Consensus Statement on Neurogenic Detrusor Overactivity: Multiple Sclerosis and Spinal Cord Injury

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ABSTRACT

In October 2011, a multidisciplinary panel of health care professionals and representatives from key associations advocating for patients with multiple sclerosis (MS) and spinal cord injury (SCI) met to discuss issues in the diagnosis, management and treatment of adults with symptoms of neurogenic detrusor overactivity (NDO). This supplement discusses the effect of NDO on the quality of life and overall health of patients with MS and SCI, identifies health care provider and patient barriers to care, describes best practices to screen for urinary dysfunction, and summarizes the panel's recommendations for management of NDO in this patient population. Antimuscarinic agents are first-line therapy, and oxybutynin is the only antimuscarinic agent approved specifically for detrusor overactivity associated

with a neurologic condition. Recently, onabotulinumtoxinA intradetrusor injection was approved by the US FDA for the treatment of detrusor overactivity in patients with neurologic conditions, such as MS and SCI. Sacral nerve stimulation is approved for idiopathic OAB but not for the treatment of neurogenic-related bladder dysfunction. Bladder augmentation or urinary diversion is typically reserved for patients who fail less-invasive therapies. Clean intermittent catheterization is performed commonly for urinary retention in patients with SCI and may also be needed for some patients with MS as their disease progresses and increases in residual urine in the bladder contribute to symptoms. Long-term follow-up of patients with NDO is important because changes in detrusor compliance and urodynamic patterns may occur over time.

Target Audience

This activity is designed for urologists, neurologists, physiatrists, and other health care professionals interested in or involved with the management of patients with multiple sclerosis or spinal cord injury who are at risk for neurogenic detrusor overactivity.

Educational Objectives

- Describe the effect of bladder dysfunction on health and health-related quality of life in individuals with multiple sclerosis (MS) and spinal cord injury (SCI)
- Identify factors and barriers influencing optimal management of neurogenic detrusor overactivity (NDO) across specialties
- Discuss the clinical aspects of NDO including its multiple etiologies, patient evaluation, varying treatment goals, and common coexisting conditions
- Review current and future options for the management of NDO in patients with MS and SCI
- Adopt new standards of care for multidisciplinary management of NDO in the practice setting

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INTRODUCTION

In October 2011 a multidisciplinary panel of prominent clinicians (urologists, neurologists, physiatrists, nurse practitioners) and representatives from key associations, including the Consortium of Multiple Sclerosis Centers, the United Spinal Association, Inc., and the Multiple Sclerosis Association of America, met to discuss issues in the assessment, diagnosis, and treatment of adults with neurologic disease or injury and symptoms consistent with overactive bladder (OAB).

In sensate individuals, neurogenic detrusor overactivity (NDO) may cause symptoms similar to OAB, such as urgency, with or without urinary incontinence, often with frequency and nocturia [1]. In individuals with spinal cord injury (SCI), the presenting symptom of NDO is more commonly urinary incontinence. The term OAB, as defined by urgency, with or without urgency urinary incontinence, often with frequency and nocturia, refers to "idiopathic" OAB, in which there is no identifiable cause. In patients with neurologic diseases, lower urinary tract dysfunction may arise from the bladder itself as the result of detrusor overactivity or underactivity (including areflexia), or from the urethral sphincter, in the form of detrusor-sphincter dyssynergia. Neurogenic detrusor overactivity, formerly called "detrusor hyperreflexia" refers to the presence of involuntary bladder contractions on urodynamic study in a patient with a known neurologic condition [1].

These and other terms used throughout this article are defined in Table 1 [1,2]. Signs and symptoms suggestive of obstruction—low urine flow, intermittency of urine stream, and incomplete bladder emptying—also are seen in some patients with neurologic disorders due to impaired bladder contractility or the loss of coordination between bladder and sphincter, a condition referred to as "detrusor-sphincter dyssynergia," which is typically seen in patients with SCI [3]. Therefore, in the evaluation of lower urinary tract dysfunction in patients with neurologic disease or injury, the potential for both bladder and sphincter dysfunction must be considered.

Two common neurologic causes of detrusor overactivity are multiple sclerosis (MS) and SCI, and these two patient populations will be the focus of this report. Approximately 400,000 people in the United States have MS, and 10,400 new cases are diagnosed annually [4]. Spinal cord injury affects approximately 265,000 individuals in the United States, and 12,000 new cases occur each year [5].

The major differences in these two neurological diseases are the progressive nature of MS and that urinary problems in patients with MS may be related to storage and/or emptying problems. Other complications in patients with MS are mobility impairment, cognitive changes, fatigue, and environmental barriers. The most frequent symptoms are those of frequency, urgency, and urgency urinary incontinence [6]. At least one moderate to severe urinary symptom is reported by 65% of patients with MS [7]. In some studies, 21% to 50% of patients experience frequent episodes of urinary incontinence in addition to hesitancy, and 2% to 52% report obstructive symptoms with urinary retention [7-10]. The onset of symptoms occurs an average of 6 years (range, 5 to 9 years) after the diagnosis of MS. According to de Sèze et al, [11] detrusor and sphincter problems are inevitable and may be a presenting symptom in 10% to 17.5% of patients [11,12]. Neurogenic detrusor overactivity is the most common urodynamic finding, in association with either a synergistic or dyssynergic striated

Table 1. Definitions [1,2].

