

Approved by the AUA  
Board of Directors

September 2021

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

© 2021 by the American Urological Association

American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU)

## The AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction

Panel Members: David A. Ginsberg, MD; Timothy B. Boone, MD PhD; Anne P. Cameron, MD; Angelo Gousse, MD; Melissa R. Kaufman, MD; Erick Keays; Michael J. Kennelly, MD; Gary E. Lemack, MD; Eric S. Rovner, MD, Lesley H. Souter, PhD; Claire C. Yang, MD; Stephen R. Kraus, MD

### Executive Summary

#### Purpose

The term neurogenic lower urinary tract dysfunction (NLUTD) refers to abnormal function of either the bladder, bladder neck, and/or its sphincters related to a neurologic disorder. Prior terminology commonly used "neurogenic bladder" to describe this condition. With the understanding that this is not just an issue confined to the bladder, NLUTD is now the preferred way to describe the various voiding issues seen in patient with a neurologic disorder. The clinician treating patients with NLUTD needs to balance a variety of factors when making treatment decisions. In addition to the patient's urologic symptoms and urodynamic findings (if applicable), other issues that may influence management options of the lower urinary tract include cognition (which can be impacted by the neurologic disorder), hand function, type of neurologic disease (progressive versus stable), mobility, bowel function/management, and social and caregiver support (if needed). This Guideline allows the clinician to understand the options available to treat patients, understand the findings that can be seen in NLUTD, and appreciate which options are best for each individual patient. This allows for decisions to be made with the patient, in a shared decision-making manner, such that the patient's quality of life can be optimized in regards to their bladder management.

#### Methodology

A comprehensive search for studies assessing patients undergoing evaluation, surveillance, management, or follow-up for NLUTD was conducted from January 2001 through October 2017 and was rerun in February 2021 to capture newer literature. The primary search returned 20,496 unique citations. Following a title and abstract screen, full texts were obtained for 3,036 studies. During full-text review, studies were primarily excluded for not meeting the PICO criteria. One hundred eight-four primary literature studies met the inclusion criteria and were included in the evidence base.

### Guideline Statements

#### Initial Evaluation of the Patient with NLUTD

1. At initial evaluation, clinicians should identify patients as either:
  - a. low-risk, or
  - b. unknown-risk, who will require further evaluation to allow for complete risk stratification.

*(Clinical Principle)*

2. At initial evaluation, all patients with NLUTD should undergo a detailed history, physical exam, and urinalysis. *(Clinical Principle)*
3. At initial evaluation, patients with NLUTD who spontaneously void should undergo post-void residual measurement. *(Clinical Principle)*
4. At initial evaluation, optional studies in patients with NLUTD include a voiding/catheterization diary, pad test, and non-invasive uroflow. *(Expert Opinion)*
5. At initial evaluation, in patients with low-risk NLUTD, the clinician should not routinely obtain upper tract imaging, renal function assessment, or multichannel urodynamics. *(Moderate Recommendation; Evidence Level: Grade C)*
6. At initial evaluation, in patients with unknown-risk NLUTD, the clinician should obtain upper tract imaging, renal function assessment, and multichannel urodynamics. *(Moderate Recommendation; Evidence Level: Grade C)*
7. In the patient with an acute neurological event resulting in NLUTD, the clinician should perform risk stratification once the neurological condition has stabilized. *(Clinical Principle)*
8. Clinicians should not perform routine cystoscopy in the initial evaluation of the NLUTD patient. *(Clinical Principle)*

#### **Autonomic Dysreflexia**

9. During urodynamic testing and/or cystoscopic procedures, clinicians must hemodynamically monitor NLUTD patients at risk for autonomic dysreflexia. *(Clinical Principle)*
10. For the NLUTD patient who develops autonomic dysreflexia during urodynamic testing and/or cystoscopic procedures, clinicians must terminate the study, immediately drain the bladder, and continue hemodynamic monitoring. *(Clinical Principle)*
11. For the NLUTD patient with ongoing autonomic dysreflexia following bladder drainage, clinicians should initiate pharmacologic management and/or escalate care. *(Clinical Principle)*

#### **Surveillance of the patient with NLUTD**

12. The clinician must educate patients with NLUTD on the signs and symptoms that would warrant additional assessment. *(Clinical Principle)*
13. In patients with low-risk NLUTD and stable urinary signs and symptoms, the clinician should not obtain surveillance upper tract imaging, renal function assessment, or multichannel urodynamics. *(Moderate Recommendation; Evidence Level: Grade C)*
14. In patients with moderate-risk NLUTD and stable urinary signs and symptoms, the clinician should assess the patient with:
  - a. annual focused history, physical exam, and symptom assessment.
  - b. annual renal function assessment.
  - c. upper tract imaging every 1-2 years.*(Moderate Recommendation; Evidence Level: Grade C)*
15. In patients with high-risk NLUTD and stable urinary signs and symptoms, the clinician should assess the patient with:
  - a. annual focused history, physical exam, and symptom assessment.
  - b. annual renal function assessment.
  - c. annual upper tract imaging.
  - d. multichannel urodynamic studies, with or without fluoroscopy, which may be repeated when clinically indicated.*(Moderate Recommendation; Evidence Level: Grade C)*

16. In patients with low-risk NLUTD who present with new onset signs and symptoms, new complications (e.g., autonomic dysreflexia, urinary tract infections, stones), and/or upper tract or renal function deterioration, the clinician should re-evaluate and repeat risk stratification. *(Clinical Principle)*

17. In patients with moderate- or high-risk NLUTD who experience a change in signs and symptoms, new complications (e.g., autonomic dysreflexia, urinary tract infections, stones), or upper tract or renal function deterioration, the clinician may perform multichannel urodynamics. *(Clinical Principle)*

18. In the NLUTD patient with concomitant hematuria, recurrent urinary tract infections, or suspected anatomic anomaly (e.g., strictures, false passage), clinicians should perform cystoscopy. *(Moderate Recommendation; Evidence Level: Grade B)*

19. In NLUTD patients, clinicians should not perform screening/surveillance cystoscopy. *(Strong Recommendation; Evidence Level: Grade B)*

20. In NLUTD patients with a chronic indwelling catheter, clinicians should not perform screening/surveillance cystoscopy. *(Strong Recommendation; Evidence Level: Grade B)*

21. In NLUTD patients with indwelling catheters, clinicians should perform interval physical examination of the catheter and the catheter site (suprapubic or urethral). *(Moderate Recommendation; Evidence Level: Grade C)*

22. In NLUTD patients with indwelling catheters who are at risk for upper and lower urinary tract calculi (e.g., patients with spinal cord injury, recurrent urinary tract infection, immobilization, hypercalcuria) clinicians should perform urinary tract imaging every 1-2 years. *(Moderate Recommendation; Evidence Level: Grade C)*

### **Urinary Tract Infection**

23. In asymptomatic NLUTD patients, clinicians should not perform surveillance/screening urine testing, including urine culture. *(Moderate Recommendation; Evidence Level: Grade C)*

24. Clinicians should not treat asymptomatic bacteriuria in patients with NLUTD. *(Moderate Recommendation; Evidence Level: Grade C)*

25. In NLUTD patients with signs and symptoms suggestive of a urinary tract infection, clinicians should obtain a urinalysis and urine culture. *(Moderate Recommendation; Evidence Level: Grade C)*

26. In NLUTD patients with a febrile urinary tract infection, clinicians should order upper tract imaging if:

- a. the patient does not respond appropriately to antibiotic therapy.
- b. the patient is moderate- or high-risk and is not up to date with routine upper tract imaging, regardless of their response to therapy.

*(Clinical Principle)*

27. In NLUTD patients with a suspected urinary tract infection and an indwelling catheter, clinicians should obtain the urine culture specimen after changing the catheter and after allowing for urine accumulation while plugging the catheter. Urine should not be obtained from the extension tubing or collection bag. *(Clinical Principle)*

28. In NLUTD patients with recurrent urinary tract infections, clinicians should evaluate the upper and lower urinary tracts with imaging and cystoscopy. *(Clinical Principle)*

29. In NLUTD patients with recurrent urinary tract infections and an unremarkable evaluation of the upper and lower urinary tract, clinicians may perform urodynamic evaluation. *(Conditional Recommendation; Evidence Level: Grade C)*

30. In NLUTD patients who manage their bladder with an indwelling catheter, clinicians should not use daily antibiotic prophylaxis to prevent urinary tract infection. *(Strong Recommendation; Evidence Level: Grade B)*

31. In NLUTD patients who manage their bladders with clean intermittent catheterization and do not have recurrent urinary tract infections, clinicians should not use daily antibiotic prophylaxis. (*Moderate Recommendation; Evidence Level: Grade B*)

### **Non-Surgical Treatment**

32. Clinicians may recommend pelvic floor muscle training for appropriately selected patients with NLUTD, particularly those with multiple sclerosis or cerebrovascular accident, to improve urinary symptoms and quality of life measures. (*Conditional Recommendation; Evidence Level: Grade C*)

33. Clinicians may recommend antimuscarinics or beta-3 adrenergic receptor agonists, or a combination of both, to improve bladder storage parameters in NLUTD patients. (*Conditional Recommendation; Evidence Level: Grade C*)

34. Clinicians may recommend alpha-blockers to improve voiding parameters in NLUTD patients who spontaneously void. (*Conditional Recommendation; Evidence Level: Grade C*)

35. Clinicians should recommend intermittent catheterization rather than indwelling catheters to facilitate bladder emptying in patients with NLUTD. (*Strong Recommendation; Evidence Level: Grade C*)

36. For appropriately selected NLUTD patients who require a chronic indwelling catheter, clinicians should recommend suprapubic catheterization over an indwelling urethral catheter. (*Strong Recommendation; Evidence Level: Grade C*)

37. In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision-making and discussion regarding increased risk of antibiotic resistance. (*Conditional Recommendation; Evidence Level: Grade C*)

38. In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer bladder instillations to reduce the rate of urinary tract infections. (*Expert Opinion*)

39. Clinicians may counsel NLUTD patients with recurrent urinary tract infection who use various forms of catheter management that cranberry extract has not been demonstrated to reduce the rate of urinary tract infections. (*Conditional Recommendation; Evidence Level: Grade B*)

40. In NLUTD patients with spinal cord injury or multiple sclerosis refractory to oral medications, clinicians should recommend onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life measures. (*Strong Recommendation; Evidence Level: Grade A*)

41. In NLUTD patients, other than those with spinal cord injury and multiple sclerosis, who are refractory to oral medications, clinicians may offer onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life measures. (*Conditional Recommendation; Evidence Level: Grade C*)

42. In NLUTD patients who spontaneously void, clinicians must discuss the specific risks of urinary retention and the potential need for intermittent catheterization prior to selecting botulinum toxin therapy. (*Clinical Principle*)

### **Surgical Treatment**

43. Clinicians may offer sphincterotomy to facilitate emptying in appropriately selected male patients with NLUT but must counsel them of the high-risk of failure or potential need for additional treatment or surgery. (*Conditional Recommendation; Evidence Level: Grade C*)

44. Clinicians may offer urethral bulking agents to NLUTD patients with stress urinary incontinence but must counsel them that efficacy is modest and cure is rare. (*Conditional Recommendation; Evidence Level: Grade C*)

45. Clinicians should offer slings to select NLUTD patients with stress urinary incontinence and acceptable bladder storage parameters. (*Moderate Recommendation; Evidence Level: Grade C*)

46. Clinicians may offer artificial urinary sphincter to select NLUTD patients with stress urinary incontinence and acceptable bladder storage parameters. (*Conditional Recommendation; Evidence Level: Grade C*)

47. After a thorough discussion of risks, benefits, and alternatives, clinicians may offer bladder neck closure and concomitant bladder drainage methods to select patients with NLUTD and refractory stress urinary incontinence. (*Expert Opinion*)

48. Clinicians may offer posterior tibial nerve stimulation to select spontaneous voiding NLUTD patients with urgency, frequency, and/or urgency incontinence. (*Conditional Recommendation; Evidence Level: Grade C*)

49. Clinicians may offer sacral neuromodulation to select NLUTD patients with urgency, frequency, and/or urgency incontinence. (*Conditional Recommendation; Evidence Level: Grade C*)

50. Clinicians should not offer sacral neuromodulation to NLUTD patients with spinal cord injury or spina bifida. (*Moderate Recommendation; Evidence Level: Grade C*)

51. Clinicians may offer augmentation cystoplasty to select NLUTD patients who are refractory to, or intolerant of, less invasive therapies for detrusor overactivity and/or poor bladder compliance. (*Conditional Recommendation; Evidence Level: Grade C*)

52. Clinicians may offer continent catheterizable channels, with or without augmentation, to select NLUTD patients to facilitate catheterization. (*Conditional Recommendation; Evidence Level: Grade C*)

53. Clinicians may offer ileovesicostomy to select patients with NLUTD and must counsel them on the risks, benefits, alternatives, and the high-risk of needing additional treatment or surgery. (*Conditional Recommendation; Evidence Level: Grade C*)

54. Clinicians should offer urinary diversion to NLUTD patients in whom other options have failed, or are inappropriate, to improve long-term quality of life. (*Moderate Recommendation; Evidence Level: Grade C*)

55. Other potential treatments for NLUTD should be considered investigational and patients should be counseled accordingly. (*Expert Opinion*)

#### **Follow-up and post treatment**

56. In NLUTD patients with impaired storage parameters and/or voiding that place their upper tracts at risk, clinicians should repeat urodynamic studies at an appropriate interval following treatment. (*Expert Opinion*)

57. In NLUTD patients with impaired storage parameters that place their upper tracts at risk and are refractory to therapy, clinicians should offer additional treatment. (*Expert Opinion*)

58. In NLUTD patients who have undergone lower urinary tract reconstruction incorporating a bowel segment(s), the clinician should assess the patient annually with:

- a. focused history, physical exam, and symptom assessment.
- b. basic metabolic panel.
- c. urinary tract imaging.

(*Expert Opinion*)

59. Clinicians may perform urodynamics following sphincterotomy to assess outcome. (*Conditional Recommendation; Evidence Level: Grade C*)

60. In NLUTD patients who have undergone lower urinary tract reconstruction utilizing bowel, and who also develop gross hematuria or symptomatic recurrent urinary tract infection, clinicians should perform cystoscopy. (*Moderate Recommendation; Evidence Level: Grade C*)

## Introduction

The term neurogenic lower urinary tract dysfunction (NLUTD) refers to abnormal function of either the bladder, bladder neck, and/or its sphincters related to a neurologic disorder. Prior terminology commonly used “neurogenic bladder” to describe this condition. With the understanding that this is not just an issue confined to the bladder, NLUTD is now the preferred way to describe the various voiding issues seen in patient with a neurologic disorder. NLUTD is a broad term in several respects. A wide array of potential neurologic etiologies can lead to lower urinary dysfunction. As demonstrated by the Functional Classification System, NLUTD can impact a.) the bladder’s ability to store or empty urine at a socially acceptable time and location; and b.) the sphincter’s ability to relax at the time of voiding as well as maintain continence during bladder filling. For example, some patients can have urinary incontinence (UI) while others may have urinary retention requiring intermittent catheterization (CIC). In addition, NLUTD is not necessarily confined to only one of these categories and is often a mixture of several issues; for example, patients could have both UI and urinary retention. NLUTD can also occur concomitantly with urinary symptoms and lower urinary tract symptoms (LUTS) that are not neurogenic in origin. Examples of this would include a man with NLUTD, secondary to Parkinson’s disease (PD) also having obstructive voiding symptoms from an enlarged prostate, or a women with NLUTD secondary to a cerebrovascular accident (CVA) also with symptoms of stress urinary incontinence (SUI). Lastly, NLUTD symptoms can evolve over time. For example, patients with NLUTD secondary to diabetes may initially be asymptomatic, then progress to overactive bladder (OAB)-type symptoms and ultimately evolve to a bladder with incomplete emptying and possible overflow incontinence.<sup>1</sup>

NLUTD is often categorized by the neuroanatomic location (suprapontine, suprasacral spinal cord, or sacral) of the neurologic deficit contributing to the abnormal lower urinary tract function. Depending on the location of the neurological lesion, common pathophysiological patterns of NLUTD manifest. Diagnoses of the brain and brainstem leading to NLUTD include brain tumors, PD, normal pressure hydrocephalus, CVA, and traumatic brain injury. The most common of these diseases is CVA. In the United States, approximately 795,000 people experience a CVA every year<sup>2</sup> with 28-79% having symptoms of UI post-CVA.<sup>3-7</sup>

The two most common causes of NLUTD from spinal cord lesions are multiple sclerosis (MS) and spinal cord injury (SCI). The estimated prevalence of MS in 2010 in the United States, culminated over ten years, ranged from 288 to 309 per 100,000, which corresponds to a total of 523,437 to 727,344 cases of MS.<sup>8</sup> Studies have suggested that up to 50-90% of patients with MS have LUTS<sup>9</sup> with up to 65% of respondents to a 2005 North American Research Committee On Multiple Sclerosis survey noting moderate to severe urinary symptoms.<sup>10</sup> It should be appreciated that LUTS in the MS population could be secondary to emptying symptoms, storage symptoms, or a combination of both. According to the National Spinal Cord Injury Statistical Center, there are approximately 17,700 new cases of SCI each year and 247,000 to 358,000 persons in the United States are living with SCI as of 2018.<sup>11</sup> The majority of patients with a SCI have some degree of NLUTD with over 80% requiring use of a catheter (e.g., condom, intermittent, indwelling) post-injury.<sup>12</sup>

Common causes of NLUTD at the peripheral nerve level include diabetes and iatrogenic injuries from surgeries such as abdominoperineal resection and radical hysterectomy. It is estimated that 34.2 million Americans, or 10.5% of the total population, had diabetes in 2018,<sup>13</sup> with up to 80% of diabetics experiencing some type of lower urinary tract complication during their lifetime.<sup>14</sup>

NLUTD can have a significant impact on patients’ quality of life (QoL). The degree to which this impacts patients is demonstrated by the fact that, given the choice, SCI patients did not have a preference if choosing between an improvement in the bladder/bowel function versus obtaining the ability to walk.<sup>15</sup> Prior to World War II, the primary cause of death for patients with a SCI was renal failure secondary to suboptimal management of their bladder.<sup>16</sup> Presently, with better understanding of the importance of bladder storage pressures, renal failure and renal complications are less common causes of death. This speaks to one of the main goals for the clinician caring for patients with NLUTD: understanding risk of upper urinary tract damage and managing the patient in such a way that risk is minimized. However, there are often a variety of other issues that the clinician caring for the patient with NLUTD may need to address. In addition to LUTS, such as UI and retention, patients with NLUTD may experience recurrent urinary tract infection (UTI) and autonomic dysreflexia (AD), which this Guideline will address. Non-urinary conditions such as sexual dysfunction, male infertility, and bowel dysfunction are also

common in patients with NLUTD but are not within the scope of this Guideline. **It should also be noted that this is a Guideline for adult patients with NLUTD and pediatric NLUTD will not be discussed.**

The initial urologic evaluation and subsequent surveillance of the NLUTD patient differs depending on the etiology and severity of the neurologic injury or disease. In addition to the standard history, physical examination, and urinalysis (UA), there are a variety of tools that are used in the evaluation of NLUTD patients. These may include evaluations and tests such as voiding diaries, questionnaires (e.g., NBSS, Qualiveen), measurement of post-void residual (PVR), uroflow, urodynamics (UDS), renal ultrasound (US), and cystoscopy. All NLUTD patients do not need all of these studies. This Guideline will help clinicians caring for patients with NLUTD understand what the appropriate initial evaluation should entail. Once that is done, the patient is then placed into one of the three levels of risk: low; medium; high (Figure 1). The level of risk then determines what would be the appropriate surveillance over time.

The clinician treating patients with NLUTD needs to balance a variety of factors when making treatment decisions. In addition to the patient's urologic symptoms and urodynamic findings (if applicable), other issues that may influence management options of the lower urinary tract include cognition (which can be impacted by the neurologic disorder), hand function, type of neurologic disease (progressive versus stable), mobility, bowel function/management, and social and caregiver support (if needed). This Guideline allows the clinician to understand the options available to treat patients with various types of LUTS, understand the findings that can be seen in NLUTD, and appreciate which options are best for each individual patient. This would allow for decisions to be made with the patient, in a shared decision-making manner, such that the patient's quality of life can be optimized in regard to their bladder management.

### Panel Formation

The Panel was created in 2016 by the American Urological Association Education and Research, Inc. (AUAER). This guideline was developed in collaboration with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members

with specific expertise in this area in conjunction with SUFU. Additionally, the Panel included patient representation. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

## Methods and Methodology

### Literature Search Strategy

A comprehensive search for relevant systematic reviews assessing patients undergoing evaluation, surveillance, management, or follow-up for NLUTD was conducted using MEDLINE, Embase, and the Cochrane Library for systematic reviews databases in October 2017. The search was rerun in February 2021 to identify systematic reviews published from October 2017 through 2021. Where no existing systematic reviews were identified, or when identified reviews were incomplete in some fashion, PubMed (MEDLINE) and Embase databases were systematically searched using standardized vocabulary and keywords derived using the *a priori* developed PICO (population, interventions, comparisons, and outcomes) elements. Control articles, which were deemed important and relevant by the Panel, were compared with the literature search strategy output and the strategy was updated as necessary to capture all control articles. Databases were searched for studies published from January 2001 through October 2017 and the search was rerun in February 2021 to capture the newer literature.

### Study Selection Criteria and Process

All hits from the literature search were input into reference management software (EndNote X7), where duplicate citations were removed. Abstracts were reviewed by the methodologist to determine if the study addressed the Key Questions and if the study met study design inclusion criteria. For all research questions, randomized controlled trials, observational studies, and case-control studies were considered for inclusion in the evidence base. Although studies of any sample size were included, where data was available, only studies that enrolled at least 30 patients were used to inform recommendation statements. Case series, letters, editorials, *in vitro* studies, studies conducted in animal models, and studies not published in English were excluded from the evidence base *a priori*.

Full-text review was conducted on studies that passed the abstract screening phase. Studies that met the PICO criteria were chosen for inclusion in the evidence base. Figure 1 summarizes the study selection process.

**Figure 1. Primary Literature Search Flow Diagram**

		Potentially relevant citations identified by search of MEDLINE and EMBASE databases (de-duplicated): n = 20,496
Citations excluded after title and abstract review: n = 17,460		
		Studies included in full-text review: n = 3,036
Studies excluded after full-text review: n = 2,852		
1,443	-	Irrelevant
79	-	Only abstract available
938	-	Narrative review
62	-	No outcomes of interest reported
28	-	Reference included in identified systematic review
302	-	Sample size smaller than 30 patients
		Studies included in Qualitative Synthesis n = 184

**Data Extraction**

Data were extracted from all studies that passed full-text review by the methodologist.

**Quality Assessment***Individual Study Quality and Potential for Bias*

Quality assessment for all retained studies was conducted. Using this method, studies deemed to be of low quality would not be excluded from the systematic review, but would be retained, and their methodological strengths and weaknesses discussed where relevant. To define an overall study quality rating for each included study, risk of bias as determined by validated study-type specific tools, was paired with additional important quality features. To evaluate the risk of bias within the identified studies, the Assessment of Multiple Systematic Reviews (AMSTAR)<sup>17</sup> tool was used for systematic reviews, the Cochrane Risk of Bias Tool<sup>18</sup> was used for randomized studies, and a Risk of Bias in Non-Randomized Studies – of Intervention (ROBINS-I)<sup>19</sup> was used for observational studies. Additional important quality features, such as study design, comparison type, power of statistical analysis, and sources of funding were extracted for each study.

*Certainty of Evidence by GRADE*

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)<sup>20</sup> system was used to determine the aggregate evidence quality for each outcome, or group of related outcomes, informing each guideline statement. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low and very low, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision and publication bias across the studies.<sup>21</sup> Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

The AUA employs a 3-tiered strength of evidence system to underpin evidence-based guideline statements. Table 1 summarizes the GRADE categories, definitions and how these categories translate to the AUA strength of evidence categories. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C.



### AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 2). Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, when benefits and harms are finely balanced, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body

of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens; therefore, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged. A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence.

### Results

#### *Search for Existing Systematic Reviews*

The search for existing systematic reviews identified 45 possible reviews on evaluation, surveillance, management, or follow-up of patients with NLUTD. Twenty-five were chosen for inclusion in the evidence base. When multiple systematic reviews reported on the same outcome and included the same primary literature, only the most complete systematic review was retained. All

**Table 1: Strength of Evidence Definitions**

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
<b>A</b>	High	We are very confident that the true effect lies close to that of the estimate of the effect
<b>B</b>	Moderate	We are moderately confident in the effect estimate.
		The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
<b>C</b>	Low	Our confidence in the effect estimate is limited.
		The true effect may be substantially different from the estimate of the effect.
	Very Low	We have very little confidence in the effect estimate.
		The true effect is likely to be substantially different from the estimate of effect.

Table 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) is substantial</li> <li>-Applies to most patients in most circumstances and future research is unlikely to change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) is substantial</li> <li>-Applies to most patients in most circumstances but better evidence could change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) appears substantial</li> <li>-Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)</li> </ul>
Moderate Recommendation (Net benefit or harm moderate)	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) is moderate</li> <li>-Applies to most patients in most circumstances and future research is unlikely to change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) is moderate</li> <li>-Applies to most patients in most circumstances but better evidence could change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Benefits &gt; Risks/Burdens (or vice versa)</li> <li>-Net benefit (or net harm) appears moderate</li> <li>-Applies to most patients in most circumstances but better evidence is likely to change confidence</li> </ul>
Conditional Recommendation (Net benefit or harm comparable to other options)	<ul style="list-style-type: none"> <li>-Benefits=Risks/Burdens</li> <li>-Best action depends on individual patient circumstances</li> <li>-Future Research is unlikely to change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Benefits = Risks/Burdens</li> <li>-Best action appears to depend on individual patient circumstances</li> <li>-Better evidence could change confidence</li> </ul>	<ul style="list-style-type: none"> <li>-Balance between Benefits and Risks/Burdens unclear</li> <li>-Net benefit (or net harm) comparable to other options</li> <li>-Alternative strategies may be equally reasonable</li> <li>-Better evidence likely to change confidence</li> </ul>

20 excluded systematic reviews were excluded based on overlapping primary literature when compared to the systematic reviews chosen for inclusion in the evidence base.

#### *Search for Primary Literature*

The primary literature systematic review was used to address all outcomes not covered by the included systematic reviews. It was anticipated that primary literature would report on outcomes in addition to what was pooled in the 24 included systematic reviews. As such, the literature search for primary literature was not altered following selection of the systematic review into the evidence base. Instead, where overlap was recognized between studies included in the identified systematic reviews and identified primary studies, primary studies were either removed from the evidence base, or when primary literature reported on additional outcomes, overlapping outcomes were not extracted in the primary literature. This methodology ensured that data were not included twice in the evidence base, as this may result in an overestimate of effect.

#### *Literature Search Results*

The primary search returned 20,496 unique citations. Following a title and abstract screen, full texts were obtained for 3,036 studies. During full-text review, studies were primarily excluded for not meeting the PICO criteria (irrelevant, n=1,443). One hundred eight-four primary literature studies met the inclusion criteria and were included in the evidence base (Figure 1).

#### **Peer Review and Document Approval**

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and management of NLUTD. In addition to reviewers from the AUA PGC, Science and Quality Council, and Board of Directors, the document was reviewed by representatives from SUFU as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from May 26 – June 7, 2021 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 34 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 23 reviewers provided comments, including 3 external reviewers. At the end of the peer

review process, a total of 825 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, Science and Quality Council, and Board of Directors, as well as the governing bodies of SUFU for final approval.

#### **Guideline Statements**

##### **Initial Evaluation of the Patient with NLUTD**

**STATEMENT ONE: At initial evaluation, clinicians should identify patients as either:**

- a. low-risk, or
- b. unknown risk, who will require further evaluation to allow for complete risk stratification.

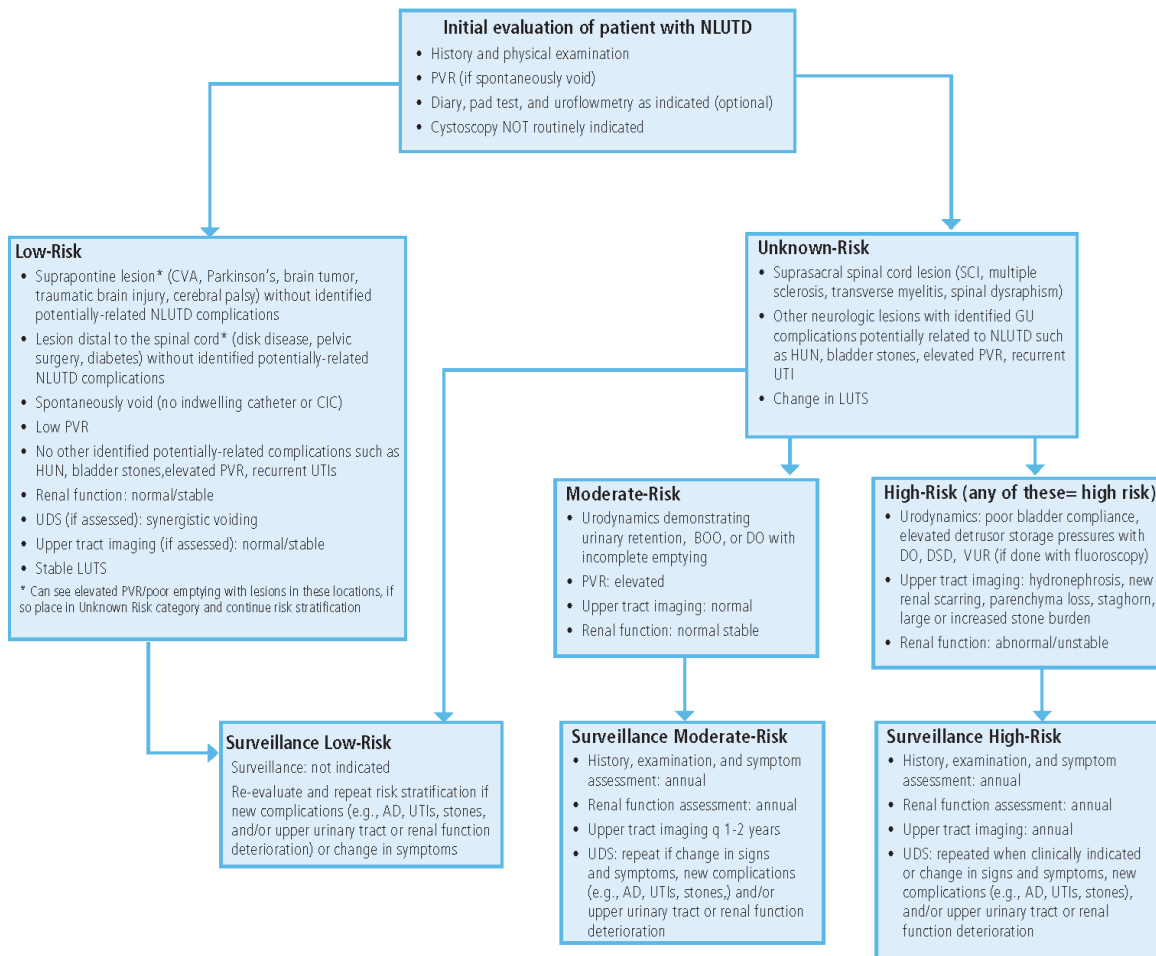
##### ***(Clinical Principle)***

The stratification of risk is of utmost importance when following patients with NLUTD. In addition to treating bothersome symptoms associated with NLUTD, the clinician needs to be aware of the various parameters that place patients at future risk for damage to the upper urinary tract. This can be a challenge when managing NLUTD patients as there are a variety of neurologic diseases and insults that can result in NLUTD and, even within specific neurologic diagnoses, there is a spectrum of disease severity. The Panel strongly feels that clinicians who treat patients with NLUTD are able to assess their potential for risk and damage to the upper urinary tract and follow these patients accordingly based on this risk stratification (Figure 2).

To a certain degree stratification can be done based on location of the neurologic disease or insult. For example, patients with suprapontine lesions (e.g., CVA, brain tumor, traumatic brain injury) tend to have detrusor overactivity (DO) with synergistic voiding and low PVRs; thus, they would be placed in the low-risk category. However, elevated PVRs could be seen in certain patients after CVA or in patients with cerebral palsy and pseudodyssynergia; placing them in the moderate-risk category. In addition, lesions distal to the spinal cord tend to have low bladder storage pressures; however, poor contractility could result in elevated PVRs and over time loss of bladder compliance can be seen in this patient population as well, another example of how lesion location can cross over into several risk stratification categories.

Patients with suprasacral spinal cord lesions (SCI, MS, transverse myelitis) are at greater risk for both DO and

Figure Two: Neurogenic Lower Urinary Tract Dysfunction Risk Stratification Flow Chart



AD: autonomic dysreflexia; BOO: bladder outlet obstruction; CVA: cerebrovascular accident; CIC: clean intermittent catheterization; DO: detrusor overactivity; DSD: detrusor sphincter dyssynergia; GU: genitourinary; HUN: hydronephrosis; LUTS: lower urinary tract symptoms; NLUTD: neurogenic lower urinary tract dysfunction; PVR: post-void residual; SCI: spinal cord injury; UTI: urinary tract infection; UDS: urodynamics; VUR: vesicoureteral reflux.

detrusor-external sphincter dyssynergia (DESD). These patients would be placed in the unknown-risk category until further evaluation (UDS, upper tract imaging, assessment of renal function) is performed allowing for more specific stratification. These studies allow for evaluation for kidney abnormalities such as hydronephrosis or renal scarring, assessment of renal function and the presence of potentially concerning urodynamics findings such as poor bladder compliance, DO and DESD. Once patients are appropriately stratified based on their evaluation (Table 3), the Panel has provided recommendations within the Guideline as to how these patients should undergo regular urologic surveillance.

**STATEMENT TWO: At initial evaluation, all patients with NLUTD should undergo a detailed history, physical exam, and urinalysis. (Clinical Principle)**

NLUTD represents a broad spectrum of medical conditions and illnesses which result in variable effects to the lower urinary tract. Although, to some degree, the individual clinical findings can be predicted by the neurological condition or illness, there are several factors which may preclude accuracy in the initial assessment. Potential limitations of cognition, as well as motor and sensory deficits in some individuals with NLUTD, can make information gathering and physical examination challenging and time consuming. Such limitations also

may reduce the diagnostic and prognostic accuracy of the initial evaluation prompting additional studies. A thorough initial assessment including a comprehensive history, directed physical examination, and UA is critical in directing subsequent evaluation and management. Such an initial assessment will guide the clinician in forgoing, or pursuing, further studies such as imaging and multichannel UDS. Critical elements of the history and physical examination in the individual with NLUTD are outlined below. Many of these elements are common to all patients with NLUTD, while others may be unique to only certain types of NLUTD (e.g., evaluating for AD in a patient with a SCI at T6 or above). Important and notable factors to elicit in this population, which may impact management, include: cognitive ability; upper and lower extremity function; spasticity and dexterity, which impacts the ability to do CIC; mobility; supportive environment; and prognosis from the neurological condition (i.e., progressive, acute, stable, resolving). Validated questionnaires including symptom assessment instruments (e.g. OAB-q, NBSS) may be administered to capture baseline data as well as assess for changes over time and response to interventions.

**Critical elements of the history and physical examination in the individual with NLUTD:**

**History:**

- Characterization of the neurological condition resulting in NLUTD: time of onset, severity, progres-

**Table 3: NLUTD Risk Stratification**

	Low-Risk	Moderate-Risk	High-Risk
<b>Renal Function</b>	Normal/stable	Normal/stable	Abnormal/unstable
<b>PVR (voiding patients):</b>	Low	Elevated	N/A
<b>Urinary Tract Imaging</b>	Normal/stable (if assessed)	Normal findings	Hydronephrosis, new renal scarring, loss of renal parenchyma, or staghorn/ large stone burden
<b>Urodynamics</b>	Synergetic voiding (if assessed)	Neurogenic retention DO with incomplete emptying	Poor compliance VUR (if UDS done with fluoroscopy) High storage pressures with DO and DSD

Patients are categorized into the highest risk strata they meet (e.g., a patient meeting the high-risk criteria in any one category is high-risk).

DO: detrusor overactivity; DSD: detrusor sphincter dyssynergia; PVR: post-void residual; UDS: urodynamic studies; VUR: vesicoureteral reflux

sion, prognosis, potential for recovery, disability, presence of ventriculoperitoneal shunt

- Lower urinary tract management: voluntary voiding, CIC, indwelling catheter
- LUTS: frequency, urgency, hesitancy, straining, nocturia, nocturnal enuresis, pad use/diapers, pain
- Catheterization use: type, frequency, size, pain
- Incontinence: stress, urge, insensate
- Sexual function and desire
- Fertility function and desire (gynecologic/reproductive history)
- Bowel function and regimen (if appropriate)
- Skin integrity: decubitus ulcers
- AD: presence, triggers, and typical symptoms
- Renal function tests and imaging
- Current and prior assessments and management related to urinary, sexual, infertility, and bowel issues:
  - \* Behavioral, medical, and surgical
  - \* Efficacy: success, failure, limitations
  - \* Adverse events (AE) and complications
- Complications: stones, UTIs, catheter issues (e.g., encrustations, catheter clogging), skin breakdown
- Functional limitations: lifestyle, mobility, hand function
- Socio-economic situation and/or support (home) environment
- Assessment of goals of evaluation and therapy in the context of the neurological condition (e.g., SCI versus dementia)
- Co-existent genitourinary (GU) conditions, prior GU surgery (e.g., benign prostatic hyperplasia (BPH), urethral stricture, fistula, SUI)
- Past medical history
- Past surgical history
- Medications
- Allergies (including latex allergy)
- Lifestyle factors: smoking, alcohol, or addictive drug use`

#### Physical Exam:

- General mental status, cognition
- Assessment of mobility and upper extremity function
- Abdominal and flank exam
- Pelvic and vaginal examination in females
- Genital examination and digital rectal exam
- Rectal: tone, masses, reflexes, prostate assessment (in males)
- Skin integrity of pelvis, perineum, buttocks, lower back, and lower extremities
- Directed neurological assessment: sensory, motor, spasticity, etc.
  - \* Evaluation of bulbocavernosus, anal, and cremasteric reflexes
  - \* Tone of anal sphincter and voluntary contraction of the anal sphincter and pelvic floor muscles

UA (dipstick and/or microscopic) is performed to assess for hematuria, pyuria, glucosuria, proteinuria, and other findings which may prompt further evaluation. Abnormalities should be interpreted in the context of the patients underlying condition, symptoms, and the presence or absence of a urinary catheter. An initial abnormal dipstick UA may prompt a formal microscopic examination of the urine. Additional evaluations in individuals with NLUTD demonstrating an abnormal UA are discussed in relevant sections later in this Guideline.

Ultimately, the initial evaluation is part of the risk stratification process which may or may not lead to further investigations, such as urinary tract imaging or multi-channel UDS, in some individuals.

**STATEMENT THREE: At initial evaluation, patients with NLUTD who spontaneously void should undergo post-void residual measurement. (Clinical Principle)**

PVR is defined as the volume of urine left in the bladder at the end of micturition.<sup>22</sup> PVR provides valuable information regarding bladder emptying. An elevated PVR suggests an abnormality of bladder emptying due to detrusor underactivity (DU), bladder outlet obstruction (BOO), or both. A chronically elevated PVR can result in LUTS, as well as complications such as UTIs, bladder stones, and upper urinary tract deterioration.

Notably, a low PVR does not absolutely exclude significant NLUTD and risk. Although uncommon, a poorly compliant, low-capacity bladder, with or without vesicoureteral reflux (VUR), may be associated with a low PVR but still carry a substantial risk to the upper urinary tract in the setting of a competent or fixed, non-relaxing bladder outlet.

There is no universally agreed upon definition of an elevated PVR,<sup>23, 24</sup> either as an absolute value or as a percentage of bladder emptying (“voiding efficiency”), although a volume of greater than 300 cc has been suggested as a definition for non-neurogenic chronic urinary retention.<sup>25</sup> In the NLUTD population, there is no definite upper limit of bladder volume below which constitutes a normal PVR, nor is there a lower limit of volume above which defines an abnormal or elevated PVR. An elevated PVR which could potentially be associated with a clinically relevant abnormality or condition (e.g., LUTS, UTI, upper tract deterioration) is generally considered abnormal and should prompt further evaluation with multichannel UDS<sup>23</sup> and treatment as indicated.

PVR can be measured using several techniques including transabdominal bladder scanner, real-time US, or urethral catheterization. Although non-invasive, the accuracy of transabdominal US imaging for PVR may be compromised by several factors including body habitus (obesity), prior lower abdominal or pelvic surgery, presence of ascites or pelvic cysts, and vaginal prolapse involving the bladder. Urethral catheterization is the most accurate method and provides an uncontaminated urine specimen for further study, but is also the most invasive.

