Management of neurogenic detrusor overactivity

Cassra B. Clark, MD, Radhika Ragam, MD, Akhil K. Das, MD, Patrick J. Shenot, MD

Department of Urology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

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Introduction: *Neurogenic lower urinary tract dysfunction (NLUTD) refers to altered function of the urinary bladder, bladder outlet, and external urinary sphincter related to a confirmed neurologic disorder. Neurogenic detrusor overactivity (NDO) is a subset of NLUTD that frequently results in incontinence and may be associated with elevated bladder storage and voiding pressures resulting in upper urinary tract damage.*
Materials and methods: *This article provides an update on the evaluation and management of patients with NDO. Basic bladder physiology as well as classification of NLUTD, initial urologic evaluation, and management*

options ranging from the most conservative to surgical interventions will be covered.
Results: *NDO may be managed by conservative, pharmacologic, and surgical methods. Untreated or inadequately managed NDO may result in significant urologic morbidity and mortality, making careful evaluation and lifelong management necessary to optimize quality of life and prevent secondary complications.*
Conclusions: *Patients with NDO should have life-long urologic surveillance and follow up. The extent of regular evaluation and testing should be based on the principal of risk stratification. Treatment for NDO should be considered not only for clinical symptoms such as incontinence, but also aimed at preserving renal function.*

Key Words: bladder augmentation, neurogenic bladder, urinary incontinence

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) refers to altered function of the urinary bladder, bladder outlet, and external urinary sphincter related to a confirmed neurologic disorder. Common causes of NLUTD include spinal cord injury (SCI), multiple sclerosis (MS), myelomeningocele, Parkinson's disease, and cerebrovascular accident (CVA). While CVA is a most common of these conditions, multiple sclerosis and spinal cord injury/dysfunction are the most common neurologic disorders to result in clinically significant NLUTD.[1,2] The vast majority of patients with SCI have NLUTD, and about 85% of patients with MS have lower urinary tract symptoms (LUTS).[3]

Neurogenic detrusor overactivity (NDO) is a subset of NLUTD that frequently results in urinary frequency, urgency, and urge incontinence. It may be associated with elevated bladder storage and voiding pressures. Elevated bladder pressures, can lead not only loss of urinary control, but to upper urinary tract damage and renal failure.

Address correspondence to Dr. Cassra B. Clark, Department of Urology, Thomas Jefferson University, 1025 Walnut Street, Suite 1100, Philadelphia, PA 19107 USA

Classification of neurogenic lower urinary tract dysfunction

The functional system for classification of NLUTD is simple, intuitive, and widely accepted. The function of the bladder is to store urine at appropriate pressures and volumes without incontinence, and empty completely at the appropriate place and time. This system divides lower urinary tract dysfunction into two broad categories: 1) failure to store and 2) failure to empty. Failure to store urine can result from either bladder dysfunction such as NDO or impaired bladder compliance, or outlet dysfunction such as intrinsic sphincter deficiency. Failure to empty may result from bladder dysfunction such as impaired bladder contractility. Outlet obstruction, such as detrusor external sphincter dyssynergia, may also lead to failure of bladder emptying.

Historically, sequela of poorly managed lower urinary tract dysfunction has been a significant cause of morbidity and mortality in patients with NDO, particularly those with SCI. Mortality rates from genitourinary complications in SCI patients have declined significantly, from approximately 50% in the 1950s to less than 3% today.[4] The goal of NLUTD management, in general, and NDO specifically, is to prevent upper urinary tract deterioration, minimize

urinary incontinence, prevent urinary tract infections and urolithiasis, and avoid autonomic dysreflexia.[5]

Initial urologic evaluation

Initial evaluation includes a detailed history and physical examination, urinalysis, and bladder or catheterization diary. Patients who spontaneously void should be carefully evaluated. A post void residual should be obtained in nearly all who spontaneously void. Further evaluation can be tailored based on stratification of risk for lower and upper urinary tract complications. Initial evaluation of patients at high risk for urologic complications would generally include upper tract imaging, assessment of renal function, and urodynamic evaluation. It is important to recognize that an acute neurologic event such as SCI often is followed by a phase of spinal shock. Therefore, urodynamic evaluation should be deferred until the neurologic condition is stabilized and spinal shock has resolved.