Overactive bladder syndrome	Urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of infection or other obvious pathology.
Bladder compliance	Relationship between change in bladder volume and change in detrusor pressure (Δvolume/Δpressure).
Detrusor overactivity (DO)	A urodynamic observation characterized by involuntary detrusor contractions (IDCs) during the filling phase, which may be spontaneous or provoked. DO may be further characterized as neurogenic DO, which means it is associated with a relevant neurologic condition (eg, SCI, MS) or idiopathic DO, which means there is "no defined cause" (nonneurogenic).
Neurogenic detrusor activity	This term replaced "detrusor hyperreflexia."
Idiopathic detrusor overactivity	This term replaced "detrusor instability."
Detrusor leak-point pressure	A measure of detrusor pressure in a patient with decreased bladder compliance. It is defined as the lowest detrusor pressure at which urine leakage occurs in the absence of either detrusor contraction or increased abdominal pressure. The higher the outlet resistance, the higher the detrusor leak-point pressure.
Normal detrusor function	Characterized by a voluntary initiated continuous contraction that leads to complete bladder emptying within a normal time span and in the absence of obstruction.
Detrusor underactivity	A contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span in the absence of obstruction.
Acontractile detrusor	No demonstrable contraction during urodynamics.
Detrusor areflexia	Absence of reflex bladder emptying resulting in an acontractile detrusor (see above). Term is used to refer to the lack of bladder contraction due to neurologic disease or injury.
Bladder outlet obstruction	Generic term for obstruction during voiding, characterized by increased detrusor pressure and reduced urine flow rate.
Detrusor-external-sphincter dyssynergia (DESD)	Occurs when there is an involuntary increase in external sphincter activity associated with DO and also with voiding. It is caused by a neurologic lesion in the suprasacral spinal cord (ie, above the sacral micturition center). The detrusor contracts involuntarily against a relatively closed sphincter, which results in high pressure and can cause impaired bladder compliance over time. DESD may be considered a urodynamic risk factor for upper urinary tract deterioration, especially in a male patient.
Detrusor internal sphincter dyssynergia (DISD)	Dyscoordination of the smooth muscle of the bladder neck and proximal urethra. In the case of neurologic disease, if a suprasacral spinal cord lesion is above the level of the sympathetic ganglia (T10, L1), DISD may occur in conjunction with DESD.
Lower urinary tract symptoms (LUTS)	Term applied to include both storage and emptying symptoms.

Table 2. Urodynamic findings in multiple sclerosis [6,13].

Urodynamic Pattern	Patients (%) Affected
Detrusor overactivity	~34%-99%
Detrusor overactivity, striated detrusor-sphincter dyssynergia	~30%-65%
Impaired detrusor contractility or areflexia	~5%-37%

Table 3. Location of spinal cord injury and urodynamic findings [13,15].

Location of Lesion	Lower Urinary Tract Changes
Suprasacral, complete lesion	Detrusor overactivity, smooth sphincter synergia (with lesions below the sympathetic outflow) and striated sphincter dyssynergia
At or above spinal level of T6	May result in smooth sphincter dyssynergia
Sacral T12 to L1 and below	Detrusor areflexia with high or normal compliance is the common initial result, but decreased compliance may develop.

sphincter (Table 2) [6,13]. Eventually, 37% to 99% of patients with MS may report symptoms of OAB, and 34% to 79% may report voiding or obstructive symptoms, with chronic urinary retention occurring in 25% [11]. The prevalence of urinary symptoms correlates with disease severity; once the patient experiences difficulty walking, the probability of lower urinary tract symptoms is 100% [14].

In SCI, the majority of patients have voiding dysfunction, even if they are ambulatory with incomplete injuries [15]. The location of the lesion determines the urodynamic findings (Table 3),[13,15] and the management of patients with SCI preferably should be based on those urodynamic findings rather than inferences from the patient's neurologic history and evaluation.

EFFECT OF NEUROGENIC DETRUSOR OVERACTIVITY ON QUALITY OF LIFE AND OVERALL HEALTH IN PATIENTS WITH MS AND SCI

Experience in patients with MS and SCI indicates that symptoms of detrusor overactivity, especially incontinence, affect emotional well-being, social interactions, and relationships. Patients with MS report that incontinence is one of the most troubling aspects of the disease and greatly diminishes quality of life (QoL) [16]. Among a series of patients with MS interviewed regarding QoL, respondents reported that urinary frequency or incontinence negatively affected emotional health (31%), ability to perform household chores (22%), and ability to participate in physical recreation (28%) [9]. Similarly, in patients with SCI the presence of complicating medical problems such as incontinence appears to have a greater negative impact on QoL than the extent of SCI per se [17]. In patients with MS or SCI, effective bladder management has been shown to improve QoL and reportedly improves disability in patients with MS [18,19].

Patients with SCI and MS are at risk for multiple bladder-related morbidities, including urinary tract infection (UTI), sepsis, upper and lower urinary tract deterioration, upper and lower urinary tract calculi, autonomic dysreflexia, skin complications and depression [13,20,21]. In patients with SCI, failure to adequately manage lower urinary tract dysfunction can lead to significant morbidity and mortality. Historically, renal disease was the major cause of death for individuals with paraplegia [22]. More recently, as a result of improved diagnosis and treatment, the leading causes of death in SCI are pneumonia, septicemia, heart disease, accidents, and suicide [23,25]. However, overall survival among patients with SCI has increased.