A single elevated PVR may not be indicative of bladder emptying ability. An artifactually elevated PVR may result from rapid diuresis or psychogenic inhibition (e.g., patient difficulty with emptying due to environmental factors), among other factors. Thus, a suspected abnormally elevated PVR should be confirmed with a second measurement at another visit.<sup>23, 24</sup> A PVR should be performed at the time of diagnosis and may be checked periodically thereafter to monitor for changes in bladder emptying ability, regardless of the symptoms, or at the discretion of the physician following changes in management in the setting of NLUTD.<sup>23</sup> An additional challenge in patients with NLUTD may be an inability to empty their bladder on command; thus, it may not be possible to check a true PVR at certain visits if voluntary voiding cannot be initiated.

**STATEMENT FOUR: At initial evaluation, optional studies in patients with NLUTD include a voiding/catheterization diary, pad test, and non-invasive uroflow. (Expert Opinion)**

Multiple adjunctive studies such as a voiding diary, pad test, and non-invasive uroflowmetry may be useful in the initial assessment of some individuals with NLUTD. Due to the wide variety of neurological conditions, signs and symptoms, and severity at presentation, such studies are selectively utilized where they may provide additional diagnostic or prognostic information or direct clinical management.

A voiding diary is a simple, noninvasive, and inexpensive method of collecting somewhat objective information regarding LUTS and/or catheterization habits. A voiding and intake (or “bladder”) diary captures the timing and volumes of micturition, the number of incontinence episodes, and potentially other information such as type and volume of fluid intake; the degree of urgency (in those with intact sensation); and the severity of incontinence episodes.<sup>22</sup> The same data can be captured with a catheterization diary in those who use CIC exclusively, or in those who use CIC in combination with volitional voiding. Similar to the guidance in the *AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder (OAB) in Adults*,<sup>26</sup> the diary is considered optional in the NLUTD patient where it may assist in diagnosis or inform clinical decision making. It is notable that there exists very little normative data for diary parameters in the neurogenic population. Furthermore, although it is widely used and advocated as a diagnostic, management, and outcomes assessment tool, there is only sparse literature supporting its use in patients with NLUTD.

The baseline diary can corroborate, or sometimes conflict, with the symptomatic data obtained during history taking and provides a unique data point to be integrated into the overall assessment and management of the patient.<sup>27</sup> Patients who do not appear able to provide accurate intake and voiding information from recall should be directed to complete a diary.<sup>26</sup> Compared to patient report, the voiding diary is generally considered a more accurate assessment of at least some micturition variables in the non-neurogenic patient population.<sup>27, 28</sup> These data can have utility for patient counseling and directing initial and subsequent treatment in some NLUTD patients. Other than capturing voiding/catheterization intervals and volumes, incontinence and other symptom data, other potentially useful infor-

mation to be gleaned from bladder diaries include the diagnosis of polydipsia/polyuria and identification of fluid types, which may be detrimental to lower urinary tract function (e.g., alcohol, caffeine). The diary also provides an assessment of functional bladder volume, which can be helpful in behavioral modification strategies as well as in interpreting and performing multi-channel UDS studies. Additionally, bladder volumes recorded on the diary may assist with subsequent management protocols, especially in patients with impaired bladder compliance and elevated filling pressures, as bladder volumes can be behaviorally adjusted to avoid upper urinary tract deterioration in these patients. Finally, subsequent diaries can also be used in follow-up to assess response to various types of treatments.

The optimal duration for collecting such diary data in the non-neurogenic population has been suggested to be from 1-7 days; however, very little information is available on the optimal diary duration. In one study in the NLUTD population, a 3-day diary was considered to be reliable for most of the parameters of interest.<sup>29</sup> It has been shown that in the non-neurogenic population, test-retest reliability increases as the number of days recorded in the voiding diary increases but patient compliance decreases.<sup>30</sup> Shorter duration of collection periods (1-3 days) are generally associated with better compliance and completeness and should be balanced against the amount of information captured from a longer period of collection (4-7 days), which is associated with greater inconvenience to the patient. The International Consultation on Incontinence suggests a minimum of 3 days in the NLUTD population.<sup>31</sup>

The pad test is a noninvasive, inexpensive tool used to acquire objective data in confirming the diagnosis of incontinence, assessing its severity, and aiding in the treatment in some individuals with NLUTD. Quantitative pad testing is suggested for individuals with NLUTD by some authors.<sup>32</sup> Pad testing measures the increase in weight of the perineal pads used (weighed pre- and post-testing) and is a volumetric assessment of the amount of urine lost over the duration of testing and may be used as a diagnostic and outcomes tool. Methods range from a short provocative test to a 24-hour pad test. Quantitative pad tests are used to measure the amount of urine leakage after executing either a standardized set of activities or a normal daily routine over a fixed time period (e.g., 24 hours). These tests can range from short time pad tests, which are done in the office, to home-based pad tests, which are typically longer in duration. Qualitative pad tests typically are

utilized to detect the presence of UI when the diagnosis is in doubt or requires objective confirmation. Such tests utilize a colored dye, either administered directly into the bladder, given orally, or given parentally, which stains the urine a predetermined color allowing the examination of the pad to assess for the presence of urine leakage. Overall, there is little data on the optimal type, duration, or utility of pad tests specifically in the NLUTD population.

A non-invasive uroflow (uroflowmetry) integrates bladder function and bladder outlet function over time during a voiding event. Normative values and specific patterns have been established in the non-neurogenic population, which are suggestive of various underlying urological conditions such as BOO, DU, Valsalva voiding, and intrinsic sphincteric deficiency. Abnormalities in this test are indicative of a significant dysfunction in the voiding phase of micturition.<sup>23, 24</sup> However, there is very limited data on the utility of uroflowmetry in the NLUTD population and it only has value in individuals who spontaneously void. There are no normative values established in the NLUTD population; importantly, this test cannot distinguish between an abnormally low flow rate due to outlet obstruction or DU. In NLUTD, where the uroflow is expected to be unaffected by the relevant neurologic condition (i.e., CVA), an abnormal uroflow suggests that the clinical picture is complicated and additional diagnostic studies may be warranted. Notably, a normal uroflowmetry study does not exclude a co-existing significant underlying abnormality.

**STATEMENT FIVE: At initial evaluation, in patients with low-risk NLUTD, the clinician should not routinely obtain upper tract imaging, renal function assessment, or multichannel urodynamics. (Moderate Recommendation; Evidence Level: Grade C)**

*The statement is supported by four observational studies (Pizzi 2014, Kim 2010, Han 2010, Kim 2015) with a very serious risk of bias when reporting on urodynamic findings, but evidence was not further downgraded for any domain.*

As noted previously in this Guideline, there are patients with NLUTD who can be characterized as low-risk for complications at the initial evaluation depending on a number of clinical factors, including a neurological diagnosis resulting in NLUTD (Figure 2). Characteristics of these patients include a neurological condition with a low potential for serious genitourinary complications (e.g., suprapontine lesions such as PD, CVA, dementia,



and normal pressure hydrocephalus), an absence of a history of elevated PVR, UTIs, and stable LUTS.

Suprapontine lesions may result in a variety of urodynamic abnormalities, most commonly DO during filling/storage, with or without DU, during voiding.<sup>33-36</sup> Such UDS findings are often correlated with LUTS in affected patients, but are not associated with a significant risk of complications such as hydronephrosis, stones, or UTIs. When performed, UDS generally reveal normal compliance, DO, “balanced” or synergic voiding, and satisfactory emptying in the absence of other unexpected lower urinary tract abnormalities (e.g., BOO, urethral stricture). Typically, these patients do not harbor “occult” elevated storage pressures, and as such, multichannel UDS are unlikely to add additional clinically valuable or actionable information. In the absence of chronically elevated storage pressures, there is limited or no risk to the patient with respect to renal function. Upper urinary tract imaging and renal function studies in the low-risk NLUTD patient are very likely to be normal and not indicated at the initial evaluation in the absence of other mitigating factors (Figure 2).

Not all patients with suprapontine lesions are considered low-risk. Some have elevated PVR, recurrent UTIs, or unstable signs and symptoms on initial evaluation. These patients are at unknown-risk and these findings should prompt further investigation as indicated.

In low-risk patients, bladder function may or may not be impaired, and symptoms may or may not be present, but the underlying neurogenic vesicourethral dysfunction is not commonly associated with abnormally high-pressure storage of urine, such as that seen with impaired compliance. Multichannel UDS, the diagnostic tool used to assess intravesical storage parameters, is invasive, expensive, uncomfortable, and a potentially morbid diagnostic study. In the initial evaluation of low-risk NLUTD, multichannel UDS are unlikely to add significant value as intravesical storage pressures are generally not elevated. This study should be reserved for patients in whom the results would affect prognosis, change the diagnosis, or direct treatment,<sup>23</sup> or in those in whom additional urological pathology, such as suspected obstruction, would alter management.<sup>37</sup> Furthermore, in low-risk NLUTD patients, the urological prognosis is generally independent of the UDS findings, the diagnosis is empiric, and management can be safely initiated in the absence of urodynamic confirmation of DO or DU.

**STATEMENT SIX: At initial evaluation, in patients with unknown-risk NLUTD, the clinician should obtain upper tract imaging, renal function assessment, and multichannel urodynamics. (Moderate Recommendation; Evidence Level: Grade C)**

*This statement was supported by two observational studies (Elmelund 2017, Ozkan 2005) with an aggregate very serious risk of bias, but evidence was not further downgraded for any domain.*

In some individuals with NLUTD, the risk of complications remains unknown after the initial evaluation with a history, physical examination, PVR, and UA (Figure 2). This may be due to several factors such as the type of underlying neurological condition (i.e., suprasacral spinal conditions), the presence of a concurrent or pre-existing history of stones, an elevated PVR, recurrent UTIs, and/or fluctuating or new signs and symptoms. Accurate risk stratification in these individuals is not possible without additional evaluations, which would include multichannel UDS and upper tract assessment, including functional tests and imaging.

An initial assessment with multichannel UDS will provide additional information to allow for accurate risk stratification in the NLUTD patients who are at unknown-risk at presentation. History and neurological exam may not predict UDS findings in some types of NLUTD including those with infrapontine neurological lesions.<sup>38, 39</sup> Elevated lower urinary tract pressures during storage, as well as unfavorable detrusor leak point pressures (DLPP) alone, or in combination with other factors, are correlated with upper urinary tract deterioration in many individuals with NLUTD.<sup>40-43</sup> Multichannel UDS are an essential tool in assessing lower urinary tract storage pressures and DLPP (where clinically relevant) for an accurate diagnosis, to assess prognosis, and to direct treatment in many cases.

NLUTD patients who are not stratified by initial history, physical examination, PVR, and UA as low-risk should also undergo upper tract assessment with imaging and functional studies. Prediction of upper tract deterioration in all but the low-risk NLUTD population is currently imprecise and somewhat vague. Neurological conditions such as SCI, spina bifida (SB), transverse myelitis, and MS (in males) may present with widely variable signs, symptoms, and UDS findings. Furthermore, even after assessment with multichannel UDS, the exact DLPP and intravesical storage pressure at which the upper urinary tract is at risk is unclear. Furthermore, there is no universally agreed upon value of abnormal

bladder compliance although calculated values of less than 12.5 ml/cmH<sub>2</sub>O (compliance = D volume/D pressure) have been suggested as abnormal.<sup>44</sup> Sustained intravesical pressures in excess of 40 ml/cmH<sub>2</sub>O are associated with an increased risk of upper urinary tract deterioration.<sup>40</sup> Factors including VUR, infection, and functional bladder capacity, among other elements, can impact the risk of finding occult hydronephrosis and diminished renal function at presentation. Thus, even though multichannel UDS are essential in the evaluation of these unknown risk NLUTD patients, this should be accompanied by an upper tract assessment as well at the time of initial evaluation.

**STATEMENT SEVEN: In the patient with an acute neurological event resulting in NLUTD, the clinician should perform risk stratification once the neurological condition has stabilized. (Clinical Principle)**

Timely risk stratification in the NLUTD patient enables the clinician to counsel the patient with respect to their condition and proceed with an appropriate, cost effective, and efficient evaluation resulting in an accurate diagnosis, an assessment of prognosis, and that often directs treatment. In doing so, the clinician will avoid unnecessary and potentially morbid testing, such as multichannel UDS in those who would not benefit, while proceeding with an evaluation in those for whom it would have utility. However, there are some individuals in whom an initial risk stratification should be delayed, particularly those with spinal shock and acute brain injury.

Following an acute neurological event to the brain (e.g., stroke) or spinal cord (e.g., trauma), there are initial short-term clinical findings that change over time and are not limited to urodynamic changes.<sup>45</sup> Such changes may evolve over the course of days, weeks, months, and up to 1-2 years following the initial event. The exact timing of the evaluation should be explored in a shared decision-making context between the patient and clinician.

Spinal shock following acute SCI is generally characterized by a period of loss of neurologic activity below the level of injury, including absent somatic reflex activity and flaccid muscle paralysis. This usually results in the urodynamic findings of detrusor areflexia and preserved sphincter tone. It may occur in partial or complete SCI and may last several days or months, and usually resolves in approximately 3-6 months, but the duration can be as long as 1-2 years. Recovery from spinal

shock is manifest by the return of reflex bladder activity and lower extremity deep tendon reflexes. The exact pathophysiology of spinal shock, as well as its resolution, is not well understood. Nevertheless, profound clinical and urodynamic changes occur during the spinal shock period.<sup>46</sup> These changes are not predictive of future function of the lower urinary tract or UDS findings; thus, UDS are not invariably performed at this time and may be delayed until the period of spinal shock has resolved.

Similarly, a transient period of clinical evolution commonly results following acute brain injury such as ischemic or hemorrhagic stroke or blunt or penetrating head trauma usually attributed to a temporary period of cerebral edema. Urodynamic investigations during this period may reveal detrusor areflexia. Following treatment and recovery from the acute event, reinvestigation with UDS weeks or months later may reveal considerable changes in the pattern of lower urinary tract dysfunction.<sup>34</sup>

Thus, following acute spinal or brain injury, the clinical condition as well as the short-term changes are not prognostically valuable, nor are they reflective of the ultimate long-term neuro-urological diagnosis. Risk stratification should not be performed during this period in these patients and should be postponed until the neurological condition and consequences have stabilized. Furthermore, neurological recovery during this period is variable and depends on the type, extent, and mechanism of injury; initial treatment; and many other factors. Thus, risk stratification prior to stabilization will not be clinically meaningful and moreover, may be misleading.

**STATEMENT EIGHT: Clinicians should not perform routine cystoscopy in the initial evaluation of the NLUTD patient. (Clinical Principle)**

Similar to the general population, cystoscopy should be reserved for situations where there is a defined clinical indication or strong suspicion of an anatomic abnormality. Cystoscopy is an invasive, potentially morbid, expensive, and oftentimes uncomfortable diagnostic procedure. A diagnosis of NLUTD is not an absolute or relative indication for cystoscopy.

In the NLUTD patient, cystoscopy may be indicated at the initial evaluation in the setting of unexplained hematuria or pyuria; suspected urethral pathology such as stricture or false passage; bladder stones; or known or suspected bladder cancer. However, in the absence

of mitigating factors from history, physical examination, or UA, as noted above, lower urinary tract investigation with cystoscopy is unlikely to yield a significant finding in the NLUTD patient and is therefore not recommended. Cystoscopy may reveal abnormalities, such as trabeculation in some individuals with NLUTD, but these findings do not independently alter diagnosis, prognosis, or affect treatment and do not warrant investigation. Indications for cystoscopy in the follow-up/surveillance of NLUTD is covered in Guideline Statement 18.

### Autonomic Dysreflexia

**STATEMENT NINE: During urodynamic testing and/or cystoscopic procedures, clinicians must hemodynamically monitor NLUTD patients at risk for autonomic dysreflexia. (Clinical Principle)**

Clinicians who are managing NLUTD patients should be able to recognize those at greatest risk for AD. The patients at risk for AD who are undergoing cystoscopy and/or multichannel UDS should be hemodynamically monitored continuously during testing.<sup>47</sup> In addition, the procedure should be performed by experienced and trained staff who have a thorough understanding of AD and its associated signs and symptoms. Furthermore, pharmacotherapy to manage AD should be accessible and readily available in the facility before every urologic procedure.<sup>48, 49</sup>

AD is caused by an aberrant spinal reflex related to the SCI at or above T6. In general, patients with cervical level or upper thoracic level SCI are at greatest risk for AD. When a noxious stimulus such as bladder distention during cystoscopy and/or UDS enters the spinal cord below the level of injury, this afferent stimulus generates sympathetic overactivity leading to vasoconstriction below the neurologic lesion along with involvement of splanchnic circulation causing vasoconstriction and hypertension. The excessive compensatory parasympathetic activity leads to vasodilation above the level of the lesion and is thought to be responsible for headache, visual disturbances flushing, sweating, and nasal congestion. The reflex bradycardia is secondary to baroreceptor mediated vagal stimulation.<sup>50</sup>

Bladder distension is the most common trigger factor for AD. The distension that can result from urinary retention, catheter blockage, or lower urinary tract procedures accounts for up to 85% of cases of AD.<sup>47</sup>

It is important to note that the second most common trigger factor for AD is bowel distension due to fecal impaction. This can be noticed during placement of

the rectal catheter at the time of multichannel UDS. Other potential factors include hemorrhoids, anal fissures, and/or pressure ulcers. Education of patients, clinicians, caregivers, and family members regarding AD is vital to prevent its occurrence, facilitate its recognition, and proceed with treatment in a timely fashion.<sup>51</sup>

**STATEMENT TEN: For the NLUTD patient who develops autonomic dysreflexia during urodynamic testing and/or cystoscopic procedures, clinicians must terminate the study, immediately drain the bladder, and continue hemodynamic monitoring. (Clinical Principle)**

AD is a medical emergency specific to patients with SCI at the neurologic level T6 or above. A few patients with T7 or even T8 SCI level may also be at risk.<sup>52</sup> For NLUTD patients who develop AD during urodynamic testing/and or cystoscopy examinations, the clinician should stop the inciting procedure immediately and drain the urinary bladder. These maneuvers should be considered first-line treatment and are often the most expeditious and effective in treating the condition. Clinical improvement, as measured hemodynamically and clinically, is usually immediate once the noxious stimulus has been removed.<sup>48</sup>

Initial management also involves placing the patient in an upright position in a wheelchair to take advantage of any orthostatic reduction in blood pressure and loosening tight clothing and/or constrictive devices. Blood pressure should be monitored at least every five minutes until the patient is stable with baseline vital signs. If hemodynamic improvement does not occur after first-line treatment, then pharmacotherapy should be considered (see Statement 11).

**STATEMENT ELEVEN: For the NLUTD patient with ongoing autonomic dysreflexia following bladder drainage, clinicians should initiate pharmacologic management and/or escalate care. (Clinical Principle)**

Although bladder drainage, placing the patient in an upright position (in a wheelchair), and monitoring vital signs are the first steps in managing AD in the SCI/NLUTD patient, clinicians should immediately initiate pharmacologic management and escalate care in those with ongoing and persistent AD following bladder decompression. Patients with a systolic blood pressure greater than 150 mm Hg and/or 20 mm Hg above baseline who exhibit persistent classic symptoms such as flushing, sweating, headache, blurry vision, and a

sense of impending doom are not adequately managed.

In general, nitrates are the most commonly used medication to manage refractory AD associated blood pressure elevation because they have a direct relaxant effect on vascular smooth muscles, leading to dilation of coronary vessels and peripheral veins. The topical application of 1 to 2 inches of 2% nitroglycerine paste on the skin, above the level of the spinal cord lesion, is effective and can be easily removed in order to minimize the subsequent risk of hypotension once the hypertensive crisis subsides. Nitropaste is the most popular and versatile pharmacologic treatment for AD and should be readily available in urology units treating SCI/NLUTD patients.<sup>53</sup>

Alternatively, nifedipine, a dihydropyridine, voltage-sensitive calcium channel blocker, can be used. When it is administered in immediate-release sublingual form (10 mg capsules), it exerts coronary and peripheral vasodilator properties.<sup>54</sup> Although nifedipine significantly decreases resting mean arterial blood pressure in patients with SCI/ NLUTD, and prevents dangerous blood pressure elevations during UDS and/or cystoscopy, there is a lack of well-controlled clinical trials on nifedipine use for the management of AD. Also, nifedipine can rapidly and precipitously lower blood pressure well below baseline values and its effects may not be rapidly reversed in the clinic setting, as can be done with wiping topical nitroglycerine off, so it should be used judiciously.

If such antihypertensive compounds do not alleviate symptoms, then escalating care to an intensively monitored setting may be appropriate. Initiating intravenous administration of sodium nitroprusside may be indicated for rapid titration of blood pressure.<sup>49</sup> Other agents have also been utilized in the setting of AD. Alpha-adrenergic receptor blocking agents (e.g., terazosin, a specific alpha-1 adrenergic antagonist) appear to prevent serious harm from AD. Another alpha 1-adrenergic antagonist, prazosin (3 mg twice a day, given for 2 weeks), has been reported to reduce both the severity and duration of AD episodes in cervical and high thoracic SCI individuals.<sup>49</sup>

### Surveillance of the patient with NLUTD

**STATEMENT TWELVE: The clinician must educate patients with NLUTD on the signs and symptoms that would warrant additional assessment. (Clinical Principle)**

Patients with NLUTD can suffer from urological compli-

cations in the interval period between annual visits and, because of their neurological condition, may not have the expected signs and symptoms.

Patients should be educated to contact their clinician if they develop new or worsening AD or UI. Both could be early warnings of worsening bladder function such as DO or worsening bladder compliance.<sup>55</sup> New or more frequent UTIs and/or infections associated with fever or flank pain should also be reported to their clinician since these could be associated with worsening bladder function,<sup>55</sup> or new upper tract findings such as stones or hydronephrosis/VUR. Hematuria, even with catheterization, should be reported to their clinician since this can be an early sign of bladder cancer<sup>56</sup> or urinary lithiasis. This should prompt consideration of a hematuria workup<sup>57</sup> since gross hematuria is the most common presenting symptom of bladder cancer in patients with NLUTD, occurring in 32% of cases of bladder cancer in NLUTD.<sup>58</sup> Lastly, new difficulties in catheterizing can be the first sign of developing urethral stricture. Urological providers should work closely with the patient's physical medicine and rehabilitation provider since these symptoms could also be reported to them or be related to their neurological condition.

These reported signs and symptoms, assessed within the patient's clinical context, as well as their level of risk, may prompt lab work, imaging, an office evaluation, or office procedure such as UDS or cystoscopy, depending on the clinical scenario (see Statements 16, 17, and 18). The clinician may already have sufficient information from routine urologic care to assess the potential severity of the new signs and symptoms, and the decision to provide reassurance, investigations, or an office evaluation will be situation specific.

Although signs and symptoms can be atypical in this population, the importance of investigating them cannot be underestimated. Symptomatic NLUTD patients are far more likely to have pathologic findings than those without symptoms. Among a population of 21 SCI patients who reported new urologic symptoms (fever/rigors, hematuria, kidney/bladder pain, purulent urine, recurrent bladder infections), 20 had significant findings on renal/bladder US (including hydronephrosis and stones) and required some type of intervention. This was compared to 87 asymptomatic SCI patients who had the same renal/bladder US performed as part of routine surveillance; 63 US were normal and 24 had insignificant anomalies such as renal cysts or non-obstructing stones that did not require intervention.<sup>59</sup>

**STATEMENT THIRTEEN: In patients with low-risk NLUTD and stable urinary signs and symptoms, the clinician should not obtain surveillance upper tract imaging, renal function assessment, or multichannel urodynamics. (Moderate Recommendation; Evidence Level: Grade C)**

*The evidence base for this statement is comprised of one systematic review (Averbeck 2015) and two observational studies (Pizzi 2014, Kim 2018). The two observational studies reported on urodynamic parameters and were limited by a very serious risk of bias but evidence was not further downgraded.*

Low-risk NLUTD patients are by definition those with a neurological diagnosis that is low-risk to the upper urinary tract (i.e., stroke, PD, dementia) who void with a low PVR and have not suffered any urological complications or recurrent UTIs (Table 3). Because of their low-risk neurological conditions, these patients do not require upper tract imaging, renal function assessment, or UDS at initial presentation or in subsequent follow up (Figure 2; Statement 4). It is highly unlikely that over time these patients will develop urological complications secondary to their NLUTD; hence, there is little utility in performing more advanced screening tests. Also, should they develop a complication such as a renal stone, urinary retention, or a UTI, these conditions would present symptomatically and further evaluation could be done as indicated (Figure 2). These patients can suffer from non-neurological causes of LUTS, such as sling obstruction or BPH causing BOO, which can be treated based on clinical presentation, but often require greater counselling of the patient before treatment and potentially more workup, such as UDS, before proceeding with surgical intervention.

In a study on UDS performed on 106 post-stroke incontinent (n=84) and continent patients (n=22) patients, all had either a normal study, DO, DU, or DOIC<sup>34</sup>. None of these patients had dangerous findings such as poor bladder compliance, high storage pressures, or detrusor sphincter dyssynergia (DSD), none of which would be expected with a suprapontine neurological disease. The most frequent urodynamic finding in patients with PD is DO with balanced voiding; other findings include low PVR volumes, normal bladder compliance, and normal capacity without evidence of high-risk features.<sup>60</sup> Low-risk NLUTD patients are not at significantly higher risk for upper tract stones or hydronephrosis than the general population, which is why screening this group with upper tract imaging or renal function studies is not time

- or cost-effective. If low-risk patients develop new signs, symptoms, or complications during their follow-up period, risk re-stratification and appropriate evaluation can be done as indicated (see Statement 16). These patients, when appropriate, can be managed expectantly with follow-up by their primary care provider and with education on signs and symptoms that would require re-evaluation (see Statement 12).

**STATEMENT FOURTEEN: In patients with moderate-risk NLUTD and stable urinary signs and symptoms, the clinician should assess the patient with:**

- a. annual focused history, physical exam, and symptom assessment.
- b. annual renal function assessment.
- c. upper tract imaging every 1-2 years.

**(Moderate Recommendation; Evidence Level: Grade C)**

*This statement is informed by two systematic reviews (Averbeck 2015, Cameron 2012) and seven observational studies (Cameron 2015, Edokpolo 2013, Guzelkucuk 2015, Gao 2017, Katsumi 2010, Chen 2002, Bartel 2014) reporting on detection of new or worsening symptoms. The studies carried a very serious aggregate risk of bias but evidence was not further downgraded for any domain.*

Moderate-risk NLUTD patients have already been risk stratified (Statements 1 and 2) and are, by definition, those who require catheter drainage of their bladder (CIC or indwelling) or have an elevated PVR after voiding (see Table 3). These patients do not have dangerous UDS findings, but still remain at risk of complications, albeit lower than those in the high-risk NLUTD category. An annual focused history, physical exam, and symptom assessment, with or without applicable questionnaires, provides the opportunity to screen for complications and worsening or new symptoms that may require investigation or a change in medical management (Figure 1). Patients who catheterize can be assessed for adherence to their recommended schedule or for difficulties in passage of their catheter. This is an ideal time to adjust catheter type, to adjust frequency of catheterization, and to assess the efficacy of medical/injection therapy for NLUTD.

Renal function with serum creatinine, although a weak predictor of renal deterioration for many patients in this population with low muscle mass,<sup>61</sup> is a simple test and often is performed with other routine lab work obtained

by other providers. Serum creatinine levels in SCI patients have been shown to be significantly lower than age and gender matched ambulatory individuals; levels below the normal range are expected. A significant rise in serum creatinine from baseline, even within the normal range, should prompt careful assessment. Alternatively, a creatinine clearance measure by 24-hour urine collections is more sensitive, but time consuming.<sup>61</sup> Cystatin C levels can also be used to estimate renal function; as it is less influenced by muscle mass it is thought to be superior to serum creatinine in patients with SCI.<sup>62</sup> However, the widespread use of Cystatin C appears to be limited due to cost concerns.<sup>63</sup> Moderate-risk patients have had prior normal upper tract imaging and safe urodynamic parameters on prior screening studies; provided they have no new complications or symptoms reported in their clinical visit, a renal US every 1-2 years is sufficient to assess for asymptomatic renal calculi or other upper tract findings (Figure 2).<sup>59</sup> These patients typically have low mobility, which increases urinary calcium and subsequently results in an increased risk of stones, particularly in the first three months after injury.<sup>64</sup> Recurrent renal stones have been reported in 34-64% of persons with SCI in long-term studies,<sup>65, 66</sup> and bladder stone recurrence has been reported as high as 23%<sup>67</sup>; hence, surveillance for these stones needs to be lifelong.

Due to changes in sensation from their neurological disorder, renal calculi are often asymptomatic in moderate-risk NLUTD patients and symptoms of ureteral obstruction may present differently. In addition, because these patients are at a higher risk of UTI, staghorn calculi and infectious stones are prevalent and can lead to serious complications if discovered late or when of substantial size.

Renal US is a low morbidity imaging modality that assesses both the kidneys and bladder with better sensitivity for calculi than a kidney, ureter, and bladder X-ray (KUB)<sup>61</sup> and without the risk of ionizing radiation from CT scans. If a patient has undergone cross sectional or other equivalent upper tract imaging for other purposes during the interval between visits, it would be adequate to reference this imaging.

Nuclear medicine renal scans are a more sensitive assessment of renal obstruction than serum creatinine, intravenous pyelogram, or voiding cystourethrogram<sup>61</sup> and provide information on renal function; however, in studies on serial renal nuclear scans on individuals with SCI, there was no advantage over renal US, particularly

if the renal US was normal. A renal scan, which is more time-intensive than a renal US, is best reserved for investigating renal function deterioration based on serum creatinine, evaluating obstruction, or as a secondary imaging study if abnormalities are seen on renal US. Also, renal scans are poor at identifying renal stones and cannot be used as an alternative imaging to renal US.

Several systematic reviews support this surveillance schedule, particularly the use of routine renal US,<sup>61</sup> although actual clinical practice may differ. An analysis of a 5% sample of Medicare beneficiaries over a 2-year period showed that only 25% of SCI individuals underwent upper tract imaging, renal function assessment, and a urological clinic visit.<sup>68</sup>

There is little data on the optimal frequency of renal US in NLUTD patients. Various systematic reviews and guidelines suggest different schedules. While some advocate imaging as often as every six months,<sup>69</sup> most recommend US annually<sup>61</sup> or every 1-2 years.<sup>70</sup> The frequency is dependent on the patient's risk of upper tract deterioration.

Edokpolo and Foster<sup>55</sup> assessed the impact of routine surveillance with annual renal US. They followed 48 SCI patients who performed CIC and had safe UDS parameters on initial testing for a mean of 6.8 years with annual US. They did not perform routine UDS on this group of patients and found mild/moderate hydronephrosis in 6%, with no severe cases, and renal calculi in 13%, with no new renal scarring or thinning. This follow up strategy was deemed safe and effective.

Another study on renal US followed 1005 SCI patients with tetraplegia (n=313) or paraplegia (n=692) who had a renal bladder US at varying times after injury (mean 32.5 +/- 49.2 months). Renal calculi were detected in 6%, hydronephrosis in 5.5%, and renal atrophy in 1.2%. A trabeculated bladder was seen in 35.1%, which was found to be a risk factor in this study for stones and renal atrophy. Longer time since injury, bladder management with indwelling catheter, and higher level of injury were other risk factors for these complications, further emphasizing the need for long term surveillance since risk of complications appears to increase over time.<sup>71</sup>

Flexibility in the schedule of US imaging is at the discretion of the provider who may space out imaging to every two years in those patients who have been stable for longer periods of time and who are reliable at seek-

ing care when they have complications or symptoms. Given the burden of travel in this vulnerable population, providers should aim to have these tests and imaging studies either performed close to the patient's home or during the same visit as the clinical encounter to hopefully improve compliance.

**STATEMENT FIFTEEN: In patients with high-risk NLUTD and stable urinary signs and symptoms, the clinician should assess the patient with:**

- a. **annual focused history, physical exam, and symptom assessment.**
- b. **annual renal function assessment.**
- c. **annual upper tract imaging.**
- d. **multichannel urodynamic studies, with or without fluoroscopy, which may be repeated when clinically indicated.**

**(Moderate Recommendation; Evidence Level: Grade C)**

*The evidence base for this statement is comprised of three systematic reviews (Cameron 2012, Averbek 2015, Kavanagh 2019) and two observational studies (Elmelund 2016, Fletcher 2013). Across the studies evaluating the surveillance modalities and reporting on the outcomes of interest, the aggregate risk of bias was very serious. Evidence was not further downgraded in any domain for any reported outcome.*

High-risk NLUTD patients (Table 3) are those who have high-risk features on UDS such as poor bladder compliance, VUR, high storage pressures, or have existing upper tract significant disease (e.g., hydronephrosis, parenchymal thinning, large stone burden, unstable renal function). This group of patients is at substantial risk of renal deterioration, worsening bladder parameters, and urinary infections. An annual clinical assessment with their urological provider is the minimum clinical follow-up recommendation for this high-risk group, and they will likely require more care than this surveillance schedule for management of complications or medical treatment. In contrast to moderate-risk patients, high-risk patients require upper tract imaging annually given their risk of new stones, increasing stone burden, or renal parenchymal loss in a potentially already compromised upper tract (Figure 1).

Close surveillance is particularly important in these patients who manage their bladder with such high-risk bladder methods.<sup>72</sup> In a study of 116 SCI patients, most of whom emptied their bladder with reflex triggering or bladder expression, 58% had moderate renal

dysfunction rate and 29% had a severe renal dysfunction rate after 45 years of follow up. Upper tract dilatation and renal/ureter stones requiring intervention were the most significant risk factors for renal dysfunction.

UDS may need to be repeated in high-risk patients, even in those with stable symptoms. Worsening of bladder compliance and/or detrusor storage pressures, or the development of VUR, can be silent but are serious conditions requiring constant monitoring and action as needed. The timing of repeat UDS is left to the discretion of the urological provider since not all patients in this group will benefit from routine UDS. Some patients who are high-risk because of upper tract findings but have prior favorable UDS parameters and have their incontinence well managed with medical or surgical treatment of the bladder, are unlikely to have unexpected findings on UDS study. On the other hand, a patient with prior dangerous bladder storage parameters and continued symptoms can easily have deterioration prompting more aggressive therapy. The number of iterations of possible scenarios is vast; hence, appropriate knowledge and understanding of the patient's neurological disease and prior testing results, as well as the findings from the clinical assessment and upper tract imaging, will guide the clinician as to whether or not to repeat UDS evaluation. Existing guidelines and systematic reviews are varied in their recommendations. The European Association of Urology guideline on neuro-urology recommends UDS at "a regular interval" for the high-risk patient.<sup>69</sup> The National Institute for Health and Care Excellence guideline advocates to consider UDS as part of the surveillance regimen,<sup>73</sup> but there is no clear schedule recommended. Most guidelines advocate for UDS in the event of new symptoms or a more regular basis in high-risk patients with prior poor bladder compliance.<sup>23, 61, 70</sup>

A systematic review of 28 studies including 1368 patients found that evidence supporting the timing of UDS was lacking. UDS was found to modify treatment and often had findings even in the absence of symptoms or changes on upper tract imaging;<sup>74</sup> however, UDS is costly and not without risk to the patient. Patients can suffer urethral complications, UTI, or AD during the procedure. The Panel recommends that clinician take these morbidities into account as well as the time and travel burden to this vulnerable population.

A patient can change from high- to moderate-risk after receiving appropriate treatment and undergoing subsequent evaluation, post-treatment, repeat UDS, upper

tract imaging, or renal function studies. If this occurs, then follow-up should be based on their new risk category.

**STATEMENT SIXTEEN: In patients with low-risk NLUTD who present with new onset signs and symptoms, new complications (e.g., autonomic dysreflexia, urinary tract infections, stones), and/or upper tract or renal function deterioration, the clinician should re-evaluate and repeat risk stratification. (Clinical Principle)**

There are essentially two pathways for patients to initially enter the low-risk stratification. This can occur at initial presentation with a neurological condition that is at low-risk for upper tract deterioration, with the identification of good bladder emptying, with stable urological symptoms, and with no recurrent UTIs or complications. This can also occur in patients who were initially classified as unknown-risk who subsequently underwent risk stratification with upper tract imaging, UDS, and renal function and showed normal renal function and upper tracts and synergistic voiding on UDS. This would subsequently classify these patients as low-risk (Table 3).

Low-risk NLUTD patients do not require routine upper tract imaging, renal function assessment, or UDS (Figure 1). If they do not require further urological management for LUTS, these patients may be under the care of their primary care physician and do not require routine urological care. Despite their initial risk categorization as low-risk, they are not at zero risk of urological manifestations of NLUTD. These patients may develop new incontinence or difficulty emptying, recurrent UTIs, stones, or upper tract/renal function deterioration. These signs, symptoms, and complications may be the result of NLUTD or a manifestation of unrelated urological disease such as BPH or SUI. If their urinary tract condition has changed over time, and a clinical assessment changes their risk stratification, they should be followed up according to their new category.

**STATEMENT SEVENTEEN: In patients with the moderate- or high-risk NLUTD who experience a change in signs and symptoms, new complications (e.g., autonomic dysreflexia, urinary tract infections, stones), or upper tract or renal function deterioration, the clinician may perform multichannel urodynamics. (Clinical Principle)**

The data is mixed on the utility of routine UDS in pa-

tients with NLUTD who have stable urinary symptoms and no urological complications; however, the data is very consistent that UDS performed for specific symptoms or cause often yield important urodynamic findings that may result in treatment changes. In multiple studies following NLUTD patients with sign or symptom changes such as increased incontinence, recurrent UTIs, changes in renal function or new hydronephrosis, UDS revealed changes in bladder function such as loss of bladder compliance, high storage pressure, VUR, or worsening DO that required a change in bladder management method or medical or surgical therapy.<sup>74</sup> UDS findings may result in a change in risk stratification to high-risk if concerning features are found (see Table 3).

**STATEMENT EIGHTEEN: In the NLUTD patient with concomitant hematuria, recurrent urinary tract infections, or suspected anatomic anomaly (e.g., strictures, false passage), clinicians should perform cystoscopy. (Moderate Recommendation; Evidence Level: Grade B)**

*This statement is supported by a systematic review (Ismail 2018) with a serious risk of bias.*

Any patient with painless gross hematuria requires upper tract imaging (i.e., CT urogram or renal US) and a cystoscopy. SCI patients have a slightly elevated risk of bladder cancer which is especially pronounced after 20 years of disease. In a systematic review of 15 studies encompassing 103,397 SCI patients, the only patient factor correlating with bladder cancer was the presence of gross hematuria.<sup>58</sup> Indwelling catheter management in the SCI population does have an increased risk of squamous cell carcinoma compared to those managed with CIC.

Patients with indwelling catheters or those who perform CIC are at risk of urinary tract irritation or catheter trauma as the source of bleeding, but this cannot be determined without cystoscopic investigation. Benign bladder lesions, urethral strictures, or calculi can also be the cause of bleeding and will be effectively diagnosed with a cystoscopy and receive the correct treatment.