Conservative management

Behavioral interventions for the management of urinary incontinence secondary to NDO may be effective in selected cases. For patients who void spontaneously and have no bladder emptying deficits, timed voiding may effectively minimize or eliminate incontinence related to involuntary detrusor contractions. Adapting drinking habits to spread fluid intake throughout the course of the day, and in some cases fluid restriction, is often employed in patients with NDO to minimize incontinence and lengthen intervals between catheterization. These management options need to be carefully individualized to each patient as this population often suffers from neurogenic bowel and chronic constipation which can be exacerbated by low fluid intake. Another method to lessen detrusor overactivity and improve storage is through activation of detrusor inhibitory reflexes stimulated by activity in pelvic floor musculature.[6] Pelvic floor exercises may be offered in carefully selected patients with less severe neurologic deficits and although it may have a role in management of patients with NLUTD with multiple sclerosis or CVA, it is rarely useful in patients with SCI.

Oral pharmacologic treatment of NDO

Systemic pharmacotherapy has long been utilized in the management of urinary incontinence secondary to NDO event though many of the commonly used agents have not been widely studied in neurogenic populations. These agents are commonly used in patients with overactive bladder (OAB) to improve symptoms of urinary urgency, frequency, and urge incontinence. The objective of pharmacologic therapy in patients with neurogenic bladder is to minimize episodes of incontinence resulting from detrusor overactivity and to lower detrusor pressures, particularly during the storage phase in order to minimize the risk of upper tract complications.

The most commonly used oral systemic agents are antimuscarinics and beta-3 agonists. These are often used adjunctively with intermittent catheterization in patients who have deficits in bladder emptying. Antimuscarinic agents, also known as anticholinergics, have been consistently shown to improve clinical and urodynamic parameters in patients with NDO. They inhibit the binding of acetylcholine at M2 and M3 muscarinic receptors on detrusor smooth muscle, allowing for relaxation of the detrusor muscle.[7] The M3 receptors appear to be the most important for detrusor contraction in the healthy state, but M2 receptors may play an important role in detrusor contractions in patients with neurogenic bladder dysfunction.[8]

Antimuscarinic treatment should be considered not only in patients with symptomatic bother from NDO, but also in those with worrisome urodynamic findings. Published studies on the use of antimuscarinics are characterized by the lack of validated and standardized reported outcomes, lack of long term follow up, and absence of sufficient evidence in particular groups of patients with NDO. Most studies primarily include patients with SCI, and to a lesser extent, patients with multiple sclerosis. A systematic review and meta-analysis of 16 randomized controlled trials published between 1966 and 2011 involving 960 patients treated with antimuscarinic medications found a significant improvement in maximum cystometric capacity, and lower detrusor pressure compared to placebo.[9] In a review including other non-randomized control trials of treatment with oxybutynin, propiverine, and trospium, maximum detrusor pressure decreased by 30%-40% and bladder capacity increased by over 30%-40%. Urodynamic improvements appear to be dosed related with further decreases in detrusor pressures at higher doses.[10] Flexible dosing, in which patients self-select different doses of antimuscarinics, may improve efficacy without diminishing tolerability.

These antimuscarinic agents are inherently non-selective and bind to smooth muscle receptors of other organs resulting in the commonly reported side effects such as dry mouth, constipation, and pupillary dilation with blurred vision. These side effects are mediated by

blocking M3 receptors in the salivary glands, intestinal smooth muscle, and ciliary and iris sphincter muscles respectively. Other anticholinergic side effects may include headache, drowsiness, and tachycardia.

There is a variety of marketed antimuscarinic agents. Although there are different molecular structures, pharmacokinetic profiles, and muscarinic receptor subtype specificities, there does not appear to be a clear superiority of any one agent in managing either clinical symptoms or improving urodynamic parameters in patients with NDO. Intolerance to one antimuscarinic agent does not necessarily portend intolerance to a different agent.

