper urinary tract damage should be considered. The PVR volume at which to begin intermittent catheterisation is related to the overall bladder capacity; patients with neurogenic LUT dysfunction often have a reduced bladder capacity, and a PVR volume consistently more than 100 mL has been advocated if the patient is symptomatic.

**Intermittent catheterisation**

Incomplete bladder emptying can exacerbate detrusor overactivity and also render treatments such as antimuscarinic drugs and botulinum toxin less effective. The use of intermittent catheterisation therefore greatly improves management. Experienced health-care professionals, such as a continence adviser, should be involved in teaching the technique and exploring possible barriers to successful catheterisation. Neurological lesions resulting in poor manual dexterity, weakness, tremor, rigidity, spasticity, impaired visual acuity, or cognitive impairment affect the ability of a patient to perform self-catheterisation. Catheterisation four to six times per 24 h is recommended to manage complete urinary retention. Frequency of catheterisation depends on many factors such as bladder volume, fluid intake, and PVR volume, as well as urodynamical parameters (compliance, detrusor pressure). Patients emptying their bladder incompletely will need to use the catheter one to three times per 24 h after voiding. The incidence of symptomatic UTIs is low when done regularly.

**Other interventions**

Triggered reflex voiding can occasionally be achieved by provoking a bladder contraction through stimulation of sacral and lumbar dermatomes (eg, suprapubic tapping...
and thigh scratching), and is most successful in patients with a suprasacral spinal cord lesion. However, these manoeuvres should be recommended only in patients with a urodynamically safe bladder.29 Bladder expression using Valsalva or Credé manoeuvres (manual compression of the lower abdomen) is not usually recommended because these could be associated with a rise in intravesical pressures.29 Suprapubic vibration using a mechanical buzzer was shown to be of limited value in patients with multiple sclerosis with incomplete bladder emptying and detrusor overactivity.42 α-Adrenoceptor blockers relax the internal urethral sphincter in men, but there is no rationale for considering this treatment unless concomitant bladder outlet obstruction caused by a non-relaxing bladder neck or benign prostate enlargement is suspected.29 Botulinum toxin injections into the external urethral sphincter might improve bladder emptying in patients with SCI who have pronounced voiding dysfunction, but this intervention did not reduce PVR volumes in patients with multiple sclerosis.36

Surgical treatment
Surgical interventions can be considered in patients for whom conservative treatments have failed, although this is becoming increasingly uncommon for progressive non-traumatic neurological disorders because of the availability of less-invasive options. Table 2 shows the procedures that can be considered.

Follow-up of patients with neurogenic LUT dysfunction
In the absence of prospective long-term natural history studies, there is no consensus about how often a patient with neurogenic LUT dysfunction should be followed up. The population of patients at high risk of upper urinary tract damage should be followed up regularly with a patient-tailored approach that aims to achieve best possible quality of life and to protect the upper urinary tract.67 Follow-up should reflect regional guidelines based upon resource allocation.29

Future perspectives
There are several emerging diagnostic and therapeutic approaches that are likely to affect the management of neurogenic LUT dysfunction. Non-invasive tests to assess neurogenic LUT dysfunction are being explored, such as sensory evoked potentials88 and MRI.49 Functional MRI has been used to non-invasively assess upper urinary tract functions without the need for contrast medium in non-neurological patients312 and might become an option in those with neurogenic LUT dysfunction.

There is evidence to suggest that nocturia represents a disorder of circadian rhythm, and a preliminary study suggests that use of melatonin helps to improve nocturia;103 However, further studies are needed to prove its efficacy. There is also evidence that deep-brain stimulation of the subthalamic nucleus,104–106 pallidum,107 and thalamus.108 can improve in patients with movement disorders undergoing deep-brain stimulation of the subthalamic nucleus.98–100,110 pallidum,107 and thalamus.108

Another therapeutic strategy is tissue engineering, which has had limited success in treating high-pressure or poorly compliant bladders of patients with spina bifida.103 Studies in animal models of SCI that assessed the effects of anti-Nogo-A antibody showed earlier recovery of voiding;109 however, further studies are needed to assess the role of regenerative treatments for SCI in improving associated LUT dysfunction.111

Conclusions
LUT dysfunction is common in neurological patients and has a pronounced effect on quality of life. The high prevalence of dysfunction reflects the wide distribution of neural control of LUT functions in health. The site and nature of the neurological lesion determine the pattern of dysfunction. In general, progressive non-traumatic disorders are less often associated with upper urinary tract damage than are spinal cord injury and spina bifida.

History taking supplemented by the bladder diary provides a real-time assessment of symptoms. Although (video-)urodynamic investigations can be used to assess detrusor and bladder outlet function and provide information about detrusor pressure, compliance, and vesico-uretero-renal reflux, their place in the routine evaluation of LUT symptoms in patients with neurological disease is a topic of debate. Increasingly, neurologists are asking patients about LUT symptoms and, with an ever-expanding armamentarium of non-invasive and minimally invasive therapeutic options, they are becoming involved in the management of LUT dysfunction in partnership with urologists.

Contributors
JNP and TMK created the written content, figures, and panels, and reviewed the manuscript. CJF served as emendator.

Declaration of interests
JNP receives royalties from Cambridge University Press, has been involved in trials supported by Wellspect, FirstKind Ltd, and Allergan.
and has received speaker’s honoraria from Wellspect, Astellas, and Allergan. CJF reports grants and personal fees from Allergan, outside the submitted work. TMK is chairman of the non-profit organization Swiss Continence Foundation.

Acknowledgments

JNP undertook this work at UCLH/UCL Institute of Neurology and is supported in part by funding from the UK Department of Health NIHR Biomedical Research Centres funding scheme.

References


26 Kessler TM. Diagnosis of urinary incontinence. JAMA 2008; 300: 283.


29 Kessler TM. Diagnosis of urinary incontinence: JAMA 2008; 300: 283.