Recurrent UTIs are not rare in NLUTD patients, but in this population they can be the result of anatomic defects in the bladder such as foreign bodies or bladder diverticula that can be diagnosed with cystoscopy.<sup>75</sup>

NLUTD patients with difficult urethral catheter passage or hematuria with catheterization can have urethral strictures or a false passage from catheter trauma, par-



ticularly in those patients with external sphincter spasm during catheter passage. Cystoscopy can effectively diagnose these conditions and may prompt treatment of a stricture or a change in catheterization technique after careful observation of the patient performing CIC. Other changes aimed at minimizing urethral trauma can include changing catheter type such as switching to a coude catheter, changing catheter size or to those that are pre-lubricated. Alternatively, in the case that a urethral stricture is highly suspected as the cause of difficult catheter passage, a retrograde urethrogram can make the diagnosis of urethral strictures in male patients.<sup>76</sup>

**STATEMENT NINETEEN: In NLUTD patients, clinicians should not perform screening/surveillance cystoscopy. (Strong Recommendation; Evidence Level: Grade B)**

**STATEMENT TWENTY: In NLUTD patients with a chronic indwelling catheter, clinicians should not perform screening/surveillance cystoscopy. (Strong Recommendation; Evidence Level: Grade B)**

*The evidence base supporting statements nineteen and twenty are shared based on identified studies enrolling NLUTD patients using different bladder management strategies with subgroup analyses for those using indwelling catheters in several studies. The evidence base is comprised of two systematic reviews (Ismail 2018, Cameron 2012) and four observational studies (El-Masri 2014, Hamid 2003, Sammer 2015, Hamid 2009), which were limited only by a serious risk of bias.*

Patients with SCI are at higher risk than the general population for developing bladder cancer; however, this overall risk is only 0.3%, even when including those patients managed with indwelling catheters.<sup>58</sup> One concern that often prompts the recommendation for routine cystoscopic surveillance is that NLUTD bladder cancer patients often present with advanced disease at a younger age and with unfavorable pathology such as squamous cell carcinoma which is responsible for 25-81% of bladder cancers in the SCI population.<sup>77</sup> In a systematic review of bladder cancer in NLUTD patients, the average age of presentation was younger (mean: 56.1 years) and occurred after a long period of neurological disease (mean: 24.5 years). Half of the patients utilized indwelling catheters as a bladder management method making it a significant risk factor, along with smoking and recurrent UTIs.<sup>58</sup>

It has been suggested that surveillance cystoscopy in this population might be beneficial in the early detection of bladder cancer, given their higher risk, and might reduce overall morbidity and mortality. However, although conceptually attractive, this notion has not yet been proven. A systematic review of nine studies has shown that cystoscopy and cytology are poor screening tests for bladder cancer in NLUTD patient.<sup>61</sup> Multiple other studies have assessed the utility of screening cystoscopy in NLUTD patients without hematuria.<sup>78-81</sup> Six hundred and fourteen patients, most with long term indwelling catheters, were screened over many years. Only one malignancy was found on screening, but many patients had benign inflammatory or metaplastic lesions that led to surgical biopsy and other investigations. None of these studies deemed routine cystoscopy as useful in the detection of bladder cancer. The difficulty in this population, who have more UTIs and catheter burden, is that the bladder is subject to irritation and subsequent inflammatory lesion (e.g., erythema, bullous edema, catheter induced cystitis) formation. Routine cystoscopy leads to over detection of these benign lesions, which in turn leads to surgical biopsy and its inherent risk. In studies that looked closely at annual surveillance, patients were found to develop advanced symptomatic cancer between surveillance cystoscopy episodes making it a poor screening study.<sup>81</sup> Overall, there remains an absence of high-level evidence that supports initial or annual cystoscopic surveillance for bladder cancer in reducing morbidity and mortality in this population.<sup>77</sup> In a systematic review of 15 studies covering 332 patients with bladder cancer, gross hematuria was the leading presenting symptom of bladder cancer in 31.6% of patients;<sup>58</sup> hence, a urologic history alone is likely a better screening tool than cystoscopy. This argument also applies to patients who underwent prior augmentation cystoplasty. Routine cystoscopy was performed on 92 patients who were at least ten years status-post prior bladder augmentation. Screening cystoscopy did not identify any tumors and the only malignancy was diagnosed after cystoscopy was done for gross hematuria after a previously normal screening cystoscopy.<sup>56</sup>

The exception to this recommendation is patients with an existing history of non-muscle invasive bladder cancer that should be followed with screening cystoscopy based on their pathological risk strata according to recommendations from the *Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline*,<sup>82</sup> regardless of their NLUTD diagnosis.

**STATEMENT TWENTY-ONE: In NLUTD patients with indwelling catheters, clinicians should perform interval physical examination of the catheter and the catheter site (suprapubic or urethral). (Moderate Recommendation; Evidence Level: Grade C)**

*This statement is informed by three observational studies (Katsumi 2010, Gao 2017, Lavelle 2016) with a very serious risk of bias, plus evidence was downgraded for indirectness.*

Indwelling catheters are chronic foreign bodies present in the urinary tract and their site of entry is inherently at risk for complications. The urethra is at risk for catheter hypospadias (i.e., penile spatulation) in men and dilation of the bladder outlet and urethral loss in women. The catheter itself can cause pressure necrosis of the tissue of the urethra or even the pubic bone over prolonged periods of time. Risk factors for this complication include individuals with decreased sensation in the perineal area, impaired cognition, larger catheter size, and patients who are seated for prolonged periods of time. Patients with NLUTD have many of these risk factors and are at particular risk of this problem; up to 23% of men with NLUTD and a urethral catheter suffer from urethral erosion.<sup>83, 84</sup> Securing the catheter properly is one method to reduce this risk, but does not eliminate it.<sup>85</sup>

In women, the relatively short urethra and bladder neck gradually dilate over time, which can lead to urine leakage around the catheter. A temporary solution is often to increase the catheter size, which only increases the pressure on the urethra, further exacerbating the problem. The urethra can become so dilated that the catheter balloon is expelled and a larger (20-30 mL) balloon is often employed. As with catheter upsizing, balloon upsizing also exacerbates the problem long-term. A larger balloon causes more bladder stimulation and spasms, often resulting in the larger balloon to be expelled as well. Hence, neither increasing the size of the catheter nor balloon are recommended and rather an investigation of the cause of leakage is indicated.<sup>86</sup>

These urethral injuries can be repaired with urethroplasty if the tissue is amenable.<sup>87</sup> In women with milder urethral dilation with little loss of urethral tissue an autologous sling may suffice provided the catheter is changed to a suprapubic tube preventing future injury.<sup>88</sup> However, if the urethra is lost, particularly in women, the only solutions are bladder neck closure with suprapubic catheter placement or urinary diver-

sion.<sup>89</sup> Suprapubic catheters prevent this complication.<sup>83</sup> In patients who choose urethral catheterization, the urethra should be examined regularly so that any urethral damage can be detected early and conversion to a suprapubic tube can be considered to halt further injury.

Suprapubic catheters avoid urethral complications but can also erode through the abdominal wall if improperly secured. Granulation tissue can often occur around the suprapubic catheter site and can bleed and make tube changes more difficult. This can be easily identified and treated in the office with topical silver nitrate application.<sup>86</sup>

**STATEMENT TWENTY-TWO: In NLUTD patients with indwelling catheters who are at risk for upper and lower urinary tract calculi (e.g., patients with spinal cord injury, recurrent urinary tract infection, immobilization, hypercalcuria), clinicians should perform urinary tract imaging every 1-2 years. (Moderate Recommendation; Evidence Level: Grade C)**

*The evidence base for this statement is comprised of four observational studies (Guzelkucuk 2015, Katsumi 2010, Lavelle 2016, Gao 2017). The studies were limited by an aggregate very serious risk of bias, plus evidence was downgraded for indirectness.*

NLUTD patients with indwelling catheters are at unique risk for stones because of the chronic presence of a foreign body in their urinary tract. The catheter increases the risk of UTIs<sup>90</sup> and is a source of chronic bacteriuria, both of which are risk factors for bladder and upper tract calculi. The catheter itself can serve as a nidus for biofilm and crystal formation. When the balloon is deflated for catheter changes, these shells of calculi are often left in the bladder to serve as a seed for bladder calculi formation. In addition, UTIs and bacteriuria from urease splitting organism can result in high urine pH, which precipitates urinary crystals.

Bladder stones prevalence ranges from 8% to 41%<sup>71, 83, 90-92</sup> in patients with indwelling catheters and can go undetected without imaging until they are very large, particularly in patients who do not void and have altered sensation. The advantage of detecting these stones when small is that very small stones can be irrigated in clinic, while those that are slightly larger can be managed with a simple cystolitholapaxy.

Upper tract stones are also common in this patient population occurring in 6-32% of patients.<sup>71, 90, 92</sup> For this

reason, renal and bladder ultrasound are required. Cystoscopy only allows for assessment of the bladder and KUB is less sensitive for bladder stones compared to US. Any patient with an indwelling catheter falls under the moderate- or high-risk NLUTD category for long-term surveillance and requires surveillance based on their particular risk level (Statement 14 and Statement 15).

### Urinary Tract Infection

**STATEMENT TWENTY-THREE: In asymptomatic NLUTD patients, clinicians should not perform surveillance/screening urine testing, including urine culture. (Moderate Recommendation; Evidence Level: Grade C)**

*This statement is supported by three observational studies (Skelton 2018, Tornic 2020, Weglinski 2016) all reporting on the prevalence of asymptomatic bacteriuria and symptomatic UTI. The studies carried an aggregate very serious risk of bias but evidence was not further downgraded.*

The rationale to screen asymptomatic NLUTD patients is to treat those with positive urine cultures with antibiotics, to reduce bacteriuria, and to prevent the development of a future symptomatic UTI. However, the risk of developing a UTI in this patient population appears to be low enough to not justify treatment, thus eliminating the need for screening in the asymptomatic NLUTD population. Tornic et al. evaluated 317 NLUTD patients who had urine cultures obtained immediately prior to UDS and who were asymptomatic for UTI. Patients were followed for one year, and although 61% developed bacterial growth in cultures, only 18% developed symptomatic UTI; the overall incidence of symptomatic UTI was less than one per year.<sup>93</sup> This data suggests that while most patients had urinary bacterial colonization, only a small proportion went on to develop a UTI. Additionally, given the pressing concerns of antibiotic resistance and need for antibiotic stewardship, avoiding surveillance/screening urine cultures will decrease the likelihood of patients receiving unnecessary courses of antibiotics and developing resistant bacteria. *The Infectious Disease Society of America (IDSA) 2019 Clinical Practice Guidelines*<sup>94</sup> strongly recommends against screening asymptomatic persons with SCI or in patients with long-term indwelling catheters, which includes many NLUTD patients.

**STATEMENT TWENTY-FOUR: Clinicians should not treat asymptomatic bacteriuria in patients with**

**NLUTD. (Moderate Recommendation; Evidence Level: Grade C)**

*The statement is supported by four observational studies (Tornic 2020, Weglinki 2016, Skelton 2018, Waites 2006) with a very serious risk of bias but no further limitations.*

Antibiotic resistance is a significant problem in patients with NLUTD, given the high frequency of antibiotic use. The unnecessary use of antibiotics, such as for treating asymptomatic bacteriuria, should be avoided at all costs. Treatment of asymptomatic bacteriuria in catheter-free patients with SCI is followed by early recurrence of the bacteriuria with more resistant strains.<sup>95</sup> In addition, this treatment has no effect on the rate of subsequent asymptomatic bacteriuria or UTI in SCI patients performing intermittent catheterization.<sup>96</sup>

The exception to treating asymptomatic bacteriuria in NLUTD patients is in patients who are pregnant and prior to urologic procedures, in which urothelial disruption or upper tract manipulation is anticipated.<sup>74</sup> In patients with bacteriuria who are to undergo procedures in a heavily contaminated surgical field, pre-operative treatment of the bacteriuria is aimed at avoiding post-operative sepsis/UTI. Perioperative antimicrobial treatment or prophylaxis for contaminated or clean-contaminated procedures is a best practice.<sup>97</sup> *The IDSA 2019 Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria* suggests prior to endoscopic urologic procedures, a urine culture be obtained prior to the procedure and a targeted, short course antimicrobial treatment regimen given, rather than empiric therapy.<sup>94</sup> The *SUFU Best Practice Policy Statement on Urodynamic Antibiotic Prophylaxis in the Non-Index Patient* recommends a single oral dose of trimethoprim-sulfamethoxazole for patients with NLUTD.<sup>9</sup>

**STATEMENT TWENTY-FIVE: In NLUTD patients with signs and symptoms suggestive of a urinary tract infection, clinicians should obtain a urinalysis and urine culture. (Moderate Recommendation; Evidence Level: Grade C)**

*The evidence base is comprised of five observational studies (Linsenmeyer 2003, Massa 2009, Ronco 2011, Togan 2014, Clark 2018) reporting on outcomes informing this statement. Across the outcomes, studies carried a very serious risk of bias plus for evidence was downgraded in the inconsistency domain for studies reporting on accuracy of predicting a UTI based on symptoms.*

The diagnosis of a UTI in a patient with NLUTD can be challenging, especially in those patients with altered sensation. The classic symptoms of UTI seen in able-bodied patients such as dysuria, urgency, and frequency may be seen in NLUTD patients with intact lower urinary sensation; however, these symptoms are often not applicable to many patients with NLUTD due to changes in lower urinary tract sensation and altered modes of bladder management. In addition, the signs and symptoms suggestive of UTI can be impacted by the specific neurologic disorder causing NLUTD, the severity of the neurologic disorder, the degree of alteration of bladder sensation and type of bladder management (volitional void versus IC versus indwelling catheter).

For example, potential signs and symptoms of UTI, as defined by the International SCI UTI basic data set, include fever, urinary incontinence, leaking around an indwelling catheter, increased spasticity, malaise, lethargy, cloudy and/or malodorous urine, back and/or bladder pain, dysuria, and autonomic dysreflexia.<sup>99</sup> Alternatively, patients with MS may have signs of a relapse of their MS,<sup>100</sup> in addition to some of the signs and symptoms mentioned above, depending on their degree of bladder sensation and type of bladder management.

Due to these many variables, there are no signs and symptoms alone that are adequately specific and sensitive enough to predict the presence of a UTI in all patients with NLUTD. Due to these challenges, the Panel recommends that patients with signs and symptoms suggestive of a UTI should have a UA and urine culture, allowing for optimal diagnosis and the ability to use culture-specific antibiotics when treating a UTI in NLUTD patients.

Linsenmayer and Oakley<sup>101</sup> evaluated the accuracy of predicting UTI based on symptoms in a prospective case series of 147 consecutive SCI patients (101 male; 106 at T6 or higher). Patients presented to the urology clinic with complaints of a UTI over a nine-month period. UTI was defined as a new onset of clinical signs and symptoms (e.g., malodorous urine, cloudy urine, sediment in urine, increased frequency of urination, decreased urine output, fever, chills, nausea, malaise, lower extremity spasms, lower abdominal discomfort, bladder spasms, burning sensation, urinary leakage or incontinence, hematuria, discharge at suprapubic catheter site or at the urethral meatus, or signs and symptoms of AD in those with injuries at or above T6), a sig-

nificant bacteria colony count (defined as  $>10^4$  CFU/mL), and pyuria (defined as  $>10$  WBC/hpf). Using these definitions, 61% (n=90) of patients were able to predict the presence of UTI based on symptoms, and 39% (n=57) of patients were unable to predict the presence of UTI based on symptoms. In addition, the authors found that the type of bladder management had no impact on whether patients with SCI were able to predict the presence of a UTI based on symptoms alone.

Massa et al.<sup>102</sup> evaluated the accuracy and predictive values of signs and symptoms to identify UTI in 51 SCI patients (34 male, 26 at T6 or higher). This study was part of a larger trial evaluating the effectiveness of hydrophilic catheters in patients with chronic SCI (injured for at least six months) and recurrent UTI. During the three-month period, participants completed a monthly UTI signs and symptoms questionnaire (i.e., leukocytes in the urine, discomfort or pain over kidney or bladder, incontinence, increased frequency of catheterization, fever, increased spasticity, AD, cloudy urine, foul smell in the urine, feeling sick, feeling tired, sense of unease) and provided urine samples. Participants were also given five options to answer the question: "how certain are you that you have a UTI?" The three possible responses that were grouped as a positive response were "definitely do have a UTI," "do have a UTI," and "not sure." The two possible responses that were grouped as a negative response were "definitely do not have a UTI" and "do not have a UTI."

The authors found that patients were much better at predicting when they did not have a UTI versus when they did have a UTI. The negative predictive value for "definitely do not have a UTI" and "do not have a UTI" was 82.8%, whereas the positive predictive value of "definitely do have a UTI," "do have a UTI," and "not sure" was 32.6%. The authors also evaluated individual signs and symptoms to identify their predictive values alone. The presence of urinary leukocytes had the highest sensitivity (82.8%) and negative predictive value (93.8%). Cloudy urine had the second highest positive predictive value (61.3%) and sensitivity (65.5%). Interestingly, fever and symptoms of AD had the highest specificity at 99% but very low sensitivity (fever: 6.9%; AD: 0%) due to high false negative rates.<sup>102</sup> Alavinia et al.<sup>103</sup> found malodorous urine to have the highest sensitivity and new onset incontinence to have the highest specificity for UTI diagnosis in SCI patients. Cloudy urine had the highest positive predictive value (71%), which increased to 78% when combined with malodorous urine. However, it is not clear how these

results, which were found in 55 in subacute inpatient SCI patients, translates to all patients with NLUTD.

Ronco et al.<sup>104</sup> reviewed signs and symptoms of UTI in male patients with SCI in a prospective case series. Patients were divided into two groups: symptomatic UTI (381 episodes; 209 patients) and asymptomatic UTI (277 episodes; 205 patients). Symptomatic UTI was defined as a bacterial count of  $>10^2$  CFU/mL and at least one of the following signs or symptoms: fever, cloudy and/or malodorous urine, onset of UI or modification of bladder behavior, fatigue or sense of unease, increased spasticity, autonomic hyperreflexia. Asymptomatic UTI had the same culture criteria without any of the above signs and symptoms. There was no clinical sign or symptom that was diagnostic of UTI. The most common clinical signs associated with UTI were cloudy and/or malodorous urine (51.4%), new onset UI (51.2%), fatigue (41.7%), and fever (30.7%). The authors found no association between cloudy and/or malodorous urine, new onset urinary incontinence, fever with higher CFU, or urinary WBC levels when comparing symptomatic versus asymptomatic UTI. Their conclusion was that these signs and symptoms, in isolation, were not optimal for a diagnosis of UTI. They also found that fever was not associated with more concerning urinary findings and speculated this could be related to various other causes of infection leading to fever.

This data illustrates the challenges of diagnosing UTI with symptoms alone in the NLUTD population, especially in those patients with altered and decreased sensation. Without standard normal UTI symptoms, clinicians often rely on non-specific symptoms such as increased spasticity, abdominal discomfort, malaise, and increased symptoms of AD. All these symptoms can be secondary to UTI; however, these symptoms can also be caused by a variety of other conditions not related to UTI. For example, an increase in AD symptoms is a common sign that a patient with a SCI at T6 or higher may have a UTI. However, AD symptoms could also be secondary to bladder distention, bladder or kidney stones, constipation, hemorrhoids, and pressure ulcers. Thus, it is very important to obtain a UA and urine culture to optimally obtain a diagnosis of UTI in this patient population.

However, it can also be unclear as to how to interpret culture results in patients with NLUTD who manage their bladder by a variety of methods. Recommendations put forth by the National Institute on Disability

and Rehabilitation Research Consensus Statement in 1994 defined a UTI as  $>10^2$  CFU/mL for those who manage their bladder with CIC, and  $>10^4$  CFU/mL if using a condom catheter.<sup>105</sup> IDSA released clinical guidelines for the diagnosis of catheter-associated UTIs (CAUTI) in 2010.<sup>106</sup> While this was not focused on patients with NLUTD, the recommendations can be applied to this patient population. The IDSA identified three criteria to make a diagnosis of a CAUTI: signs and symptoms compatible with UTI, no other identifiable source of infection, and a bacterial count  $>10^3$  CFU/mL. In addition, the IDSA did not advocate using pyuria to determine whether antibiotics should be administered; however, they did state that if pyuria was absent another cause of symptoms, other than UTI, should be sought.

Finally, another argument for obtaining a urine culture is the ability to treat a UTI with culture-specific antibiotics and the importance of antibiotic stewardship. This is especially applicable to patients with NLUTD who may be at greater risk of harboring resistant organisms. A review of urine specimens from 93 SCI patients at a rehabilitation center found multidrug resistance in 48% of bacterial strains in patients with asymptomatic bacteriuria, and in 66.6% of strains from patients with symptomatic UTI.<sup>107</sup> Another study of 52 patients with NLUTD secondary to SCI underwent weekly urine cultures at a rehabilitation unit. There was an average 60% and 36% incidence of change in the results for patients managing their bladder with an indwelling catheter and CIC, respectively. Changes included positive to negative culture, negative to positive culture, and a change in organism in a positive culture.<sup>108</sup>

Clark and Welk<sup>109</sup> reviewed urine culture results over a two-year period of 146 patients with NLUTD at a tertiary care urology clinic. Of the 81 individuals with at least two positive cultures, there was 55.8% concordance (i.e., similar organisms between cultures), which decreased significantly for each 30-day period between urine cultures ( $p=0.02$ ). Interestingly, antibiotic sensitivity concordance was higher than what was seen for the specific bacterial organism (ciprofloxacin: 77.3%; nitrofurantoin: 78.5%, trimethoprim-sulfamethoxazole: 75%) and was not impacted by increasing time between cultures. This illustrates the importance of checking prior culture results if empiric antibiotics are to be started once a UA and culture have been obtained, but not yet resulted, in NLUTD patients with signs and symptoms of a UTI.

**STATEMENT TWENTY-SIX: In NLUTD patients with a febrile urinary tract infection, clinicians should order upper tract imaging if:**

- a. **the patient does not respond appropriately to antibiotic therapy.**
- b. **the patient is moderate- or high-risk and is not up to date with routine upper tract imaging, regardless of their response to therapy.**

**(Clinical Principle)**

Clinicians need to maintain a high degree of concern when NLUTD patients have a febrile UTI. NLUTD patients may have a structural or functional abnormality of their lower urinary tract, resulting in a “complicated” UTI at baseline. In addition, the potential alteration of normal sensation may impact signs and symptoms, such as flank or abdominal pain, that would normally inform the caregiver of a potentially more dangerous condition. While not specific, fever remains a warning sign that should not be ignored and if it does not respond to appropriate therapy may be a sign of issues such as hydronephrosis, pyonephrosis or renal abscess, and/or urinary tract stones.<sup>59, 110</sup>

NLUTD patients should have a UA and culture (see Statement 26) and culture specific antibiotics should be appropriately administered. If there is a high degree of suspicion for a UTI then empiric antibiotics should be initiated with the antibiotic changed, if needed, based on the culture result. The clinician may choose an antibiotic based on a recent, prior culture, if available.<sup>109</sup> NLUTD patients with a febrile UTI that does not respond to appropriate antibiotic therapy should undergo evaluation of the upper tract (e.g., US, CT) to evaluate for diagnoses such as stones and hydronephrosis.

Patients with moderate-risk NLUTD are to have upper tract imaging every one to two years and patients with high-risk NLUTD are to have upper tract imaging annually (see Figure 1; Statements 10 and 11). The need for appropriate radiographic assessment in these patients is still required, even if they have an appropriate response to antibiotics. Therefore, it is imperative that patients continue to be risk stratified (see Table 3) and evaluated appropriately based on their level of risk.

**STATEMENT TWENTY-SEVEN: In NLUTD patients with a suspected urinary tract infection and an indwelling catheter, clinicians should obtain the urine culture specimen after changing the catheter and after allowing for urine accumulation**

**while plugging the catheter. Urine should not be obtained from the extension tubing or collection bag. (Clinical Principle)**

In 2009, IDSA published guidelines for the diagnosis, prevention, and treatment of CAUTI in adults.<sup>106</sup> While it was not focused on the NLUTD patient, many of the recommendation can be applied. IDSA recommends obtaining urine specimens aseptically through the catheter port in patients with short-term indwelling catheterization and suspected UTI. Short-term is not defined in the IDSA document, but would not apply to NLUTD patients who manage their bladder with an indwelling urethral or suprapubic catheter. Due to concerns related to biofilm possibly impacting the adequate assessment of the urine, the recommendation from the IDSA is to obtain urine for culture from a freshly placed catheter. In addition, it is specifically stated that urine should not be obtained from the drainage bag.

The studies that support this statement are older and primarily evaluated elderly patients who managed their bladder with chronic indwelling catheters for a variety of reasons; these were not studies that specifically evaluated the topic in NLUTD patients. Bergqvist et al. evaluated a total of 50 paired urine specimens (one from the catheter end and one via suprapubic aspiration) that were obtained from 43 men who were either waiting for prostate surgery or unfit/unwilling to have prostate surgery for urinary retention.<sup>111</sup> The length of time with the catheter was: 13 men (26%): catheter for ten days or less; 13 men (26%): catheter for 11-30 days; 24 men (48%): catheter > 30 days. Fourteen of the specimens were negative, which correlated between both techniques. However, when bacteriuria was identified, there was a lack of agreement in 12 of 36 specimens. The concern was that specimens obtained via a chronically placed catheter were not optimal and the authors recommended suprapubic bladder aspiration when obtaining urine in patients with a chronic indwelling catheter. While suprapubic aspiration is not the recommendation of the Panel, this does speak to the potential benefit of obtaining urine for culture from a newly placed catheter over one that has not been changed.

Two other studies focused on the concept of placement of a new catheter to obtain urine in patients with chronic indwelling catheters which reflects present day practice. Grahn et al.<sup>112</sup> evaluated 20 elderly nursing home residents (n=2 male, n=18 female) who were managed with a long-term catheter for >6 months. A catheter specimen was obtained via needle aspiration from the

distal end of the catheter that had not been changed for at least 30 days; the bladder specimen was obtained from the end of a freshly placed catheter that was clamped for 30 minutes. There was a difference in 22 of 41 isolated bacterial strains in 17 of 20 patients. Urine from the bladder was more likely to result in urine specimens with a CFU/ml of  $<10^5$ . CFU/mL counts of  $<10^5$  were noted in 7 of 45 catheter strains compared to 16 of 45 strains from the bladder ( $p<0.05$ ). There were 17 instances where the CFU count from the catheter exceeded the quantity of the same strain in the bladder by at least tenfold. Using a CFU/mL of  $>10^5$  to identify significant bacteriuria, the authors noted that while the catheter specimens had a sensitivity of 90%, the specificity was only 43%.

Tenney et al. evaluated urine specimens in 62 women ( $>60$  years) with long-term indwelling catheters (12 who managed their bladder with a catheter for 1-3 months; 26 for 4-12 months; 24  $>$ one year).<sup>113</sup> Paired specimens were obtained similarly as to the prior study: one via needle aspiration from the distal end of the catheter that had not been changed, and one from the end of a freshly placed catheter. The authors found significantly more bacterial species from urine obtained from the older catheter (246 versus 157;  $p<0.001$ ) as well as a tenfold higher mean concentration of bacteria from the older catheter ( $p<0.001$ ). The duration of bladder management with an indwelling catheter did not affect the results; however, patients with the individual catheter in place for a longer period of time ( $>3$  weeks) were more likely to have bacterial counts  $>10^5$  ( $p<0.05$ ).

**STATEMENT TWENTY-EIGHT: In NLUTD patients with recurrent urinary tract infections, clinicians should evaluate the upper and lower urinary tracts with imaging and cystoscopy. (Clinical Principle)**

Similar to the evaluation of hematuria, it is considered good clinical practice to evaluate both the upper and lower urinary tracts for sources of recurrent UTI. Imaging is needed for examining the upper urinary tracts. The risks of direct visualization via ureteroscopy far outweighs the benefit in this situation and is not recommended. Contrast studies are not required in the initial evaluation. Since the risks of lower urinary tract evaluation via cystoscopy are low, it is a necessary part of the evaluation of recurrent UTIs. *The AUA Guideline for Recurrent Uncomplicated UTIs in Women*<sup>75</sup> defines recurrent UTI as two episodes of acute bacterial cystitis

within six months or three episodes within one year. However, there is no clear-cut definition of recurrent UTI in the NLUTD patient population. The Panel has elected not to define recurrent UTI in patients with NLUTD and leaves it to the discretion of the clinician.

**STATEMENT TWENTY-NINE: In NLUTD patients with recurrent urinary tract infections and an unremarkable evaluation of the upper and lower urinary tract, clinicians may perform urodynamic evaluation. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement is informed by studies reporting on rate of UTI (Skelton 2018, Tornic 2020, Weglinksy 2016, Manack 2011, Game 2008, Wefer 2010) and abnormal findings by urodynamic studies (Abello 2020, Bywater 2018, Chou 2006, Nosseir 2007, Wang 2016, Dromerick 2003). For each outcome, studies carried a very serious risk of bias and evidence was further downgraded for indirectness.*

Patients with NLUTD have an increased risk of recurrent UTI with an estimated rate of 2.5 episodes of infection per patient per year.<sup>114</sup> Manack et al. reviewed data of 48,327 patients with  $>1$  neurogenic bladder-specific diagnosis and found that over a one-year period, 38.6% had a UTI (36.4% lower; 2.2% upper).<sup>115</sup> There are a variety of theories as to why NLUTD patients are at greater risk of UTI, including method of bladder management/catheterization, alteration of protective flora, defective glycosaminoglycan layer, impaired immune response, defective apoptosis, bladder ischemia, elevated PVR, VUR, and disturbed hydrokinetics.<sup>116, 117</sup> Several of these potential causes are related to abnormalities in lower urinary tract function that can be seen in patients with NLUTD and diagnosed by UDS. Therefore, it is appropriate to consider UDS evaluation in NLUTD patients with recurrent UTIs that have an unremarkable evaluation of the upper and lower urinary tract.

Lapides hypothesized in 1979 that reduced blood flow to the bladder is a risk factor for UTI.<sup>118</sup> Bladder underperfusion in NLUTD could be secondary to poor compliance, DO, and/or high voiding pressures. Indirect evidence to support this theory, and the potential benefit of obtaining UDS in NLUTD patients with recurrent UTIs, comes from two studies that demonstrated UTI reduction after successful injection of onabotulinumtoxinA. In addition to improvements in bladder capacity and incontinence, Game' et al.<sup>119</sup> demonstrated a decrease in symptomatic UTIs from 1.75 to 0.2 during a 6

-month period after injection of onabotulinumtoxinA in 30 patients with NLUTD and Wefer et al.<sup>120</sup> showed a decrease in UTI prevalence from 68% to 28% in 213 patients with NLUTD after injection of onabotulinumtoxinA. Similar improvements in UTI incidence were noted after sacral deafferentation and bladder augmentation in NLUTD patients that also showed improved bladder capacity and pressures. UDS is also helpful in the identification and evaluation of elevated PVR and VUR which can commonly be seen with patients with NLUTD; there is evidence that both increased PVR and VUR can increase the risk of UTI incidence in patients with NLUTD.<sup>121-125</sup> Alterations in hydrokinetics refers to what would be seen with patients with DSD. This would theoretically result in turbulent flow and urinary stasis, potentially resulting in a higher bacterial colony count primarily and secondarily increasing the UTI risk due to elevated PVR and VUR.<sup>117</sup> Finally, clinicians may consider UDS evaluation in patients with NLUTD and LUTS that are attributed to recurrent UTI, even if evaluation is not consistent with a true infection. LUTS in patients such as this may be a sign of underlying NLUTD that would benefit from further evaluation with UDS.

**STATEMENT THIRTY: In NLUTD patients who manage their bladder with an indwelling catheter, clinicians should not use daily antibiotic prophylaxis to prevent urinary tract infection. (Strong Recommendation; Evidence Level: Grade B)**

*The statement is informed by a systematic review (Morton 2002) of fifteen studies using multiple bladder management and was limited by a serious risk of bias.*

Although antibiotics reduce or delay the onset of bacteriuria and UTI in chronically catheterized patients, many experts and guideline panels discourage prophylactic antibiotic use, primarily because of the development of antibiotic resistance. A systematic review by Morton et al. evaluated the use of antimicrobial prophylaxis in patients with spinal cord dysfunction. A total of 15 studies (eight in acute SCI patients defined as <90 days post-injury and seven in non-acute SCI, defined as >90 days post-injury, or other chronic conditions resulting in spinal cord dysfunction) were included in the review. While the majority of studies reviewed did focus on patients managing their bladder with CIC, studies that evaluated outcomes in patients managing their bladder with an indwelling catheter were included. The conclusion from the systematic review was that antimicrobial prophylaxis did not significantly decrease symptomatic infections in patients with spinal cord dys-

function. In addition, approximately a two-fold increase in antimicrobial-resistant bacteria was seen.<sup>126</sup>

**STATEMENT THIRTY-ONE: In NLUTD patients who manage their bladders with clean intermittent catheterization and do not have recurrent urinary tract infections, clinicians should not use daily antibiotic prophylaxis. (Moderate Recommendation; Evidence Level: Grade B)**

*The evidence base is comprised of two systematic reviews (Morton 2002, Niel-Weise 2012), one RCT (Fisher 2018), and two observational studies (Edokpolo 2012, Fakas 2010). Included studies carried an aggregate serious risk of bias but evidence was not downgraded for any other domain.*

This recommendation was largely based on the strength of two systematic reviews that did not find evidence to support the use of prophylactic antibiotics for patients with NLUTD who manage their bladder with CIC and do not have issues with recurrent UTI. Morton et al. reviewed outcomes of antibiotic prophylaxis in SCI patients (both acute and chronic) from 15 studies published between 1980 and 1995. Their review noted a statistically significant decrease in bacteriuria in acute (<90 days) SCI patients ( $p < 0.5$ ) and a difference that approached statistical significance ( $p = 0.06$ ) in non-acute SCI patients. However, antibiotic prophylaxis did not significantly decrease the rate of symptomatic UTIs and resulted in an approximate 2-fold increase in bacterial resistance. The type of bladder management used by the patients in these various studies included both CIC and indwelling catheter; the majority were using CIC.<sup>126</sup>

A subsequent systematic review, published in 2012, evaluated a variety of outcomes related to the use of antibiotic prophylaxis.<sup>127</sup> Specific to this question, the authors addressed the question of whether antibiotic prophylaxis was better than giving antibiotics when clinically indicated. This analysis included three crossover trials and one parallel group trial. There were some differences regarding patient population (including pediatric patients) and UTI definition. One study reported fewer UTIs in the control group and one study noted fewer UTIs in the group of patients on antibiotic prophylaxis. An additional study evaluated differences between febrile and afebrile UTI (the only study to report outcomes in this manner) and reported antibiotic prophylaxis resulted in less afebrile UTIs, but did not have an impact on febrile UTIs. The final conclusion of the systematic review was that there was not



adequate evidence to make recommendations to this practice. Based on this data, the Panel does not recommend prophylactic antibiotics in NLUTD patients who manage their bladder with CIC and do not have recurrent UTI; this recommendation is similar to other Guidelines as well.<sup>128-131</sup>

What is unclear is if antibiotic prophylaxis would be beneficial in patients who manage their bladder with CIC and have recurrent UTIs. Fisher et al. evaluated the efficacy of prophylactic antibiotics in 404 patients (all of whom did not have NLUTD) who managed their bladder with CIC. Half of the cohort received once-daily antibiotic over a 12-month period. Patients on antibiotic prophylaxis were less likely to have a symptomatic, antibiotic-treated UTI; 1.3 cases/person-year were noted in the prophylaxis group compared to 2.6 cases/person-year in the control group ( $p < 0.0001$ ). However, there was a statistically significant higher rate of antibiotic resistance in the prophylaxis group: nitrofurantoin resistance was seen in 24% of the prophylaxis group compared to 9% in the control group ( $p = .038$ ); trimethoprim resistance was seen in 67% of the prophylaxis compared to 33% in the control group ( $p = 0.0003$ ); and co-trimoxazole resistance was seen in 53% of the prophylaxis group compared to 24% in the control group ( $p = .002$ ).<sup>132</sup> The difficulty balancing fewer infections with the concern about higher rates of bacterial resistance speaks to the challenges when deciding upon the use of prophylactic antibiotics for patients on CIC that do have recurrent UTI (see Statement #37).

### Non-Surgical Treatment

**STATEMENT THIRTY-TWO: Clinicians may recommend pelvic floor muscle training for appropriately selected patients with NLUTD, particularly those with multiple sclerosis or cerebrovascular accident, to improve urinary symptoms and quality of life measures. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base informing this statement is comprised of two systematic reviews (Thomas 2008, Block 2015), one RCT (Thomas 2014), and one observational study (Xia 2014) reporting one urinary symptoms and quality of life. Across the outcomes of interest, the aggregate risk of bias was serious, and evidence was downgraded for inconsistency of results across the studies reporting on quality of life domains.*

Various types of behavioral and physiotherapeutic ap-

proaches have been employed for managing symptoms associated with NLUTD. Although current literature does encompass several RCTs, sample sizes are small ( $\leq 20$  participants per group), interventions not standardized, and patient groups diverse.<sup>133, 134</sup> The majority of studies addressed use of pelvic floor exercises as the primary therapeutic intervention. Although limited with regards to statistical power, data suggests non-invasive interventions, which are associated with minimal side effects, may be offered and are of particular benefit to select patients. In general, pelvic floor exercise reliably enhances strength and endurance of pelvic floor muscles across diverse patient groups. Improvements in the pelvic floor musculature were associated with reduction of LUTS and may be correlated with improvements on various QoL questionnaires. Of note, the preponderance of evidence has been obtained from patients with MS or CVA, with less data available for other NLUTD etiologies.

An observational analysis of MS patients evaluated effects of pelvic floor muscle training with EMG biofeedback on lower urinary tract function ( $n = 37$ ).<sup>135</sup> Following a 9-week intervention, multiple parameters demonstrated significant improvement including urinary frequency, incontinence episodes, 24-hour pad test, various QoL questionnaires, and pelvic floor muscle endurance. All intervention effects were maintained at 24 weeks follow-up.

Four RCTS evaluated patients post-CVA with LUTS. Female CVA patients were randomized to engage in gait training and stretching as well as urinary and pelvic floor education (control  $n = 17$ ) versus general rehabilitation plus pelvic floor muscle training ( $n = 18$ ) for 6 weeks.<sup>136</sup> Women performing pelvic floor exercises demonstrated significantly increased vaginal squeeze pressures, as well as improved LUTS and QoL compared to controls.

Male patients with LUTS following CVA were randomized to 12 weeks of standard rehabilitation without lower urinary tract elements ( $n = 15$ ) versus standard rehabilitation plus pelvic floor muscle training and bladder education ( $n = 16$ ).<sup>137</sup> Men in the instruction arm demonstrated significantly improved pelvic floor muscle function and strength as well as QoL scores compared to controls. Similar improvements in frequency and episodes of urgency incontinence were seen across both groups. All pelvic floor enhancements were maintained during an additional six months of follow up.

A similar study of female CVA patients randomized

women to 12 weeks of standard rehabilitation without lower urinary tract elements (n=14) versus standard rehabilitation plus pelvic floor muscle training and bladder education (n=12).<sup>138, 139</sup> Women who engaged in pelvic floor muscle training demonstrated significantly improved daytime frequency, 24-hour pad test, and pelvic floor strength and endurance compared to controls. However, both groups had comparable QoL scores on the Short Form 36 (SF-36) and the Incontinence Impact Questionnaire (IIQ).

Post-CVA patients undergoing a systematic voiding program, which included comprehensive voiding, continence assessment, and bladder training (n=124), were compared to a control arm, which included support of facilitators to optimize involvement and goal achievement (n=125).<sup>140</sup> For the primary outcomes of incontinence at six- and 12-weeks post-stroke, no differences were noted among groups.

SB patients were included in a randomized design which compared three months of usual care by their family physician (n=27) to intensive education about continence and skin care, bladder re-education, behavior management, pelvic floor exercises, timed/double voiding, and catheter care (n=27).<sup>141</sup> The active treatment group exhibited significant improvements on the American Urological Association Symptom Index (AUASI), the Urogenital Distress Inventory (UDI6), the IIQ7, and the Wexner-Fecal Incontinence Score (WFIS) compared to the control group. Some subscales on various QoL measures also improved significantly.

Two of the available published systematic reviews concluded there was no definitive evidence for any particular pelvic floor intervention;<sup>142, 143</sup> the third review concluded that in patients with MS, behavioral therapy interventions improve QoL and reduce incontinence episodes but this review inappropriately pooled dissimilar trials in the meta-analysis.<sup>144</sup> Overall, due to the minimal associated risks, the Panel recommends engaging appropriate patients with pelvic floor physiotherapy as select patients may demonstrate benefit for their LUTS.

**STATEMENT THIRTY-THREE: Clinicians may recommend antimuscarinics, or beta-3 adrenergic receptor agonists, or a combination of both, to improve bladder storage parameters in NLUTD patients. (Conditional Recommendation; Evidence Level: Grade C)**

**STATEMENT THIRTY-FOUR: Clinicians may recommend alpha-blockers to improve voiding param-**

**eters in NLUTD patients who spontaneously void. (Conditional Recommendation; Evidence Level: Grade C)**

*Statement 33 is supported by four systematic reviews (Madersbacher 2013, Madhuvrata 2012, Stothers 2016, El Helou 2020), five RCTs (Abrams 2003, Amarenco 2017, Glykas 2012, Cho 2021, Yonguc 2010), and eight observational studies (Krebs 2013, van Rey 2011, Watanabe 2010, Hadiji 2014, Vasudeva 2021, Han 2019, Krebs 2020, Peynonnet 2018). The aggregate risk of bias across the studies reporting on outcomes informing this statement was serious plus evidence was downgraded for inconsistency of results and imprecision in the reported outcomes.*

*Statement 34 is informed by two RCTs (Abrams 2003, Sung 2020) and one observational study (Gomes 2014) reporting on voiding parameters. The risk of bias for studies reporting on the parameters was serious and evidence was further downgraded for imprecision.*

Multiple classes of pharmacologic interventions are mainstays of medical therapy for patients with NLUTD. Antimuscarinics reliably increase maximum cystometric capacity (MCC) and voided/catheterized volumes, decrease detrusor pressure, and may improve urgency and incontinence across diverse NLUTD pathologies. There is no evidence for the superiority of any particular medication. Although AEs at recommended doses are generally minor with the most frequently reported being dry mouth, recent data has highlighted more critical potential concerns with anticholinergic therapy.

The Panel acknowledges and appreciates recent attention to the potential risks of long-term treatment with anticholinergic agents with regards to cognitive impairment and dementia. There exists conflicting literature regarding the actual association and risk profile, with overall low-certainty evidence.<sup>145, 146</sup> The Panel advocates a shared decision-making process with the patient to discuss the benefits of therapy balanced with the data reflecting anticholinergic use and potential cognitive decline or development of dementia. In selected NLUTD patients, use of alternative agents less likely to cross the blood-brain barrier without demonstrated cognitive risk may be appropriate.