Unlike SCI, MS rarely causes upper urinary tract damage from the standpoint of high-pressure urine storage, but can do so in men [6]. Participants in the consensus panel asserted that long-standing, untreated urinary retention and recurrent pyelonephritis can result in upper-tract damage. Patients with MS are at increased risk for lower UTI, with rates ranging from 13% to 80% reported in the literature [6]. In a recent US survey of patients with MS, 29.2% had a diagnosis of UTI during a 1-year period [26]. Febrile UTIs (pyelonephritis, orchitis, or prostatitis) occur on average in 9% of patients with MS (range, 2% to 23%) [6]. Urinary tract infections have been implicated in exacerbations of symptoms in patients with MS and are a cause of death in this population more often than in the general population [27-30].

CLINICAL ASPECTS: ACCESS TO CARE

In the evaluation of lower urinary tract dysfunction in patients with MS and SCI, provider and patient barriers to care are important considerations. Principal providers of care for patients with MS are neurologists and primary care doctors, whereas patients with SCI are cared for by neurologists and physiatrists. At the primary provider level, family practitioners, internists, neurologists, physiatrists, nurse practitioners/physician assistants may not be prepared to address bladder issues. They may lack training on screening for bladder dysfunction, may be unprepared to discuss the subject with patients, and may not be aware of all available and recent therapeutic modalities. Physicians should consider referring patients with significant bladder dysfunction to a urologist for assessment.

For the patient with MS, unless care is provided for by a multispecialty MS center, referral is a common option for most neurologists. Patients with MS receive MS-specific care from neurologists, physiatrists, or neurologic specialists such as nurse practitioners or physicians assistants. Primary care needs are usually obtained through community-based care programs. Patients who receive care in specialty MS centers generally have their bladder symptoms assessed and treated as part of their care program. Urologic referral is often made following persistent UTIs or symptoms that are refractory to standard protocols. Community-based neurologists usually refer patients for urologic assessment at the onset of persistent symptoms, since individual practices are not equipped to address these complex MS problems. Urologists are generally consulted for lower urinary tract dysfunction not amenable to simple treatment; thus, neurologists, physiatrists, and primary care providers should be prepared to identify these patients and provide timely referral. Even amongst urologists, great variation exists in urologic practice in terms of initial evaluation, follow-up, and surveillance among spinal injury units [31], which Boone (2004) has attributed to a lack of evidence-based decision-making [32]. Moreover, there are no definitive consensus guidelines in the urologic literature on how to manage lower urinary tract symptoms in patients with MS and SCI.

A number of patient-related barriers to care have been identified. Patients often are reluctant to discuss bladder issues with health care providers because of embarrassment and/or sociocultural stigma related to urinary incontinence. They may feel that their lower urinary tract symptoms are a lower priority relative to other disease-related concerns. Patients may not be aware that serious complications can result from mismanagement of incontinence. Other barriers include the perception that bladder issues are not life-threatening, fear of needing invasive surgical intervention, a lack of awareness that effective treatment options are available, and a lack of access to treatment options covered under insurance plan benefits.

EVALUATION OF BLADDER SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS AND SPINAL CORD INJURY

A one-page questionnaire is helpful to screen for urinary issues in outpatient departments providing care to patients with MS or SCI and to help identify patients who would benefit from referral to a specialist. Questionnaires can be downloaded from the following websites:

www.befreefromoab.ie/resources/symptom-questionnaire.html

www.prolutssh.com/oab.html

Another questionnaire that is pertinent to MS is in development—the ACTIONABLE MS Urinary Function Screening Tool [33].

Multiple Sclerosis

It is believed that urologic symptoms in patients with MS tend to increase with age, length of time from diagnosis, and disease progression [14]. Nevertheless, patients with MS can present with bladder dysfunction even early in their disease—a disease that is unpredictable and variable. Upper urinary tract complications are uncommon in patients with MS [34]. However, patients with MS are at an increased risk for lower UTIs, which can be associated with disease exacerbation and increased mortality [27-30]. Figure 1 summarizes the essential elements in the evaluation of lower urinary tract dysfunction in the patient with MS.

Spinal Cord Injury

Considering the risk for upper urinary tract damage if underlying lower urinary tract dysfunction is not managed adequately, patients with SCI should undergo baseline urodynamic studies and, if appropriate, should be evaluated by a urologist. The risk for upper tract damage is far greater in patients with SCI than in patients with progressive neurologic diseases such as MS, even when associated with severe disability and spasticity [13]. Risk factors for upper urinary tract deterioration in patients with suprasacral SCI include high-pressure storage (poor compliance), high detrusor leak-point pressure (> 40 cm H_2O), chronic bladder overdistension, and vesicoureteral reflux with