Newer antimuscarinic agents may be more selective for cholinergic detrusor receptors therefore minimizing systemic side effects. Extended release formulations of antimuscarinic medications avoid high peaks in drug levels and result in less dry mouth and constipation than the immediate release preparations.[11] Transdermal and intravesical formulations of oxybutynin offer the advantage of reducing the severity of the anticholinergic side effects of dry mouth and constipation by avoiding the first pass of oxybutynin through the liver. One pharmacologically active metabolic product resulting from first pass metabolism of oxybutynin is desethyloxybutynin, which appears to be responsible for many of the antimuscarinic side effects of immediate release oxybutynin. Oxybutynin is primarily metabolized in the liver and bowel wall by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Intravesical oxybutynin has been used on an "off-label basis" to minimize the effect of first pass metabolism.[12]

Beta-3 agonists, including mirabegron and vibegron, activates detrusor beta-3 receptors to cause relaxation of detrusor muscle. Mirabegron received FDA approval in 2012 for treatment overactive bladder Although it is clearly effective in increasing bladder capacity as well as decreasing urinary frequency and urge incontinence in patients with idiopathic OAB, it has not been extensively studied as a first line treatment in patients with NDO.[13] In a prospective randomized placebo controlled study of 66 patients with NDO resulting from SCI or multiple sclerosis, the use of mirabegron significantly increased the volume at first detrusor contraction and significantly improved patient reported outcomes.[14]

Mirabegron has been shown to result in meaningful improvements in patient reported outcomes in patients with OAB when used as an add-on treatment to antimuscarinic medications, particularly solifenacin. Although the evidence for use of beta-3 agonists in patients with NDO is still limited, these medications are well-tolerated and have an excellent safety profile. They should be considered as either an alternative to antimuscarinic therapy or as an add-on treatment for patients with persistent symptoms despite treatment with antimuscarinics or botulinum toxin injections.[15]

Intra-detrusor botulinum toxins

Intra-detrusor injection of botulinum toxin has widespread use in patients with NDO resulting from an array of neurologic conditions including multiple sclerosis, SCI, Parkinson's disease, CVA, and myelomeningocele. It has clearly been proven to be a safe and effective long term therapy in this patient population.[16] In clinical practice, it is most commonly utilized in patients who exhibit intolerance to, or have symptoms refractory to antimuscarinic therapy. It may be utilized with or without intermittent catheterization. Patients who spontaneously void must be willing to perform intermittent catheterization post-treatment due to the risk of urinary retention.

OnabotulinumtoxinA (Botox) was approved as a treatment for NDO in 2011. It is generally administered cystoscopically in twenty divided doses of 200 units. This treatment can generally be administered in an office setting with topical anesthesia using 2% lidocaine instilled in the bladder. In rare cases, patients with severe autonomic dysreflexia may require a general anesthetic. In our experience, topical and intravesical lidocaine administration, minimizing bladder distention during treatment, and the use of a flexible cystoscope minimizes the development of autonomic dysreflexia in the vast majority of patients.

Botulinum toxins prevent the release of acetylcholine on the pre-synaptic parasympathetic nerve ending resulting in detrusor relaxation.[17] These agents have been shown to significantly improve bladder capacity, increase volume at first detrusor contraction, reduce maximum detrusor pressure, and reduce episodes of urinary incontinence in comparison to placebo.

Due to the local effect of botulinum toxin, systemic side effects are exceedingly rare. The most common adverse events in this population include urinary tract infections, hematuria related to injection, and urinary retention. Urinary retention is of no concern in patients on intermittent catheterization. In patients who void spontaneously, the risk of urinary retention and need for intermittent catheterization should be discussed prior to treatment.

The durability of response is variable but typically ranges from 6 to 9 months. Retreatment is generally patient directed and requested when the beneficial effects of treatment begin to subside. In patients

with adverse urodynamic parameters, we typically recommend clinical reassessment including urodynamic evaluation 3 months after the first injection.

Other preparations of botulinum toxin, while less commonly utilized, appear to offer similar outcomes. AbobotulinumtoxinA (Dysport) is generally used at a dose of 750 IU. In one study, it was used as successful salvage therapy in over half of patients after failed treatment with onabotulinumtoxinA.[18]

Surgical management of NDO

Surgical management of NDO with either bladder augmentation or urinary diversion is generally reserved for situations where medical methods have failed to achieve acceptable continence. Surgical intervention is also indicated in situations where ongoing adverse urodynamic findings, such as poor bladder compliance, risks progressive upper urinary tract deterioration that may progress to renal failure.