Additional evidence suggests that the use of alpha-blockers combined with antimuscarinics can ameliorate symptoms across several etiologies of NLUTD in the setting of relatively minor AEs. Emerging, and therefore less robust, evidence exists for use of the more

recently approved beta-3 agonist, in the NLUTD population.

Six of the 21 included studies were RCTs, crossovers, or randomized designs that compared active treatments. Half of these trials included sample sizes likely to provide adequate statistical power; however, most trials demonstrated a high or unclear risk of bias. In addition, the RCTs administered a range of medications (e.g., alpha-blockers, antimuscarinics) for relatively short periods. Consequently, there is insufficient high-quality evidence for particular medications in specific patient categories over clinically relevant periods of time. The remaining observational studies generally reported findings consistent with the RCTs but follow up durations were limited, and patient groups were diverse.

Published systematic reviews addressing use of oral medications in NLUTD patients highlight similar methodological issues, including a relative absence of long-term follow-up data, lack of sufficient evidence for particular patient groups or medications, and relative absence of consistent reporting of outcomes using validated and standardized measures.

Madersbacher et al.<sup>147</sup> evaluated 30 studies and concluded that a dose relationship exists for antimuscarinics with regards to urodynamic parameters. For several common agents, placebo-controlled studies demonstrated a 30-40% decrease in maximum detrusor pressure (MDP) with an associated 30-40% increase in MCC. Flexible dose studies, which resulted in higher doses, appeared to improve efficacy without decreasing tolerability. Continence/incontinence was not addressed in detail in most studies. The most frequently reported AE was dry mouth with higher rates reported for oxybutynin IR compared to tiroprium, tolterodine, and propiverine. Higher medication doses were not necessarily associated with higher rates of AEs, but studies that administered combinations of medications generally reported higher AE rates. Overall, this systematic review indicated that the available literature was limited in quality by relatively short follow-up durations, small sample sizes in many studies with inadequate statistical power, lack of consideration for clinically important outcomes (i.e., continence, QoL), and diverse patient categories.

A meta-analysis of randomized trials of antimuscarinic medications noted significantly improved MCC (weighted mean difference [WMD] = 49.49 ml; 95% CI: 15.38-84.2;  $p < 0.05$ ), reflex volumes (RV) (WMD =

49.92 ml; 95% CI: 20.0-79.8 ml;  $p < 0.05$ ), patient-reported improvement/cure rates (RR=2.8; 95% CI: 1.64 - 4.8,  $p < 0.05$ ), and decreased MDP (WMD = -38.30; 95% CI -53.17 to -23.43;  $p < 0.05$ ) when compared to placebo.<sup>148</sup> There was no evidence for the superiority of one medication over another. Dry mouth rates were significantly higher with antimuscarinics (Relative Risk (RR) = 4.23; 95% CI: 1.85-9.67,  $p < 0.05$ ) compared to placebo. Other AE rates were statistically similar between active treatment and placebo groups.

Stothers et al.<sup>149</sup> conducted an integrative review of prospective and randomized trials of antimuscarinic medications to assess use of standardized clinical evaluation tools. The authors concluded that standardized tools were infrequently used and obtaining data relevant to specific types of NLUTD patients, particularly SCI patients, requires the use of standardized urodynamics methodology, standardized urinary tract terminology, bladder diaries, the American Spinal Injury Association impairment scale, and symptom scores validated in SCI patients.

Although the Panel concurs that class-specific administration may be employed by clinicians across NLUTD pathologies, several explicit conditions may display benefit more than others with regards to individual medical therapy. These disease-specific concerns are detailed below.

### **SCI patients**

Administration of alpha-blockers can decrease PVRs and maximum urethral pressure (MUP) and increase MCC and voided volume; most AEs were minor.

Administration of antimuscarinics can increase MCC, RV, voided volume, and compliance and decrease MDP, incontinence episodes, and 24-hour frequency. Use of antimuscarinics in SCI patients may increase PVR however AEs were generally minor.

Administration of the beta-3 agonist mirabegron may increase MCC and compliance, and decrease detrusor pressure, 24-hour frequency, and incontinence episodes with minimal associated AEs.

### Alpha-blockers

*Tamsulosin.* A RCT evaluated effects of tamsulosin in SCI patients with an open label extension.<sup>150</sup> Patients were randomized to placebo (n = 92), tamsulosin 0.4 mg (n = 88), or tamsulosin 0.8 mg (n = 83) for one month. Of the original 263 patients, 134 completed the

one-year open label extension. The primary outcome was maximum urethral pressure. During the randomized phase, the active treatment groups had greater MUP decreases (-12.2 and -9.6 cm H<sub>2</sub>O in the 0.4 and 0.8 mg groups, respectively) compared to placebo (-6.5 cm H<sub>2</sub>O) although the differences were not statistically significant. Patients had a mean change of -18.0 cm H<sub>2</sub>O in MUP (significantly different from baseline). Voided volume increased significantly for the 0.8 mg group during the randomized phase (by 28.2 ml). In addition, during the randomized phase, incontinence episode frequency and pad utilization improved for the 0.4 mg group compared to baseline. During the open label phase, QoL scores on patient reported questionnaires improved significantly compared to baseline. Subjective ratings indicated 71% of patients were noted to be either slightly (44%) or much improved (27%). AEs were generally transient; the most frequently reported were dizziness, abnormal ejaculation, and fatigue. During the randomized phase, more patients discontinued for AEs in the placebo group (4.4%) compared to the two active drug groups (2.3 and 2.5%, respectively). During the open label extension, 9.6% of patients discontinued for AEs. Although the AEs precipitating discontinuation were not specified, the authors conclude that long-term tamsulosin is well-tolerated and improves bladder storage and emptying in SCI patients.

**Terazosin.** Perkas<sup>151</sup> administered up to 5 mg daily in 28 male SCI patients for approximately 10 days. Fifty percent of patients reported improved voiding but UDS documented improvement in only 42% (decreased voiding pressure). Three patients discontinued the medication for AEs of syncope, lethargy, and rash.

An observational study employing one month of 5 mg terazosin administration in 22 SCI patients demonstrated improved bladder compliance with a significant mean pressure decrease of 36 cm H<sub>2</sub>O.<sup>152</sup> MCC increased significantly by 125 mL. Of the four patients with AD, three experienced cessation of symptoms while using terazosin. Most patients reported reduced incontinence episodes with complete resolution of incontinence reported by four patients. Ten patients continued to utilize terazosin after study conclusion with continued efficacy at a mean of 7.75 months. Five patients withdrew from the study for AEs including syncope and peripheral edema.

#### Antimuscarinics

**Trospium.** For SCI patients with DO, one RCT compared 20 mg trospium twice daily (n = 29) to placebo

(n = 32) for three weeks.<sup>153</sup> In the trospium group, significant improvements included: MCC increased by 138.1 mL; MDP decreased by 37.8 cm H<sub>2</sub>O; compliance increased by 12.2 mL/cm H<sub>2</sub>O. AEs were minor (i.e., nausea, dry mouth, constipation) and more frequently reported in the placebo group although the reporting system for AEs is unclear.

**Solifenacin.** One observational study administered 10 mg solifenacin to 35 SCI patients with neurogenic detrusor overactivity (NDO) for 13 months.<sup>154</sup> Solifenacin significantly improved bladder capacity (30 mL increase), MDP (7.0 cm H<sub>2</sub>O decrease), RV (62.5 mL increase), and compliance (25.0 mL cm H<sub>2</sub>O). Eight patients discontinued for lack of efficacy; two patients discontinued for intolerable AEs.

**Oxybutynin.** O'Leary et al.<sup>155</sup> administered 10 mg to 30 mg controlled-release oxybutynin daily to ten patients with NDO with 3-month follow-up. All patients were allowed to titrate the dose, and all chose a final effective dosage of greater than 10 mg, with four patients taking the maximum of 30 mg per day. MCC increased significantly from 274 to 380 mL. Frequency (24 hours) decreased from 12 to 8 voids and incontinence episodes per week decreased significantly from 13 to 6 episodes. PVR increased significantly from 26 to 51 mL but no patient reported a serious AE during the study.

#### Drug combinations

A three-arm medication combination trial compared patients (21 SCI, 3 SB, 2 MS, 1 viral encephalomyelitis) who were administered oxybutynin + trospium (n=8), oxybutynin + tolterodine (n=8), and tolterodine + trospium (n=11) over six months.<sup>156</sup> All patients previously failed maximum recommended doses of single medications and the double dose paradigm described previously by Horstmann et al.<sup>157</sup> All three groups improved comparably and significantly with large reductions in incontinence episodes and increases in bladder capacity, RV, and compliance. Two patients in different treatment groups withdrew from the study for intolerable AEs (i.e., dry mouth and blurred vision). Similar AEs reported by five additional patients were graded mild to moderate.

Comparison of oxybutynin to trospium or a combination of both medications for one month was performed in incontinent (n = 156) and continent (n = 75) SCI patients.<sup>158</sup> Although MCC increased significantly and involuntary detrusor contractions (IDC) decreased significantly, most patients did not achieve full continence

and NDO was not well controlled in approximately one-third of the continent patients. AEs were not systematically evaluated but 30 of the 97 patients on two medications reported experiencing dry mouth.

The Panel appreciates that many practitioners will employ combination therapy with anticholinergic and beta-3 adrenergic receptor agonists based upon data from non-neurogenic OAB patients.<sup>159</sup> Although the literature review for this guideline did not reveal contemporary studies providing significant safety and efficacy data for this combination, the Panel acknowledges after shared decision-making with the patient regarding risks and benefits, concomitant therapy with beta-3 adrenergic receptor agonists and antimuscarinics presents a reasonable treatment option.

#### Beta 3 adrenergic receptor agonist

*Mirabegron.* One observational study reported on effects of mirabegron (initiated at 25 mg daily and increased to 50 mg after two weeks) in 15 SCI patients with NDO followed for 7 weeks.<sup>160</sup> Twenty-four hour frequency was significantly reduced (from 8.1 to 6.4), incontinence episodes significantly decreased (from 2.9 to 1.3), MCC improved (from 365 to 419 mL), compliance improved (from 28 to 54 mL/cm H<sub>2</sub>O), and detrusor pressure during storage additionally improved (from 45.8 to 30 cm H<sub>2</sub>O). AEs were minimal and included worsening incontinence and constipation. Systematic reviews have confirmed clinical improvements with beta-3 adrenergic receptor agonists for NLUTD.<sup>161</sup>

#### **MS patients**

The administration of antimuscarinics can increase MCC and voided volume and reduce frequency, nocturia, incontinence events, urgency episodes, and urgency severity with generally minor AEs.

#### Antimuscarinics

*Oxybutynin compared to propantheline.* Gajewski et al.<sup>162</sup> randomized MS patients to oxybutynin (15 mg daily; n = 19) or propantheline (45 mg daily; n = 15) for seven weeks. MCC improved significantly more in the oxybutynin group (144 mL) than the propantheline group (35 mL). Oxybutynin resulted in significant improvements in frequency, nocturia, urgency, and urgency incontinence with 67% reporting subjective improvement compared to 36% with propantheline. Although AEs were mild to moderate and experienced by most patients, approximately one-quarter of patients in each group withdrew from the study for severe AEs.

*Solifenacin.* Thirty MS patients were administered solifenacin (5 – 10 mg daily) and followed for two months.<sup>163</sup> Frequency and number of pads used per day decreased significantly as did urgency severity while voided volume increased. Of the 30 patients, 20 chose to continue the medication after study completion. Two patients withdrew from the study for AEs with the majority reporting none or “acceptable” AEs.

#### **Parkinson’s Disease patients**

The administration of the antimuscarinic solifenacin decreased 24-hour frequency, nocturia, and incontinence episodes in the setting of minor AEs.

The administration of the alpha-blocker doxazosin improved maximum flow rate and self-reported urinary symptoms with mild AEs.

#### Antimuscarinics

*Solifenacin.* With a RCT, PD patients were assigned to placebo (n=13) or solifenacin (5-10 mg daily; n=10) for three months. The randomized phase was followed by an eight-week open label extension in which all patients received active drug. Twenty-four-hour frequency improved significantly in the randomized phase with solifenacin but not placebo. During the open label extension, significant decreases occurred in incontinence and nocturia episodes. AEs occurred in a minority of patients and were classified as mild.<sup>164</sup>

#### Alpha blockers

*Doxazosin.* Gomes et al.<sup>165</sup> followed 33 patients who were administered doxazosin ER (4 mg daily) for three months. Maximum flow rate improved significantly (from 9.3 to 11.2 mL/sec) as did QoL scores. Transient and mild dizziness was the most commonly reported AE with one patient discontinuing for these symptoms. Patients with a Unified Parkinson’s Disease Rating Scale score <70 were more likely to exhibit clinically significant improvements.

#### **Patients with various causes of NLUTD**

Antimuscarinics can increase MCC, RV, and catheterized volume, and decrease MDP, leak point pressure, number of incontinence episodes, frequency, and nocturia. Reduction in number of urgency episodes and improved QoL also was reported with minor AEs.

Alpha blockers may increase maximum flow rate, reduce PVR, and improve IPSS scores. AEs were generally minor although phenoxybenzamine was associated with high rates (25%) of discontinuation.

### Antimuscarinics

*Oxybutynin versus solifenacin.* The SONIC trial was a randomized study which compared placebo (n = 44) to oxybutynin immediate-release (IR) 15 mg daily (n = 47), solifenacin 5 mg daily (n = 50) or solifenacin 10 mg daily (n = 53).<sup>166</sup> Patients with SCI or MS were followed for one month. MCC was the primary outcome and increased significantly in all three active treatment conditions compared to placebo with the largest increases seen with oxybutynin IR (165.4 mL) and solifenacin 10 mg (134.2 mL). Compared to placebo, significant improvements were seen in all treatment groups in the following parameters: increased RV; decreased MDP; decreased DLPP; decreased incontinence episodes. Multiple QoL questionnaires favored solifenacin compared to placebo. AEs were mild with dry mouth and UTI the most commonly reported with three patients discontinuing for side effects.

*Tolterodine.* A crossover trial compared placebo to tolterodine (4 mg daily) in 14 patients followed for two weeks.<sup>167</sup> Tolterodine treatment resulted in significantly larger catheterized volumes and reduced incontinence compared to placebo. When patients were allowed to choose their dose of tolterodine (4-12 mg) or oxybutynin (10-15 mg) in an open label comparison phase, the drugs exhibited similar efficacy in terms of catheterization volumes, incontinence, and MCC. Dry mouth severity was similar between tolterodine (4 mg) and placebo but was worse for oxybutynin compared to tolterodine when patients selected generally higher doses.

One observational study administered tolterodine extended-release (4 mg daily) to 39 patients for three months.<sup>168</sup> Bladder capacity at first sensation, compliance, and MCC increased significantly as did RV. Twenty-four hour frequency, number of urgency episodes, number and volume of incontinence episodes, and voided volumes all improved significantly with treatment. AEs were mild (i.e., dry mouth, constipation) and occurred in 9% of patients.

### Alpha blockers

*Phenoxybenzamine.* One observational study administered phenoxybenzamine (15 to 30 mg daily) to 43 patients.<sup>169</sup> At six months, fewer than half the patients continued with the medication. In the 21 patients who persisted on active treatment, PVRs were generally reduced. One-quarter of patients discontinued for AEs (e.g., severe orthostatic hypotension, severe tachycar-

dia). Six patients developed incontinence and all male patients had ejaculatory failure.

### Intravesical administration of oxybutynin

Although identified studies included in the analysis were composed of small sample sizes, treatment protocols were congruent and length of follow-up adequate to assess efficacy and AEs associated with intravesical oxybutynin. Available information suggests intravesical oxybutynin reliably increased maximum bladder capacity, decreased MDP, and increased bladder compliance when chronically administered in NLUTD patients. Additionally, functional improvements in UDS parameters were associated with decreased incontinence episodes. Importantly, available data indicates that AEs may occur less frequently with intravesical oxybutynin administration compared to oral formulations.

For SCI patients deemed refractory to oral treatment, Pannek et al.<sup>170</sup> administered intravesical (15 mg three times daily) oxybutynin in combination with oral oxybutynin (5 mg four times daily with reductions as necessary) to 25 patients. At six-months follow-up, the addition of intravesical oxybutynin resulted in significantly increased bladder capacity, from 349 mL to 420 mL, with decrease in MDP from 54 to 26.5 cm H<sub>2</sub>O. In addition, the number of patients with an MDP <40 cm H<sub>2</sub>O increased from a baseline of four to 21. Of five patients with AD, three reported symptom resolution. Of the 15 patients experiencing incontinence before treatment, 11 reported symptom alleviation. The most commonly reported AEs were UTI and dry mouth. No patients discontinued treatment because of AEs.

Also exclusively in SCI patients, George et al.<sup>171</sup> aimed to ameliorate NDO with various bladder instillations of oxybutynin, propantheline, and capsaicin (n=18). Medications were instilled sequentially without a washout period between agents. No significant changes in any measured objective or subjective parameters were noted after oxybutynin. The most commonly reported AEs were dry mouth and thirst. Because this study only administered the medication for one day, its utility is minimal but included for comprehensiveness.

With regards to diverse etiologies of NLUTD, three studies were evaluated for intravesical oxybutynin efficacy and safety. A randomized design compared 17 patients on oral oxybutynin (5 mg three times daily) to 18 patients receiving intravesical oxybutynin (0.1% solution three times daily) for a one-month interval. Patients had a variety of causes of NLUTD.<sup>172</sup> The MCC

increased significantly by 116.6 mL in the intravesical group compared to 18.1 mL in the oral group. Both groups demonstrated similar improvements in MDP, RV, compliance, incontinence episodes, catheterization frequency, DLPP, and volume at time of incontinence episode. AEs were more common among patients who received oral dosing (82.4%) compared to the intravesical administration (55.6%). With intravesical instillation, significantly lower rates of visual, gastrointestinal, nervous system, and skin AEs were reported compared to oral administration. Patients had the option to continue therapy once the trial was complete; 15 of 18 patients continued intravesical treatment and maintained efficacy for one year.

Prasad and Vaidyanathan<sup>173</sup> administered intravesical oxybutynin (5 mg three times daily) in 14 patients with varied causes of NLUTD. After nine months of treatment, MCC increased significantly (from 132 to 284 mL) and compliance increased significantly (from 2.0 to 5.5). During the course of therapy, the number of catheterizations performed per day decreased significantly from an average of 16 at baseline down to eight. For patients experiencing incontinence, episodes resolved in 80%. No AEs were reported.

No published systematic reviews were identified which addressed the intravesical use of oxybutynin in patients with NLUTD. Literature regarding application of intravesical agents other than oxybutynin was not included and more contemporary agents with extended-release mechanisms may not be appropriate in this application. Overall, the Panel advocates use of intravesical oxybutynin in select patients with NLUTD who are currently performing CIC due to the potential to improve UDS storage parameters and decrease incontinence episodes combined with acceptable tolerability with regards to systemic side effects.

**STATEMENT THIRTY-FIVE: Clinicians should recommend intermittent catheterization rather than indwelling catheters to facilitate bladder emptying in patients with NLUTD. (Strong Recommendation; Evidence Level: Grade C)**

*he evidence base for this statement is comprised of four systematic reviews (Fumincelli 2017, Moore 2007, Rognoni 2017, Kinnear 2020) covering separate outcomes, three RCTs (Cardenas 2011, Vapnek 2003, Costa 2013), and 33 observational studies (Adriaansen 2017, Afsar 2013, Bothig 2012, Bjerklung 2007, Dahlberg 2004, Edokpolo 2012, El Masri 2014, Hagen 2014, James 2014, Katsumi 2010, Krassioukov 2015, Krebs*

*2016, Krebs 2013, Krebs 2015, Ku 2006 (BJU Int), Ku 2006 (Spinal Cord), Lavelle 2016, Lopes 2014, Liu 2010, Liu 2015, Luo 2012, Oh 2006, Ord 2003, Ozbas 2012, Ploypetch 2013, Mukai 2016, Nwadiaro 2007, Sugimura 2008, Singh 2011, Turi 2006, Svihra 2018, Yilmaz 2014, Yasami 2017). The aggregate risk of bias across studies reporting on outcomes informing this statement was serious plus evidence was further downgraded for inconsistency. Confounding within the identified studies was also noted and thoroughly discussed in text.*

Despite limitations in the retrieved body of evidence including inadequate sample sizes, suboptimal controls, variable definition of clinical outcomes, large gaps in follow-up, and a preponderance of data for SCI patients over other NLUTD conditions, the Panel determined the risk profile and complications of an indwelling catheter favored recommendation for intermittent catheterization. The Panel additionally acknowledges intermittent catheterization may not be feasible in certain situations but should be preferred when the capability exists.

Overall, hydrophilic catheters may be associated with lower rates of UTI and urethral trauma than other catheter types, specifically among SCI patients. The highest rates of UTI and recurrent UTI occur in patients managed with transurethral indwelling catheters, in patients who undergo botulinum toxin injections, and in patients on various forms of antibiotic prophylaxis. Rates of bladder stone occurrence generally increase as follow-up duration increases; suprapubic catheters are associated with higher rates of bladder stones than intermittent catheterization or urethral catheters. QoL studies suggest that the poorest QoL is associated with indwelling catheters and the need to have intermittent catheterization performed by a caregiver and the best QoL is associated with the ability to self-catheterize.

*Hydrophilic and non-hydrophilic catheters.* There is a mixture of results in the body of literature evaluating the ability of hydrophilic catheters to decrease the risk of UTI for patients that manage their bladder with CIC. There are three systematic reviews that have evaluated this topic. The first was published in 2007 and included four parallel group trials that evaluated outcomes related to symptomatic UTI.<sup>174</sup> Due to heterogeneity of the various studies, pooling of data could not be done. Reasons for heterogeneity included types of hydrophilic catheters, catheterization technique (sterile versus clean), catheter usage (single versus multiple use), and definition of UTI. The systematic review did not provide

details regarding the number of patients with recurrent UTI prior to entering the various trials. The trials had wide confidence intervals that did not demonstrate a difference and crossed the no-difference line. Due to this, and study heterogeneity, a summary estimate was not produced from this document on this topic.

Rognoni and Taricone published the second systematic review in 2017.<sup>175</sup> Nine studies were identified and six were used in the meta-analysis evaluating UTI risk. The studies reviewed were all RCTs and were published between 1990-2016. Hydrophilic catheters were compared to single use catheters and to multiple use non-coated catheters. This review did allow for pooling of data and a meta-analysis. When hydrophilic catheters were compared to single use catheters, pooling of four studies demonstrated a significant reduction in UTI with the hydrophilic catheter (RR=0.84; 95% CI: 0.75-0.94; p=0.003). Similarly, when hydrophilic catheters were compared to single or multiple-use catheters, pooling of six studies demonstrated a significant reduction in UTI with the hydrophilic catheter (RR=0.84; 95% CI: 0.75-0.94; p=0.003). Limitations of this systematic review included heterogeneity related to definition of UTI between the studies and a large number of dropouts during the trials that could have contributed to attrition bias. Similar to the other systematic review, details regarding the number of patients with recurrent UTI prior to entering the various trials was not provided.

Several RCTs directly addressed outcomes with hydrophilic versus non-hydrophilic catheters in SCI patients. After less than three months following injury, traumatic SCI patients were randomized to the use of a hydrophilic catheter (n=108) or an uncoated model (n=116) and followed for six months.<sup>176</sup> The incidence of UTI and time to first symptomatic infection requiring antibiotic therapy was significantly delayed in the hydrophilic group compared to the uncoated group. High dropout rates were encountered (58% and 40%, respectively) due to alterations in bladder management strategy.

Vapnek et al.<sup>177</sup> randomized patients to hydrophilic (n=31) or uncoated catheter groups (n=31) for 12 months. Patients utilizing hydrophilic catheters demonstrated less hematuria and UTI compared to uncoated catheter group. However, there were dissimilar baseline characteristics and types of catheter management.

A retrospective cohort study that was published in 2013 and evaluated compliance with CIC in newly injured SCI patients was not included in the Rognoni systematic review due to the retrospective study design.<sup>178</sup> The

study involved a mailed questionnaire to SCI patients four years following discharge from in-patient rehabilitation. At discharge, 104 patients were using CIC which decreased to 60 at follow-up. Of the 60 patients who continued to manage their bladder with CIC, 28 used hydrophilic and 32 used non-coated catheters. The study reported that the frequency of UTI at follow-up in patients using non-coated catheters was not significantly different than in those using hydrophilic (p=0.499); however, raw rates of UTI were not reported for either group and urine culture could not be obtained for most of the patients in the study.

#### *Clean versus sterile technique.*

Moore et al.<sup>179</sup> randomized recent tetraplegic patients requiring intermittent catheterization to follow clean (n = 16) or sterile (n = 20) techniques for six weeks. Symptomatic UTIs developed in 37% of the clean group compared to 45% in the sterile group. The authors concluded that use of clean technique, which has cost and time saving benefits, does not place patients at risk for higher rates of UTIs.

#### *Time-dependent versus volume dependent intermittent catheterization*

Polliack et al.<sup>180</sup> randomized patients to two techniques for catheterization frequency (n = 11 to time-dependent; n = 13 to volume-dependent as measured by portable ultrasound) for approximately three weeks. The volume-dependent group demonstrated significantly lower numbers of catheterizations per day and no UTIs compared to three patients in the time-dependent group.

#### *Catheter length*

Overall, preference for catheter length was dependent on patient gender with similar clinical outcomes.<sup>181, 182</sup> Compact catheters were rated as superior in terms of disposal, discretion, inserting, storing, carrying, and control.<sup>183</sup>

#### *Pre-lubricated vs. patient-applied lubrication*

A comparison of 18 patients utilizing pre-lubricated non-hydrophilic versus patient-lubricated catheters was conducted for a duration of seven weeks.<sup>184</sup> Rates of UTI were higher with the patient-lubricated catheters (22.2%) compared to the pre-lubricated model (7.4%) as were rates of asymptomatic bacteriuria (33.3% versus 14.8%) with elevated mean urethral cell counts indicative of trauma (15.1 versus 6.3). Patients rated the pre-lubricated model as easier to insert and extract,



more comfortable, and easier to handle than the patient-lubricated catheter.

#### *Intermittent versus indwelling catheter*

Turi et al.<sup>185</sup> randomized patients to CIC (n = 40) or an indwelling urethral catheter (n = 40) for an unknown duration of follow-up. Fewer patients in the CIC group experienced pyelonephritis (5%), epididymo-orchitis (2.5%), or urosepsis (0%) compared to the indwelling catheter group which had rates of 25%, 7%, and 5% of these AEs, respectively.

#### *Adverse events across catheter types*

A variety of observational studies were extracted on multiple etiologies of NLUTD and AEs from catheter-related interventions. Most AEs exhibit a large range and variable follow-up confounding determination if specific catheter types are associated with higher or lower rates of AEs. Despite these limitations, the Panel concluded that the overall data favored intermittent catheterization in comparison to indwelling catheters of any type. Although the majority of study arms addressed intermittent catheterization, indwelling catheters, or suprapubic catheters, others included comparison groups such as spontaneous voiding and surgical interventions.<sup>78, 83, 90, 186-207</sup>

#### *Urinary tract infection*

One critical metric for preference of catheter modality involves risk with regards to UTI. Morbidity of infections is a primary driving factor for many therapeutic decisions for NLUTD patients and is often intimately associated with catheter management.

For the three methods of catheter utilization (intermittent catheterization, indwelling urethral catheter, and suprapubic catheter) pooled data regarding the percent of patients who experienced UTI during the follow-up periods favors CIC. Limitations include inconsistent UTI definitions across studies. Higher rates of UTI do not predictably occur as follow-up durations increase; within the first 18 months of catheter use, a large range of UTI rates is displayed. Most importantly, at the longer time duration, UTI incidence appears to favor CIC as compared to either indwelling catheter modalities.

Bladder management methods were interrogated in a large patient database (n = 1104) with a mean symptom duration of 20.3 years.<sup>202</sup> The authors determined that bladder management, botulinum toxin injections, and prophylactic treatment of UTIs all were sig-

nificant predictors of UTIs. The highest rate of annual symptomatic UTIs occurred among patients using transurethral indwelling catheters (83.3%); this management method increased the odds of experiencing a UTI by 10-fold and the risk of recurrent UTI (50.0%) by 4-fold compared to patients who voided spontaneously (rates of 29.6% and 9.9%, respectively). Patients with suprapubic catheters (UTIs: 58.3%; recurrent UTIs: 17.5%), intermittent catheterization (UTIs: 70.5%; recurrent UTIs: 31.2%), and reflex voiding (UTIs: 61.5%; recurrent UTIs: 24.8%) also had increased risk for UTIs compared to patients who voluntarily void.

Patients who had botulinum toxin injections experienced UTIs at a rate of 76.8% and recurrent UTIs at a rate of 36.2%; values for patients who did not undergo injections were 59.0% and 23.0%, respectively. Use of prophylaxis (i.e., antibiotics or other substances) resulted in UTI rates of 72.2% and recurrent UTI rates of 32.2%; patients who did not use prophylaxis had rates of 55.3% and 20.5%, respectively.

#### *Bladder calculi*

An important component of bladder management strategy that provokes morbidity and further interventions is the development of bladder stones. Combined data on lower urinary tract stones reveals a distinct relationship with follow-up duration and stone formation. Stone rates increase with increasing follow-up with data going out to 10-12 years; there are too few studies with longer durations from which to draw conclusions after that. Stone rates for patients that manage their bladder with suprapubic catheter studies are generally higher than for those that manage their bladder with intermittent catheterization or indwelling urethral catheters. For upper tract calculi, the relationship to length of follow up was less clear.

#### *QoL*

Utilizing a broad array of patient-reported standardized questionnaires and subjective assessments across multiple NLUTD states, several general themes emerged. For most studies, patients with spontaneous voiding displayed the highest QoL scores. Additionally, intermittent catheterization was generally preferred over any indwelling catheter methods. However, a large prospective analysis revealed utilizing a standardized QoL outcome measure that patients may prefer indwelling catheters or surgery over certain iterations of intermittent catheterization.<sup>208</sup> Another important consistency across studies was patient dissatisfaction with intermit-

tent catheterization when dependent on a caregiver to perform.<sup>209-219</sup>

**STATEMENT THIRTY-SIX: For appropriately selected NLUTD patients who require a chronic indwelling catheter, clinicians should recommend suprapubic catheterization over an indwelling urethral catheter. (Strong Recommendation; Evidence Level: Grade C)**

*Statement 36 was supported by four observational studies (Ahluwalia 2006, Colli 2011, Cronin 2011, Edokpolo 2011) with very serious risk of bias. Additionally, evidence was further downgraded for both inconsistency and indirectness.*

Although existing literature was composed of observational studies limited by small sample sizes, variable reporting of follow-up duration, and contradictory rates of AEs, the Panel interpreted these data with shared experience of catheter management to favor suprapubic catheterization (SPC). No published systematic reviews specifically addressed suprapubic catheter surgery.

Ahluwalia et al.<sup>220</sup> followed 219 patients (mean age: 75 years) for a mean of 50 months after suprapubic catheter insertion. The majority of patients reported satisfaction with the SPC (72%) and a preference for the SPC compared to their prior urethral catheter (89%). The intraoperative complication rate was reported at 10% (anesthesia 1.8%, bowel injury 2.3%, catheter malposition 2.7%). The 30-day complication rate was 19% with the most common reported as UTI with sepsis (4.6%), surgical site infection (3.65%), bleeding (1.82%), and SPC malfunction (2.28%). During follow-up, 43.5% of patients experienced an AE that required clinical intervention. These included UTI (21.1%) and SPC site infection (15.4%).

Procedural outcomes were assessed in 585 patients undergoing initial SPC placement and 439 patients with SPC exchange performed by Interventional Radiologists utilizing ultrasound, fluoroscopic, or CT guidance.<sup>221</sup> Technical success rates, defined as appropriate placement into the bladder, were 99.6% in the initial SPC placement group and 92.3% in the exchange group. The clinical success rate, defined as placement that resolved symptoms of urinary retention was 98.1% in the initial SPC group. Minimal AEs were reported, including catheter malposition (0.34% in initial SPC group; 0 in exchange group), minor hemorrhage (3.3% and 1.8%, respectively), peri-catheter urine leak (1.9% and 1.1%, respectively), and SPC associated pain (0.86% and

0.68%, respectively). One major AE of bowel injury requiring surgery was reported in the initial placement arm (0.17% and 0, respectively).

Additional observational studies with small sample sizes reported minor immediate postoperative rates of complications<sup>222</sup> while follow-up of 29 patients for 38.2 months after surgery revealed a 90-day complication rate of 52%.<sup>223</sup> Additional AEs were surgical site infection (21%), urethral incontinence (17%), urethral fistula (21%), UTI with sepsis (37%), and SPC malfunction (24%). All studies with clinically relevant follow up reported higher rates of future interventions necessary following SPC placement ranging from 5.9% to 34%.<sup>223, 224</sup>

The preference of the Panel for recommending SPC placement was exemplified by a small report of six female patients with complete urethral destruction from long-term indwelling catheters who underwent SPC placement with transvaginal closure of the bladder neck.<sup>225</sup> At 21 months follow-up, all patients were continent with no upper tract deterioration. Although the Panel recognizes that progression to urinary diversion other than suprapubic catheter may be ideal, often such procedures may be unfeasible due to high morbidity from prior abdominal interventions.

**STATEMENT THIRTY-SEVEN: In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision-making and discussion regarding increased risk of antibiotic resistance. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement was informed by one systematic review (Morton 2002), two RCTs (Darouiche 2014, Fisher 2018), and three observational studies (Poirier 2016, Salomon 2006, Krebs 2016) reporting on rate of UTI. The risk of bias across the studies was serious plus evidence was downgraded for inconsistency.*

In the literature, there is lack of uniformity regarding the definition of recurrent UTI in the NLUTD patient. The various definitions varied in urinary symptoms, urine culture colony forming unit/mL threshold, differentiation of bacterial persistence versus reinfection by bacterial species, and number of UTIs per year. Given these limitations, various types of prophylaxis protocols have been employed for managing recurrent UTI in pa-

tients with NLUTD. Although older prophylaxis literature<sup>126</sup> concludes that there is no evidence to support the use of antimicrobials to reduce the rate of UTI's; recent literature has noted contradictory results.<sup>132</sup> Overall there is limited evidence regarding the benefits of oral antimicrobial prophylaxis to reduce the rate of recurrent UTI in NLUTD patients who perform CIC. The majority of studies on this topic are observational studies of limited quality, small sample size, and heterogeneous in terms of protocols and measures. Additionally, the evidence from a large database study<sup>202</sup> notes that the use of antimicrobial prophylaxis is associated with higher rates of recurrent UTIs.

For evidence-based treatment of recurrent UTI in NLUTD patients that perform CIC, there is limited evidence that exists in support of antibiotic prophylaxis. The evidence report for this guideline identified one systematic review, a meta-analysis of 15 trials,<sup>126</sup> one RCT<sup>132</sup> and two observational trials<sup>226, 227</sup> that evaluated antibiotics for prevention of recurrent UTI in NLUTD patients on CIC.

A meta-analysis of 15 studies (7 acute and 8 non-acute phases) concluded that there was no evidence to support the regular use of antimicrobial prophylaxis to reduce the rate of UTI for NLUTD patients on CIC.<sup>126</sup> For acute patients (within 90 days of injury), antibiotic prophylaxis (mainly supported by trials that tested nitrofurantoin and methenamine) was significantly associated with a reduction in bacteriuria with a trend for the same effect in non-acute patients. However, the analysis noted a twofold increase in the proportion of antimicrobial-resistant bacteria cultured from patients on antibiotics; this was not noted with methenamine. The authors conclude that the use of prophylaxis potentially results in serious harm in the absence of a reduction in UTIs.

While Morton's systematic review is relevant to the issue of UTI prevention, it must be noted that all of the trials included in the report pre-dated the literature cut off for our systematic review. While the quality of the systematic review is high, the Panel felt the data may be less applicable and should be interpreted in light of the given lapse of time and interval recent evidence.

One RCT<sup>132</sup> and two observational trials<sup>226, 227</sup> demonstrated that antibiotics reduce the rate of UTI in NLUTD patients that perform CIC. The two small sample sized observational studies (n=38 and n=50) used weekly oral cycling antibiotic (WOCA) protocols and had follow-up at 2 years.<sup>226, 227</sup> The WOCA regimen consisted of

the alternate administration of two different antibiotics once a week based upon prior cultures obtained. The various antibiotics utilized included amoxicillin (3000 mg), cefixime (400 mg), fosfomycin-trometamol (6000 mg), nitrofurantoin (300 mg), and trimethoprim/sulfamethoxazole (320–1600 mg). Patients received a single antibiotic (treatment A) during week A and a different one (treatment B) the following week (week B). Under the WOCA protocols, both trials observed a significant reduction in symptomatic UTI/patient-year from baseline  $9.4 \pm 5.34$  to  $1.84 \pm 2.814$  per patient-year ( $p < 0.01$ )<sup>227</sup> and  $9.45 \pm 6.40$  to  $1.57 \pm 2.12$  per patient-year ( $p < 0.001$ ).<sup>226</sup> Additionally, both studies demonstrated a significant reduction in febrile UTI/patient-year from baseline 0.75 to 0.31 per patient-year ( $p = 0.04$ )<sup>227</sup> and  $5.25 \pm 7.29$  to  $0.18 \pm 0.66$  per patient-year ( $p < 0.001$ ).<sup>226</sup> The WOCA regimen significantly reduced the number and length of hospitalizations and the level of antibiotic consumption days without emergence of multidrug resistant bacteria.

A multicenter, open label, randomized-controlled superiority trial (n=404) performed in the United Kingdom demonstrated continuous antibiotic prophylaxis is effective in reducing UTI frequency in CIC users with recurrent UTIs over a 12-month period.<sup>132</sup> 39% of the study population (n=80 in prophylaxis group, n=79 in no prophylaxis group) had NLUTD. The conclusion of the primary analysis was unchanged by inclusion of the various stratification factors including neurologic bladder dysfunction. The antibiotics given in the study were 50 mg nitrofurantoin, 100 mg trimethoprim, or 250 mg cephalexin on a daily regimen. During the 12-month study, the incidence of symptomatic, antibiotic-treated UTIs in the prophylaxis group was 1.3 cases per person-year (95% CI 1.1–1.6) and 2.6 cases per person-year (2.3–2.9) for no prophylaxis control group. The analysis revealed a 48% reduction in the incidence of UTIs associated with prophylaxis treatment (IRR=0.52; 95% CI 0.44–0.61;  $p < 0.0001$ ) in favor of prophylaxis. The median number of symptomatic, antibiotic-treated UTIs observed over 12 months was 1 (range 0–2) in the prophylaxis group and 2 (range 1–4) in the no prophylaxis control group. The microbiologically-confirmed incidence of UTIs was 0.74 cases per person-year (95% CI 0.58–0.94) in the prophylaxis group and 1.5 cases per person-year (1.3–1.8) in the no prophylaxis group, a 51% reduction in the microbiological incidence of UTI (IRR=0.49 (0.39–0.60) in favor of prophylaxis.

A major concern regarding the use of antimicrobial prophylaxis is the development of antimicrobial re-

sistance in addition to the potential side effects of the medication. Similar to prior systematic review data,<sup>126</sup> this study demonstrated increased antibiotic resistance for each antibiotic used in the prophylaxis group which may limit the appeal of a daily antimicrobial prophylaxis strategy. Shared decision-making and full discussion regarding the potential harms related to acquiring an antibiotic resistant infection should be factored into the decision for antibiotic prophylaxis for UTI prevention.

**STATEMENT THIRTY-EIGHT: In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer bladder instillations to reduce the rate of urinary tract infections. (Expert Opinion)**

The body of evidence regarding bladder instillations to reduce the rate of UTI is limited due to the quantity, quality, and design of the studies in addition to the heterogeneity of the population, type of bladder management and instillation solution utilized. There were insufficient studies and inadequate evidence for any single strategy to reduce the rate of UTI in NLUTD patients that perform CIC.

One RCT<sup>95</sup> investigating acetic acid, neomycin/polymyxin, and saline bladder irrigation and one observational study<sup>228</sup> involving gentamicin bladder instillation were identified. The aggregate risk of bias for these two studies is very serious.

#### Self-Intermittent Catheterization

In an observational retrospective study (n=22) of NLUTD patients with recurrent UTI's exclusively managed on self-intermittent catheterization, Cox et al.<sup>228</sup> monitored patients before and after gentamicin instillation and demonstrated fewer symptomatic UTIs (median 4 versus 1 episodes;  $p < 0.004$ ), fewer courses of UTI treatment (median 3.5 versus 1;  $p < 0.01$ ), and had less overall oral antibiotic usage. The gentamicin protocol used was a 30–60 mL (14.4–28.8 mg) dose of gentamicin solution instilled into the bladder after the last catheterization and left indwelling until the next catheterization. In this short-term study, the rate of gentamicin resistance did not increase and AEs were self-limited and rare. As there are no data on long-term follow-up of patients treated with intravesical aminoglycosides, caution is still warranted regarding antibiotic resistance development, adverse events, and optimal duration of treatment.