Figure 1. Evaluation of lower urinary tract dysfunction in patients with multiple sclerosis.
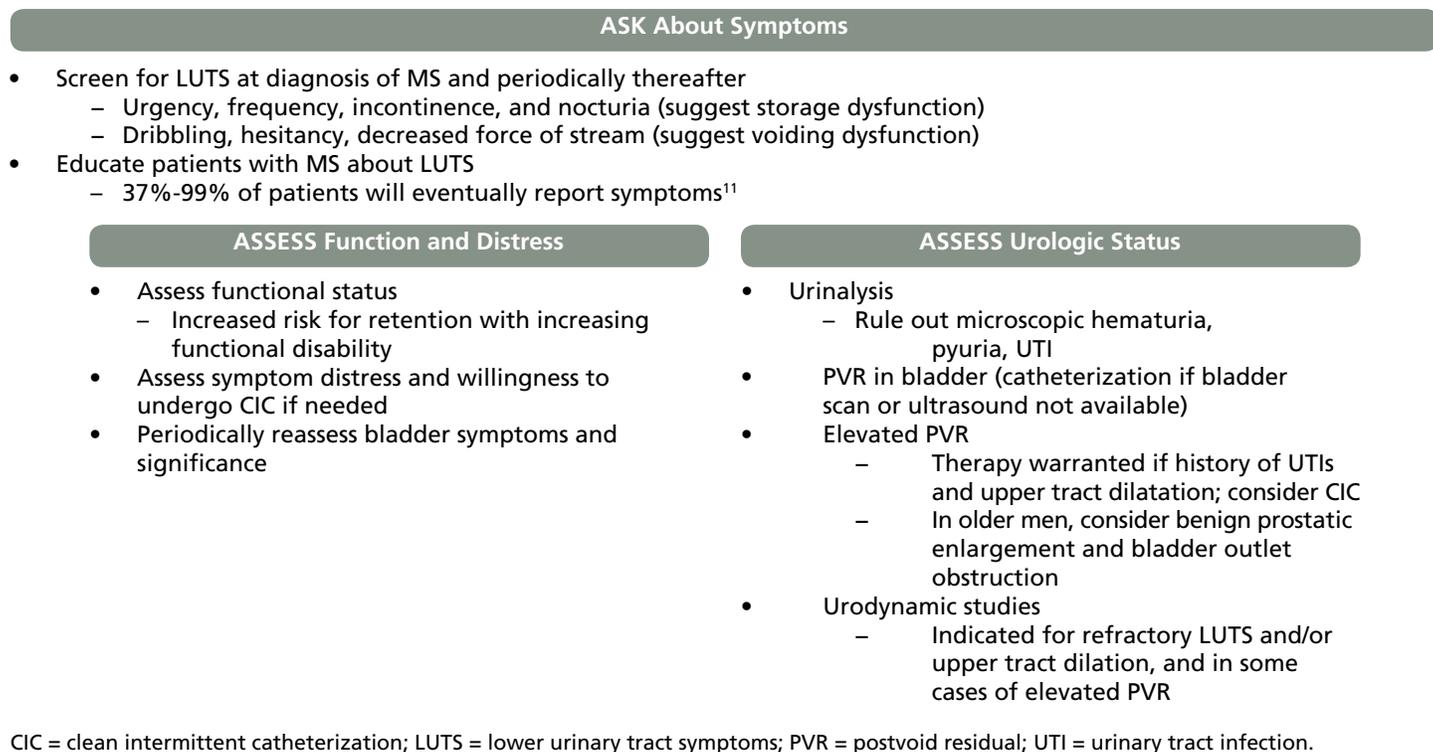
ASK About Symptoms

- Screen for LUTS at diagnosis of MS and periodically thereafter
    - Urgency, frequency, incontinence, and nocturia (suggest storage dysfunction)
    - Dribbling, hesitancy, decreased force of stream (suggest voiding dysfunction)
- Educate patients with MS about LUTS
    - 37%-99% of patients will eventually report symptoms[11]

ASSESS Function and Distress

- Assess functional status
    - Increased risk for retention with increasing functional disability
- Assess symptom distress and willingness to undergo CIC if needed
- Periodically reassess bladder symptoms and significance

ASSESS Urologic Status

- Urinalysis
    - Rule out microscopic hematuria, pyuria, UTI
- PVR in bladder (catheterization if bladder scan or ultrasound not available)
- Elevated PVR
    - Therapy warranted if history of UTIs and upper tract dilatation; consider CIC
    - In older men, consider benign prostatic enlargement and bladder outlet obstruction
- Urodynamic studies
    - Indicated for refractory LUTS and/or upper tract dilation, and in some cases of elevated PVR

CIC = clean intermittent catheterization; LUTS = lower urinary tract symptoms; PVR = postvoid residual; UTI = urinary tract infection.

Figure 2. Evaluation of lower urinary tract dysfunction in patients with spinal cord injury.

Spinal Shock

- CIC or indwelling catheter

Post Spinal Shock Period

- Urodynamics
- CIC ± antimuscarinic
- Periodic radiologic evaluation to rule out hydronephrosis, stones

Urologic Assessment

- Baseline urodynamics
- Evaluate urine for:
    - Change in continence status
    - Cloudy urine (high WBC count) or foul-smelling urine in the presence of other symptoms
    - Fever
    - Increased spasticity or tone
- Periodic/annual urologic follow-up; more frequent follow-up if patient reports:
    - Frequent UTI
    - Pelvic or bladder pain
    - Hematuria
- Annual upper tract surveillance/renal ultrasound to assess for calculi and hydronephrosis

