

# INVESTIGATION AND MANAGEMENT OF NEUROGENIC BLADDER DYSFUNCTION

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**B**ecause of the complex nature of the neural control of the lower urinary tract, complaints about bladder function are common in patients with neurological disease. The main neural circuits controlling the two functions of the bladder—that is, storage and voiding—are trans-spinal so that intact cord connections between the pons and the sacral segments are necessary to sustain physiological control. Furthermore, input from higher centres is critical in the assessment of appropriate timing of voiding and many types of cortical disease can affect the centres involved with this. In addition to the spinal pathways and input from higher centres, the peripheral innervation to the bladder is through the pelvic plexus, sacral, and pudendal nerves.

However, despite this complexity of neural control, when considered from the point of view of possible dysfunctions, these are limited to those causing a failure of storage or those causing a failure of emptying. Most commonly patients with neurological disease have problems with the former and have incontinence. Some patients, however, may have urinary retention. In addition, there is a large group of patients, particularly those with disruption cord disease, who have a combination of incomplete emptying and bladder overactivity.

Although the patients' symptoms are generally a good guide as to the predominant underlying bladder disorder if it is detrusor overactivity, this is not the case in those with additional incomplete emptying; it is in these cases that investigations determining management are most important.

## INVESTIGATIONS

The investigations of patients with neurogenic bladder dysfunction are aimed at both improving symptoms and also preserving renal tract health.

### Prevention of upper tract damage

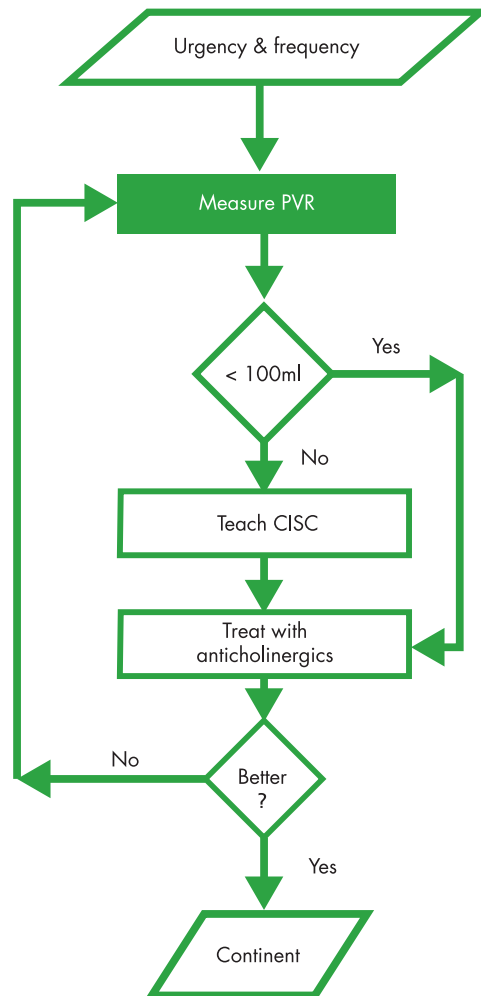
Following spinal cord trauma and in patients with spina bifida, upper urinary tract damage may occur secondary to the neurogenic bladder dysfunction. This is due to high detrusor pressures both throughout the filling phase (so called poor "compliance") as well as superimposed detrusor contractions occurring against a closed sphincter caused by the disorder known as "detrusor-sphincter dyssnergia". Patients with such conditions should be under the care of a urologist who will arrange annual surveillance of the upper urinary tract, using ultrasound to check there is not any ongoing insidious renal tract damage. In patients with chronic spinal disorders such as multiple sclerosis, although the extent of neurological disability may be as severe as in the patient who has had a traumatic spinal cord lesion, upper tract involvement is fortunately extremely uncommon. It is only likely to be a problem if the patient has had recurrent urinary tract infections and has an indwelling catheter. In general, therefore, investigations in patients with progressive neurological disease should be aimed primarily at improving bladder management options.

### Symptom management

If urinary frequency, urgency, and urge incontinence are major complaints it is highly likely that there is underlying detrusor overactivity. The best method of demonstrating this is to perform cystometry which will show involuntary contractions of the detrusor muscle. The formal International Continence Society definition of detrusor overactivity is that it is "a urodynamic observation characterised by involuntary detrusor contraction during the filling phase which may be spontaneous or provoked"; no limit is specified as to the amplitude of the contraction, but there is a rider that confident interpretation of low pressure waves (that is, < 5 cm H<sub>2</sub>O) depends on high quality urodynamic technique. The result is a small capacity bladder that develops unwanted contractions which the patient may be unable to suppress. A practical approach to such a patient is to consider treatment with anticholinergics, but only after measurement of the post-micturition residual volume (fig 1).