Additionally, clinicians must understand the procedure is time-consuming and requires personal commitment

and motivation on the part of the individual performing the task. Consequently, shared decision-making regarding the individual risk-benefit assessment of gentamicin bladder irrigation is encouraged.

#### Indwelling Urethral or Suprapubic Catheter

Waites et al.<sup>95</sup> randomized chronically catheterized NLUTD patients with asymptomatic bacteriuria to 3 methods of bladder irrigation performed twice daily for 8 weeks in a community setting. Bladder irrigants used were normal saline (n = 30), 0.25% acetic acid (n = 30), and neomycin-polymyxin GU irrigant containing 40 mg/mL neomycin sulfate and 200,000 units/mL polymyxin B (n = 29). 30 mL of irrigant remained in the bladder for 20 minutes. There were no statistically significant differences among groups in bacterial load, pyuria, or inflammation.

**STATEMENT THIRTY-NINE: Clinicians may counsel NLUTD patients with recurrent urinary tract infection who use various forms of catheter management that cranberry extract has not been demonstrated to reduce the rate of urinary tract infections. (Conditional Recommendation; Evidence Level: Grade B)**

*The evidence base assessing the use of cranberry extract to reduce the rate of UTI is comprised of two RCTs (Gallien 2014, Lee 2007) and one observational study (Hess 2008). Studies were limited by a serious risk of bias but evidence was not further downgraded in any other domain. Studies had reasonable sample sizes, clinically relevant follow-up durations of six months or more and low to unclear risk of bias. Although outcome measures varied in the studies, the results were consistent across most studies indicating that there is no consistent evidence to support the use of cranberry extract to reduce the rate of UTIs in NLUTD patients on various forms of catheter management.*

The systematic review identified five randomized controlled trials: two evaluated cranberry versus placebo/no cranberry;<sup>229, 230</sup> two crossover studies from cranberry to placebo;<sup>231, 232</sup> one cranberry versus cranberry + methenamine versus placebo.<sup>233</sup> Four RCTs studied cranberry in a tablets/capsules and one studied cranberry extract powder for oral solution, each at various dosages.<sup>230</sup> Risk of bias was low in two RCTs<sup>230, 233</sup> and unclear in three RCTs.<sup>229, 231, 232</sup> One RCT<sup>230</sup> evaluated only MS patients and four RCTs enrolled SCI patients on various bladder management methods.<sup>229, 231-233</sup> Most trials had reasonable sample sizes (range n=37–305)

and clinically relevant follow-up durations (6 - 12 months). Despite the heterogeneous patient population, bladder management method, cranberry dose, and outcome measures studied, the results were consistent across all but one trial demonstrating that cranberry does not reduce the rate of UTIs in NLUTD patients.

### MS Population

Gallien et al.<sup>230</sup> randomized MS patients to 36 mg of proanthocyanidins per day of cranberry extract (n = 82) or placebo (n = 89) twice daily and all patients were followed for one year. 33.9% of the study group managed their bladder with clean intermittent catheterization. There were no group differences in time to first symptomatic UTI across one year (Hazard Ratio = 0.99; 95% CI 0.5 to 1.60; p>0.05). The percentage of patients who had at least one UTI for one year was 40.0% in the placebo group and 41.2% in the cranberry group. The mean number of UTIs for patients who had at least one UTI for one year was 2.2 in the placebo group and 2.3 in the cranberry group.

### SCI Population

Waites et al.<sup>229</sup> randomized 48 SCI patients using CIC or an external collection device to 2 g of concentrated cranberry extract tablets (n = 26) or placebo (n = 22), each for six months. There were no significant differences between groups in the percent of patients who had a symptomatic UTI during follow-up (38.5% in the cranberry group; 36.4% in the placebo group). Lee et al.<sup>233</sup> randomized SCI patients using varied bladder management methods to receive oral cranberry + placebo tablets (n = 78), oral methenamine + cranberry tablets (n = 75), oral methenamine + placebo tablets (n = 75), or oral placebo + placebo tablets (n = 77). The dose of cranberry was 1600 mg and the methenamine dose was 2 g. There were no statistically significant differences across groups in six-month UTI-free survival rates (range from 53.5% to 56%). Linsenmeyer et al.<sup>232</sup> randomized 37 SCI patients using indwelling catheters to 1200 mg cranberry or placebo tablets, each for one month. There were no statistically significant differences between groups for bacterial count, WBC counts or WBC and bacterial counts in combination. Hess et al.<sup>231</sup> randomized 57 SCI patients using varied methods of bladder management to 1000 mg cranberry extract or placebo tablets, each for six months. The number of UTIs, percent of patients experiencing at least one UTI, and the incidence of UTI prorated to one year were all reduced in the cranberry

group (7, 13%, and 0.3, respectively) compared to the placebo group (21, 34%, and 0.9, respectively). The authors noted that patients with a glomerular filtration rate >75 ml/min benefitted the most. Limitations to this study's positive findings are the crossover study design without a washout period and the heterogeneous methods of bladder management used by the patients.

**STATEMENT FORTY: In NLUTD patients with spinal cord injury or multiple sclerosis refractory to oral medications, clinicians should recommend onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life measures. (Strong Recommendation; Evidence Level: Grade A)**

*Statement 40 is supported by three systematic reviews (Yuan 2017, Li 2018, Mangera 2014), ten RCTs (Ehren 2017, Chancellor 2013, Kennelly 2013, Grise 2010, Chartier-Kastler 2016, Rovner 2013, Ferreira 2018, Tullman 2018, Cruz 2011, Herschorn 2011, Ginsberg 2012), and three observational studies (Kennelly 2017, Dominique 2020, Sussman 2013) with a non-serious risk of bias and no downgrading for any domain.*

Based upon the high-quality, well-conducted systematic reviews and RCTs with placebo-control groups, and adequate sample sizes to achieve sufficient statistical power, the body of evidence supports the use of onabotulinumtoxinA to manage NDO in patients with SCI or MS.<sup>234-239 240-243</sup> Most of the trials had a low-risk of bias. There was Grade A evidence to support the conclusions regarding both initial injections as well as repeated injections of onabotulinumtoxinA.

In patients with SCI or MS, a single set of intradetrusor injections of onabotulinumtoxinA reduces UI episodes, increases MCC, and decreases MDP compared to placebo groups. Other clinical and UDS parameters as well as QoL outcomes also generally demonstrate improvement.

There are no differences in efficacy between the 200 U and 300 U dose.

The most frequently reported AEs are UTI, urinary retention, and the need for patients not using CIC pre-trial to begin using CIC to manage retention.

In patients with SCI or MS, repeated series of intradetrusor injections of onabotulinumtoxinA restore the improvements experienced with the first set of injections and efficacy does not appear to diminish with re-

peat treatment in most patients.

### Efficacy of Initial Injection

Two of the most recent high-quality systematic reviews with meta-analysis evaluated pooled data from RCTs, with placebo-control groups, that evaluated the use of onabotulinumtoxinA in SCI patients only and SCI and MS patients.<sup>241, 243</sup> All trials in these systematic reviews evaluated injections into the detrusor of 200 U and 300 U onabotulinumtoxinA and one study evaluated only 300 U onabotulinumtoxinA injections. All studies spared the trigone with their intradetrusor injections template. The analysis of pooled data demonstrated that onabotulinumtoxinA significantly reduced the daily frequency of UI and MDP during first IDC, and improved MCC in SCI and MS patients with UI due to NDO.<sup>241, 243</sup>

Yuan et al.'s meta-analysis indicated that onabotulinumtoxinA significantly reduced UI episodes by -1.41 episodes (95% CI -1.70 to -1.12,  $p < 0.05$ ). The mean difference in UI episodes per day from baseline for the 200 U and 300 U doses were -1.38 (95% CI: -1.83 to -0.94) and -1.42 (95% CI: -1.81 to -1.04), respectively. Using a meta-regression method, no obvious dose-dependent differences were found between the 200 U and 300 U dose groups ( $p = 0.974$ ). In the pooled data, there was a decreased MDP during the first IDC of -32.98 (95% CI: -37.33 to -28.62) compared to the placebo group. A subgroup dose analysis demonstrated a decrease in MDP during the first IDC of -32.71 cm H<sub>2</sub>O (95% CI: -39.32 to -26.10) for 200 U and -31.85 cm H<sub>2</sub>O (95% CI: -38.08 to -25.62) for 300 U. MCC increased by 135.5 mL (95% CI: 118.2 to 152.8 mL;  $p < 0.05$ ) compared to placebo groups (200U: 140.38; 95% CI: 114.43–166.34; 300 U: 136.56; 95% CI: 110.91–162.21).<sup>243</sup>

Li et al.'s meta-analysis included 17 studies of patients with NDO secondary to SCI. When compared with placebo, treatment with onabotulinumtoxinA demonstrated significant improvement in UI episodes (Mean Difference (MD): -12.45; 95% CI: -19.90 to -5.00;  $p = 0.001$ ), volume at IDC (MD: 163.42 mL; 95% CI: 96.41–230.43 mL;  $p < 0.00001$ ), and MCC (MD: 134.75 mL; 95% CI: 105.06–164.44 mL;  $p < 0.00001$ ). No significant difference was found between 200 U and 300 U of onabotulinumtoxinA in UI episodes (MD: -1.27; 95% CI: -6.82 to 4.27;  $p = 0.65$ ), MCC (MD: -2.32 mL; 95% CI: -36.19 to 31.56 mL;  $p < 0.89$ ), the number of patients with no IDC (MD: 0.77; 95% CI: 0.53–1.12;  $p = 0.18$ ), PVR (MD: -79.85 mL; 95% CI: -120.41 to -39.29 mL;  $p = 0.0001$ ), and bladder compliance (MD:

3.10 mL/cmH<sub>2</sub>O; 95% CI: -7.47 to 13.67 mL/cmH<sub>2</sub>O;  $p < 0.57$ ). Overall, there was not a significant clinical or urodynamic difference between effects at the 200 U versus the 300 U dose.<sup>241, 243</sup>

One RCT investigated the 100 U dose and randomized non-catheterized MS patients to either onabotulinumtoxinA or placebo. After six weeks of treatment, onabotulinumtoxinA reduced UI at week 6 (-3.3 episodes/day versus -1.1 episodes/day;  $p < 0.001$ ) and a significantly greater proportions of onabotulinumtoxinA-treated patients achieved 100% UI reduction (53.0% versus 10.3%;  $p < 0.001$ ). When compared to placebo, treatment with onabotulinumtoxinA demonstrated significant improvement in urinary urgency (-4.3 versus -1.6 episodes/day;  $p < 0.001$ ), micturition (-2.5 versus -0.8 episodes/day;  $p < 0.001$ ), and voided volume (-27.8 versus 5.1 mL;  $p < 0.001$ ). Significantly improved urodynamic bladder storage parameters were noted in the onabotulinumtoxinA 100U group. MCC increased by 127.2 mL (95% CI: 91.8 to 162.5 mL;  $p < 0.001$ ) and there was a decreased MDP during the first IDC of -19.6 cm H<sub>2</sub>O (95% CI: -35.1 to -4.0 cm H<sub>2</sub>O).<sup>242</sup>

The UDS data in the onabotulinumtoxinA placebo-controlled RCT studies support the patient-reported clinical effects of increased voided volume and decreased UI episodes.<sup>241, 243</sup> Abolishment of IDCs, increased bladder capacity, and improved bladder compliance are all important goals of management in NLUTD patients to minimize the untoward negative effects on the upper urinary tracts.

### Efficacy of Initial Injection: Quality of Life Measures

It is well known that UI has a negative impact on a person's health-related QoL (HRQoL). Unfortunately, objective outcome measures utilized in clinical studies often do not capture the patient's goals, expectations, or treatment satisfaction. Consequently, patient-reported outcome measures are a standardized approach to measure information that is important to patients and are highly encouraged in investigating QoL conditions such as urinary incontinence. In the RCTs evaluating botulinum toxin A, the HRQoL questionnaires utilized were the Incontinence Quality of Life (I-QoL), modified Overactive Bladder Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ), and the Patient Global Assessment (PGA).

Although heterogeneous in their HRQoL measures, all of the RCTs that evaluated patient reported outcomes

demonstrated significantly improved HRQoL parameters in the onabotulinumtoxinA active treatment group compared to placebo.<sup>244, 241, 243</sup> In the DIGNITY trials, at weeks 6 and 12, patients who received onabotulinumtoxinA (200 U or 300 U) demonstrated important improvements versus placebo in I-QOL Questionnaire total score, modified OAB-PSTQ, and PGA.<sup>244, 245</sup> Similar to the clinical and urodynamic effect, there is no clinically relevant difference in patient reported outcomes between the onabotulinumtoxinA 200 U and 300 U doses.<sup>244, 245</sup>

Regarding patient's goals, Chartier-Kastler et al.<sup>246</sup> reported significantly greater proportions of patients in the onabotulinumtoxinA groups (200 U and 300 U) making significant progress toward, or complete achievement of, their goals in comparison to placebo. A sub-analysis of disease etiology and treatment goals and goal attainment was performed noting similar goals between MS and SCI patients. Although there were noted minor differences in baseline goals, disease etiology had no impact on overall goal attainment with either dose of onabotulinumtoxinA (200 U or 300 U).<sup>246</sup> Of interest was the awareness that for those patients who needed to self-catheterize after onabotulinumtoxinA 200 U or 300 U, CIC did not impact patient satisfaction with onabotulinumtoxinA treatment.

Improved quality of life was also reported in an RCT randomizing non-catheterizing MS patients to 100 U onabotulinumtoxinA or placebo. Tullman et al.<sup>242</sup> reported greater improvement in I-QOL total summary score that was >3 times the minimally important difference at week 6 and was maintained through week 12 ( $p < 0.001$ , both time points). These various HRQoL results support the clinical efficacy of onabotulinumtoxinA 200 U and 300 U, as measured with changes in daily UI episodes and improved bladder storage parameters.

### **Efficacy of Initial Injection: Adverse Events**

The beneficial effects of botulinum toxin A must be weighed against the most frequently reported AEs which include UTI, urinary retention, and the need for patients not using CIC pre-treatment to require the use of CIC post-injection. The meta-analysis by Yuan et al.,<sup>243</sup> which reviewed six RCTs, indicated that botulinum toxin A is significantly associated with the likelihood of having a UTI (OR = 1.68; 95% CI 1.20 to 2.35;  $p < 0.05$ ) and urinary retention (OR = 6.80; 95% CI 3.46 to 13.35;  $p < 0.05$ ). Similar conclusions were noted by Li et al.<sup>241</sup> with increased rates of symptomatic

UTI, urinary retention, hematuria, and AD significantly increased with onabotulinumtoxinA compared to placebo.

The occurrence of UTIs in the NLUTD population is common, particularly in patients who are using CIC and have elevated storage pressure and postvoid residual. Although there was heterogeneity in the definition of UTI (symptomatic or asymptomatic bacteriuria) and bladder management method, all of the RCTs noted UTI as the most prevalent adverse event with ranges from 21 – 70%.<sup>243</sup> In non-catheterizing MS patients, Tullman et al.<sup>242</sup> reported a 25.8% UTI rate for the onabotulinumtoxinA-treated patients and 6.4% of placebo-treated patients. The UTIs were symptomatic in 13.6% and 1.3% in the onabotulinumtoxinA- and placebo-treated groups, respectively.

Urinary retention rates are primarily related to MS patients who were not on CIC at study entry. In a study where non-catheterized MS patients were randomized to receive 100 U onabotulinumtoxinA or placebo, Tullman et al.<sup>242</sup> reported a 15.2% CIC rate due to urinary retention in the onabotulinumtoxinA group and 2.6% in the placebo group for a median duration of 64.0 and 2.0 days, respectively. In the DIGNITY pooled analysis, MS patients demonstrated a dose-dependent increase in the need to initiate CIC for urinary retention (31.4% and 47.1% in the onabotulinumtoxinA 200 and 300 U groups, respectively) compared with the placebo group (4.5%). Nearly half of these patients used CIC for  $\leq 36$  weeks while the other half used CIC for  $\geq 36$  weeks. For those who initiated de novo CIC, treatment satisfaction remained high in the onabotulinumtoxinA 200 U dose group compared to those who did not initiate CIC, but not in the onabotulinumtoxinA 300 U dose group. Due to the high-risk of long-term CIC, patient - is important when discussing onabotulinumtoxinA treatment with MS patients who do not require CIC at baseline.

Distant spread of botulinum toxin has been noted to cause muscular weakness. In RCTs, the range of muscular weakness post-onabotulinumtoxinA (range 0 – 13.4%) was similar to placebo (range 0 – 14.29%) and the few reports noted the adverse event were transient and resolved without further treatment.<sup>247-249</sup> The DIGNITY studies noted similar annualized MS exacerbation rates for onabotulinumtoxinA and placebo groups. Cruz et al.<sup>247</sup> reported an annualized MS exacerbation of 0.19, 0.36, and 0.20 and Ginsberg et al.<sup>249</sup> reported an annualized MS exacerbation rate of 0.22, 0.14 and 0.37 in the placebo, and 200 and 300 U groups, respectively.

These data indicate; however, that patients may experience neurological AEs in addition to the more commonly reported events of UTIs and urinary retention.

### **Efficacy of Repeated Injections**

The systematic review identified one moderately high-quality meta-analysis of 18 observational studies that assessed repeated onabotulinumtoxinA injections, primarily in SCI and MS NLUTD patients.<sup>250</sup> OnabotulinumtoxinA (dose ranges 200 U – 300 U) was used in 13 studies, abobotulinumtoxinA (dose range 500 U – 1000 U) was used in four studies and both were used in one study. The number of repeat injections and mean injection interval ranged from 3 - 9 months and 8.3 - 14.9 months, respectively. The analysis of pooled data demonstrated that botulinum toxin A significantly increased MCC, RV, bladder compliance, and reduced MDP compared to baseline in NLUTD patients. There were no statistically significant differences (Standard Mean Difference < 0.2) in MCC (149.8 mL to 155.3 mL), MDP (-23.5 and -26.8 cm H<sub>2</sub>O), RV (104.3 mL and 129.3 mL), and bladder compliance (18.2 and 18.4 mL/cm H<sub>2</sub>O) between the outcomes after the first and last injections, suggesting stable efficacy over repeat injections. The most frequently reported AEs were UTI, urinary retention, and hematuria. Various limitations of this meta-analysis include heterogeneous study designs, variety of toxin used and doses of toxin, in addition to selection bias and limited quality and quantity of studies.

The long-term effects of onabotulinumtoxinA were demonstrated in three RCTs with follow up ranging from 12 months to 4 years.<sup>238, 251, 252</sup> Each trial demonstrated significant clinical improvements in UI, UDS parameters, and QoL. The largest (n=396) open label 4-year extension phase of the DIGNITY trials<sup>247, 249</sup> with pooled patients across the original trials reported on six treatment cycles (although some patients had up to thirteen).<sup>247, 249, 252</sup> Despite a nearly 40% drop out, discontinuations for lack of efficacy were few (n=8; 2.0%) as were discontinuations for AEs (n=12; 3.0%). Consistent reductions in the number of daily UI episodes (range -3.2 - -4.1) and increased voided volumes (133.2 – 156.1 mL) were observed along with sustained I-QoL improvements following long-term repeated treatment. Treatment duration varied across patients with <6 months in 22% of patients, ≥ 6-12 months in 52% of patients, and >12 months in 26% of patients. No new safety signals emerged as UTIs and urinary retention, as well as the need for de novo CIC,

remained the most frequently reported AEs.

### **Injection Location**

A meta-analysis of 2 RCTs compared 55 SCI patients to onabotulinumtoxinA 300 U injections into the detrusor or submucosa.<sup>241</sup> Acknowledging their small sample size, short duration, and unclear risk of bias both groups improved regarding the number of catheterizations per 24 hours, the number of UI episodes over 24 hours, catheterized volume, MCC, RV, MDP during filling, and bladder compliance at 3 months. There were no significant differences between groups in clinical and UDS parameters (UI episodes (MD: -1.21; 95% CI: -5.30 to 2.88; p=0.56), mean functional bladder capacity (MD: -54.26; 95% CI: -81.91 to -26.61; p=0.0001), VFIDC (MD: -37.69; 95% CI: -83.60 to 8.22; p<0.00001), and Pdet (MD: -7.99; 95% CI: -21.98 to 6.00; p=0.26).<sup>241</sup>

### **AbobotulinumtoxinA**

The body of evidence regarding abobotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve QoL measures is limited due to the quantity, quality, design, and limited follow-up of the studies. Although the preliminary findings of abobotulinumtoxinA appear similar to those of onabotulinumtoxinA, multicenter larger RCTs compared to placebo with defined NLUTD patient populations, dosing, injection method, and standardized outcome assessments along with longer term follow-up will be needed. The systematic review identified two RCTs<sup>234, 235</sup> compared to placebo investigating abobotulinumtoxinA in NLUTD patients with UI refractory to oral medications. The risk of bias is low in these two trials.

Ehren et al.<sup>235</sup> randomized patients with varied causes of UI to placebo (n=14) or abobotulinumtoxinA 500 U (n=17) with 6-month follow-up. The active treatment group experienced significant improvements in UI episodes, MCC, MDP, and QoL as noted in the Qualiveen questionnaire, and there were no AEs related to the treatment. Denys et al.<sup>234</sup> randomized 47 patients to receive either 15 or 30 intradetrusor injections of placebo or abobotulinumtoxinA 750 U and followed them for 3 months. Both abobotulinumtoxinA groups experienced significant improvements in daily UI episodes, MCC, MDP, and RV compared to the placebo groups, and there were no differences in treatment efficacy based on number of injections. The most commonly reported AE was UTI that appeared to increase with the number of injections and abobotulinumtoxinA dose in-



dependently. The UTI rate was 14.3% in the placebo 15 injections group, 57.1% in the placebo 30 injections group, 37.5% in the abobotulinumtoxinA 15 injections group, and 41.2% in the abobotulinumtoxinA 30 injections group. Muscle weakness was noted in three SCI patients in the 15 injection abobotulinumtoxinA group but resolved without intervention.

The systematic review identified one RCT comparing 2 doses of abobotulinumtoxinA (500 U and 750 U) in a mixed neurogenic population who were followed for one year.<sup>253</sup> Clinical and urodynamic variables improved similarly between groups with complete continence observed in 56.4% of the 500 U group and in 73.7% of the 750 U group ( $p=0.056$ ). 10.3% of patients experienced AEs including hematuria/fever, pyelonephritis, fatigue with vertigo, muscle weakness, constipation, difficulty with CIC, and fever.

In NLUTD patients with SCI and MS refractory to oral medications, the body of evidence is Grade A for use of onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve QoL measures.<sup>235, 239 241, 243</sup> In NLUTD patients with SCI or MS, intradetrusor injections of onabotulinumtoxinA reduces UI episodes, increases MCC, and decreases MDP compared to placebo groups. Other clinical and UDS parameters as well as QoL outcomes also generally demonstrated improvement. There are no differences in efficacy between the 200 U and 300 U dose; however, there is an increasing dose-dependent relationship regarding risk of retention and need for CIC. In patients with SCI or MS, repeated series of intradetrusor injections of onabotulinumtoxinA restore improvements experienced with the first set of injections and efficacy does not appear to diminish.

**STATEMENT FORTY-ONE: In NLUTD patients, other than those with spinal cord injury and multiple sclerosis, who are refractory to oral medications, clinicians may offer onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life measures. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement is informed by two RCTs (Ehren 2007, Grise 2010) and seven observational studies (Kennelly 2017, Giannantoni 2009, Jiang 2014, Peyronnet 2018, Peyronnet 2017, Stoehrer 2009, Ko 2019). The risk of bias for outcomes of interest reported by these studies was very serious. Additionally, evidence was downgraded for indirectness and imprecision.*

Outside of SCI and MS, the body of evidence for onabotulinumtoxinA to treat NLUTD patients with UI refractory to oral medications is Grade C for efficacy and adverse events. Due to a lack of high quality, adequately powered trials, the data can only be extracted from observational trials with small sample size and variable methodologies.

The systematic review identified one RCT<sup>235</sup> with placebo control groups that evaluated the effects of 500 U of abotulinumtoxinA in a mixed neurogenic population; however, the non-MS/non-SCI group only accounted for 16% ( $n=5/31$ ) of patients.<sup>235</sup> During follow-up, the active treatment group experienced significant improvements in UI episodes, MCC, MDP, and QoL and no AEs were reported during the 6-month follow-up. The risk of bias was low but due to the few non-MS/non-SCI patients in the study there is limited evidence for the larger NLUTD population.

The systematic review also identified one RCT<sup>253</sup> comparing two doses of abobotulinumtoxinA (500 U and 750 U) in a mixed neurogenic population followed for 1 year; however, the non-MS/non-SCI group only accounted for 12.9% ( $n=10/77$ ). Clinical and UDS variables improved similarly between groups with complete continence observed in 56.4% of the 500 U group and in 73.7% of the 750 U group ( $p=0.056$ ). The review did not find any RCTs with a non-MS/non-SCI mixed neurogenic population for onabotulinumtoxinA.

Numerous observational studies have reported on the effects of a single set of botulinum toxin A in a non-MS/non-SCI NLUTD population.

#### **Parkinson's Disease**

Data on the use of botulinum toxin A in patients with PD is limited due to small sample size, lack of controls, short follow-up, and single center observational trials. Overall, there is a suggestion of improvement in symptoms with similar side effects noted with MS and SCI botulinum toxin trials. Due to PD's older male predominance, the coexistence of BOO along with detrusor dysfunction raises the concerns for the development of urinary retention post-injection.

Knupfer et al.<sup>254</sup> evaluated the effects of 200 U onabotulinumtoxinA in 10 PD patients ( $n=4$  female,  $n=6$  male; median age: 67.9 years) with refractory LUTS with 4-month follow-up. The injection location was intradetrusor and included the trigone. At four months, patients experienced significant clinical improvements in urinary frequency, pad use, and QoL based upon ICIQ scores.

UDS parameters improved significantly including increased MCC ( $196.2 \pm 88.29$  mL preoperatively,  $332.6 \pm 135.45$  mL postoperatively) and decreased MDP (mean:  $57.9 \pm 33.1$  cm H<sub>2</sub>O preoperatively,  $18 \pm 16.55$  cm H<sub>2</sub>O postoperatively). A non-significant increase in PVR occurred (from  $61.28 \pm 75.91$  mL to  $77.0 \pm 119.78$  mL postoperatively) without the need for CIC. The duration of effect was a mean of  $9.75 \pm 4.85$  months for the four patients who received re-injection.

Anderson et al.<sup>255</sup> followed 20 PD patients (n=12 male, n=8 female; median age: 71.5 years) with refractory UI after onabotulinumtoxinA 100 U office injections for six months. Moderate to marked symptom relief at three months was noted on QoL questionnaires (PGA) and a 50% incontinence decrease over six months relative to pretreatment was reported in 59% of patients ( $p < 0.02$ ). Of note, 25% of patients failed to complete the 6-month endpoint. Significantly increased PVR, classified as partial retention, occurred in three men at the 1-month follow-up (mean: 310 mL). No patient required intermittent catheterization but two men were given alpha-blocking agents.

Giannantoni et al.<sup>256</sup> evaluated the effects of 100 U onabotulinumtoxinA in 8 PD patients (n=1 male, n=7 female; mean age: 66 years) with refractory UI with six month follow up. OnabotulinumtoxinA demonstrated clinical improvements in UI, daytime urinary frequency, and nocturia along with improved QoL and VAS scores. On urodynamic assessments, significant improvements in MCC were noted at all time points, and 37.5% of patients had abolishment of IDCs. PVR volume increased 1 month after treatment but decreased markedly at three and six months. Two female patients (25%) had elevated PVR (300 mL) necessitating CIC twice daily. One patient needed CIC for one month and the other required a caregiver to perform CIC for three months.

Kulaksizoglu et al.<sup>257</sup> followed 16 PD patients (n=10 female, n=6 male; mean age: 67.2 years) with refractory UI who were treated with abobotulinumtoxinA (500 U) injections for 12 months. Symptom relief was noted at three and six months with decreased urinary frequency and improvement in UI. Mean functional bladder capacity increased significantly compared to baseline at all time points but reached the peak by 6 - 9 months. Both the patient's QoL as well as caregiver's burden was significantly improved up to nine months. There were no AEs reported.

Giannantoni et al.<sup>258</sup> evaluated the effects of 200 U onabotulinumtoxinA in four PD patients and two multi-

system atrophy (MSA) patients. OnobotulinumtoxinA demonstrated significant improvements in daytime and nighttime frequency with resolution of UI and improvements in I-QOL at one and three months. UDS showed significant improvements in MCC, volume at first IDC, and IDC maximum pressure. No systemic AE or UTI's developed but the two MSA patients needed daily CIC. The MSA patients had documented elevated PVR's and detrusor dysfunction prior to the onabotulinumtoxinA treatment which provides a signal that the MSA patient may be a higher at-risk population for urinary retention.

### Central Nervous System Lesions

In a retrospective observational trial, Jiang et al.<sup>259</sup> compared the effects of 100 U onabotulinumtoxinA in 40 patients with mild CNS lesions including chronic CVA (n=23), PD (n= 9), and dementia (n=8) to 160 OAB patients without CNS lesion. Similar significant clinical and UDS improvements were noted at three months in UI, urgency, urgency severity score, and MCC in both groups, with and without CNS lesions. There was no difference in PVR between the two groups. The PdetQmax and Qmax did not change in patients with CNS lesions, and there was no significant difference between the groups. The CVA group had a higher incidence of straining to void, but all other AEs were similar. The urinary retention rates reported for CNS lesions were CVA (17.4%), PD (11.1%), dementia (0%), and OAB patients without CNS lesion (10%). Patient selection in this vulnerable patient population is important. Patients with advanced CNS lesions and poor sensory awareness are not ideal candidates for botulinum toxin as they may be at higher risk for impaired bladder sensation after botulinum therapy and risk the development of urinary retention and UTI. Patients with CNS disorders should be informed of the possible risk of urine retention and bladder management strategies need to be discussed prior to botulinum toxin therapy. Patients with CNS disorders may not be able to cognitively or physically perform CIC and may need a caregiver or temporary catheter for management of incomplete bladder emptying/urine retention.

### Spinal Dysraphism in Adults

Spinal Dysraphism (SD) is the most common congenital cause of neurogenic bladder with 90% of patients presenting with NLUTD. Unlike SCI or MS neurological lesions, SD lesions are typically incomplete with variable presentations. There are sparse reports regarding botulinum toxin for adult patients with SD.

Peyronnet et al.<sup>260</sup> reported on a multicenter retrospective chart review of 125 adult SD patients who underwent a total of 561 intradetrusor botulinum toxin A injections over a 14-year period. OnabotulinumtoxinA 200 U, 300 U, and abobotulinumtoxinA 750 U were used in 34.7%, 49.2%, and 16.1%, respectively. After the first injection, urgency and UI resolved in 62.3% with resolution of UI in 73.5% of patients. UDS parameters showed significant improvement in MCC, MDP, and bladder compliance by 6 - 8 weeks compared to baseline. On multivariate analysis, female gender and older age were predictors of successful first botulinum toxin injections, while poor bladder compliance was associated with a lower global success rate. AEs occurred in 3.6% of cases which included UTI (2.3%), muscular weakness (0.5%), pain (0.5%) and gross hematuria (0.2%), which were all mild and transient.

#### Other NLUTD Conditions

Besides MS, SCI, PD, CVA or SD, the systematic review did not find any other NLUTD conditions uniquely studied using botulinum toxin for the treatment of UI. However, many observational studies investigating botulinum toxin had included NLUTD conditions other than MS and SCI. Of the more than 20 observational botulinum toxin studies including mixed NLUTD conditions in their analysis, only two studies had a reasonably large cohort of non-MS or non-SCI NLUTD patients (> 20% of the overall study group).

In a retrospective case-control study over 7 years, Peyronnet et al.<sup>261</sup> reported on 211 NDO patients treated with onabotulinumtoxinA (200 U and 300 U) and abobotulinumtoxinA (750 U). Of the 211 patients, the number of patients with other NLUTD (non-MS and non-SCI) were 15 patients (28.3%), 11 patients (12.7%) and 18 (23.1%) patients in the onabotulinumtoxinA 200 U, onabotulinumtoxinA 300 U, and abobotulinumtoxinA 750 U arm, respectively. Overall clinical improvements in UI were noted in all doses with higher rates of UI resolution in patients treated with onabotulinumtoxin 300 U compared to abobotulinumtoxin 750 U, based on match-paired analysis (94.9% versus 76.9%;  $p=0.02$ ). No subgroup analysis of the "other" NLUTD cohort was performed likely due to the varied conditions and overall low numbers of unique NLUTD conditions.

Stoehrer et al.<sup>262</sup> reported on their seven year experience with botulinum toxin injections (onabotulinumtoxinA 300 U and abobotulinumtoxinA 750U) in 277 NLUTD patients. The "other" condition

cohort of patients accounted for 24.1% (n=67) of the study population. Significant UDS parameters were improved (MCC, MDP, RV, and compliance) in those studied along with sustained clinical improvements in UI. Adverse events were rare (2%) and two cases of temporary self-limiting generalized weakness with speech and swallowing difficulty was reported.

#### Patients with an Augmentation Enterocystoplasty

Persistent NDO may persist after NLUTD patients undergo an augmentation enterocystoplasty procedure. Botulinum toxin A has been investigated as a treatment regimen for these patients, but the evidence is very sparse. Martinez et al. performed a multi-institutional retrospective study (n=21) in which 86% of patients endorsed subjective improvement in terms of decreased urgency, frequency, increased catheterized volumes, and decreased leakage between catheterizations.<sup>263</sup> The patient population included 24% of patients with idiopathic origin of bladder dysfunction, and heterogenous origin of bladder dysfunction in the rest of the population. This study did not exclude based on dose or frequency of botulinum toxin A, but found subjective improvement for those injected with 200 U compared to 300 U was 85% and 87%, respectively. The ENTEROTOX study represented a French multicenter retrospective study (n=33) to evaluate clinical efficacy, UDS effect, and safety of botulinum toxin A injections in patients with NDO after augmentation cystoplasty (AC).<sup>264</sup> Injection was effective (defined by a request for reinjection) in 58% of patients with mean MCC increased by 23% (333 +/- 145 mL versus 426 +/- 131 mL;  $p=.007$ ) on post-injection UDS. This study also contained a heterogenous patient population in terms of etiology of bladder dysfunction, dose, type of botulinum toxin A, and injection sites. Both studies showed a low rate of AEs amongst study participants. The validity of this evidence is limited by sample size, does not isolate NLUTD, and does not standardize methods given the retrospective nature of the studies. Prospective studies are needed to further evaluate the efficacy of botulinum toxin A for NLUTD in the context of AC, though safety profile shows little risk amongst the small population examined above.

The evidence level regarding onabotulinumtoxinA in NLUTD patients refractory to oral medications is Grade A for SCI and MS patients with randomized, well-conducted, large scale studies with low-risk of bias. Unfortunately, there are insufficient high-quality, adequately powered, and low-risk of bias trials available to

make the same recommendation for patients with other (non-SCI and non-MS) conditions of NLUTD such as PD, CVA, SB, and others. Based upon the small sample sizes of the other conditions (non-MS and non-SCI) noted in the onabotulinumtoxinA RCTs, and the limitations of the observational studies reviewed (small sample size, bias, and lack of long-term follow-up), the body of evidence strength for onabotulinumtoxinA in NLUTD with non-SCI or non-MS conditions is Grade C. The balance between clinical benefits of onabotulinumtoxinA and risk of treatment in this population is unclear; clinicians may offer onabotulinumtoxinA to NLUTD patients refractory to oral medications, to improve bladder storage parameters, decrease episodes of incontinence, and improve QoL measures.

**STATEMENT FORTY-TWO: In NLUTD patients who spontaneously void, clinicians must discuss the specific risks of urinary retention and the potential need for intermittent catheterization prior to selecting botulinum toxin therapy. (Clinical Principle)**

OnabotulinumtoxinA has demonstrated improvement in NLUTD patient's QoL with more patients experiencing decreased UI episodes and improved bladder storage parameters (capacity, compliance, and resolution of IDCs) in SCI and MS patients with UI due to NDO. One of the most common AEs after onabotulinumtoxinA injections is incomplete bladder emptying or urinary retention, which may require a period of bladder catheterization. Reports from single injection RCTs involving NLUTD patients revealed a urinary retention rate range of 2.6 – 54% for the onabotulinumtoxinA treatment groups, and 1.9 – 5.0% for the placebo treatment groups. A meta-analysis by Yuan et al.<sup>243</sup> reviewed six placebo-controlled RCTs and indicated that onabotulinumtoxinA is significantly associated with the likelihood of having urinary retention (OR = 6.80; 95% CI: 3.46 to 13.35;  $p < 0.05$ ).<sup>243</sup> The meta-analysis by Li et al. reviewed 17 studies and noted a urinary retention rate of 20.49% ( $n=150$ ) for onabotulinumtoxinA and 3.67% ( $n=15$ ;  $p < 0.00000$ ) for placebo.<sup>241</sup>

In the DIGNITY trials,<sup>239, 247, 249, 265</sup> classifying urinary retention and the need for the initiation of CIC post-treatment as AEs was based on the investigator's clinical judgement. In MS patients who were not catheterizing at baseline, there was a dose-dependent increase in urinary retention rate (31.4% and 47.1% in the onabotulinumtoxinA 200 U and 300 U groups, respectively) compared with the placebo group (4.5%).

Nearly half of these patients used CIC for  $\leq 36$  weeks while the other half used CIC for  $\geq 36$  weeks. With repeated treatments, de novo CIC rates dropped markedly in subsequent treatment cycles (29.5%, 3.4%, and 6.0% in treatment cycles 1-3, respectively) and were higher in patients receiving 300 U (43.0, 15.0, and 4.8% in treatment cycles 1–3, respectively).<sup>239</sup> The urinary retention rates are primarily related to MS patients who were not on CIC at study entry and the risk of retention appears to be dose related. In the non-catheterized MS patients randomized to receive 100 U onabotulinumtoxinA or placebo, Tullman et al.<sup>242</sup> reported a 15.2% CIC rate due to urinary retention in the onabotulinumtoxinA group and 2.6% in the placebo group, for a median duration of 64.0 and 2.0 days, respectively.

The Panel realizes that there are several limitations and unclear bias in reviewing the urinary retention data, including the heterogeneous patient population, toxin type, toxin dose, and injection location, not to mention the variable definitions of incomplete bladder emptying/urine retention and what criteria constitutes a requirement for CIC used in the trials.

Nonetheless, the Panel feels that all spontaneously voiding NLUTD patients considering botulinum toxin treatment must be counseled regarding the risk of requiring CIC (or possibly an indwelling catheter, if not able to perform CIC) for up to several weeks to months after the procedure.

Clinicians should be cognizant that CIC may be challenging for some NLUTD patients due to physical or cognitive limitations. In that case, there should be an appropriately trained caregiver to perform catheterization.<sup>266</sup> Adequate logistics including education, training, and supplies in addition to social, emotional, and time availability must be considered in this population. For this reason, the Panel advocates for shared decision-making when discussing botulinum toxin therapy with NLUTD patients who void spontaneously.

Given the known risk of incomplete bladder emptying and/or urinary retention, the Panel consensus it that all clinicians must discuss the specific risks of urinary retention and the potential need for intermittent catheterization prior to selecting botulinum toxin therapy. This recommendation is also consistent with Statement 18 in the *Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: an AUA/SUFU Guideline*: "Clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the care-

fully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. Standard (Evidence Strength Grade B)<sup>26</sup>

### Surgical Treatment

**STATEMENT FORTY-THREE: Clinicians may offer sphincterotomy to facilitate emptying in appropriately selected male patients with NLUTD, but must counsel them of the high-risk of failure or potential need for additional treatment or surgery. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base for this statement is comprised of one systematic review (Reynard 2003) and three observational studies (Vainrib 2014, Pan 2009, Pannek 2009). The risk of bias across the studies reporting on outcomes informing this statement was very serious but evidence was not further downgraded for any domain.*

Although detrusor relaxation with oral anticholinergic treatment in combination with intermittent catheterization is the primary way to treat NLUTD patients with DSD due to SCI,<sup>267</sup> external urethral sphincterotomy may be performed in patients who are unwilling or unable to perform CIC. While sphincterotomy is irreversible, patients who experience reflex voiding, can maintain urinary drainage and containment with a condom catheter, and have poor hand function or an unwillingness to perform CIC are appropriate candidates for the procedure. Sphincterotomy can increase the effectiveness of bladder emptying, decrease UTIs, and preserve urinary tract function.<sup>267</sup> However, patients must be counseled that this procedure requires regular follow-up and repeat procedures may be required.<sup>268</sup>

Sphincterotomy is performed endoscopically at the 12 o'clock position with electrocautery resection or laser incision. In a study by Pan et al.,<sup>269</sup> 84 men with documented spinal injury underwent primary sphincterotomy for DSD (n=73), recurrent UTI (n=39), and upper tract dilation (n=11) and were followed for 6.35 years (mean). Failure of the procedure was identified in 57 patients (68%, median time to failure 36 months) and 30 patients underwent a second procedure for the following indications: DSD (n=18); recurrent UTI (n=10); upper tract dilatation (n=2). Thirteen patients did not require further intervention, and 17 who eventually

failed had a mean duration of success of 80.2 months. Overall, definitive control of DSD with a single sphincterotomy was achieved in 32% of SCI patients, emphasizing the need for continued evaluation and high likelihood of the need for further intervention.