CIC = clean intermittent catheterization; UTI = urinary tract infection; WBC = white blood cell.
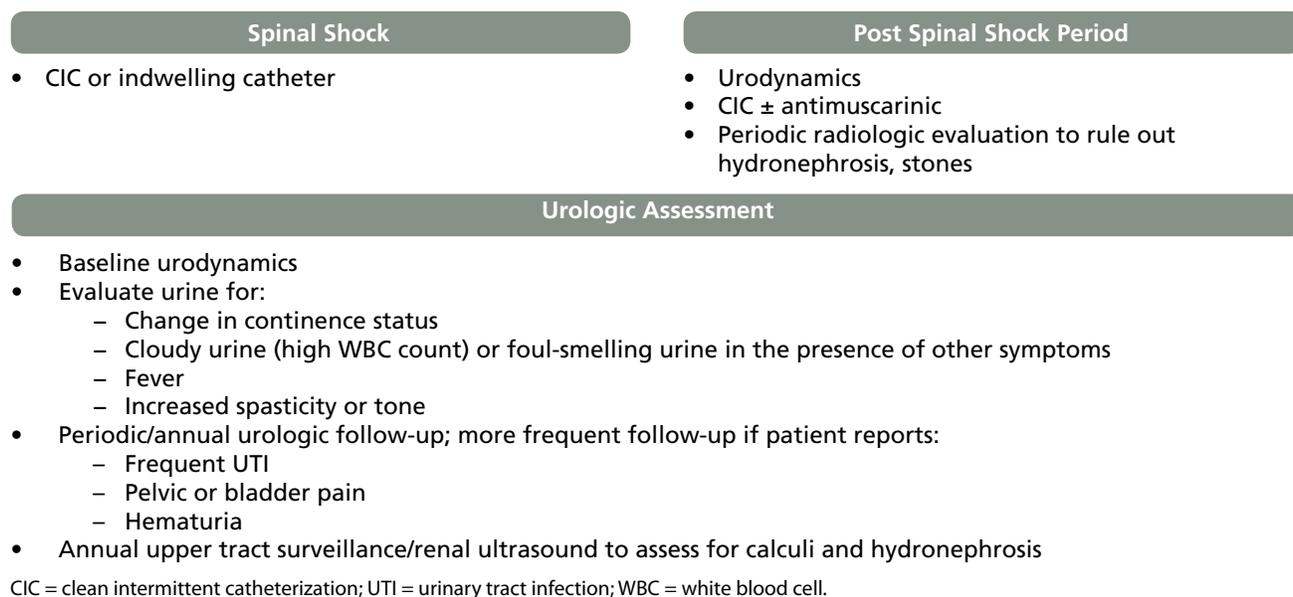
Table 4. Patient factors to consider when selecting therapy [13].

- Prognosis of underlying disease, especially if progressive
- General health
- Limiting factors, eg, inability to perform certain tasks (hand dexterity, dressing, transfers)
- Body habitus and sensation
- Mental status
- Motivation
- Desire to remain catheter or appliance free
- Desire to avoid surgery
- Sexual activity status
- Reliability
- Ability to learn
- Psychosocial environment, interest, reliability and cooperation of family
- Economic factors

infection [13]. However, lower detrusor leak-point pressures have also been shown to be a risk factor [35].

In the multidisciplinary care of patients, the urologist should assume the management of lower urinary tract dysfunction. Essential components in the evaluation of lower urinary tract dysfunction in patients with SCI are summarized in Figure 2.

Goals of Treatment

For patients with MS or SCI who have lower urinary tract dysfunction, the primary goals of therapy are to preserve or improve renal function (ie, upper urinary tract), prevent or control infection, maintain adequate storage and emptying at low intravesical pressure, maintain adequate control of bladder emptying without incontinence, avoid the need for a catheter or stoma, and ensure social and vocational acceptability and adaptability [13]. A given regimen should be changed or augmented if any of the following occur: upper or lower urinary tract deterioration; recurrent sepsis or fever of urinary tract origin; inadequate storage, emptying, or control; unacceptable side effects; or skin changes secondary to incontinence or collecting device [13].

MANAGEMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

According to Wein and Dmochowski, [13] "Management of the urinary tract in SCI patients must be based on urodynamic

findings and principles rather than inferences from the neurologic history and evaluation. Similarly, although the information regarding "classic" complete lesions is for the most part valid, one should not make neurologic conclusions solely on the basis of urodynamic findings."

Before initiating treatment for a neurologic patient with symptoms of NDO, it is important to discuss the patient's expectations and goals as well as the physician's treatment objectives. In particular, patients with SCI need to be educated with regard to the importance of preservation of the upper renal tract, while those with MS need to understand the role that lower UTI can have on their overall physical well-being, disease progression, and function. A number of factors to consider when choosing therapy are listed in Table 4 [13].

Lifestyle Changes, Behavioral Modification, Clean Intermittent Catheterization

Lifestyle changes and behavioral modification are the first line of treatment and may be helpful in combination with pharmacologic therapy in selected patients. Such changes are more likely to have a substantial effect in patients with MS than in those with SCI. Dietary changes to reduce bladder irritation involve decreasing the consumption of caffeine, artificial sweeteners, or alcohol, and avoiding acidic and spicy foods. Either excessive or insufficient fluid intake may aggravate symptoms [36].

Behavioral modification is ideal for ambulatory patients with neurogenic bladder who are voiding volitionally. Timed (scheduled) voiding can help to minimize functional problems such as getting to the bathroom and removing clothing in time [36]. This intervention can be initiated and maintained by caregivers. The usual schedule is every 3 hours during the daytime [37]. Use of pelvic floor exercises (ie, Kegel maneuver) has been shown to be beneficial in patients with MS [19] and in those with incomplete SCI [38].

Clean intermittent catheterization (CIC) is considered the gold standard for the management of urinary retention or incomplete bladder emptying in patients with neurogenic lower urinary tract dysfunction caused by either detrusor underactivity or detrusor-sphincter dyssynergia [38]. Antimuscarinic agents and intradetrusor injection of onabotulinumtoxinA (OnaBoNT-A) used for the treatment of detrusor overactivity in neurogenic bladder dysfunction may precipitate urinary retention requiring CIC. Self-catheterization requires adequate hand function and sufficient cognitive ability to perform [15]. Patients and/or caregivers require instruction in technique and risks—aseptic

Table 5. Clean intermittent catheterization (CIC) [15,34,36,38].