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**Figure 1** Practical algorithm for the management of patients with symptoms of detrusor overactivity.

Because spinal lesions cause neurogenic detrusor overactivity the predominant symptoms in such patients will be urgency and urge incontinence. However, the spinal disease is also likely to affect the neural pathways involved in bladder emptying so that incomplete bladder emptying may also exist. Although this may be relatively asymptomatic it can contribute significantly to the overall bladder dysfunction. Typically a patient with multiple sclerosis will present with complaints of urgency, frequency, and urge incontinence but only on direct questioning will admit to a poor stream, possibly difficulty with initiating micturition, and a sense of incomplete bladder emptying. The latter symptom is particularly unreliable because although most patients who complain of incomplete bladder emptying are correct, many of those who claim to be emptying to completion will not be.

Figure 1 shows the essential management algorithm of patients with complaints of urge incontinence. The only necessary measurement is an estimate of the post-micturition residual volume. Although now widely followed, this algorithm was initially opposed in urological circles as being “inadequate” as cystometry was not included. In certain circumstances full cystometry is indicated, coupled possibly with a video study to provide an anatomical study of the lower urinary tract. These investigations are best carried out

**Table 1** Indications for referral to urology

1	Recurrent urinary tract infections
2	Evidence of impaired renal function
3	Pain thought to be arising from the upper or lower urinary tract
4	Haematuria

by the urological team and absolute indications for a urological opinion are shown in table 1.

Measurement of the residual volume can be carried out using a small portable ultrasound device. The cost of these instruments has now dropped considerably and most nurse-led continence services will have access to one. The device is shown in fig 2.

Except for the debated value of sphincter electromyography (EMG) in patients with parkinsonism and bladder symptoms, clinical neurophysiology contributes little to the investigation of patients with established neurological disease.

### MEDICAL TREATMENT

The mainstay of the treatment of the symptoms of urgency, frequency, and urge incontinence is anticholinergic medication. Several alternative drugs are available for treatment of the overactive detrusor but, for most, clinical use is based on the results of preliminary, open studies rather than randomised, controlled clinical trials. Anticholinergics may be efficacious in many patients but they do have side effects, and patients often stop taking them. Their common mode of action is on the muscarinic receptors of the detrusor muscle, and whether they act predominantly on the M2 or M3 receptors seems to have little influence on their clinical efficacy.



**Figure 2** Continence nurse specialist with the portable ultrasound device for estimating the post-micturition residual volume of urine.

The antimuscarinic, anticholinergic agent atropine is rarely used in treatment of detrusor overactivity because of its systemic side effects, which preclude its use. Propantheline bromide is non-selective for muscarinic receptor subtypes and has a low bioavailability. It was a first choice agent for detrusor overactivity in the 1980s but has been largely supplanted by newer agents since. Trospium chloride is a quaternary ammonium compound and, although non-selective for the muscarinic receptor subtypes, it is a very efficacious anticholinergic. Tolterodine is a potent and competitive antagonist of the muscarinic receptor. Although no selectivity has been shown for individual receptor subtypes, it appears to show tissue selectivity for the bladder over the salivary glands. Oxybutynin has antimuscarinic, muscle relaxant, and local anaesthetic actions. It has been demonstrated to have a higher affinity for muscarinic M1 and M3 receptors than M2, but the clinical significance of this is unclear. The therapeutic effect of the immediate release formulation on detrusor overactivity is associated with a high incidence of side effects and its dose should be titrated. Side effects are typically antimuscarinic (dry mouth, constipation, blurred vision, drowsiness). With the recognised problem of central acetylcholine deficiency as a significant neurotransmitter in dementia, it is probably sensible to use anticholinergics that do not cross the blood-brain barrier such as tolterodine or trospium chloride in patients with cognitive impairment.

The most common side effect of the anticholinergic agents is dry mouth; it seems likely that this complaint is worse when blood concentrations are high and preparations which produce less in the way of peaks and troughs (that is, "long acting forms") are preferable. The "XL"/slow release preparations are made so by containing the active constituent in a capsule. This has a minute hole in it through which the medication is released as it passes through the small intestine. Under some circumstances patients may report passing the capsule in their faeces but this does not mean they have failed to absorb the medication.