A review of studies of patients who underwent a sphincterotomy reported that while MCC generally did not change, patients showed improvements in PVR, MDP, end filling detrusor pressure, and DLPP.<sup>267-269</sup>

There are a few studies reporting the use of botulinum toxin for chemical sphincterotomy. Gallien et al. performed a multicenter, placebo-controlled, randomized, double blind trial exploring the effects of a single transperineal injection of onabotulinumtoxinA 100 U into the striated sphincter in patients with DSD. Eighty-six patients with MS were divided into placebo and treatment groups. One month post-injection there was no statistical difference in decrease in PVRs between the two groups. A larger voided volume with reduced maximal voiding pressure was identified in the treatment group.<sup>270</sup> A small double-blind study by de Seze et al.<sup>271</sup> compared a single transperineal injection of onabotulinumtoxinA 100 U versus lidocaine injection into the external sphincter in 13 patients with SCI. Post-injection, the onabotulinumtoxinA group showed a reduction in PVR by more than 50% and a reduction in AD. Given the limited efficacy over time with chemical sphincterotomy, it is not recommended for routine management of DSD in NLUTD.

Initial sphincterotomy may fail and patients must be followed for recurrent UTIs, AD, dysreflexia, elevated DLPP, and residual urine volume.<sup>272</sup> DLPP above 40 cm H<sub>2</sub>O has been associated with a risk of upper tract damage<sup>42</sup> and pressure-based management to keep storage pressures low has been shown to reduce lower and upper tract complications. Long-term issues associated with sphincterotomy include skin breakdown from the condom catheter, an inability to keep the condom in place resulting in urinary incontinence, the need for repeat procedures, and postoperative bleeding, which may result in post-operative blood transfusion.<sup>268, 269</sup>

While sphincterotomy may be an attractive option for patients that have reflex bladder contractions and prefer to manage their bladder with a condom catheter, patients must be made aware of the high-risk of failure and potential need for further intervention. Patient selection is important and appropriate counseling allows for decisions to be made with the patient in a shared decision making manner.

**STATEMENT FORTY-FOUR: Clinicians may offer urethral bulking agents to NLUTD patients with stress urinary incontinence but must counsel them that efficacy is modest and cure is rare. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement is informed by two observational studies (Hamid 2003, Tabibian 2003) with very serious risk of bias and further downgraded for imprecision.*

Before considering treatment with a bulking agent for SUI in patients with NLUTD, patients must be counseled that while bulking agents are a minimally invasive treatment option with low-risk for AEs, there is a paucity of literature that has evaluated this treatment in this particular patient population, success rates are not high, and long-term outcomes are poor.

In a retrospective study, Tabibian and Ginsberg<sup>273</sup> reviewed the charts of 11 male patients (mean age 35 years) who underwent transurethral collagen injections for SUI. All had NLUTD secondary to SCI except for one with SB. Outcomes were reviewed in nine patients; six patients underwent one injection, one had two injections, and two had three injections. Success was defined as patient satisfaction and pad use. Two patients (22.2%) had near complete symptom resolution, two (22.2%) reported at least 50% improvement, two (22.2%) noted moderate improvement but continued to require pads and three patients (33.3%) did not have any improvement in symptoms. The number of injections did not appear to affect the outcome, no AEs were reported, and no long-term complications were attributable to the injections. However, the study was limited by observational design, the lack of long-term follow-up, and small sample size.

Another retrospective study by Hamid et al.<sup>274</sup> looked at the efficacy of polydimethylsiloxane (PDS) submucosal injections in 14 men (mean age 41 years; mean duration of injury 9.6 years) with SUI secondary to SCI. After a mean follow-up of 37.5 months, 37.5% were completely dry both symptomatically and urodynamically. Of the remaining patients, 21.4% were at least 50% improved (based on pad use) while 42.8% had no improvement, even after repeat treatment.

Historically, studies on bulking agents used PDS and bovine collagen. Though collagen is no longer available, PDS along with several other bulking agents are currently being used. It is not known if the type of bulking agent has an impact on outcomes in the NLUTD patient

with SUI. In addition, compared to non-NLUTD patients, it is unclear how the need for regular CIC in many patients with NLUTD would impact outcomes with bulking agents.

**STATEMENT FORTY-FIVE: Clinicians should offer slings to select NLUTD patients with stress urinary incontinence and acceptable bladder storage parameters. (Moderate Recommendation; Evidence Level: Grade C)**

*Statement 45 is supported by one systematic review (Frag 2016) and one observational study (Shin 2020). Evidence level was based on a very serious risk of bias in these studies but no further downgrading.*

The Panel recommends that slings should be considered for NLUTD patients with SUI who are able to void on their own. Assessment of bladder storage parameters with UDS should be performed prior to any SUI procedure in patients with relevant NLUTD where bladder compliance could be worsened by an outlet procedure, resulting in elevated storage pressures and risk to the upper urinary tracts. For patients with significant sphincteric dysfunction, this may require bladder neck/urethral occlusion (often done either with a catheter balloon or manual compression) to allow for adequate bladder filling. This would be particularly applicable to patients with moderate- or high-risk NLUTD. The risk of subsequent voiding dysfunction and the possibility of neurogenic disease, which may cause future voiding problems should be discussed with the patient. For example, if there is concern for the future need for CIC, then the Panel recommends avoiding synthetic slings. In the situation where an occlusive sling is being considered, the Panel recommends not using synthetic material. Instead, consideration should be given to autologous fascia or other biologic grafts.

Slings demonstrated significant improvement in incontinence compared to pre-sling measures in patients with SUI and NLUTD. A meta-analysis by Farag et al.<sup>275</sup> identified 30 studies of SUI surgical treatments, 15 of which utilized slings (n=286 cases). This included autologous fascial slings (n=177), sling wraps (n=63), female synthetic slings (n=20), and male synthetic slings (n=26). In those studies that examined the effectiveness of slings, the success and failure rates were 58% and 22% respectively; however, the definition of success was not reported for each study. Post-hoc analysis reported no statistical differences in success rates between AUS and sling, but both interventions fared better than bulking agents. Conclusions regarding the

efficacy of slings compared to other interventions are limited given the age of the studies (published between 1990 – 2013), the lack of studies with Grade A evidence (i.e., no RCTs), and poorly described outcome definitions. More recently, Shin et al. reported on midurethral sling outcomes in women with and without relevant neurologic disease with regards to SUI and OAB outcomes.<sup>276</sup> The SUI success rates in women with neurologic disease versus without neurologic disease were the same (93.7% compared to 95%, respectively;  $p=0.440$ ) However, de novo OAB symptoms were found to be higher in women with neurologic disease (21.05% versus 5.26%;  $p<0.001$ )

The patient with SUI who also has NLUTD should not be considered in the same context as the patient who has SUI without neurogenic disease. In addition, all patients with SUI and a neurologic diagnosis are not the same. For example, the debilitated patient with severe SUI due to urethral loss secondary to a chronic indwelling urethral catheter is very different than the healthy woman with SUI and minimally advanced MS. Every patient needs to be individually evaluated with special attention focused on issues such as the severity of SUI, the degree of neurologic impairment, the possibility of progression of the neurologic disease, and the impact the NLUTD could have on voiding parameter post-sling placement.

**STATEMENT FORTY-SIX: Clinicians may offer artificial urinary sphincter to select NLUTD patients with stress urinary incontinence and acceptable bladder storage parameters. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement is informed by five observational studies (Kaiho 2018, Bersch 2009, Chartier Kastler 2011, Singh 2011, Costa 2013) with an aggregate very serious risk of bias for the outcomes of interest. Additionally, evidence was downgraded for inconsistency of results.*

Artificial urinary sphincter (AUS) demonstrates significant improvements in SUI in select male and female patients with NLUTD. While AUS has been demonstrated to be successful in managing SUI, the risk of voiding dysfunction needs to be considered in all relevant neurogenic populations and the possibility of needing subsequent CIC should be discussed. Assessment of bladder storage parameters with UDS should be performed prior to any AUS placement in patients with relevant NLUTD where bladder compliance could be worsened by an outlet procedure, resulting in elevated storage pressures and risk to the upper urinary tracts. For patients

with significant sphincteric dysfunction, this may require bladder neck/urethral occlusion (often done either with a catheter balloon or manual compression) to allow for adequate bladder filling. This would be particularly applicable to patients with moderate- or high-risk NLUTD. In addition, adequate upper extremity function to allow for AUS manipulation needs to be confirmed prior to proceeding with implantation.

Placement of AUS in men with NLUTD should not be considered the same as placement in men with post-prostatectomy incontinence. Bladder storage parameters are a concern in the NLUTD patient and placement of an AUS could potentially exacerbate impaired compliance. This can create risk to the upper tract and urodynamic confirmation of acceptable bladder storage pressures is required prior to placement.

The literature search for this guideline returned eight studies that evaluated AUS outcomes in patients with SUI due to NLUTD<sup>277-284</sup> This included four studies in SCI patients, one in patients with SB, and one in patients with mixed neurologic disease. While significant improvements in continence were seen across the study populations, standardized rates of improvement are difficult to characterize due to the wide variability in definitions of success, cure, improvement, and outcome variables. Conclusions from the literature are also limited by heterogeneous populations, study design (i.e., observational studies with relatively small sample sizes), and confounding variables such as concomitant surgeries (e.g., AC).

In a retrospective study of 51 adult male incontinence patients who had either SB ( $n=16$ ) or SCI ( $n=35$ ) and underwent AUS insertion, Chartier et al.<sup>285</sup> reported 60% of patients were completely continent and 22% were moderately continent after seven years follow-up. In another study of male ( $n=75$ ) and female ( $n=15$ ) young adults (mean age 26 years) with NLUTD and AUS implantation, Singh et al.<sup>193</sup> reported that after a mean follow-up of four years, 92% were fully continent. Wide ranges of improvements with variable definitions of success were reported; up to 77.7% cured, 9.8% using one or more pads per day.

The use of the AUS in women is less common but has shown good success. Costa et al. conducted a large retrospective review of all women at their center who underwent AUS at the bladder neck via an open surgical approach.<sup>286</sup> Of 344 patients, 54 were defined as having NLUTD due to acquired or congenital disease. In women with versus without NLUTD, complete conti-

nence was achieved in 90.74% versus 84.78%, respectively, ( $p=0.25$ ). Non-mechanical complications in all women included infection (4.8%), vaginal erosion (3.2%), urethral erosion (1.9%), labia-major erosion (1.9%), and bladder erosion (1.1%). Mechanical complications of the device decreased to 8.8% after a modification of surgical technique involving bilateral incision of the endopelvic fascia. While the differences in rates of each type of complication between neurogenic and non-neurogenic were not reported, NLUTD was a risk factor for shorter device survival.

The possibility of needing CIC should be addressed and the patient should be counseled that while CIC in the context of an AUS is possible, patients undergoing AUS placement must be willing to accept higher risks of both AUS erosion and/or infection than what is seen in the non-NLUTD patient population. Therefore, patients should be counseled that they may need additional surgeries, revision, explants, and the possibility of surgery after AUS placement. Singh et al.<sup>193</sup> reported a re-operation rate of 28% in conjunction with infections, erosions, device failure, bladder perforation, and rectal perforation; 78% needed to perform intermittent catheterization. Patki et al.<sup>287</sup> reported 43% of successful implants required one revision.

Location of the AUS cuff can be variable depending on the patient population. While bladder neck (BN) cuff placement may reduce risk of erosion, especially in the context of CIC, the surgery is considered more extensive and should only be performed by clinicians with the necessary experience and expertise. Chartier et al.<sup>285</sup> reported a 5.9% (3 of 51 patients) cuff erosion rate using a BN cuff. The expansion of robotic assistance with AUS placement may minimize this limitation in the future.

Use of the AUS in the patient with NLUTD requires extensive consideration that is not well reflected by the literature. AUS use in adult women should be considered rare and under limited circumstances. The Panel consensus is that placement of a transvaginal cuff is considered a poor option. The increased use of a robotic approach may result in AUS placement in women becoming a more attractive option as more surgeons become comfortable with this technique.<sup>288</sup> Lastly, one potential limitation of AUS placement is adequate upper extremity function. Just as would be recommended for non-NLUTD patients, any surgeon placing an AUS in a patient with NLUTD must make sure that there is adequate hand dexterity to properly manipulate the device.

**STATEMENT FORTY-SEVEN: After a thorough discussion of risks, benefits, and alternatives, clinicians may offer bladder neck closure and concomitant bladder drainage methods to select patients with NLUTD and refractory stress urinary incontinence. (Expert Opinion)**

Bladder neck closure (BNC) for bladder outlet incontinence is an irreversible procedure and is an option for patients who are refractory to any other form of urethral reconstruction due to prior interventions that may have injured the BN or external sphincter, or who have severe urethral pathologies, such as strictures or urethrocutaneous fistula.<sup>289</sup> Although BNC is associated with continence rates of 75 – 100%, fistulization with recurrent incontinence after the initial closure can occur in up to 25% of cases.<sup>89, 290</sup>

Careful attention and planning to assure safe bladder storage pressure following BNC is important to protect upper urinary tract function. This is particularly relevant for those patients undergoing BNC and concomitant construction of a continent catheterizable stoma. Assessment of bladder storage parameters with UDS should be performed in patients with relevant NLUTD where bladder compliance could be worsened by an outlet procedure such as BNC, resulting in elevated storage pressures and risk to the upper urinary tracts. This would not be an issue if the surgical plan is to perform BNC and place a suprapubic catheter which would allow for continuous bladder drainage. For patients with significant sphincteric dysfunction, this may require bladder neck/urethral occlusion (often done either with a catheter balloon or manual compression) to allow for adequate bladder filling. This would be particularly applicable to patients with moderate- or high-risk NLUTD.

In females with NLUTD, the most common cause of severe urethral damage is the use of a chronic urethral catheter. Transvaginal or transabdominal BNC can be combined with a chronic indwelling suprapubic catheter,<sup>224</sup> continent catheterizable stoma, or ileovesicostomy<sup>289</sup> to provide urinary drainage.

Two retrospective reviews provide the largest series on BNC in patients with NLUTD. Shpall and Ginsberg<sup>289</sup> reported on 21 males and 18 females with a variety of neurologic diagnoses: 23 SCI, 5 cerebral palsy, 4 MS, 4 myelomeningocele, 2 spinal tumor. Indications for BNC included urethrocutaneous fistulae, incompetent urethra, urethral stricture, and pressure ulcer. A fistula of the BNC occurred in 6 (15%) patients. Four required a second surgery to close the fistula (3 transabdominal, 1



transvaginal), one patient's fistula closed spontaneously with prolonged drainage, and one patient did not undergo further repair.

In a study by Colli and Lloyd,<sup>224</sup> the outcome of BNC with suprapubic catheter placement was reported in 35 patients with NLUTD (SCI 71%; MS 23%; CVA 9%). The overall complication rate was 17%, with one vesicovaginal fistula. The authors showed BNC with suprapubic catheter diversion is a viable option for patients with urethral damage beyond repair.

While BNC is done via a retropubic approach for male patients, it can be performed retropubically or transvaginally for women. Most of the literature evaluating these outcomes has come from case series looking at women with eroded urethras due to long-term urethral catheters; not all women in these series had NLUTD. Rovner et al.<sup>291</sup> reviewed outcomes on 11 patients with a devastated outlet due to long-term urethral catheter drainage with 10 of 11 undergoing successful initial BNC with a transvaginal posterior urethral flap. Willis et al.<sup>292</sup> reviewed outcomes in 64 women (35 transvaginal; 29 retropubic) and did not note differences in outcomes based on the method/approach of BNC (85.7% versus 81.5% success rate;  $p=0.74$ ) but did note shorter operative time and hospital stay with the transvaginal approach. In contrast, Ginger et al.<sup>223</sup> found a higher fistula rate in patients with NLUTD (24 female; 5 male) undergoing BNC via a transvaginal approach ( $p=0.01$ )

Loss of male fertility and the need for assisted reproduction should be discussed before BNC. An alternative to surgical BNC is a tight fascial sling. Use of a fascial sling at the BN would allow a urethral catheter to be placed emergently and provide easier navigation with a ureteroscope to manage an upper tract stone. However, sling placement is not an option for many of these patients who have severe urethral loss and are without an adequate amount of tissue to allow for a successful sling procedure; thus, other options such as a BNC must be considered.

**STATEMENT FORTY-EIGHT: Clinicians may offer posterior tibial nerve stimulation to select spontaneous voiding NLUTD patients with urgency, frequency, and/or urgency incontinence. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base was comprised of two systematic reviews (Zecca 2016, Schneider 2015) and two obser-*

*vational studies (Tudor 2020, Kabay 2021). The risk of bias for benefits of care was serious, and evidence was further downgraded for inconsistency. Additionally, MS patients were represented in both systematic reviews leading to a potential overestimate of effect in this patient population.*

Posterior tibial nerve stimulation (PTNS) is approved for patients with non-neurogenic OAB; however, it has been shown to offer benefit to select patients with NLUTD where bladder problems are mainly isolated to storage symptoms. This benefit has primarily been demonstrated in patients with neurologic diagnoses such as MS, PD, and CVA who have OAB symptoms and continue to be able to voluntarily void on their own.

A systematic review of seven observational studies looked at the effectiveness of PTNS on patients who had NLUTD secondary to MS.<sup>293</sup> Across all studies, patients demonstrated improvement in daily urgency episodes, weekly incontinence episodes, volume at first sensation, bladder capacity, voided volumes, PVR, urinary frequency, and nocturia. The stimulation schedule varied: two studies employed single bilateral sessions; four studies employed unilateral weekly 30 minutes sessions for twelve weeks; one study utilized daily 20-minute sessions for 12 weeks. In patients who underwent daily therapy ( $n=70$ ), 83.3% of patients reported an improvement in warning time ( $p<0.001$ ), urgency ( $p=0.023$ ), and voids per day ( $p<0.01$ ) at study end. Similar results were found in studies where patients underwent weekly sessions for 30 minutes.

Of note, a study that evaluated long-term efficacy of PTNS in patients with MS<sup>294</sup> was included in the PTNS systematic review (Zecca 2016).<sup>293</sup> A total of 83 patients underwent twelve weekly PTNS sessions with 74 moving on to maintenance therapy after an initial improvement with their LUTS. The frequency of stimulation needed to maintain efficacy was PTNS treatments every 4 weeks in 9/74 (12%) patients, every 3 weeks in 18/74 (24%) patients, every 2 weeks in 44/74 (60%) patients and weekly in 3/74 (4%) patients. Outside of a study, it is unclear if patients will be willing to undergo such treatments at such a frequency nor is it clear if this would be reimbursed at a frequency shorter than the standard duration of every four weeks.

A study by Kabay et al.<sup>295</sup> also looked at the effectiveness of initial PTNS therapy followed by a maintenance protocol. Thirty-four MS patients underwent unilateral, weekly PTNS treatments for 12 weeks. At the end of the initial treatment phase, 29 were "positive respond-

ers" (i.e., voiding parameters improvement over 50%) and subsequently underwent a tapering protocol of 6, 9 and 12 months of therapy (i.e., every 2 weeks for 3 months; every 3 weeks for 3 months; and once a month for 3 months). Of the 29 patients that entered the protocol, 21 completed treatment for one year. Compared to baseline, these 21 patients showed a statistically significant improvement ( $p < 0.001$ ) in daytime frequency, nocturia, UI, urgency episodes, and incontinence episodes, at 6, 9, and 12 months.

Although limited studies have been performed in patients with NLUTD due to PD, PTNS has demonstrated improvements in urgency episodes, bladder capacity, MDP, maximum flow rate, and bladder compliance. Studies are generally limited by short follow-up, small sample size, and high dropout rates. In a RCT by Perissinotto et al.,<sup>296</sup> 13 PD patients were randomized to transcutaneous tibial nerve stimulation (TTNS) or to a sham procedure. Patients who were allocated to treatment ( $n=8$ ) were given 30-minutes of TTNS twice a week for five weeks. At the end of ten weeks, those who underwent the intervention showed a statistically significant reduction in urgency episodes as compared to baseline ( $p=0.004$ ). In terms of nocturia, although there were no differences in the number of episodes between the treatment and placebo group at baseline, those who underwent an active intervention showed a reduction in the number of episodes ( $p < 0.01$ ) after five weeks, while those who were randomized to sham saw no difference before and after treatment. Significant UDS differences were also found in regard to strong desire to void and urgency. However, while improvements were seen between other pre- and post-treatment variables (e.g., volume at first desire to void, volume at strong desire, volume at urgency, MCC, bladder compliance, DO, maximum flow rate, MDP, PVR) they were not statistically significant.

One RCT trial looked at the effects of PTNS in male NLUTD patients who had history of a CVA. PTNS was compared to stretching of the lower extremity and demonstrated improvements in urgency and frequency; however, no statistical improvement was seen in urge incontinence. The applicability of this study is limited by the study design which included a non-standardized stimulation schedule consisting of two sessions per week for six weeks. In two separate trials studying CVA patients, those randomized to TTNS demonstrated improvement in urinary frequency, nocturia, urgency, and urge incontinence as compared to a control group.

However, these studies were limited by short follow-up and inability to blind subjects.<sup>297</sup>

One study met search criteria looking at the use of PTNS in patients with NLUTD due to SCI. While improvements were seen in CIC volumes and incontinence, study limitations limit extrapolation to clinical use. The study was randomized, however the comparative arm received medication and there was no comparison to sham or placebo. Furthermore, this study used adhesive skin surface electrodes and not the true percutaneous approach used by PTNS.<sup>298</sup>

In a retrospective study that looked at outcomes after PTNS in patients with neurogenic versus idiopathic overactive bladder, Tudor et al. showed that improvements did not differ between neurogenic versus idiopathic patients.<sup>299</sup>

While promising, the use of PTNS in NLUTD could be further elucidated. As summarized by Schneider et al. in a meta-analysis of studies employing PTNS in various NLUTD patients including MS, PD, stroke, SCI and others, data in support of PTNS in patients with select NLUTD suggests it is effective and safe; however, the quality of evidence is limited and more reliable evidence from well-designed RCTs are needed.<sup>300</sup> Also of note, studies evaluating MS patients included within the Schneider meta-analysis were also included within the aforementioned Zecca systematic review,<sup>293</sup> potentially leading to an overestimate of effect in this patient population.

**STATEMENT FORTY-NINE: Clinicians may offer sacral neuromodulation to select NLUTD patients with urgency, frequency, and/or urgency incontinence. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base was comprised of one systematic review (Kessler 2010) and two observational studies (Chaabane 2011, Zhang 2019). The risk of bias for benefits of care was serious, and evidence was further downgraded for inconsistency.*

While sacral nerve modulation therapy (SNM) was originally approved for OAB, urge urinary incontinence, non-obstructive urinary retention, and fecal incontinence, its mechanism of action lends to possible extension of use to outside the original indications. SNM has been shown to be effective in select patients with NLUTD including those with NLUTD due to MS, stroke, and PD.

Observational studies with small numbers of patients

have shown that SNM has moderate success in patients with MS including improvements in urinary frequency, incontinence episodes and voiding (for patients with retention), including PVR and/or voided volumes. AEs were considered minimal (e.g., lead migration, need for battery change or device malfunction).<sup>301-305 306</sup>

One limitation in the use of SNM in the MS patient has been the device's MRI incompatibility. However, newer devices are MRI conditional and have longer battery life expectancies, which has expanded their applicability and will likely broaden opportunities for research and use in patients with MS. In addition, placing a neuro-modulation device in a patient with a progressive disease such as MS can be an issue; as the disease process worsens the patient's lower urinary tract function may progress and worsen as well. This possible outcome is reflected in a report by Chaabane et al.<sup>307</sup> who noted loss of efficacy in three of seven implanted patients with MS; all three of those patients had loss of efficacy after a MS relapse.

While the data is limited on the use of implantable SNM in CVA or PD patients, several studies have reported on the success of SNM in pools of mixed neurologic diseases, including MS, CVA, PD, cerebral palsy, acquired brain injuries, viral and vascular myelitis, encephalitis, central nervous system tumors, Friedreich ataxia, dysautonomia, incomplete SCI, multiple system atrophy, and spinocerebellar atrophy. Although limited by small sample size and study design, these observational studies demonstrated improvements in urinary incontinence, urgency episodes, MCC, voided volumes and urinary frequency. AEs included mainly infections and device malfunction, some of which required explanation.<sup>307-311</sup>

A more recent study by Zhang et al.<sup>306</sup> reported on the use of SNM in a larger sample of pooled patients with NLUTD including those due to spinal cord injury (traumatic and post-operative), congenital malformation of the spine, pelvic surgery, diabetes and PD. Types of bladder dysfunction included; neurogenic OAB, neurogenic retention, and voiding difficulties. Overall, 107/182 (58.8%) NLUTD patients went on to receive a second stage or placement of the SNM generator. Stable statistically significant improvements were seen at follow-up (endpoint) compared to baseline data in: urinary frequency, urgency, nocturia, daily urine volume, daily urinary leakage, and residual urine. There were 14 adverse events (13.1%) in the neurogenic group who received full implant including six with recurrence

of symptoms, five implant site infections, two system disconnections and one subjective noncooperation. Unfortunately, outcomes and AE's were reported as a pooled group thus limiting ability to delineate SNM outcomes in each disease process.

**STATEMENT FIFTY: Clinicians should not offer sacral neuromodulation to NLUTD patients with spinal cord injury or spina bifida. (Moderate Recommendation; Evidence Level: Grade C)**

*This statement is informed by two observational studies (Lombardi 2014, Lombardi 2011) with very serious risk of bias but outcome evidence was not further downgraded for any domain.*

SNM should not be used in patients with NLTUD due to SCI or SB due to the high variability in the bladder dysfunction and the disease processes themselves. Studies have shown SNM may improve various outcomes in patient with SCI and SB including incontinence, chronic urinary infections, and upper tract protection; however, these were heterogenous clinical situations and subsequent revisions and other procedures were also required.

Three observational studies<sup>312-314</sup> reviewed SNM in patients with incomplete SCI without posterior rhizotomy. In those with retention, improvements were seen in voided volumes. For those with OAB symptoms, patients demonstrated increased bladder capacity, decreased urge incontinence episodes, and decreased end filling pressures. AEs included surgical site infections, pain at the generator site, detectable or bothersome lower extremity sensations, and loss of efficacy.

**STATEMENT FIFTY-ONE: Clinicians may offer augmentation cystoplasty to select NLUTD patients who are refractory to, or intolerant of, less invasive therapies for detrusor overactivity and/or poor bladder compliance. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base was comprised of one systematic review (Hoen 2017) and one observational study (Reid 2020) with an aggregate serious risk of bias and further downgrading for inconsistency.*

Although AC is the most common reconstructive procedure for managing NLUTD when bladder capacity, bladder compliance, or DO that is refractory to medications or botulinum toxin, the quality and number of studies reviewing this surgery for NLUTD patient is sparse. Despite these shortcomings, all studies reviewed show

AC to be associated with high rates of continence and upper tract protection with the trade-off of the frequent need for subsequent procedures to manage complications and long-term follow-up. Prior to proceeding with AC, patients with NLUTD must be made aware of the potential long-term risks (e.g., stones, perforation, bowel dysfunction, mucus production) and the need for life-long follow-up after lower urinary reconstruction. In addition, the hand and cognitive function necessary to perform regular CIC must be assessed and be present by either the patient or a family member/caregiver that would conceivably be able to perform this on a regular basis.

There is only one systematic review evaluating the safety and efficacy of AC in adults with NLUTD.<sup>315</sup> A meta-analysis of the eligible studies for inclusion in the review was not possible due to the paucity and quality of the data, so a narrative synthesis was performed on 20 publications covering AC in adults with NLUTD. The primary outcome measures were QoL, renal function, and changes in anatomy. Secondary measures were UDS findings, continence outcomes, and long-term complications, as well as the need for additional interventions including repair of bladder perforation. Four studies included 140 patients with most reporting satisfaction with the results of AC; however, QoL measures were not standardized. Renal function stabilized in 247 patients post-operatively with no deterioration and 11 studies showed continence improvement and resolution of VUR in 108 of 150 renal units. Serious AEs were rare, but the risk of stones, bowel dysfunction, and mucus-related complication exceeded 10%, further emphasizing the need for life-long follow-up after AC.

Notable findings from two of the larger studies include no need for concomitant ureteral reimplantation at the time of AC<sup>316</sup> and efficacy equivalence with earlier post-operative recovery using an extraperitoneal approach to AC.<sup>317</sup> One of the theoretical potential long-term concerns post-AC is an increased risk of bladder cancer. Recent literature shows the risk of bladder cancer in patients with AC is very low, ranging from 0.6% to 4.5%.<sup>77</sup> Routine surveillance cystoscopy is not recommended in the absence of indications such as hematuria or recurrent UTI.

Reid and colleagues compared AC in two 10-year series at the same institution comprising 126 patients with congenital or acquired SCI or disease.<sup>318</sup> Dry rates were 83% and 85% in both series demonstrating the long-term efficacy of AC to manage low capacity and

poor compliance. Early (< 3 months) and late (> 3 months) post-operative complications were 15% and 17%, respectively, with no mortality.

**STATEMENT FIFTY-TWO: Clinicians may offer continent catheterizable channels, with or without augmentation, to select NLUTD patients to facilitate catheterization. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base for this statement is comprised of one systematic review (Phe 2017) with a serious risk of bias.*

Continent catheterizable channels (CCC) may be offered to NLUTD patients who are able to perform self-catheterization but have a devastated urethra that cannot be catheterized (e.g., urethral stricture, perineal pressure ulcer eroding into the urethra) or require BNC closure (i.e., complete loss of the urethra due to a chronic indwelling urethral catheter). An additional indication would be patients with normal hand dexterity and urethral function that prefer a CCC due to ease of catheterization; this is most often seen in female patients that may have difficulty performing CIC per the urethra. Pre-operative counseling is required before any CCC surgery to advise the patient on potential complications, expectations, and outcomes. Pre-operative counseling and decision making may be optimized with a multidisciplinary team that, in addition to urology, may include rehabilitation physicians, occupational therapists, neurologists, stomal therapists/nurses and physiotherapists. This is especially important for patients with cognitive and/or upper extremity limitations and these issues must be taken into consideration as surgical planning and decisions are made.

A systematic review of 11 retrospective studies looked at the effectiveness of CCC in NLUTD patients<sup>319</sup> in whom urethral catheterization could not be performed. No meta-analysis was possible due to the low quality and number of studies meeting the inclusion criteria. The publications reviewed involved 213 patients with mixed NLUTD for a median follow-up of 36 months. The primary outcomes were the ability to catheterize the CCC (84%) and stomal continence rate (>75%). There were no consistent QoL results and re-operations were required in 40% of patients. CCC stenosis occurred in 4-32% (median 14%) of patients requiring re-operation in addition to the need for further surgery for neovesicocutaneous fistulae, bladder stones, and bladder perforation. Mitrofanoff, Monti or Casale tubes were utilized in 55%, invaginated valves (Kock,

Benckekroun, Mainz 1) in 23%, and non-invaginated efferent tubes (Indiana, Miami) in 21% of patients. Concomitant AC or a pouch was performed in 78% and 23% required simultaneous outlet surgery (e.g., fascial sling, suburethral sling, BNC, AUS).

Cheng and colleagues with the Neurogenic Bladder Research Group combined their outcomes with continent cutaneous ileocecostoplasty in 114 patients over a 10-year period.<sup>320</sup> Concomitant procedures managing the outlet were required in 45% of the study population with a pubovaginal or omental flap being the more common adjunct procedure. Major complications occurred in 16% of the patients requiring readmission in 21%. Furthermore, at a median follow-up of 40 months, 42% of the patients underwent 80 additional procedures with 20% of those requiring at least one channel procedure. The need for revision of a continent channel revision is common and should be discussed pre-operatively with all patients.

There is limited evidence that evaluates CCC outcomes for patients that undergo the procedure to facilitate catheterization. Walsh et al.<sup>321</sup> reviewed outcomes in six women with SCI at C7 or higher. With construction of the CCC, the mean time required to perform CIC decreased from an average of 27 (10-40) to 7.8 minutes (1-15) and all patients were able to catheterize while in their wheelchair. In addition, Zommick<sup>322</sup> evaluated outcomes in 21 patients with cervical spinal cord injury who underwent CCC construction. Twenty of 21 continued to be catheterized per the CCC (12 by the patient, 8 by family member or caregiver). These results speak to the option of self-catheterization that may only be attainable for certain NLUTD patients after CCC construction and the importance of the multidisciplinary evaluation and discussion prior to the proceeding with this type of reconstruction, especially in NLUTD patients that may rely on others to perform catheterization.

**STATEMENT FIFTY-THREE: Clinicians may offer ileovesicostomy to select patients with NLUTD and must counsel them on the risks, benefits, alternatives, and the high-risk of needing additional treatment or surgery. (Conditional Recommendation; Evidence Level: Grade C)**

*This statement is informed by two observational studies (Tan 2008, Husmann 2020) with a very serious risk of bias when reporting on the outcomes of interest. Evidence was not further downgraded for any domain.*

Ileovesicostomy as an option for patients unable to per-

form self-catheterization secondary to poor hand function, immobility, challenging body habitus, or condom catheter induced skin breakdown. The goal of ileovesicostomy is to allow for low pressure storage via a urostomy while avoiding the need for a ureterovesical anastomoses. In addition, this is theoretically a reversible procedure. However, there is a concern that with longer follow-up, patients have increased risk for requiring revision or alternate surgery to facilitate urinary drainage.

The literature search for this guideline provided three retrospective single institution studies<sup>323-325</sup> with small sample sizes that evaluated the effectiveness, risks, and benefits of ileovesicostomy in different patient populations. Across all studies, the need for subsequent procedures was high, ranging from 33 to 75%, with stomal revision as the most common reason for reoperation followed by bladder and kidney stone removal.<sup>323</sup>

The largest study by Tan et al.<sup>325</sup> retrospectively reviewed the operative logs of 50 patients (21 male; 29 female) who underwent incontinent ileovesicostomy urinary diversion from 1999 to 2003. Mean follow-up was 26.3 months with a range of 1 – 79 months. The two most common etiologies of NLUTD were SCI (42%) and MS (38%). Prior to surgery, 88% were incontinent despite previous bladder management interventions and 37 were managed with an indwelling urethral and/or suprapubic catheter. Other pre-operative management interventions included: pubovaginal sling (65.5%), BNC (20%), suprapubic closure (20%), enterocystoplasty (12%), and urinary fistula repair (6%). Post-procedure analysis showed a urethral continence rate of 72% (n=36) at a mean follow-up of 26 months (range 1-79 months). Of note, continence appears to improve with time. The authors reported a 42% continence rate at six months, 44.8% at one year, and continence in 22 of 32 patients with follow-up greater than one year.

Seventy-seven reoperations were required in 27 patients, including: ileovesicostomy revision – 6; stoma revision – 8, BNC – 7; urinary fistula closure – 33; pubovaginal or perineal sling – 9; bladder onabotulinumtoxinA injection - 11; collagen injection - 3; wound (incision) repair - 7. The risk of reoperation was significantly related to the number of total complications (p<0.001) and stomal complications (p=0.0417). Of the 16 patients with four or more complications, 100% required reoperation, whereas 73.7% of the 19 patients

with stomal complications required reoperation for stomal or other complications. It did not appear that concurrent sling or BNC increased the likelihood of complications or reoperation. Overall, of the 27 patients requiring reoperation, 25 patients were still incontinent at some time point post-procedure, 13 of whom regained continence at last follow-up.

The authors recommended BNC over a sling procedure and careful attention to body habitus where the ostomy appliance is concerned to improve outcomes. The downside of BNC is the inability to access the lower urinary tract per the native urethra; thus, the risk and benefits should be carefully discussed with the patient prior to performing this procedure. In addition, ileovesicostomy may not be an optimal management option in obese patients due to concerns regarding ostomy placement and the need for a longer ileal segment which may drain poorly. Long-term and regular follow-up is required post-ileovesicostomy to ensure adequate emptying and to screen for issues such as stones.

Finally, all options should be evaluated when considering ileovesicostomy construction. Husmann and Viers<sup>326</sup> evaluated outcomes in patients undergoing BNC and SPC drainage (n=21), BNC and ileovesicostomy (n=17), or cystectomy with ileal conduit (n=10) for severe urethral destruction. The highest rates of urosepsis (ileovesicostomy: 82%; ileal conduit: 60%; SPC: 29%) and need for subsequent surgical intervention (ileovesicostomy: 88%; ileal conduit: 50%; suprapubic tube: 52%) were noted with the patients that underwent BNC and ileovesicostomy.

**STATEMENT FIFTY-FOUR: Clinicians should offer urinary diversion to NLUTD patients in whom other options have failed, or are inappropriate, in order to improve long-term quality of life. (Moderate Recommendation; Evidence Level: Grade C)**

*Statement 54 is informed by six observational studies (Chartier Kastler 2002, Deboudt 2016, Guillotreau 2012, Gobeaux 2012, Adiaansen 2017, Singh 2011) reporting on quality of life using various tools. The studies suffered from a very serious risk of bias, plus evidence was further downgraded for inconsistency in the reported outcomes.*

Incontinent or continent urinary diversion for end-stage bladder or urethral dysfunction, intractable fistula, or non-healing decubitus ulceration is the last resort when all other options fail to provide safe and adequate stor-

age of urine. Careful counseling is required for both types of urinary diversion and consideration of upper extremity and hand function, along with assessment of the patient's social and home environment for support, is imperative.

The literature review identified several articles that evaluated outcomes of ileal conduit in the NLUTD patient population. Chartier-Kastler<sup>327</sup> reviewed outcomes in 33 patients (19 women, 14 men) with several different neurologic conditions (21 SCI; 4 MS; 3 myelitis; 5 central neurological disease). Indications for conduit included a variety of complications related to management of their lower urinary tract; at a mean follow-up of 48 months all catheter and incontinence-related problems had resolved. Legrand et al. reviewed outcomes in 53 MS patients with a median follow-up of 75 months that underwent cystectomy and conduit construction. The overall post-operative complication rate was 50%; however, the majority (n=23 cases) of reported complications were minor (Clavien grades I-II) with an additional 6 major complications (Clavien III-IV) also reported. Due to improved urinary issues and health-related QoL (based on the Qualiveen questionnaire) the authors stated that this was an acceptable option in the MS patient with NLUTD refractory to other treatment options.

Several reports examined the surgical method of ileal conduit surgery. Deboudt et al.<sup>328</sup> compared the morbidity and mortality in 65 patients with NLUTD following open (n=11), laparoscopic (n=14) and robotic (n=40) cystectomy and ileal conduit urinary diversion. This is the largest series to date comparing these techniques over a mean follow-up of 29 months. They found robotic-assisted cystectomy and ileal conduit diversion to be feasible and safe with superior overall outcomes. Guillotreau et al.<sup>329</sup> reviewed outcomes in 44 patients with MS and found a laparoscopic approach to cystectomy and ileal conduit construction to be safe with a low complication rate.

The literature review provided less than 100 cases where continent urinary diversion was used to manage NLUTD. Supratrigonal cystectomy with Hartmann pouch was performed in 61 patients with NLUTD and a mean follow-up of 5.8 years.<sup>330</sup> They reported a 90% improved continence rate with an overall complication rate of 37%, 83% of which were Clavien grade <2. Similar reports of improved QoL and improved continence were reported by Pazooki et al.<sup>186, 331</sup> with the Kock reservoir in 10 SCI patients and Zommick et al.<sup>322</sup>

with either the Kock reservoir or Indiana pouch. None of these studies used a NLUTD-specific quality of life instrument such as Qualiveen or the NBSS.<sup>332</sup> Adriaasen et al. reviewed Qualiveen scores of 282 patients with chronic (>10 years) SCI who managed their bladder with a variety of methods and found those who underwent urinary diversion reported the least impact of NLUTD on their QoL.<sup>217</sup>

Given the delayed complication rate of 21-50% for patients undergoing supravescical diversion, cystectomy should be considered at the time of reconstruction. Significant long-term complications in three studies with a median follow-up of > 4 years raise important findings when considering urinary diversion with an ileal conduit. Kato et al. performed ileal conduits in 16 patients with NLUTD secondary to tetraplegia and reported the need for subsequent cystectomy in 50% who suffered from empyema of the bladder.<sup>333</sup> Singh et al.<sup>193</sup> reviewed outcomes in 93 (71 with NLUTD) patients after supravescical diversion; 48 patients (52%) had issues with recurrent bladder infection and pyocystis with five ultimately requiring cystectomy. Of the 19 patients that did not undergo cystectomy at the time of ileal conduit construction in the series from Chartier-Kastler et al., four had issues with pyocystis and three patients ultimately required cystectomy.<sup>327</sup> Gender may play a role when discussing the option of concomitant cystectomy with patients prior to supravescical diversion. For women with pyocystis a "Spence procedure," which is essentially creation of a vesicovaginal fistula, can allow for adequate drainage of the defunctionalized bladder if pyocystis occurs, possibly obviating the need for cystectomy in women undergoing supravescical diversion.<sup>334</sup> Concurrent supratrigonal cystectomy or cystoprostatectomy should be strongly considered at the time of urinary diversion in male NLUTD patients.