- CIC effective in patients with:
  - Detrusor underactivity or acontractility
  - Detrusor-sphincter dyssynergia associated with increased detrusor pressures and/or increased PVR, if overactivity (if present) can be controlled
- Catheter size: 12-14 French units
- Fluid intake: moderate, spaced throughout the day
- Frequency: varies based on factors such as bladder capacity, compliance, and ability
- Bladder volume: should remain < 400 mL

PVR = postvoid residual

catheterization is the method of choice [38]. Additional details are presented in Table 5 [15,34,36,38]. In patients with SCI who are undergoing CIC, asymptomatic bacteriuria does not warrant antibiotic therapy [38,39]. In most patients, use of CIC is preferable to a chronic indwelling Foley catheter or suprapubic tube.

A recent survey of the National Spinal Cord Injury Database emphasizes the importance of supportive counseling to help patients avoid the need for indwelling catheters [40]. In this analysis, the patient's bladder management method was determined at discharge from rehabilitation and at each 5-year follow-up for 30 years. Among individuals using CIC and condom catheterization at discharge home, only 20% and 34.6%, respectively, continued to use these methods. At long-term follow-up, 41.8% of patients initially undergoing CIC and 23.1% of those initially using condom catheters switched to an indwelling catheter. Among patients initially discharged with an indwelling catheter, 71.1% continued using this method for 30 years [40].

Medical Interventions

A number of medical interventions are used for the treatment of patients with NDO, as listed in Table 6 [6,38,41-66].

First-Line Therapy: Antimuscarinic Agents

Antimuscarinic agents, traditionally referred to as "anticholinergic agents," [38] remain the first-line therapeutic option for NDO, and oxybutynin is the only antimuscarinic agent approved for

detrusor overactivity associated with a neurologic condition (although trials in adults are limited) [67,68]. Based on clinical experience and a limited number of studies, patients with NDO may need higher doses of antimuscarinic agents than do those with OAB [38,52,69-71].

Currently, antimuscarinic use in NDO is recommended by the European Association of Urology, [38,69] a UK consensus group on the treatment of patients with MS, [34] and an expert panel on the management of patients with neurogenic bladder [72]. Moreover, a survey of the US members of the Society for Urodynamics and Female Urology noted that 84% believe antimuscarinic agents and CIC are the best option for bladder management in persons with SCI who have detrusor overactivity [73].

Adverse effects of antimuscarinic agents are related to a lack of uroselectivity [67]. The most common side effect associated with antimuscarinic agents is dry mouth, but a review of studies in patients with idiopathic OAB found no indication that this had an effect on the numbers of patients who withdrew from treatment [68]. Other common side effects include constipation and blurred vision [67]. Constipation can be of concern in patients with neurologic disease since many already experience this as a result of their neurological problem. It can be quite serious in SCI and very disabling in MS. It is important that patients are provided with nutritional counseling to ensure regular bowel movements and prevent impaction and/or bowel leakage around the impaction resulting in bowel incontinence.

In 2010, angioedema was reported to be an uncommon adverse effect associated with this class of drugs. Because antimuscarinic agents can exacerbate urinary retention, a baseline postvoid residual volume should be obtained in patients with MS not performing intermittent catheterization prior to therapy, and patients should be evaluated periodically while on antimuscarinic therapy [74].

Cognitive changes may occur with the use of antimuscarinic agents. A recent review of randomized, controlled trials evaluating cognitive function in patients with OAB receiving oxybutynin, darifenacin, tolterodine, solifenacin, and/or trospium chloride found that oxybutynin was occasionally reported to be associated with cognitive impairment, whereas darifenacin was not [75]. Other studies have found that trospium chloride does not penetrate the central nervous system and has no significant effect on learning or recall [76,77].

Newer formulations of older antimuscarinic therapies such as extended-release formulations and transdermal applications

have decreased the incidence of side effects while maintaining desired efficacy. Intravesical oxybutynin has also been evaluated in limited studies involving detrusor overactivity of neurologic etiology [78]. Its use, however, requires catheterization and can be cumbersome.

Note that alpha-1 adrenergic receptor antagonists are not recommended for the oral therapy of patients with NDO, given a lack of evidence of efficacy [67].

Second-Line Therapy

Several management options are available for patients who do not respond adequately to treatment with antimuscarinic (anticholinergic) agents.

OnabotulinumtoxinA Intradetrusor Injection

In 2011, OnaBoNT-A intradetrusor injection was approved by the US FDA for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI and MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication [79]. In the bladder, OnaBoNT-A acts at the presynaptic cholinergic junction where it prevents the release of acetylcholine from the presynaptic nerve terminal. This prevents stimulation of the detrusor muscle. It is also thought that in addition to its efferent effects on the detrusor, OnaBoNT-A may affect the afferent limb of the contraction cycle through a multimodal effect on a number of sensory pathways [80].

There are limitations to the total amount of OnaBoNT-A that an individual may receive over a period of time [79]. Prior to use, it is important to ask patients with SCI or MS if they have received OnaBoNT-A for a medical (eg, spasticity) or cosmetic reason in the past or any other botulinum toxin product within the past 3 months. For detrusor overactivity associated with a neurologic condition, the recommended total dose of OnaBoNT-A is 200 Units, as 1 mL (~6-7 Units) injections across 30 sites into the detrusor, excluding the trigone. The total dose of OnaBoNT-A injected anywhere throughout the body should not exceed 360 Units administered in a 3-month interval, according to the FDA. Autonomic dysreflexia has been associated with intradetrusor injections and SCI patients at risk (injury at level T5 and higher) should be appropriately managed. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with OnaBoNT-A 200 Units compared with placebo (1.5% vs 0.4%, respectively). In double-blind, placebo-controlled clinical trials of combined MS and SCI populations, the proportion of patients not using CIC at baseline who required catheterization

for urinary retention following intradetrusor injection was 30.6% with OnaBoNT-A 200 Units compared with 6.7% with placebo [79]. Therefore, patients considering this therapeutic option must be agreeable to performing CIC.