Most commonly anticholinergic medication is used either alone or, if the patient is failing to empty their bladder adequately, in combination with clean intermittent self catheterisation. The latter procedure is most conveniently taught by a nurse continence advisor. There is an extensive network of these specialist nurses in the UK and often they are able to go into the patient's home to teach them the technique in their own environment. The patient is taught to identify the urethral orifice (obviously easier in men than women) and insert a catheter into the bladder to drain it. The catheter is then removed. Over the last 10 years there have been significant developments in the type of catheter available and now those most popularly used are coated with a lipophilic film which upon contact with fluid becomes highly lubricated and easy to pass. Some of the manufacturers now provide the catheter in a sachet containing fluid. These catheters are inevitably more expensive than the multiple use catheters that relied on applying KY jelly as a lubricant.

Patient reaction and acceptance of intermittent catheterisation is extremely variable. Some patients take to it well, particularly if they have spoken to another patient who has benefited from performing the technique. Others always find it difficult and do not persist with it. Since there is very little to be lost by the patient learning the technique of self

catheterisation, one approach is to teach most patients how to do it if they have a significant post-micturition residual volume (consistently above 100 ml) and are capable of performing the procedure, and see then if it helps them symptomatically.

Recurrent urinary tract infections can undeniably be a problem and its best if the patient learns to recognise the early symptoms of an infection and has available a short course of antibiotics to take as appropriate. Arrangements should be made for a urine specimen to be easily sent off to the laboratory before starting the antibiotics. Long term low dose antibiotics are not usually recommended. Nor is it advisable for asymptomatic patients to send regular specimens to the laboratory since those doing self catheterisation are likely to grow organisms from the urine although not actually have a urinary tract infection.

If, despite clean intermittent self catheterisation and taking an adequate dose of anticholinergic, incontinence is still a problem, the synthetic antidiuretic hormone desmopressin taken either at night or during the day (but not both) may be considered. This reduces urinary frequency for a number of hours and patients find it helpful if, for example, they are going on a long journey or out for a social occasion when they want to be free from urinary urgency. It is important, however, to stress to the patient that they must take this only once in 24 hours or be at risk of water intoxication.

## SECOND LINE TREATMENTS

Second line therapies aimed at lessening detrusor overactivity have been largely based on the principle of de-afferenting the bladder. Neurogenic detrusor overactivity can be caused either by loss of inhibition on the pontine micturition centre, as happens with supra-pontine pathologies, or if there has been disconnection of the pontine micturition centre from the sacral part of the cord, the emergence of a new reflex at spinal level. In these circumstances de-afferentation of the bladder using an intravesical vanilloid has been tried. First capsaicin was used but this was pungent and an unlicensed medicine, and was replaced by resiniferatoxin (RTX). Resiniferatoxin is obtained from the plant *Euphorbia resiniferi* and is known to be an ultra-potent capsaicinoid with a thousand times the neurotoxicity for unmyelinated C fibres as capsaicin, for an equal pungency so that an instillation of RTX is significantly less uncomfortable. Unfortunately multicentre trials to demonstrate the efficacy of RTX were unsuccessful, probably because its propensity to adsorb to plastic was not recognised. There are, however, some centres in the world that have persevered with this treatment and obtained impressive results in both neurogenic and non-neurogenic detrusor overactivity. It is hoped that this medication will become commercially available in the future.

A highly promising recent development has been the use of intra-detrusor injections of botulinum toxin. First described from Switzerland in the treatment of patients with spinal cord disease, it has been found to be effective in other causes of neurogenic bladder overactivity as well as non-neurogenic cases. The injections are given through a cystoscope at between 20 and 30 different sites in the detrusor muscle wall, avoiding the trigone. The introduction of injections through a flexible cystoscope has meant that the entire process can be achieved as an outpatient procedure, taking less than 20

minutes. The beneficial effect seems to be remarkable, in that it increases bladder capacity and virtually eliminates the sense of urgency, the effect lasting for between 6–9 months. Fortunately the efficacy of second and subsequent injections does not seem to be diminished and reports are now appearing of patients who have had repeat injections on at least four occasions with continuing benefit. As with botulinum toxin injections at other sites, very few adverse events have been reported. The range of patients for whom this treatment will be suitable remains to be defined.