Robot-assisted cystectomy, comparing extracorporeal versus intracorporeal ileal conduit diversion for NLUTD, was reported by Mazouin et al. across six centers in 97 patients.<sup>335</sup> The major indications were urinary retention with loss of hand function and UI. There were no significant differences in perioperative outcomes comparing the approaches to ileal conduit diversion.

Patients with NLUTD must continue to have regular follow-up after ileal conduit construction (see Statement 58). Shimko et al.<sup>336</sup> reviewed long-term complications of conduit urinary diversion after radical cystectomy for bladder cancer. The authors reported a variety of com-

plications that continued to occur over a 20-year period of follow-up. NLUTD patients tend to be younger than the bladder cancer patient population, and have a longer life expectancy, so the need for continued follow-up post-conduit formation is clearly required. With a median follow-up of 75 months, 11 of 53 patients with MS who underwent ileal conduit construction required surgery for a late complication and Singh et al.<sup>193</sup> reported upper tract changes post-conduit in 34% of patients.

**STATEMENT FIFTY-FIVE: Other potential treatments for NLUTD should be considered investigational and patients should be counseled accordingly. (Expert Opinion)**

Use of non-standardized options for the treatment of NLUTD should be limited due to their infancy in development or lack of adequate outcomes data supporting their use and should only be performed in the context of a well-designed clinical trial.

Our literature review found one acceptable study reporting on the use of an adjustable continence mechanism for the treatment of SUI in patients with NLUTD. Ammirati et al.<sup>337</sup> reported successful outcomes in all 16 patients (13 male; 3 female) with NLUTD (mostly lower-level SCI, cauda equina, and myelomeningocele). While outcomes were reported at 48 months, weaknesses with this study (i.e., small sample size, retrospective design, no pre-defined outcome measures) limit its applicability for wide-spread use. While no peri-operative complications were reported, the authors reported five out of the 13 devices required explantation due to malfunction, erosion, or infection.

An earlier study by Mehnert also reported continence improvements though adverse events including erosion, migration, infection, bladder stone formation, and difficulty performing CIC were reported. This study's applicability is also limited due to small sample size and its retrospective design. While positive outcomes might support its use, SUI in NLUTD should not be treated the same as non-NLUTD. The adjustable continence mechanism should undergo more rigid clinical research to better understand its efficacy and risks in the NLUTD population, especially in those patients that manage their bladder with CIC.

The use of SNM is not recommended for the treatment of NLUTD in patients with SCI and SB as mentioned earlier (Statement 50). However, SNM implantation in the early phases of NLUTD due to SCI is thought to have an impact on the evolution of bladder dysfunction

by altering neural reflexes or impacting neuroplasticity of relevant neuropathways. Sievert et al. reported that early SNM in ten acutely injured SCI patients prevented detrusor overactivity and incontinence, ensured normal bladder capacity while also improving bowel and erectile function.<sup>338</sup> While promising, the use of neuromodulation as a mean to modify the progression of early NLUTD remains investigational.<sup>339</sup>

The Xiao procedure is based on the rerouting of nerves to establish a somatic to autonomic reflex arc with the aim of restoring volitional bladder and bowel control in patients with NLUTD due to SCI or SB. In the initial study, Xiao reported 67% achieved satisfactory emptying and low PVR, reduction in UTIs, and resolution of overflow UI. However, the procedure has not achieved widespread acceptance and follow-up to the Xiao study has been limited and inconsistent.<sup>340</sup>

Peters et al. performed a pilot study in the US; however, the results were not as successful, all patients developed at least transient leg weakness and most were still incontinent.<sup>341</sup> Tuite et al. performed a randomized, prospective, double-blind controlled trial in patients with SB who were undergoing untethering surgery. Ten patients were randomized to untethering alone and ten underwent untethering and the Xiao procedure. No difference in ability to control urination, achieve continence, or demonstrate urodynamic bladder contraction in response to cutaneous stimulation was seen. The lack of reproducibility, in conjunction with the possible risks and morbidities reported with this surgery, warrants that the Xiao procedure only be considered in investigational settings with appropriate patient counseling.<sup>342</sup>

The use of tissue engineering offers an innovative approach for bladder reconstruction or replacement. Techniques including seeding, scaffolding, use of different cell types, and regenerative factors are continuously expanding. While attractive as a modality, the use of tissue engineering in patients with NLUTD remains in its infancy and should be limited to investigational activities.

The Brindley sacral anterior root stimulator (SARS) neurostimulator was first described in 1982 with outcomes reported in 1984 and FDA approval obtained, through a Humanitarian Device Exemption, in 1998. The procedure involves implanting the neurostimulator device which consists of electrodes placed on the bilateral S2-S4 nerves which are connected to an internal receiver stimulator placed subcutaneously in the abdo-

men. The surgery is typically done in conjunction with a posterior sacral rhizotomy from S2 to S5.<sup>343</sup> Cardozo et al. reported early results in 13 patients who received the surgery, and all demonstrated ability to void volitionally, low PVRs, and acceptable bladder capacities. Results from 21 patients at one year included 85.7% able to void more than 200 mL, 71.4% with low PVR (< 50 ml), reductions in UTIs and CIC frequency, less AD, decreased need for medical therapy, and improved bowel management.<sup>344</sup>

More recently, Castano-Botero et al. reported on outcomes of SARS using their modified Barcelona extradural surgical technique.<sup>345</sup> All 104 patients (n=95 men) had SCI characterized as: 32.7% cervical, 65.4% thoracic, 1.9% lumbar. After SARS implant, improvements from baseline were seen in number of patients with incontinence (100% to 14%;  $p<0.001$ ), incidence of UTI (91% to 15%;  $p<0.001$ ) and number of patients with dysreflexia (66.3% to 5.8%;  $p<0.001$ ). After SARS implant, 94% obtained a bladder capacity of greater than 400 mL and 91% achieved effective voluntary voiding with a PVR less than 50 mL. AEs included implant infection in 1.9%, extrusion of electrode in 1.9% and extrusion of receiver block in 1.9%.

While SARS offers promising outcomes, the surgery requires an irreversible sacral rhizotomy which is often associated with increased morbidity and can lead to loss of certain functions in patients with incomplete injuries. Furthermore, the surgery is difficult to apply in clinical practice given its inherent complexities and it is not commonly performed. The implantation of sacral anterior root neurostimulators such as those employing the Brindley or the modified Barcelona techniques should be limited to investigational settings or specialty centers familiar with the surgery and use of the device.

#### Follow-up and post treatment

**STATEMENT FIFTY-SIX: In NLUTD patients with impaired storage parameters and/or voiding that place their upper tracts at risk, clinicians should repeat urodynamic studies at an appropriate interval following treatment. (Expert Opinion)**

Subgroups of patients with neurological disorders affecting bladder function are clearly at risk for upper tract damage, particularly if elevated bladder storage pressures remain untreated. Any patient with impaired compliance is likely at risk. From the perspective of etiology, patients with cervical and high thoracic SCI and SB may be at greatest risk for elevated storage pres-



tures though other conditions such as transverse myelitis, Guillain Barre, and cerebral palsy have been noted to have serious deleterious effects as well in some instances.<sup>61, 68, 70, 72</sup> Efforts aimed at reducing intravesical pressures should be assessed for their effectiveness, which is most readily done by repeat multichannel UDS.<sup>74</sup> Treatments may include increasing the frequency of catheterization in those on CIC, oral therapy, onabotulinumtoxinA injections, or AC. In select populations, each of these interventions has been found to be clinically successful.<sup>156, 166, 246, 346, 347</sup> Successful interventions (including onabotulinumtoxinA injections and AC) have been shown to effectively improve bladder compliance and reduce the severity of DO. Upper tract imaging has documented improvement in upper tract drainage in those appropriately treated,<sup>55, 348</sup> though it is clear that risk of renal damage, particularly following SCI, is lifelong and ongoing surveillance is required.<sup>72</sup> While the interval for urodynamic assessment remains an area of controversy and is poorly studied, an interval of two years or less in those at risk is reasonable once pressures have been normalized; however, decreased frequency of testing is possible if the patient remains clinically stable. Specific recommendations depend on the particular neurological condition and degree of risk based on the patient's baseline (and subsequent) findings.<sup>70, 128, 349, 350</sup> Providers following NLUTD patients with impaired storage pressures must be aware of concerning urodynamic findings and other high-risk parameters (i.e., neurologic etiology, hydronephrosis, loss of renal function) and urodynamically re-evaluate the patient at appropriate intervals. To optimally appreciate what volumes the bladder should be filled to during UDS, it is helpful to have patients complete a voiding/catheterization diary prior to the study.

**STATEMENT FIFTY-SEVEN: In NLUTD patients with impaired storage parameters that place their upper tracts at risk and are refractory to therapy, clinicians should offer additional treatment. (Expert Opinion)**

The goal of therapy directed at elevated storage pressures is to improve upper tract drainage which should serve several goals, the most important of which are to preserve renal function and reduce the risk of recurrent symptomatic UTIs. When that is not accomplished by initial efforts, additional interventions should be offered. Stepwise therapy based on invasiveness is reasonable, as long as repeated UDS are conducted to assess effectiveness at appropriate intervals. For example, if a pa-

tient with elevated intravesical pressures (i.e., poor compliance or severe DO) is instructed to perform CIC at 4 hours, but continues to have incontinence or repeated infections, then additional treatments should not be delayed as upper tract abnormalities in untreated patients at elevated risk are not uncommon.<sup>71</sup> Similarly, if patients remain symptomatic or UDS documents persistently elevated storage pressures, despite anticholinergic or beta agonist therapy, then consideration should be given for more advanced therapies such as onabotulinumtoxinA injections or AC since sustained long-term improvements in incontinence, QoL, and upper tract drainage have been noted with both of these therapies.<sup>239, 315, 346, 351</sup> For patients refractory to all therapies, constant urinary drainage (SPC or suprapubic urinary diversion) should be strongly considered.<sup>90, 224, 325, 327</sup>

**STATEMENT FIFTY-EIGHT: In NLUTD patients who have undergone lower urinary tract reconstruction incorporating a bowel segment(s), the clinician should assess the patient annually with:**

- a. focused history, physical exam, and symptom assessment.
- b. basic metabolic panel.
- c. urinary tract imaging.

**(Expert Opinion)**

As with any patient undergoing lower urinary tract reconstruction, those with NLUTD require lifelong surveillance as complications are not uncommon.<sup>352</sup> Many of these patients may have some degree of pre-existing renal dysfunction or have a prior history of recurrent UTIs. Patients who previously underwent bladder augmentation using bowel, or those with history of either continent or incontinent diversion, may be at risk for metabolic disturbances depending on the degree of pre-existing renal dysfunction, the presence of comorbidities, the length and type of bowel segment utilized, and the type of diversion created (those with continent diversions at higher risk).<sup>346, 353</sup> As such, at a minimum, the Panel recommends lifelong surveillance with history/physical examination and an assessment of any symptoms potentially related to the urinary tract reconstruction (i.e., incontinence, infections, hematuria). A basic metabolic panel to assess for electrolyte or acid-base abnormalities is similarly recommended to diagnose and help direct treatment for asymptomatic metabolic disturbances. If terminal ileum is used as part of the reconstruction, B12 levels should be monitored over time and supplemented if appropriate. Last-

ly, repeated upper urinary tract assessment is recommended to assess for any signs of upper urinary tract obstruction, which could be related to the reconstruction.<sup>354</sup> Early diagnosis of these abnormalities can lead to prompt, directed intervention and avoidance of additional morbidity. It should be noted that patients that only underwent construction of a continent urinary stoma, without AC, would not be at risk for electrolyte or acid-base abnormalities that can be seen after augmentation. Thus, yearly evaluation without a basic metabolic panel would be sufficient.

**STATEMENT FIFTY-NINE: Clinicians may perform urodynamics following sphincterotomy to assess outcome. (Conditional Recommendation; Evidence Level: Grade C)**

*The evidence base is comprised of two observational studies (Takahashi 2018, Pan 2009) reporting on long-term urodynamic findings following sphincterotomy. The aggregate risk of bias was very serious, but evidence was not further downgraded.*

Sphincterotomy has been found to be an effective treatment for patients with DSD and elevated storage pressures, particularly in the setting of SCI.<sup>269</sup> In particular, sphincterotomy has been shown to lower the risk of renal damage<sup>355</sup> and recurrent bladder infections, presumably by decreasing DLPP. To assess the efficacy of sphincterotomy and document the reduction in intravesical storage pressures, multichannel UDS is recommended in the postoperative period.<sup>356</sup> Since the long-term data for sphincterotomy indicates that impaired bladder emptying and elevated intravesical pressures can recur following treatment, sometimes insidiously, ongoing monitoring of both upper and lower urinary tract emptying and bladder storage pressures is appropriate.

**STATEMENT SIXTY: In NLUTD patients who have undergone lower urinary tract reconstruction utilizing bowel, and who also develop gross hematuria or symptomatic recurrent urinary tract infection, clinicians should perform cystoscopy. (Moderate Recommendation; Evidence Level: Grade C)**

*The statement is informed by two observational studies (Hamid 2009, Higuchi 2010) carrying a very serious risk of bias. Evidence was not further downgraded for any domain.*

The role of routine surveillance cystoscopy in the asymptomatic, stable NLUTD patient is not supported

by current literature (see Statement 19).<sup>79, 129</sup> However, the role of endoscopic evaluation in NLUTD patients who have undergone lower urinary tract reconstruction utilizing a bowel segment, such as AC, remains very controversial. Hamid et al. performed a prospective analysis of 92 consecutive NLUTD patients who had undergone routine scheduled cystoscopy 10 years after AC. After a median follow up of 15 years (10-33 years), bladder cancer was not identified in a single asymptomatic patient.<sup>56</sup> It is now being recognized that lower urinary tract malignancy in NLUTD patients with lower urinary tract reconstruction utilizing bowel almost always present with signs and symptoms such as gross hematuria, unexplained recurrent UTI or suprapubic pain. In NLUTD patients who present with these signs and/or symptoms, a full evaluation including cystoscopy, urine cytology, and computerized tomography scan of the abdomen and pelvis is warranted. The clinician should not assume that recurrent unexplained UTI or gross hematuria is related to traumatic CIC, cystitis, or pouchitis, until proven otherwise.

The actual risk of lower urinary tract malignancy in NLUTD patients who have undergone AC is not well defined. Several studies have suggested that the risk of lower urinary tract malignancy in the NLUTD patient who have undergone lower urinary tract reconstruction using bowel segment is higher than the general population although the level of evidence for this conclusion was noted to be poor in a recent review<sup>357</sup> and the results should be interpreted with caution by the clinician. The follow-up probability to develop a malignant tumor (s) after AC ranged from 0-5.5% and estimated incidence ranged from 0 to 272.3 per 100,000 patients/year. Adenocarcinoma was the most common histological type (51.6%). Malignant lesions predominantly occurred at the entero-urinary anastomosis (50%). The mean latency period was 19 years and most malignant lesions were diagnosed more than 10 years after surgery (90%).<sup>357</sup>

Non-invasive techniques such as urine cytology and urinary tumor markers have been proposed: however, these studies need further evaluation as it is not clear how they apply to NLUTD patients after lower urinary tract reconstruction.<sup>358</sup> It is important to note that malignant tumors were often diagnosed at an advanced stage within surveillance protocols time intervals.<sup>358</sup> Studies regarding carcinogenesis and surveillance strategies should be considered to develop a more efficient follow-up protocol and allow early diagnosis.<sup>68</sup>

## Future Directions

### Assessment of Bladder Dysfunction: Condition-Specific Questionnaires

Numerous lower urinary tract questionnaires exist for men and women with a variety of conditions. While there certainly is overlap in the urinary symptoms experienced by patients with and without underlying neurological conditions, it is clear that the severity of urinary symptoms may differ considerably.<sup>359</sup> For this reason, and because it is also clear that sensation may differ considerably in patients with neurological conditions from those patients that are neurologically intact, it is desirable to assess symptoms in a consistent manner in patients with NLUTD. When possible, the panel advocates use of condition-specific lower urinary tract questionnaires and recommends development and refinement of additional questionnaires to better assess urinary tract dysfunction in patients with NLUTD.<sup>360</sup>

### Improving Current Strategies/Implementing current strategies for new indications

The use of botulinum toxin in patients with neurogenic detrusor overactivity represents a tremendous advancement in the care of many patients with NLUTD. Quality of life has been substantially improved in many patients who otherwise might have been subjected to invasive, morbid and irreversible procedures. While these invasive procedures remain effective and are at times still necessary, they are often associated with both operative risk and postoperative complications. However, the need for repeat injections, the discomfort experienced by some, and the expense pose obstacles for some patients and providers to obtain treatment with intravesical injection of botulinum toxin on a regular basis. The Panel supports the ongoing investigation of alternate injection strategies, as well as the development of different delivery techniques for botulinum toxin so that this agent can be offered more widely.<sup>361</sup>

Neuromodulation strategies have similarly been extremely effective at ameliorating LUTS/OAB in patients ineffectively treated by other interventions. The use of either peripheral or central neuromodulation in patients with NLUTD has not been widely studied, though small, typically single center cohort observational trials have offered some hope for efficacy in certain NLUTD populations. Further study may allow for a better understanding of which type of stimulation may be more beneficial for specific patient types with NLUTD. With the expected influx of several implantable tibial nerve stimu-

lation devices, it would be reasonable to expect this technology to be evaluated in patients with NLUTD. In addition, it remains possible that various forms of neuromodulation, both invasive and non-invasive, may show promise after SCI.<sup>362</sup> This includes therapy as an option to treat symptoms<sup>363, 364</sup> or, with early intervention<sup>338, 365</sup> as a disease modifying strategy to possibly minimize the progression and severity of NLUTD symptoms over time that can be seen after SCI. The Panel recommends further studies of these techniques, particularly as the latest technology for sacral neuromodulation is MRI-conditional and allows for full body imaging using conventionally available magnets. Other routes of stimulation, such as SARS and the Xiao procedure, remain options as well.<sup>342, 366</sup> However, they each have potential issues impacting widespread acceptance. As discussed in Statement 52, there are technical challenges with SARS as well as the risk of loss of certain functions (with concomitant sacral rhizotomy) and the outcomes with Xiao procedure have not been found to be consistently positive. With further study and technology, the Panel is hopeful that these procedures could be more viable treatment options for patients with NLUTD.

Finally, the concept of implanted urethral catheters with valves to promote “natural voiding” (and eliminate or minimize the need for CIC) continues to be studied. There is presently a device that has an FDA indication to treat detrusor underactivity in women using an intraurethral valve pump.<sup>367</sup> This device does not have a specific indication for NLUTD. There is also a device being evaluated in male patients with chronic urinary retention.<sup>368</sup> The Panel is hopeful that with further research and advancement of technology, devices that would allow for improved bladder emptying for both men and women with NLUTD (and which also minimizes possible issues such as device migration, infection, encrustation, discomfort and pump clogging) will be a treatment option in the future.

### Novel Strategies for Urinary Diversion and Augmentation

Various forms of intestinal urinary diversion are not uncommonly required for patients with NLUTD (as well as for patients requiring bladder removal for malignant neoplasms). While bowel is nearly always readily available and quite versatile, its use can be associated with significant metabolic and enteric complications. Prior attempts at bladder replacement have focused on synthetic or bioengineered material; however, to this date

none have been particularly successful. A variety of naturally derived, synthetic and bioengineered scaffolds have been developed over the years with the goal being the construction and promotion of an optimal environment for natural cellular ingrowth. While initial clinical reports for utilizing scaffolds were favorable, more recent clinical updates indicate that utilizing autologous smooth muscle cells and urothelial cells seeded onto a biodegradable composite scaffold at the time of bladder augmentation did not lead to improvement in bladder storage pressures and was associated with significant postoperative morbidity.<sup>369</sup> Clearly, further investigation of this potential alternative to bowel for patients requiring lower urinary tract reconstruction is desired.

Recent reports have noted the feasibility of bladder allograft transplantation with vascular anastomoses, at least in cadaveric models.<sup>370</sup> This represents an exciting possibility and we await further assessment of such a concept to determine if this technically challenging procedure can result in a functional and safe lower urinary tract and, if so, whether it represents a viable option for patients with NLUTD.

Overall, the Panel encourages exploration of novel approaches to surgical urinary diversion and reconstruction including the exploration of non-intestinal concepts, and further development and refinement of tissue-engineered scaffolds to promote endogenous bladder restoration.<sup>371</sup>

### **Treatment of the Neurologic Condition**

Treatment of the neurologic condition leading to NLUTD is an attractive option – not only could this improve or minimize the bothersome symptoms related to NLUTD but it theoretically could also impact the other, non-urinary symptoms seen in these patients as well. One potential option would be the use of stem cells which has largely been evaluated in patients with acute SCI. Preclinical data has been promising and a review of clinical trials identified ten studies (5 completed, 5 ongoing) that evaluated outcomes in human subjects. Initial data appear to show increased MCC, improved bladder compliance and decreased detrusor pressures; however, urinary incontinence was not improved nor was the need for CIC eliminated.<sup>372</sup>

Further, high-quality studies are needed to understand if this will be a viable option for future patients with NLUTD secondary to SCI. Additional consideration in regard to stem cell therapy include the treatment of underactive bladder and SUI. Human trials have evalu-

ated the use of stem cells to treat SUI; however, there are still questions to be answered (efficacy, optimal stem cell type, stem cell dose, location of implantation, etc.) before this is a viable therapy.<sup>373</sup> In addition, if this does become a viable therapy it is not clear if this therapy would be applicable to NLUTD patients that require CIC. High quality trials evaluating the use of stem cells for underactive bladder have yet to be completed and this has not been specifically evaluated in the NLUTD patient population; however, this is another potential therapy that could improve bladder emptying in those with underactive bladder that require CIC or an indwelling catheter.<sup>374</sup>

An example of one therapy presently used is deep brain stimulation which is used to treat motor symptoms in patients with PD and other neurological disorders. A systematic review of the effects of DBS on lower urinary tract function found that stimulation of the subthalamic nucleus led to a significant increase in maximum bladder capacity. Other urodynamic parameter changes were not clinically relevant and the authors concluded that deep brain stimulation may have a beneficial effects on lower urinary tract function.<sup>375</sup> An additional therapy to potentially treat PD is stem cells. While this is a potentially promising concept, it is unclear if this would be a realistic therapy and trials would clearly be required to evaluate this option.<sup>376</sup>

The Panel is hopeful that improving therapies to treat the various neurologic conditions that often result in NLUTD will also lead to either an improvement or resolution in the various urinary symptoms associated with that condition.

<b>Abbreviations</b>	
AC	Augmentation cystoplasty
AD	Autonomic dysreflexia
AE	Adverse events
AUAER	American Urological Association
BN	Bladder neck
BNC	Bladder neck closure
BOO	Bladder outlet obstruction
BPH	Benign prostatic hyperplasia
CAUTI	Catheter-associated urinary tract infection
CCC	Continent catheterizable channels
CIC	Clean intermittent catheterization
CVA	Cerebrovascular accident
DLPP	Detrusor leak point pressures
DO	Detrusor overactivity
DU	Detrusor underactivity
EMG	Electromyographic
GU	Genitourinary
HTLV-1	Human T-Lymphotropic Virus 1
IDSA	The Infectious Disease Society of America
IIQ	Incontinence impact questionnaire
KUB	Kidney, ureter, and bladder X-ray
LUTS	Lower urinary tract symptoms
MCC	Maximum cystometric capacity
MDP	Maximum detrusor pressure
MS	Multiple sclerosis
MUP	Maximum urethral pressure
NDO	Neurogenic detrusor overactivity
NLUTD	Neurogenic lower urinary tract dysfunction
OAB	Overactive bladder
PD	Parkinson's disease
PGC	Practice Guidelines Committee
PICO	Populations, Interventions, Comparisons, Outcomes
PTNS	Posterior tibial nerve stimulation
PVR	Post void residual

<b>Abbreviations</b>	
QoL	Quality of life
SB	Spina bifida
SCI	Spinal cord injury
SNM	Sacral nerve modulation therapy
SPC	Suprapubic catheterization
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
SUI	Stress urinary incontinence
SVP	Systematic voiding program
UA	Urinalysis
UDS	Urodynamics
US	Ultrasound
UI	Urinary incontinence
UUI	Urgency incontinence
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

**References**

1. Daneshgari F, Liu G, Birder L et al: Diabetic bladder dysfunction: Current translational knowledge. *J Urol* 2009; **182**: S18.
2. Roger VL, Go AS, Lloyd-Jones DM et al: Heart disease and stroke statistics--2011 update: A report from the American Heart Association. *Circulation* 2011; **123**: e18.
3. Kolominsky-Rabas PL, Hilz MJ, Neundoerfer B et al: Impact of urinary incontinence after stroke: Results from a prospective population-based stroke register. *Neurourol Urodyn* 2003; **22**: 322.
4. Williams MP, Srikanth V, Bird M et al: Urinary symptoms and natural history of urinary continence after first-ever stroke--a longitudinal population-based study. *Age Ageing* 2012; **41**: 371.
5. Brocklehurst JC, Andrews K, Richards B et al: Incidence and correlates of incontinence in stroke patients. *J Am Geriatr Soc* 1985; **33**: 540.
6. Brittain KR, Perry SI, Peet SM et al: Prevalence and impact of urinary symptoms among community-dwelling stroke survivors. *Stroke* 2000; **31**: 886.
7. Borrie MJ, Campbell AJ, Caradoc-Davies TH et al: Urinary incontinence after stroke: A prospective study. *Age Ageing* 1986; **15**: 177.
8. Wallin MT, Culpepper WJ, Campbell JD et al: The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology* 2019; **92**: e1029.
9. Nazari F, Shaygannejad V, Mohammadi Sichani M et al: The prevalence of lower urinary tract symptoms based on individual and clinical parameters in patients with multiple sclerosis. *BMC Neurol* 2020; **20**: 24.
10. Mahajan ST, Patel PB and Marrie RA: Under treatment of overactive bladder symptoms in patients with multiple sclerosis: An ancillary analysis of the narcoms patient registry. *J Urol* 2010; **183**: 1432.
11. Center NSCIS: <https://www.Nscisc.Uab.Edu/public/facts%20and%20figures%20-%202018.Pdf>, 2018.
12. Cameron AP, Wallner LP, Tate DG et al: Bladder management after spinal cord injury in the United States 1972 to 2005. *J Urol* 2010; **184**: 213.
13. Control CfD: <https://www.Cdc.Gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.Pdf>. 2018;
14. Daneshgari F and Moore C: Diabetic uropathy. *Semin Nephrol* 2006; **26**: 182.
15. Lo C, Tran Y, Anderson K et al: Functional priorities in persons with spinal cord injury: Using discrete choice experiments to determine preferences. *J Neurotrauma* 2016; **33**: 1958.
16. Hackler RH: A 25-year prospective mortality study in the spinal cord injured patient: Comparison with the long-term living paraplegic. *J Urol* 1977; **117**: 486.
17. Shea BJ, Grimshaw JM, Wells GA et al: Development of amstar: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; **7**: 10.
18. Higgins JP, Altman DG, Gotzsche PC et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
19. Sterne JA, Hernan MA, Reeves BC et al: Robins-i: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
20. Guyatt G, Oxman AD, Akl EA et al: Grade guidelines: 1. Introduction-grade evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383.
21. Balshem H, Helfand M, Schunemann HJ et al: Grade guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64**: 401.
22. Gajewski JB, Schurch B, Hamid R et al: An international continence society (ICS) report on the terminology for adult neurogenic lower urinary tract dysfunction (anludt). *Neurourol Urodyn* 2018; **37**: 1152.
23. Winters JC, Dmochowski RR, Goldman HB et al: Urodynamic studies in adults: AUA/SUFU guideline. *J Urol* 2012; **188**: 2464.
24. Kobashi KC, Albo ME, Dmochowski RR et al: Surgical treatment of female stress urinary

- incontinence: Aua/sufu guideline. J Urol 2017; **198**: 875.
25. Stoffel JT, Peterson AC, Sandhu JS et al: Aua white paper on nonneurogenic chronic urinary retention: Consensus definition, treatment algorithm, and outcome end points. J Urol 2017; **198**: 153.
  26. Lightner DJ, Gomelsky A, Souter L et al: Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: Aua/sufu guideline amendment 2019. J Urol 2019; **202**: 558.
  27. Cameron AP, Wiseman JB, Smith AR et al: Are three-day voiding diaries feasible and reliable? Results from the symptoms of lower urinary tract dysfunction research network (lurn) cohort. Neurourol Urodyn 2019; **38**: 2185.
  28. Stav K, Dwyer PL and Rosamilia A: Women overestimate daytime urinary frequency: The importance of the bladder diary. J Urol 2009; **181**: 2176.
  29. Konstantinidis C, Kratiras Z, Samarinas M et al: Optimal bladder diary duration for patients with suprapontine neurogenic lower urinary tract dysfunction. Int Braz J Urol 2016; **42**: 766.
  30. Groutz A, Blaivas JG, Chaikin DC et al: Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: A multicenter study of micturition diary and pad tests. J Urol 2000; **164**: 698.
  31. Incontinence ICo: Incontinence 2017.
  32. Gajewski JB and Drake MJ: Neurological lower urinary tract dysfunction essential terminology. Neurourol Urodyn 2018; **37**: S25.
  33. Sakakibara R, Panicker J, Finazzi-Agro E et al: A guideline for the management of bladder dysfunction in parkinson's disease and other gait disorders. Neurourol Urodyn 2016; **35**: 551.
  34. Pizzi A, Falsini C, Martini M et al: Urinary incontinence after ischemic stroke: Clinical and urodynamic studies. Neurourol Urodyn 2014; **33**: 420.
  35. Lee SH, Cho ST, Na HR et al: Urinary incontinence in patients with alzheimer's disease: Relationship between symptom status and urodynamic diagnoses. Int J Urol 2014; **21**: 683.
  36. Campos-Juanatey F, Gutierrez-Banos JL, Portillo -Martin JA et al: Assessment of the urodynamic diagnosis in patients with urinary incontinence associated with normal pressure hydrocephalus. Neurourol Urodyn 2015; **34**: 465.
  37. Nitti VW, Adler H and Combs AJ: The role of urodynamics in the evaluation of voiding dysfunction in men after cerebrovascular accident. J Urol 1996; **155**: 263.
  38. Weld KJ and Dmochowski RR: Association of level of injury and bladder behavior in patients with post-traumatic spinal cord injury. Urology 2000; **55**: 490.
  39. Satar N, Bauer SB, Shefner J et al: The effects of delayed diagnosis and treatment in patients with an occult spinal dysraphism. J Urol 1995; **154**: 754.
  40. McGuire EJ, Woodside JR, Borden TA et al: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981; **126**: 205.
  41. Ozkan B, Demirkesen O, Durak H et al: Which factors predict upper urinary tract deterioration in overactive neurogenic bladder dysfunction? Urology 2005; **66**: 99.
  42. Kim YH, Kattan MW and Boone TB: Bladder leak point pressure: The measure for sphincterotomy success in spinal cord injured patients with external detrusor-sphincter dyssynergia. J Urol 1998; **159**: 493.
  43. Elmelund M, Klarskov N, Bagi P et al: Renal deterioration after spinal cord injury is associated with length of detrusor contractions during cystometry-a study with a median of 41 years follow-up. Neurourol Urodyn 2017; **36**: 1607.
  44. Weld KJ, Graney MJ and Dmochowski RR: Differences in bladder compliance with time and associations of bladder management with compliance in spinal cord injured patients. J Urol 2000; **163**: 1228.
  45. Khanna R, Sandhu AS and Doddamani D: Urodynamic management of neurogenic bladder in spinal cord injury. Med J Armed Forces India 2009; **65**: 300.
  46. Ditunno JF, Little JW, Tessler A et al: Spinal shock revisited: A four-phase model. Spinal Cord 2004; **42**: 383.



47. Shergill IS, Arya M, Hamid R et al: The importance of autonomic dysreflexia to the urologist. *BJU Int* 2004; **93**: 923.
48. Walter M, Knüpfer SC, Cragg JJ et al: Prediction of autonomic dysreflexia during urodynamics: A prospective cohort study. *BMC Med* 2018; **16**: 53.
49. Wan D and Krassioukov AV: Life-threatening outcomes associated with autonomic dysreflexia: A clinical review. *J Spinal Cord Med* 2014; **37**: 2.
50. McGillivray CF, Hitzig SL, Craven BC et al: Evaluating knowledge of autonomic dysreflexia among individuals with spinal cord injury and their families. *J Spinal Cord Med* 2009; **32**: 54.
51. Liu N, Hu ZW, Zhou MW et al: The practice of spinal cord injury core data collection among chinese physicians: A survey-based study. *Spinal Cord* 2015; **53**: 658.
52. Wyndaele JJ: Developing a spinal cord injury research strategy. *Spinal Cord* 2015; **53**: 713.
53. Medicine CfSC: Acute management of autonomic dysreflexia: Individuals with spinal cord injury presenting to health-care facilities. *J Spinal Cord Med* 2002; **25 Suppl 1**: S67.
54. Lee BY, Karmakar MG, Herz BL et al: Autonomic dysreflexia revisited. *J Spinal Cord Med* 1995; **18**: 75.
55. Edokpolo LU and Foster HE, Jr.: Renal tract ultrasonography for routine surveillance in spinal cord injury patients. *Top Spinal Cord Inj Rehabil* 2013; **19**: 54.
56. Hamid R, Greenwell TJ, Nethercliffe JM et al: Routine surveillance cystoscopy for patients with augmentation and substitution cystoplasty for benign urological conditions: Is it necessary? *BJU Int* 2009; **104**: 392.
57. Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: Aua/sufu guideline. *J Urol* 2020; **204**: 778.
58. Ismail S, Karsenty G, Chartier-Kastler E et al: Prevalence, management, and prognosis of bladder cancer in patients with neurogenic bladder: A systematic review. *Neurourol Urodyn* 2018; **37**: 1386.
59. Vaidyanathan S, Hughes PL and Soni BM: A comparative study of ultrasound examination of urinary tract performed on spinal cord injury patients with no urinary symptoms and spinal cord injury patients with symptoms related to urinary tract: Do findings of ultrasound examination lead to changes in clinical management? *ScientificWorldJournal* 2006; **6**: 2450.
60. Kim KJ, Jeong SJ and Kim J-M: Neurogenic bladder in progressive supranuclear palsy: A comparison with parkinson's disease and multiple system atrophy. *Neurourology and Urodynamics* 2018; **37**: 1724.
61. Cameron AP, Rodriguez GM and Schomer KG: Systematic review of urological followup after spinal cord injury. *J Urol* 2012; **187**: 391.
62. Ozpolat B and Lopez-Berestein G: Liposomal-all-trans-retinoic acid in treatment of acute promyelocytic leukemia. *Leuk Lymphoma* 2002; **43**: 933.
63. Shlipak MG, Mattes MD and Peralta CA: Update on cystatin c: Incorporation into clinical practice. *Am J Kidney Dis* 2013; **62**: 595.
64. Chen Y, DeVivo MJ and Roseman JM: Current trend and risk factors for kidney stones in persons with spinal cord injury: A longitudinal study. *Spinal Cord* 2000; **38**: 346.
65. Chen Y, DeVivo MJ, Stover SL et al: Recurrent kidney stone: A 25-year follow-up study in persons with spinal cord injury. *Urology* 2002; **60**: 228.
66. Donnellan SM and Bolton DM: The impact of contemporary bladder management techniques on struvite calculi associated with spinal cord injury. *BJU Int* 1999; **84**: 280.
67. Bartel P, Krebs J, Wöllner J et al: Bladder stones in patients with spinal cord injury: A long-term study. *Spinal Cord* 2014; **52**: 295.
68. Cameron AP, Lai J, Saigal CS et al: Urological surveillance and medical complications after spinal cord injury in the united states. *Urology* 2015; **86**: 506.
69. Groen J, Pannek J, Castro Diaz D et al: Summary of european association of urology (eau) guidelines on neuro-urology. *Eur Urol* 2016; **69**: 324.

70. Averbeck MA and Madersbacher H: Follow-up of the neuro-urological patient: A systematic review. *BJU Int* 2015; **115 Suppl 6**: 39.
71. Guzelkucuk U, Demir Y, Kesikburun S et al: Ultrasound findings of the urinary tract in patients with spinal cord injury: A study of 1005 cases. *Spinal Cord* 2015; **53**: 139.
72. Elmelund M, Oturai PS, Toson B et al: Forty-five-year follow-up on the renal function after spinal cord injury. *Spinal Cord* 2016; **54**: 445.
73. National Clinical Guideline C: National institute for health and clinical excellence: Guidance. In: Urinary incontinence in neurological disease: Management of lower urinary tract dysfunction in neurological disease. London: Royal College of Physicians (UK) Copyright © 2012, National Clinical Guideline Centre., 2012.
74. Kavanagh A, Akhavizadegan H, Walter M et al: Surveillance urodynamics for neurogenic lower urinary tract dysfunction: A systematic review. *Can Urol Assoc J* 2019; **13**: 133.
75. Anger J, Lee U, Ackerman AL et al: Recurrent uncomplicated urinary tract infections in women: Aua/cua/sufu guideline. *J Urol* 2019; **202**: 282.
76. Wessells H, Angermeier KW, Elliott S et al: Male urethral stricture: American urological association guideline. *J Urol* 2017; **197**: 182.
77. Welk B, McIntyre A, Teasell R et al: Bladder cancer in individuals with spinal cord injuries. *Spinal Cord* 2013; **51**: 516.
78. El Masri WS, Patil S, Prasanna KV et al: To cystoscope or not to cystoscope patients with traumatic spinal cord injuries managed with indwelling urethral or suprapubic catheters? That is the question! *Spinal Cord* 2014; **52**: 49.
79. Hamid R, Bycroft J, Arya M et al: Screening cystoscopy and biopsy in patients with neuropathic bladder and chronic suprapubic indwelling catheters: Is it valid? *J Urol* 2003; **170**: 425.
80. Sammer U, Walter M, Knupfer SC et al: Do we need surveillance urethro-cystoscopy in patients with neurogenic lower urinary tract dysfunction? *PLoS One* 2015; **10**: e0140970.
81. Yang CC and Clowers DE: Screening cystoscopy in chronically catheterized spinal cord injury patients. *Spinal Cord* 1999; **37**: 204.
82. Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: Aua/suo guideline. *J Urol* 2016; **196**: 1021.
83. Katsumi HK, Kalisvaart JF, Ronningen LD et al: Urethral versus suprapubic catheter: Choosing the best bladder management for male spinal cord injury patients with indwelling catheters. *Spinal Cord* 2010; **48**: 325.
84. Larsen LD, Chamberlin DA, Khonsari F et al: Retrospective analysis of urologic complications in male patients with spinal cord injury managed with and without indwelling urinary catheters. *Urology* 1997; **50**: 418.
85. Cipa-Tatum J, Kelly-Signs M and Afsari K: Urethral erosion: A case for prevention. *J Wound Ostomy Continence Nurs* 2011; **38**: 581.
86. Reid S, Brocksom J, Hamid R et al: British association of urological surgeons (baus) and nurses (baun) consensus document: Management of the complications of long-term indwelling catheters. *BJU Int* 2021;
87. Meeks JJ, Erickson BA, Helfand BT et al: Reconstruction of urethral erosion in men with a neurogenic bladder. *BJU Int* 2009; **103**: 378.
88. Chancellor MB, Erhard MJ, Kiilholma PJ et al: Functional urethral closure with pubovaginal sling for destroyed female urethra after long-term urethral catheterization. *Urology* 1994; **43**: 499.
89. Stoffel JT and McGuire EJ: Outcome of urethral closure in patients with neurologic impairment and complete urethral destruction. *Neurourol Urodyn* 2006; **25**: 19.
90. Lavelle RS, Coskun B, Bacsu CD et al: Quality of life after suprapubic catheter placement in patients with neurogenic bladder conditions. *Neurourol Urodyn* 2016; **35**: 831.
91. Sheriff MK, Foley S, McFarlane J et al: Long-term suprapubic catheterisation: Clinical outcome and satisfaction survey. *Spinal Cord* 1998; **36**: 171.