A growing body of evidence supports the use of OnaBoNT-A intradetrusor injection in patients with symptoms of detrusor overactivity due to MS and SCI, including prospective, open-label treatment trials, and randomized, controlled trials [43,53-58,81]. Most clinical trials report significant improvement in clinical and urodynamic outcomes in patients with MS and SCI following treatment with OnaBoNT-A intradetrusor injections. In a recent multicenter, randomized, double-blind, placebo-controlled study in 154 patients with MS and 121 with SCI who were experiencing a mean of 33.5 episodes per week of urinary incontinence due to NDO at baseline, treatment with 200 Units OnaBoNT-A significantly reduced the number of weekly episodes at 6 weeks compared with placebo (-21.8 vs -13.2; P<.01) [57]. At 6 weeks, a significantly greater proportion of patients receiving OnaBoNT-A compared with placebo (38% vs 7.6%) were fully continent (ie, dry). Onset of effect typically occurs 2 weeks postinjection, and the median duration of response in the pivotal trials was 295 days to 337 days (42-48 weeks) [79]. No loss of efficacy and no systemic side effects have been observed with repeated injections [67,79,82]. OnaBoNT-A intradetrusor injections have been associated with improved QoL, which was correlated with decreases in micturition frequency, urgency, and incontinence episodes [83]. In patients with SCI refractory to antimuscarinic agents who received at least one OnaBoNT-A injection, satisfaction with treatment was high, and the rate of annual withdrawals was low [84].

In patients with detrusor overactivity associated with a neurologic condition, the most common adverse events associated with OnaBoNT-A in double-blind, placebo-controlled trials were urinary tract infection occurring within the first 12 weeks after intradetrusor injection (OnaBoNT-A, 24% vs placebo 17%) and urinary retention (OnaBoNT-A, 17% vs placebo 3%) [79]. Note that the prescribing information for OnaBoNT-A (and all botulinum products) includes a boxed warning regarding the potential spread of toxin effects beyond the area of injection, which may result in swallowing and breathing difficulties. The risk for symptoms is likely greatest in children treated for spasticity, but symptoms can also occur in adults, particularly in those who have an underlying condition that would predispose them to such symptoms [79].

Sacral Nerve Stimulation/Sacral Neuromodulation

Sacral nerve stimulation (InterStim® implantable pulse generator,

Table 6. Medical interventions for overactive bladder of neurogenic origin.

Therapy	Adult Dosage	Trials in NDO
First Line: Antimuscarinic Agents		
Oxybutynin*	Tablets/syrup: 2.5-5.0 mg BID or TID; maximum recommended dose 5 mg QID Extended-release tablets: 5-30 mg QD	1 RCT in children with NDO[41]; multiple RCTs in adults with NDO due to MS or SCI[42-45]
Tolterodine†	Tablets: 1-2 mg BID Long-acting tablets: 2-4 mg QD	RCT, adults NDO due to MS or SCI[46]; single-arm trial NDO[47]
Darifenacin†	Extended-release tablets: 7.5-15 mg QD	RCTs in NDO due to MS or SCI[48,49]
Fesoterodine†	Extended-release tablets: 4-8 mg QD	No clinicals trials in NDO[6]
Solifenacin†	Tablets: 5-10 mg QD	Open-label trial, adults with MS[50]
Trospium†	Tablets: 20 mg BID	2 English language trials in NDO[51,52]
Second Line		
OnabotulinumtoxinA intradetrusor injections‡	200 Units as 1 mL (~6-7 Units) injections across 30 sites into detrusor; total dose not to exceed 360 Units in a 3-month interval	RCTs and multicenter studies, adults with MS or SCI[53-58]
Sacral neuromodulation§	Sacral nerve stimulator implant(s); see product technical manuals for full prescribing information or call Medtronic at 1-800-328-0810	Lack of RCTs, low numbers of patients, few studies in NDO due to MS or SCI[38,59-65]
Third Line		
Bladder augmentation or urinary diversion		Patients with SCI or MS rarely analyzed separately[61,66]; rarely used

BID = twice daily; TID = three times daily; QD = once daily; QID = four times daily; RCT = randomized, controlled trial.

* Immediate-Release Tablets and Syrup: Approved for relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (ie, urgency, frequency, urinary leakage, urge incontinence, dysuria). Extended-Release Tablets: Approved for overactive bladder with symptoms of urge incontinence, urgency, frequency, and in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (eg, spina bifida). Patients must be able to empty the bladder.

† Approved for overactive bladder with symptoms of urge incontinence, urgency, frequency. Patients must be able to empty the bladder.

‡ Approved for detrusor overactivity associated with neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

§ Approved for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments. Sacral neuromodulation (InterStim®) is not approved for the treatment of neurogenic overactive bladder.

Medtronic, Inc., Minneapolis, MN) is FDA approved for the treatment of urinary retention and the symptoms of OAB, including urinary urgency incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments [85]. Importantly, the safety and effectiveness of bilateral sacral neuromodulation has not been established for patients with neurologic disease origins such as MS; pregnancy, the unborn fetus, and delivery; and pediatric use under the age of 16 (Medtronic, Inc., Medical affairs phone communication).