### MEDICINAL CANNABINOID EXTRACTS

A preliminary open label study looking at the effect of sublingual cannabis spray to treat detrusor overactivity in advanced multiple sclerosis produced some encouraging results. It appears that the medication lessens the sense of urgency and reduces the number of episodes of incontinence, and patients were able to achieve improved bladder control, without unwanted psychotropic effects. The study included only patients with quite advanced multiple sclerosis who were facing the prospect of requiring an indwelling catheter, and many of them found it had a beneficial effect on other aspects of their neurological disability. A multi-centre placebo controlled double blind study in patients with multiple sclerosis is now in progress.

### FUTURE PHARMACOLOGICAL DEVELOPMENTS

The emerging understanding of the pharmacology of the neural control of the bladder suggests that there will probably soon be medications available with a central level effect that improve the efficiency of both the phase storage and of emptying. Studies are currently underway looking at the effect of 5-hydroxytryptamine (5-HT) antagonists as well as alpha delta ligands. It seems likely that in the not too distant future there will be a number of oral alternatives to the antimuscarinics to treat overactive bladder symptoms. Unfortunately at the moment there is no medication that improves neurogenic incomplete bladder emptying or retention.

### USE OF STIMULATORS

In patients with complete spinal cord transection, direct sacral root stimulation through an implanted stimulator may restore a degree of pelvic organ control; however, a dorsal rhizotomy is required to abolish reflex detrusor contractions. Such an implant is not used in patients with incomplete cord lesions. The technique, which stimulates the pelvic plexus through electrodes inserted through a sacral foramen, is known as “neuromodulation” and is mostly reserved for patients with severe idiopathic detrusor overactivity or complete urinary retention. Because of the expense of the stimulator device and the considerable surgical re-operation rate for the implant or the stimulating lead, these are not used for patients with progressive neurological disease in the UK.

### LONG TERM CATHETERS

Unfortunately in advanced neurological disease, long term indwelling catheters become the mainstay of urinary control. Many factors may complicate or impact on the choice of bladder management including neurological, urological, sexual, psychological, and social. Indeed, sometimes the preservation of quality of life for carers or lack of adequate nursing may dictate the use of indwelling catheters with little

regard for the potential longer term consequences. A recent survey estimated that 30% of patients with advanced multiple sclerosis utilised an indwelling catheter (40% urethral, 60% suprapubic).

The convenor or condom catheter is a sheath which is applied to the penis in a similar manner to a condom. It is the least satisfactory means of chronic urinary drainage as it does not drain the bladder per se and significant volumes of residual urine may remain in the bladder. This type of device is best employed, if at all, in the short term only. The sheath is prone to loose or poor fitting, and skin excoriation and infection are other problems encountered.

Although urethral catheterisation does provide effective bladder drainage it is not an ideal long term solution. Erosion of the urethra may occur in both men and women, whereas men are also prone to developing urethral stricture disease, although neither of these problems tends to arise with its short term use.

Most urologists agree that a suprapubic catheter is the preferred route for long term bladder drainage if an indwelling catheter is required. A reduction in maximal detrusor pressure, improvement in bladder morphology, and a resolution of reflux have been reported. Renal function is usually well preserved. A bowel injury or haematoma can occur at catheter insertion, but this is rare and should not happen if ultrasound guidance is utilised.

Complications common to both urethral and suprapubic catheterisation include urine bypassing the catheter leading to incontinence, and recurrent infections and catheter blockage. Bypassing is more prevalent with a urethral catheter as the inflated balloon rests on the sensitive trigonal area and may precipitate bladder spasms. Anticholinergics are the treatment of choice for catheter induced bladder spasm.

Recurrent urine infection and its sequelae cause significant difficulties in both forms of catheterisation. Initially a biofilm develops on the catheter, usually stemming from a urine infection with a urease-producing organism, and this ultimately may lead to encrustation and catheter blockage. All silicone catheters are less irritant and possess anti-adhesive properties, and their time to encrustation is twice that of the hydrogel-coated latex catheter. A minimum 16 French (minimum size) all silicone catheter is recommended for long term bladder drainage, and it should be changed at least every three months, depending on problems with infections and encrustation. Bearing in mind that the urine in patients with long term catheters is *always* colonised with a variety of microbials, urine should only be sent for microscopy and culture when a symptomatic infection is suspected. Antibiotics should only be used sparingly and prophylaxis in these patients should be resisted.

It has been speculated that chronic bladder catheterisation may be a risk factor for developing bladder cancer, but this remains unproven to date. Finally, as a general rule, a surveillance ultrasound of the upper tracts and a serum creatinine should be performed every 1–2 years to ensure stable renal anatomy and function.

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