Bladder augmentation is the preferred method of surgical treatment of NDO. It provides the advantage of keeping the native urinary tract otherwise intact as access to the upper tracts via preservation of the native ureteral orifices. This is important as this population has a higher risk of upper tract urolithiasis. The functional and clinical outcomes of bladder augmentation using a bowel segment in patients with NDO are consistent and predictable.[19] Reliable improvements in bladder compliance, urinary incontinence, and quality of life are consistent.[20] Although any bowel segment may be used, ileum and colon are most commonly chosen in clinical practice.

There are a number of absolute and relative contraindications to bladder augmentation. The most important absolute contraindication is inability to perform intermittent catheterization, such as those with quadriplegia, or those unwilling to perform intermittent catheterization. Bladder augmentation should not be considered in patients with a history of bladder cancer. Metabolic alterations may result when augmented bowel segments are exposed to urine as these segments have preserved absorptive and secreting properties. Evaluation for chronic kidney disease remains important in order to minimize the risk of clinically meaningful hyperchloremic metabolic acidosis that may develop in patients undergoing bladder augmentation with ileal or colonic segments. In general, candidates for bladder augmentation should have a creatinine clearance over 40 mL/min.

Other patient specific factors include inflammatory bowel disease or prior extensive bowel resection. Functional bowel loss may affect absorption of not only nutrients, but also water from small and large bowel. A change in bowel habits in this population, particularly loose or frequent bowel movements, may dramatically impact quality of life.

While metabolic complications are uncommon in properly selected patients, there are several long term complications of bladder augmentation including the formation of bladder stones, intraperitoneal bladder rupture, and the development of adenocarcinoma or urothelial carcinoma. The risk of bladder stone formation can be minimized by implementing a bladder irrigation regimen to prevent mucus accumulation. Intraperitoneal bladder rupture is uncommon in adult patients with bladder augmentation. Great care with patient selection to assure compliance with recommended catheterization regimens and prompt attention to difficulty with catheterization minimizes this potentially life-threatening complication.

Incontinent or continent urinary diversion may be offered as a final option for patients who have failed more conservative management. In patients able to do intermittent catheterization through a catheterizable, abdominal stoma, continent diversion may be considered. This option carries many of the same long term risks as bladder augmentation including metabolic complications and urolithiasis.[21] Continent diversion should only be offered in patients with adequate renal function due to the large segment of intestine exposed to urine. Other potential complications include ureteral-intestinal anastomotic stricture, stomal stenosis, stomal incontinence, peristomal hernias, and urolithiasis.

Incontinent urinary diversion is usually considered a last resort option. In properly selected and motivated patients, urinary diversion can offer significant improvement in long term quality of life. The ileal conduit is the most commonly utilized form of incontinent urinary diversion. Although it generally allows preserved renal function in the short to medium term period, patients with longstanding incontinent urinary diversion with ileal conduits may see a gradual decline in renal function.

The incontinent ileovesicostomy also allows continuous drainage of urine using an intestinal stoma. Advantages of this reconstruction is that it avoids the need for cystectomy and maintains normal anatomy of the ureterovesical junction allowing access to the upper tracts for endoscopic management of stones.[22] Disadvantages include the potential increase of malignancy due to preservation of the bladder segment as well as the potential for urethral incontinence. The ileovesicostomy is effective in preserving renal function by allowing low-pressure storage and

drainage of urine. We have observed some patients develop urinary stasis which can result in frequent urinary tract infections. Patient selection is critical and it is important to assure a functional bladder outlet prior to considering ileal vesicostomy to minimize the risk of urethral incontinence. Complications are similar to other types of incontinent urinary diversion including stomal stenosis, peristomal hernias, and urolithiasis.[23] Patients should be counseled regarding the significant risk of needing additional treatment or surgery following ileovesicostomy.

Conclusions

Patients with NDO should have life-long urologic surveillance and follow up. The extent of regular evaluation and testing should be based on the principal of risk stratification. Routine upper tract imaging and urodynamics is not indicated in NDO patients at low risk of renal and urologic complications; an example would be a patient with urge incontinence from a CVA who is adequately medically managed. In contrast, patients with worrisome storage parameters that risk upper tract damage require periodical evaluation. We recommend annual clinical assessment in patients with high risk NLUTD for assessment of symptoms, physical examination, evaluation of renal function, and upper tract imaging. The frequency of urodynamic studies in this patient population should be individualized. Treatment for NDO should be considered not only for clinical symptoms such as incontinence, but also aimed at preserving renal function. □

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