Randomized, controlled trials of sacral neuromodulation are lacking, and there have been few off-label studies in patients with NDO associated with SCI and MS [59]. However, a recent review of the literature found a 92% overall success rate (defined as >50% improvement in bladder diary variables, number of leakages, pad use, number of voids, and number of catheters) with permanent implants in patients with NDO due to MS, SCI, pelvic surgery, and disc disease, with a mean follow-up of 26 months [59]. Other studies suggest that patients with incomplete SCI experiencing lower urinary tract symptoms may benefit from sacral neuromodulation [86,87].

In patients with MS, sacral neuromodulation has been investigated for both urinary retention and detrusor overactivity [61,62]. At present, candidates for sacral neuromodulation may include patients with MS who have mild symptoms, are able to get to the bathroom in time, have no mobility issues, and have no need for future magnetic resonance imaging studies, which are commonly utilized in this patient group [61,88].

A review of charts for 25 consecutive patients with MS who received implants between 2001 and 2009 found that urgency and frequency were decreased significantly in patients in whom the main complaint was detrusor overactivity, and that CIC was significantly decreased in patients with urinary retention due to detrusor-sphincter dyssynergia. Quality of life was improved in patients with both urinary retention and those with incontinence [62]. However, longer follow-up studies are needed.

Posterior Tibial Nerve Stimulation

Posterior tibial nerve stimulation is an alternative form of nerve stimulation. The precise mechanism of action is unclear. It is thought that posterior nerve stimulation inhibits bladder activity by depolarizing somatic sacral and lumbar afferent fibers [89]. There are limited studies available, evaluating the use of posterior tibial nerve stimulation in patients with NDO; however, preliminary findings appear promising [90-93].

Indwelling Catheter

In select individuals, an indwelling Foley catheter or suprapubic tube may be an appropriate intervention. However, in a female patient with NDO, leakage from the urethra with suprapubic drainage may be a persistent issue. Suprapubic tubes tend to be better tolerated over the long-term and avoid the risk of urethral erosion. As with Foley catheters, suprapubic tubes should be changed on a regular basis. The impact of indwelling catheters on the risk of developing bladder cancer

is controversial [94-96]. Bacterial colonization is common and patients should be cultured and treated if there is fever, and/or a change in urinary symptoms.

Surgical Intervention

When more conservative approaches have failed in patients with SCI or MS in whom catheterization is impossible or incontinence cannot be controlled, urinary diversion may be a more suitable alternative to an indwelling catheter [38,61]. However, these procedures are associated with multiple risks, and complications such as infections, calculi, and ureteroenteric strictures [38,66]. For patients with MS, these procedures generally are considered only for those with secondary progressive/primary progressive disease who have failed nonsurgical treatments and have an increased Expanded Disability Status Scale [61]. According to Stoffel, [61] most patients with MS whom he has seen for surgical intervention will require incontinent urinary diversion because they are unable to catheterize an augmented bladder.

Long-term follow-up of patients with NDO is critical. In 2001, Ciancio et al [97] reported that a significant proportion (55%) of patients with MS with and without new symptoms will develop changes in their detrusor compliance and urodynamic pattern. Caution should be exercised in recommending irreversible options [13]. Surgical intervention for MS appears to be decreasing with improved pharmacologic management.

CONCLUSIONS

A recent retrospective analysis of medical and pharmacy claims for more than 46,000 patients with neurogenic bladder dysfunction related to incontinence—including more than 9,000 patients with MS and more than 4,000 with SCI—suggests that the management of these patients is suboptimal as indicated by high rates of UTI and hospitalizations [26]. Experts concur that a team approach involving the primary care provider, neurologist, urologist, physiatrist, and nurse practitioner, as well as any other personnel or family members involved in the patient's care, is essential in order to optimize medical and urologic management. This is not generally the case: During a 1-year follow-up, only 36% of SCI patients and 26% of MS patients were seen by a urologist; 18.5% and 53%, respectively, were seen by a neurologist; and 18% and 7.5%, respectively, received physical medicine and rehabilitation [26].

Education is needed across the specialties involved in the care of neurologically impaired patients. More emphasis needs to be placed on the urologic assessment and management of these patients, especially those with SCI in whom protection of the

upper urinary tract is a primary goal. Patients and caregivers also need to be educated about the various resources available to them in the community.

With regard to drug therapy for NDO, current US and European guidelines recommend an antimuscarinic agent as first-line therapy. The availability of newer, more selective antimuscarinic agents, including darifenacin, solifenacin, trospium chloride, tolterodine, and fesoterodine, as well as extended-release formulations has improved the tolerability of antimuscarinic therapy without compromising efficacy.

For patients with detrusor overactivity and incontinence due to a neurologic condition such as MS and SCI who have an inadequate response to or are intolerant of antimuscarinic medications, a recently approved alternative/additional therapy is OnaBoNT-A intradetrusor injection [53-58,81]. Onset of effect occurs by 2 weeks postinjection. Patients should be considered for reinjection when the clinical effect of the previous injection diminishes (median time to qualification for retreatment in the double-blind, placebo-controlled clinical studies was 42-48), but no sooner than 12 weeks from the prior bladder injection [79]. There is no loss of efficacy with repeated injections. As urinary retention is a risk with intradetrusor injection of OnaBoNT-A, patients should agree to perform CIC if needed for urinary retention after treatment. This is time limited.

Bladder augmentation/urinary diversion are less commonly performed in patients with NDO due to improvements in pharmacologic therapy and may be decreased further with the approval of OnaBoNT-A.

Importantly, clinicians and patients alike need to understand the potentially detrimental effects of poorly managed or unmanaged NDO on disease outcomes and recognize that a number of effective management options are available.

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