92. Gao Y, Danforth T and Ginsberg DA: Urologic management and complications in spinal cord injury patients: A 40- to 50-year follow-up study. *Urology* 2017; **104**: 52.
93. Tornic J, Wollner J, Leitner L et al: The challenge of asymptomatic bacteriuria and symptomatic urinary tract infections in patients with neurogenic lower urinary tract dysfunction. *J Urol* 2020; **203**: 579.
94. Nicolle LE, Gupta K, Bradley SF et al: Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the infectious diseases society of america. *Clin Infect Dis* 2019; **68**: 1611.
95. Waites KB, Canupp KC, Roper JF et al: Evaluation of 3 methods of bladder irrigation to treat bacteriuria in persons with neurogenic bladder. *J Spinal Cord Med* 2006; **29**: 217.
96. Maynard FM and Diokno AC: Urinary infection and complications during clean intermittent catheterization following spinal cord injury. *J Urol* 1984; **132**: 943.
97. Lightner DJ, Wymer K, Sanchez J et al: Best practice statement on urologic procedures and antimicrobial prophylaxis. *J Urol* 2020; **203**: 351.
98. Cameron AP, Campeau L, Brucker BM et al: Best practice policy statement on urodynamic antibiotic prophylaxis in the non-index patient. *Neurourol Urodyn* 2017; **36**: 915.
99. Goetz LL, Cardenas DD, Kennelly M et al: International spinal cord injury urinary tract infection basic data set. *Spinal Cord* 2013; **51**: 700.
100. Medeiros Junior WLG, Demore CC, Mazaro LP et al: Urinary tract infection in patients with multiple sclerosis: An overview. *Mult Scler Relat Disord* 2020; **46**: 102462.
101. Linsenmeyer TA and Oakley A: Accuracy of individuals with spinal cord injury at predicting urinary tract infections based on their symptoms. *J Spinal Cord Med* 2003; **26**: 352.
102. Massa LM, Hoffman JM and Cardenas DD: Validity, accuracy, and predictive value of urinary tract infection signs and symptoms in individuals with spinal cord injury on intermittent catheterization. *Journal of spinal cord medicine* 2009; **32**: 568.
103. Alavinia SM, Omidvar M, Farahani F et al: Enhancing quality practice for prevention and diagnosis of urinary tract infection during inpatient spinal cord rehabilitation. *J Spinal Cord Med* 2017; **40**: 803.
104. Ronco E, Denys P, Bernede-Bauduin C et al: Diagnostic criteria of urinary tract infection in male patients with spinal cord injury. *Neurorehabil Neural Repair* 2011; **25**: 351.
105. Research NioDaR: The prevention and management of urinary tract infections among people with spinal cord injuries. National institute on disability and rehabilitation research consensus statement. January 27-29, 1992. *SCI Nurs* 1993; **10**: 49.
106. Hooton TM, Bradley SF, Cardenas DD et al: Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases society of america. *Clin Infect Dis* 2010; **50**: 625.
107. Togan T, Azap OK, Durukan E et al: The prevalence, etiologic agents and risk factors for urinary tract infection among spinal cord injury patients. *Jundishapur J Microbiol* 2014; **7**: e8905.
108. Lewis RI, Carrion HM, Lockhart JL et al: Significance of asymptomatic bacteriuria in neurogenic bladder disease. *Urology* 1984; **23**: 343.
109. Clark R and Welk B: The ability of prior urinary cultures results to predict future culture results in neurogenic bladder patients. *Neurourol Urodyn* 2018; **37**: 2645.
110. Vaidyanathan S, Singh G, Soni BM et al: Silent hydronephrosis/pyonephrosis due to upper urinary tract calculi in spinal cord injury patients. *Spinal Cord* 2000; **38**: 661.
111. Bergqvist D, Bronnestam R, Hedelin H et al: The relevance of urinary sampling methods in patients with indwelling foley catheters. *Br J Urol* 1980; **52**: 92.
112. Grahn D, Norman DC, White ML et al: Validity of urinary catheter specimen for diagnosis of urinary tract infection in the elderly. *Arch Intern Med* 1985; **145**: 1858.
113. Tenney JH and Warren JW: Bacteriuria in women with long-term catheters: Paired

- comparison of indwelling and replacement catheters. *J Infect Dis* 1988; **157**: 199.
114. Siroky MB: Pathogenesis of bacteriuria and infection in the spinal cord injured patient. *Am J Med* 2002; **113 Suppl 1A**: 67s.
115. Manack A, Motsko SP, Haag-Molkenteller C et al: Epidemiology and healthcare utilization of neurogenic bladder patients in a us claims database. *Neurourol Urodyn* 2011; **30**: 395.
116. Vigil HR and Hickling DR: Urinary tract infection in the neurogenic bladder. *Transl Androl Urol* 2016; **5**: 72.
117. Vasudeva P and Madersbacher H: Factors implicated in pathogenesis of urinary tract infections in neurogenic bladders: Some revered, few forgotten, others ignored. *Neurourol Urodyn* 2014; **33**: 95.
118. Lapidus J: Mechanisms of urinary tract infection. *Urology* 1979; **14**: 217.
119. Game X, Castel-Lacanal E, Bentaleb Y et al: Botulinum toxin a detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. *Eur Urol* 2008; **53**: 613.
120. Wefer B, Ehlken B, Bremer J et al: Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin a (botox) therapy in germany. *World J Urol* 2010; **28**: 385.
121. Andreoni C, Portis AJ and Clayman RV: Retrograde renal pelvic access sheath to facilitate flexible ureteroscopic lithotripsy for the treatment of urolithiasis in a horseshoe kidney. *J Urol* 2000; **164**: 1290.
122. Taylor TA and Waites KB: A quantitative study of genital skin flora in male spinal cord-injured outpatients. *Am J Phys Med Rehabil* 1993; **72**: 117.
123. Merritt JL: Residual urine volume: Correlate of urinary tract infection in patients with spinal cord injury. *Arch Phys Med Rehabil* 1981; **62**: 558.
124. Dromerick AW and Edwards DF: Relation of postvoid residual to urinary tract infection during stroke rehabilitation. *Arch Phys Med Rehabil* 2003; **84**: 1369.
125. Kim BR, Lim JH, Lee SA et al: The relation between postvoid residual and occurrence of urinary tract infection after stroke in rehabilitation unit. *Ann Rehabil Med* 2012; **36**: 248.
126. Morton SC, Shekelle PG, Adams JL et al: Antimicrobial prophylaxis for urinary tract infection in persons with spinal cord dysfunction. *Arch Phys Med Rehabil* 2002; **83**: 129.
127. Niël-Weise BS, van den Broek PJ, da Silva EM et al: Urinary catheter policies for long-term bladder drainage. *Cochrane Database Syst Rev* 2012: Cd004201.
128. Kavanagh A, Baverstock R, Campeau L et al: Canadian urological association guideline: Diagnosis, management, and surveillance of neurogenic lower urinary tract dysfunction. *Can Urol Assoc J* 2019; **13**: E157.
129. Kreydin E, Welk B, Chung D et al: Surveillance and management of urologic complications after spinal cord injury. *World J Urol* 2018; **36**: 1545.
130. Everaert K, Lumen N, Kerckhaert W et al: Urinary tract infections in spinal cord injury: Prevention and treatment guidelines. *Acta Clin Belg* 2009; **64**: 335.
131. Tradewell M, Pariser JJ, Nimeh T et al: Systematic review and practice policy statements on urinary tract infection prevention in adults with spina bifida. *Transl Androl Urol* 2018; **7**: S205.
132. Fisher H, Oluboyede Y, Chadwick T et al: Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (antic): A randomised, open-label trial. *Lancet Infect Dis* 2018; **18**: 957.
133. Lucio AC, Campos RM, Perissinotto MC et al: Pelvic floor muscle training in the treatment of lower urinary tract dysfunction in women with multiple sclerosis. *Neurourol Urodyn* 2010; **29**: 1410.
134. Lucio AC, Perissinotto MC, Natalin RA et al: A comparative study of pelvic floor muscle training in women with multiple sclerosis: Its impact on lower urinary tract symptoms and quality of life. *Clinics (Sao Paulo)* 2011; **66**: 1563.

135. McClurg D, Ashe RG and Lowe-Strong AS: Neuromuscular electrical stimulation and the treatment of lower urinary tract dysfunction in multiple sclerosis--a double blind, placebo controlled, randomised clinical trial. *Neurourol Urodyn* 2008; **27**: 231.
136. Shin DC, Shin SH, Lee MM et al: Pelvic floor muscle training for urinary incontinence in female stroke patients: A randomized, controlled and blinded trial. *Clin Rehabil* 2016; **30**: 259.
137. Tibaek S, Gard G, Dehlendorff C et al: Is pelvic floor muscle training effective for men with poststroke lower urinary tract symptoms? A single-blinded randomized, controlled trial. *Am J Mens Health* 2017; **11**: 1460.
138. Tibaek S, Jensen R, Lindskov G et al: Can quality of life be improved by pelvic floor muscle training in women with urinary incontinence after ischemic stroke? A randomised, controlled and blinded study. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15**: 117.
139. Tibaek S, Gard G and Jensen R: Pelvic floor muscle training is effective in women with urinary incontinence after stroke: A randomised, controlled and blinded study. *Neurourol Urodyn* 2005; **24**: 348.
140. Thomas LH, Watkins CL, Sutton CJ et al: Identifying continence options after stroke (icons): A cluster randomised controlled feasibility trial. *Trials* 2014; **15**: 509.
141. Khan F, Amatya B, Ng L et al: Rehabilitation outcomes in persons with spina bifida: A randomised controlled trial. *J Rehabil Med* 2015; **47**: 734.
142. Dumoulin C, Korner-Bitensky N and Tannenbaum C: Urinary incontinence after stroke: Does rehabilitation make a difference? A systematic review of the effectiveness of behavioral therapy. *Top Stroke Rehabil* 2005; **12**: 66.
143. Thomas LH, Cross S, Barrett J et al: Treatment of urinary incontinence after stroke in adults. *Cochrane Database Syst Rev* 2008: CD004462.
144. Block V, Rivera M, Melnick M et al: Do physical therapy interventions affect urinary incontinence and quality of life in people with multiple sclerosis?: An evidence-based review. *Int J MS Care* 2015; **17**: 172.
145. Taylor-Rowan M, Edwards S, Noel-Storr AH et al: Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome. *Cochrane Database Syst Rev* 2021; **5**: CD013540.
146. Dmochowski RR, Thai S, Iglay K et al: Increased risk of incident dementia following use of anticholinergic agents: A systematic literature review and meta-analysis. *Neurourol Urodyn* 2021; **40**: 28.
147. Madersbacher H, Murtz G and Stohrer M: Neurogenic detrusor overactivity in adults: A review on efficacy, tolerability and safety of oral antimuscarinics. *Spinal Cord* 2013; **51**: 432.
148. Madhuvrata P, Singh M, Hasafa Z et al: Anticholinergic drugs for adult neurogenic detrusor overactivity: A systematic review and meta-analysis. *Eur Urol* 2012; **62**: 816.
149. Stothers L, Tsang B, Nigro M et al: An integrative review of standardized clinical evaluation tool utilization in anticholinergic drug trials for neurogenic lower urinary tract dysfunction. *Spinal Cord* 2016; **54**: 1114.
150. Abrams P, Amarenco G, Bakke A et al: Tamsulosin: Efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. *J Urol* 2003; **170**: 1242.
151. Perkash I: Efficacy and safety of terazosin to improve voiding in spinal cord injury patients. *J Spinal Cord Med* 1995; **18**: 236.
152. Swierzewski SJ, 3rd, Gormley EA, Belville WD et al: The effect of terazosin on bladder function in the spinal cord injured patient. *J Urol* 1994; **151**: 951.
153. Stöhrer M, Bauer P, Giannetti BM et al: Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries. A multicentre placebo-controlled double-blind trial. *Urol Int* 1991; **47**: 138.
154. Krebs J and Pannek J: Effects of solifenacin in patients with neurogenic detrusor overactivity as a result of spinal cord lesion. *Spinal Cord* 2013; **51**: 306.

155. O'Leary M, Erickson JR, Smith CP et al: Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; **26**: 159.
156. Amend B, Hennenlotter J, Schafer T et al: Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. *Eur Urol* 2008; **53**: 1021.
157. Horstmann M, Schaefer T, Aguilar Y et al: Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. *Neurourol Urodyn* 2006; **25**: 441.
158. Hadji N, Previnaire JG, Benbouzid R et al: Are oxybutynin and trospium efficacious in the treatment of detrusor overactivity in spinal cord injury patients? *Spinal Cord* 2014; **52**: 701.
159. Kelleher C, Hakimi Z, Zur R et al: Efficacy and tolerability of mirabegron compared with antimuscarinic monotherapy or combination therapies for overactive bladder: A systematic review and network meta-analysis. *Eur Urol* 2018; **74**: 324.
160. Wollner J and Pannek J: Initial experience with the treatment of neurogenic detrusor overactivity with a new beta-3 agonist (mirabegron) in patients with spinal cord injury. *Spinal Cord* 2016; **54**: 78.
161. El Helou E, Labaki C, Chebel R et al: The use of mirabegron in neurogenic bladder: A systematic review. *World J Urol* 2020; **38**: 2435.
162. Gajewski JB and Awad SA: Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. *J Urol* 1986; **135**: 966.
163. van Rey F and Heesakkers J: Solifenacin in multiple sclerosis patients with overactive bladder: A prospective study. *Adv Urol* 2011; **2011**: 834753.
164. Zesiewicz TA, Evatt M, Vaughan CP et al: Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**: 514.
165. Gomes CM, Sammour ZM, Bessa Junior J et al: Neurological status predicts response to alpha-blockers in men with voiding dysfunction and parkinson's disease. *Clinics (Sao Paulo)* 2014; **69**: 817.
166. Amarenco G, Sutory M, Zachoal R et al: Solifenacin is effective and well tolerated in patients with neurogenic detrusor overactivity: Results from the double-blind, randomized, active- and placebo-controlled sonic urodynamic study. *Neurourol Urodyn* 2017; **36**: 414.
167. Ethans KD, Nance PW, Bard RJ et al: Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity. *J Spinal Cord Med* 2004; **27**: 214.
168. Watanabe M, Yamanishi T, Honda M et al: Efficacy of extended-release tolterodine for the treatment of neurogenic detrusor overactivity and/or low-compliance bladder. *Int J Urol* 2010; **17**: 931.
169. Vereecken RL, Van Poppel H, Boeckx G et al: Long-term alpha-adrenergic-blocking therapy in detrusor-urethra dyssynergia. *Eur Urol* 1983; **9**: 167.
170. Pannek J, Sommerfeld HJ, Bötzel U et al: Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. *Urology* 2000; **55**: 358.
171. George J, Tharion G, Richar J et al: The effectiveness of intravesical oxybutynin, propantheline, and capsaicin in the management of neuropathic bladder following spinal cord injury. *ScientificWorldJournal* 2007; **7**: 1683.
172. Schroder A, Albrecht U, Schnitker J et al: Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. *Neurourol Urodyn* 2016; **35**: 582.
173. Prasad KV and Vaidyanathan S: Intravesical oxybutynin chloride and clean intermittent catheterisation in patients with neurogenic vesical dysfunction and decreased bladder capacity. *Br J Urol* 1993; **72**: 719.
174. Moore KN, Fader M and Getliffe K: Long-term bladder management by intermittent catheterisation in adults and children. *Cochrane Database Syst Rev* 2007: CD006008.

175. Rognoni C and Tarricone R: Intermittent catheterisation with hydrophilic and non-hydrophilic urinary catheters: Systematic literature review and meta-analyses. *BMC Urol* 2017; **17**: 4.
176. Cardenas DD, Moore KN, Dannels-McClure A et al: Intermittent catheterization with a hydrophilic-coated catheter delays urinary tract infections in acute spinal cord injury: A prospective, randomized, multicenter trial. *PM R* 2011; **3**: 408.
177. Vapnek JM, Maynard FM and Kim J: A prospective randomized trial of the Iofric hydrophilic coated catheter versus conventional plastic catheter for clean intermittent catheterization. *J Urol* 2003; **169**: 994.
178. Afsar SI, Yemisci OU, Cosar SN et al: Compliance with clean intermittent catheterization in spinal cord injury patients: A long-term follow-up study. *Spinal Cord* 2013; **51**: 645.
179. Moore KN, Burt J and Voaklander DC: Intermittent catheterization in the rehabilitation setting: A comparison of clean and sterile technique. *Clin Rehabil* 2006; **20**: 461.
180. Polliack T, Bluvshstein V, Philo O et al: Clinical and economic consequences of volume- or time-dependent intermittent catheterization in patients with spinal cord lesions and neuropathic bladder. *Spinal Cord* 2005; **43**: 615.
181. Biering-Sorensen F, Hansen HV, Nielsen PN et al: Residual urine after intermittent catheterization in females using two different catheters. *Scand J Urol Nephrol* 2007; **41**: 341.
182. Costa JA, Menier M, Doran TJ et al: Catheter length preference in wheelchair-using men who perform routine clean intermittent catheterization. *Spinal Cord* 2013; **51**: 772.
183. Chartier-Kastler E, Lauge I, Ruffion A et al: Safety of a new compact catheter for men with neurogenic bladder dysfunction: A randomised, crossover and open-labelled study. *Spinal Cord* 2011; **49**: 844.
184. Giannantoni A, Stasi S, Scivoletto G et al: Intermittent catheterization with a prelubricated catheter in spinal cord injured patients: A prospective randomized crossover study. In: *Journal of urology*, vol. 166, pp. 130, 2001.
185. Turi MH, Hanif S, Fasih Q et al: Proportion of complications in patients practicing clean intermittent self-catheterization (cisc) vs indwelling catheter. *J Pak Med Assoc* 2006; **56**: 401.
186. Penders J, Huylenbroeck AA, Everaert K et al: Urinary infections in patients with spinal cord injury. *Spinal Cord* 2003; **41**: 549.
187. Ord J, Lunn D and Reynard J: Bladder management and risk of bladder stone formation in spinal cord injured patients. *J Urol* 2003; **170**: 1734.
188. Kovindha A, Mai WN and Madersbacher H: Reused silicone catheter for clean intermittent catheterization (cic): Is it safe for spinal cord-injured (sci) men? *Spinal Cord* 2004; **42**: 638.
189. Levendoglu F, Ugurlu H, Ozerbil OM et al: Urethral cultures in patients with spinal cord injury. *Spinal Cord* 2004; **42**: 106.
190. Ku JH, Jung TY, Lee JK et al: Influence of bladder management on epididymo-orchitis in patients with spinal cord injury: Clean intermittent catheterization is a risk factor for epididymo-orchitis. *Spinal Cord* 2006; **44**: 165.
191. Nwadiaro HC, Nnamonu MI, Ramyil VM et al: Comparative analysis of urethral catheterization versus suprapubic cystostomy in management of neurogenic bladder in spinal injured patients. *Niger J Med* 2007; **16**: 318.
192. Sugimura T, Arnold E, English S et al: Chronic suprapubic catheterization in the management of patients with spinal cord injuries: Analysis of upper and lower urinary tract complications. *BJU Int* 2008; **101**: 1396.
193. Singh R, Rohilla RK, Sangwan K et al: Bladder management methods and urological complications in spinal cord injury patients. *Indian J Orthop* 2011; **45**: 141.
194. Bothig R, Hirschfeld S and Thietje R: Quality of life and urological morbidity in tetraplegics with artificial ventilation managed with suprapubic or intermittent catheterisation. *Spinal Cord* 2012; **50**: 247.
195. Edokpolo LU, Stavris KB and Foster HE, Jr.: Intermittent catheterization and recurrent urinary tract infection in spinal cord injury. *Top Spinal Cord Inj Rehabil* 2012; **18**: 187.

196. Shen L, Zheng X, Zhang C et al: Influence of different urination methods on the urinary systems of patients with spinal cord injury. *J Int Med Res* 2012; **40**: 1949.
197. Spinu A, Onose G, Daia C et al: Intermittent catheterization in the management of post spinal cord injury (sci) neurogenic bladder using new hydrophilic, with lubrication in close circuit devices--our own preliminary results. *J Med Life* 2012; **5**: 21.
198. Krebs J, Bartel P and Pannek J: Residual urine volumes after intermittent catheterization in men with spinal cord injury. *Spinal Cord* 2013; **51**: 776.
199. Lopes MA and Lima ED: Continuous use of intermittent bladder catheterization--can social support contribute? *Rev Lat Am Enfermagem* 2014; **22**: 461.
200. Krassioukov A, Cragg JJ, West C et al: The good, the bad and the ugly of catheterization practices among elite athletes with spinal cord injury: A global perspective. *Spinal Cord* 2015; **53**: 78.
201. Krebs J, Wollner J and Pannek J: Urethral strictures in men with neurogenic lower urinary tract dysfunction using intermittent catheterization for bladder evacuation. *Spinal Cord* 2015; **53**: 310.
202. Krebs J, Wollner J and Pannek J: Risk factors for symptomatic urinary tract infections in individuals with chronic neurogenic lower urinary tract dysfunction. *Spinal Cord* 2016; **54**: 682.
203. Mukai S, Shigemura K, Nomi M et al: Retrospective study for risk factors for febrile UTI in spinal cord injury patients with routine concomitant intermittent catheterization in outpatient settings. *Spinal Cord* 2016; **54**: 69.
204. Svihra J, Krhut J, Zachoval R et al: Impact of clean intermittent catheterization on quality adjusted life years (qalys) in spinal cord injury patients with neurogenic urinary incontinence. *Neurourol Urodyn* 2018; **37**: 250.
205. Andretta E, Laganà F, Cossaro E et al: Transurethral indwelling catheterisation in multiple sclerosis. *Urologica* 2002; **12**: 25.
206. James R, Frasure HE and Mahajan ST: Urinary catheterization may not adversely impact quality of life in multiple sclerosis patients. *ISRN Neurol* 2014; **2014**: 167030.
207. Bjerklund Johansen T, Hultling C, Madersbacher H et al: A novel product for intermittent catheterisation: Its impact on compliance with daily life--international multicentre study. *Eur Urol* 2007; **52**: 213.
208. Myers JB, Lenherr SM, Stoffel JT et al: Patient reported bladder related symptoms and quality of life after spinal cord injury with different bladder management strategies. *J Urol* 2019; **202**: 574.
209. Dahlberg A, Perttila I, Wuokko E et al: Bladder management in persons with spinal cord lesion. *Spinal Cord* 2004; **42**: 694.
210. Oh SJ, Shin HI, Paik NJ et al: Depressive symptoms of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. *Spinal Cord* 2006; **44**: 757.
211. Liu CW, Attar KH, Gall A et al: The relationship between bladder management and health-related quality of life in patients with spinal cord injury in the UK. *Spinal Cord* 2010; **48**: 319.
212. Luo DY, Ding MF, He CQ et al: Bladder management of patients with spinal cord injuries sustained in the 2008 Wenchuan earthquake. *Kaohsiung J Med Sci* 2012; **28**: 613.
213. Castel-Lacanal E, Game X, De Boissezon X et al: Impact of intermittent catheterization on the quality of life of multiple sclerosis patients. *World J Urol* 2013; **31**: 1445.
214. Hagen EM and Rekdal T: Management of bladder dysfunction and satisfaction of life after spinal cord injury in Norway. *J Spinal Cord Med* 2014; **37**: 310.
215. Yilmaz B, Akkoc Y, Alaca R et al: Intermittent catheterization in patients with traumatic spinal cord injury: Obstacles, worries, level of satisfaction. *Spinal Cord* 2014; **52**: 826.
216. Liu JS, Dong C, Casey JT et al: Quality of life related to urinary continence in adult spina bifida patients. *Cent European J Urol* 2015; **68**: 61.
217. Adriaansen JJ, van Asbeck FW, Tepper M et al: Bladder-emptying methods, neurogenic lower



- urinary tract dysfunction and impact on quality of life in people with long-term spinal cord injury. *J Spinal Cord Med* 2017; **40**: 43.
218. Fumincelli L, Mazzo A, Martins JCA et al: Quality of life of intermittent urinary catheterization users and their caregivers: A scoping review. *Worldviews Evid Based Nurs* 2017; **14**: 324.
219. Yasami S, Khadem M, Safaei G et al: The association between bladder-emptying methods and health-related quality of life among iranian individuals with spinal cord injury. *J Spinal Cord Med* 2017; **40**: 530.
220. Ahluwalia RS, Johal N, Kouriefs C et al: The surgical risk of suprapubic catheter insertion and long-term sequelae. *Ann R Coll Surg Engl* 2006; **88**: 210.
221. Cronin CG, Prakash P, Gervais DA et al: Imaging-guided suprapubic bladder tube insertion: Experience in the care of 549 patients. *AJR Am J Roentgenol* 2011; **196**: 182.
222. Edokpolo LU and Foster HE, Jr.: Suprapubic cystostomy for neurogenic bladder using lowsley retractor method: A procedure revisited. *Urology* 2011; **78**: 1196.
223. Ginger VA, Miller JL and Yang CC: Bladder neck closure and suprapubic tube placement in a debilitated patient population. *Neurourol Urodyn* 2010; **29**: 382.
224. Colli J and Lloyd LK: Bladder neck closure and suprapubic catheter placement as definitive management of neurogenic bladder. *J Spinal Cord Med* 2011; **34**: 273.
225. Zimmern PE, Hadley HR, Leach GE et al: Transvaginal closure of the bladder neck and placement of a suprapubic catheter for destroyed urethra after long-term indwelling catheterization. *J Urol* 1985; **134**: 554.
226. Poirier C, Dinh A, Salomon J et al: Prevention of urinary tract infections by antibiotic cycling in spinal cord injury patients and low emergence of multidrug resistant bacteria. *Med Mal Infect* 2016; **46**: 294.
227. Salomon J, Denys P, Merle C et al: Prevention of urinary tract infection in spinal cord-injured patients: Safety and efficacy of a weekly oral cyclic antibiotic (woca) programme with a 2 year follow-up--an observational prospective study. *J Antimicrob Chemother* 2006; **57**: 784.
228. Cox L, He C, Bevins J et al: Gentamicin bladder instillations decrease symptomatic urinary tract infections in neurogenic bladder patients on intermittent catheterization. *Can Urol Assoc J* 2017; **11**: E350.
229. Waites KB, Canupp KC, Armstrong S et al: Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. *J Spinal Cord Med* 2004; **27**: 35.
230. Gallien P, Amarenco G, Benoit N et al: Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: A multicenter, randomized, placebo-controlled, double-blind trial. *Mult Scler* 2014; **20**: 1252.
231. Hess MJ, Hess PE, Sullivan MR et al: Evaluation of cranberry tablets for the prevention of urinary tract infections in spinal cord injured patients with neurogenic bladder. *Spinal Cord* 2008; **46**: 622.
232. Linsenmeyer TA, Harrison B, Oakley A et al: Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study. *J Spinal Cord Med* 2004; **27**: 29.
233. Lee BB, Haran MJ, Hunt LM et al: Spinal-injured neuropathic bladder antisepsis (sinba) trial. *Spinal Cord* 2007; **45**: 542.
234. Denys P, Del Popolo G, Amarenco G et al: Efficacy and safety of two administration modes of an intra-detrusor injection of 750 units dysport(r) (abobotulinumtoxin) in patients suffering from refractory neurogenic detrusor overactivity (ndo): A randomised placebo-controlled phase iia study. *Neurourol Urodyn* 2017; **36**: 457.
235. Ehren I, Volz D, Farrelly E et al: Efficacy and impact of botulinum toxin a on quality of life in patients with neurogenic detrusor overactivity: A randomised, placebo-controlled, double-blind study. *Scand J Urol Nephrol* 2007; **41**: 335.
236. Schurch B, Denys P, Kozma CM et al: Botulinum toxin a improves the quality of life of patients with neurogenic urinary incontinence. *Eur Urol* 2007; **52**: 850.
237. Schurch B and Schulte-Baukloh H: Botulinum toxin in the treatment of neurogenic bladder in

- adults and children. *European Urology Supplements* 2006; **5**: 679.
238. Giannantoni A, Di Stasi SM, Stephen RL et al: Intravesical resiniferatoxin versus botulinum-a toxin injections for neurogenic detrusor overactivity: A prospective randomized study. *J Urol* 2004; **172**: 240.
239. Kennelly M, Dmochowski R, Schulte-Baukloh H et al: Efficacy and safety of onabotulinumtoxin therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: Final results of a long-term extension study. *Neurourol Urodyn* 2017; **36**: 368.
240. Ferreira RS, D'Ancona CAL, Oelke M et al: Intradetrusor onabotulinumtoxin injections are significantly more efficacious than oral oxybutynin for treatment of neurogenic detrusor overactivity: Results of a randomized, controlled, 24-week trial. *Einstein (Sao Paulo)* 2018; **16**: eAO4207.
241. Li GP, Wang XY and Zhang Y: Efficacy and safety of onabotulinumtoxin in patients with neurogenic detrusor overactivity caused by spinal cord injury: A systematic review and meta-analysis. *Int Neurourol J* 2018; **22**: 275.
242. Tullman M, Chartier-Kastler E, Kohan A et al: Low-dose onabotulinumtoxin improves urinary symptoms in noncatheterizing patients with ms. *Neurology* 2018; **91**: e657.
243. Yuan H, Cui Y, Wu J et al: Efficacy and adverse events associated with use of onabotulinumtoxin for treatment of neurogenic detrusor overactivity: A meta-analysis. *Int Neurourol J* 2017; **21**: 53.
244. Chancellor MB, Patel V, Leng WW et al: Onabotulinumtoxin improves quality of life in patients with neurogenic detrusor overactivity. *Neurology* 2013; **81**: 841.
245. Sussman D, Patel V, Del Popolo G et al: Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxin in patients with urinary incontinence due to neurogenic detrusor overactivity. *Neurourol Urodyn* 2013; **32**: 242.
246. Chartier-Kastler E, Rovner E, Hepp Z et al: Patient-reported goal achievement following onabotulinumtoxin treatment in patients with neurogenic detrusor overactivity. *Neurourol Urodyn* 2016; **35**: 595.
247. Cruz F, Herschorn S, Aliotta P et al: Efficacy and safety of onabotulinumtoxin in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomised, double-blind, placebo-controlled trial. *Eur Urol* 2011; **60**: 742.
248. Herschorn S, Gajewski J, Ethans K et al: Efficacy of botulinum toxin a injection for neurogenic detrusor overactivity and urinary incontinence: A randomized, double-blind trial. *J Urol* 2011; **185**: 2229.
249. Ginsberg D, Gousse A, Keppenne V et al: Phase 3 efficacy and tolerability study of onabotulinumtoxin for urinary incontinence from neurogenic detrusor overactivity. *J Urol* 2012; **187**: 2131.
250. Mangera A, Apostolidis A, Andersson KE et al: An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. *Eur Urol* 2014; **65**: 981.
251. Chen YC and Kuo HC: The therapeutic effects of repeated detrusor injections between 200 or 300 units of onabotulinumtoxin in chronic spinal cord injured patients. *Neurourol Urodyn* 2014; **33**: 129.
252. Kennelly M, Dmochowski R, Ethans K et al: Long-term efficacy and safety of onabotulinumtoxin in patients with urinary incontinence due to neurogenic detrusor overactivity: An interim analysis. *Urology* 2013; **81**: 491.
253. Grise P, Ruffion A, Denys P et al: Efficacy and tolerability of botulinum toxin type a in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: Comparison of two doses. *Eur Urol* 2010; **58**: 759.
254. Knüpfers SC, Schneider SA, Averhoff MM et al: Preserved micturition after intradetrusor onabotulinumtoxin injection for treatment of neurogenic bladder dysfunction in parkinson's disease. *BMC Urol* 2016; **16**: 55.
255. Anderson RU, Orenberg EK and Glowe P: Onabotulinumtoxin office treatment for

- neurogenic bladder incontinence in parkinson's disease. *Urology* 2014; **83**: 22.
256. Giannantoni A, Conte A, Proietti S et al: Botulinum toxin type a in patients with parkinson's disease and refractory overactive bladder. *J Urol* 2011; **186**: 960.
257. Kulaksizoglu H and Parman Y: Use of botulinum toxin-a for the treatment of overactive bladder symptoms in patients with parkinson's disease. *Parkinsonism Relat Disord* 2010; **16**: 531.
258. Giannantoni A, Rossi A, Mearini E et al: Botulinum toxin a for overactive bladder and detrusor muscle overactivity in patients with parkinson's disease and multiple system atrophy. *J Urol* 2009; **182**: 1453.
259. Jiang YH, Liao CH, Tang DL et al: Efficacy and safety of intravesical onabotulinumtoxin a injection on elderly patients with chronic central nervous system lesions and overactive bladder. *PLoS One* 2014; **9**: e105989.
260. Peyronnet B, Even A, Capon G et al: Intradetrusor injections of botulinum toxin a in adults with spinal dysraphism. *J Urol* 2018; **200**: 875.
261. Peyronnet B, Castel-Lacanal E, Roumiguie M et al: Intradetrusor injections of onabotulinum toxin a (botox(r)) 300 u or 200 u versus abobotulinum toxin a (dysport(r)) 750 u in the management of neurogenic detrusor overactivity: A case control study. *Neurourol Urodyn* 2017; **36**: 734.
262. Stoehrer M, Wolff A, Kramer G et al: Treatment of neurogenic detrusor overactivity with botulinum toxin a: The first seven years. *Urol Int* 2009; **83**: 379.
263. Martinez L, Tubre R, Roberts R et al: Refractory bladder dysfunction: A multi-institutional experience with intravesical botulinum toxin-a injection in adult patients who underwent previous augmentation cystoplasty. *Turk J Urol* 2020;
264. Michel F, Ciceron C, Bernuz B et al: Botulinum toxin type a injection after failure of augmentation enterocystoplasty performed for neurogenic detrusor overactivity: Preliminary results of a salvage strategy. The enterotox study. *Urology* 2019; **129**: 43.
265. Ginsberg D, FHerschorn, SGousse, AKeppenne, VALiotta, PSievert, K-DBrin, MfJenkins, BThompson, CLam, WHeesakkers, JHaag-Molkenteller, C: Onabotulinumtoxin a is effective in patients with urinary incontinence due to neurogenic detrusor activity regardless of concomitant anticholinergic use or neurologic etiology. In: *Advances in therapy*, vol. 30, pp. 819, 2013.
266. Amarenco G, Guinet A, Jousse M et al: Pencil and paper test: A new tool to predict the ability of neurological patients to practice clean intermittent self-catheterization. *J Urol* 2011; **185**: 578.
267. Pannek J and Kullik B: Does optimizing bladder management equal optimizing quality of life? Correlation between health-related quality of life and urodynamic parameters in patients with spinal cord lesions. *Urology* 2009; **74**: 263.
268. Vainrib M, Reyblat P and Ginsberg DA: Long-term efficacy of repeat incisions of bladder neck/external sphincter in patients with spinal cord injury. *Urology* 2014; **84**: 940.
269. Pan D, Troy A, Rogerson J et al: Long-term outcomes of external sphincterotomy in a spinal injured population. *J Urol* 2009; **181**: 705.
270. Gallien P, Reymann JM, Amarenco G et al: Placebo controlled, randomised, double blind study of the effects of botulinum a toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1670.
271. de Seze M, Petit H, Gallien P et al: Botulinum a toxin and detrusor sphincter dyssynergia: A double-blind lidocaine-controlled study in 13 patients with spinal cord disease. *Eur Urol* 2002; **42**: 56.
272. Reynard JM, Vass J, Sullivan ME et al: Sphincterotomy and the treatment of detrusor-sphincter dyssynergia: Current status, future prospects. *Spinal Cord* 2003; **41**: 1.
273. Tabibian L and Ginsberg DA: Transurethral collagen injection in neuropathic sphincter deficiency. *Topics in Spinal Cord Injury Rehabilitation* 2003; **8**: 54.
274. Hamid R, Arya M, Khastgir J et al: The treatment of male stress urinary incontinence with polydimethylsiloxane in compliant bladders

- following spinal cord injury. *Spinal Cord* 2003; **41**: 286.
275. Farag F, Koens M, Sievert KD et al: Surgical treatment of neurogenic stress urinary incontinence: A systematic review of quality assessment and surgical outcomes. *Neurourol Urodyn* 2016; **35**: 21.
276. Shin JH, Park KW, Park J et al: Treatment outcomes and overactive bladder symptoms after midurethral sling in female patients with or without various neurological diseases. *Neurourol Urodyn* 2020; **39**: 2379.
277. Kaiho YM, H.Takei, M.Hirayama, T.Mitsui, T.Yokoyama, M.Kitta, T.Kawamorita, N.Nakagawa, H.Iwamura, M.Arai, Y.: Surgical and patient reported outcomes of artificial urinary sphincter implantation: A multicenter, prospective, observational study. *J Urol* 2017;
278. Murphy SR, D.O'Mahony, J.McDermott, T. E.Thornhill, J.Butler, M.Grainger, R.: A comparison of the functional durability of the ams 800 artificial urinary sphincter between cases with and without an underlying neurogenic aetiology. *Ir J Med Sci* 2003; **172**: 136.
279. Ammirati EM, A.Giammo, A.Carone, R.: Management of male and female neurogenic stress urinary incontinence in spinal cord injured (sci) patients using adjustable continence therapy. *Urologia* 2017; **84**: 165.
280. Bersch UG, K.Pannek, J.: The artificial urinary sphincter in patients with spinal cord lesion: Description of a modified technique and clinical results. *Eur Urol* 2009; **55**: 687.
281. Patki PH, R.Shah, P. J.Craggs, M.: Long-term efficacy of ams 800 artificial urinary sphincter in male patients with urodynamic stress incontinence due to spinal cord lesion. *Spinal Cord* 2006; **44**: 297.
282. Phe VL, P.Granger, B.Denys, P.Bitker, M. O.Mozer, P.Chartier-Kastler, E.: Stress urinary incontinence in female neurological patients: Long-term functional outcomes after artificial urinary sphincter (ams 800tm ) implantation. *Neurourol Urodyn* 2017; **36**: 764.
283. Singh G and Thomas DG: Artificial urinary sphincter in patients with neurogenic bladder dysfunction. *Br J Urol* 1996; **77**: 252.
284. Chartier Kastler EG, S.Game, X.Denys, P.Richard, F.Leriche, A.Saramon, J. P.Ruffion, A.: Treatment of neurogenic male urinary incontinence related to intrinsic sphincter insufficiency with an artificial urinary sphincter: A french retrospective multicentre study. *BJU Int* 2011; **107**: 426.
285. Chartier Kastler E, Genevois S, Game X et al: Treatment of neurogenic male urinary incontinence related to intrinsic sphincter insufficiency with an artificial urinary sphincter: A french retrospective multicentre study. *BJU Int* 2011; **107**: 426.
286. Costa P, Poinas G, Ben Naoum K et al: Long-term results of artificial urinary sphincter for women with type iii stress urinary incontinence. *Eur Urol* 2013; **63**: 753.
287. Patki P, Hamid R, Shah PJ et al: Long-term efficacy of ams 800 artificial urinary sphincter in male patients with urodynamic stress incontinence due to spinal cord lesion. *Spinal Cord* 2006; **44**: 297.
288. Peyronnet B, Greenwell T, Gray G et al: Current use of the artificial urinary sphincter in adult females. *Curr Urol Rep* 2020; **21**: 53.
289. Shpall AI and Ginsberg DA: Bladder neck closure with lower urinary tract reconstruction: Technique and long-term followup. *J Urol* 2004; **172**: 2296.
290. Hulecki SJ and Hackler RH: Closure of the bladder neck in spinal cord injury patients with urethral sphincteric incompetence and irreparable urethral pathological conditions. *J Urol* 1984; **131**: 1119.
291. Rovner ES, Goudelocke CM, Gilchrist A et al: Transvaginal bladder neck closure with posterior urethral flap for devastated urethra. *Urology* 2011; **78**: 208.
292. Willis H, Safiano NA and Lloyd LK: Comparison of transvaginal and retropubic bladder neck closure with suprapubic catheter in women. *J Urol* 2015; **193**: 196.
293. Zecca C, Panicari L, Disanto G et al: Posterior tibial nerve stimulation in the management of lower urinary tract symptoms in patients with multiple sclerosis. *Int Urogynecol J* 2016; **27**: 521.

294. Zecca C, Digesu GA, Robshaw P et al: Maintenance percutaneous posterior nerve stimulation for refractory lower urinary tract symptoms in patients with multiple sclerosis: An open label, multicenter, prospective study. *J Urol* 2014; **191**: 697.
295. Canbaz Kabay S, Kabay S, Mestan E et al: Long term sustained therapeutic effects of percutaneous posterior tibial nerve stimulation treatment of neurogenic overactive bladder in multiple sclerosis patients: 12-months results. *Neurourol Urodyn* 2017; **36**: 104.
296. Perissinotto MC, D'Ancona CA, Lucio A et al: Transcutaneous tibial nerve stimulation in the treatment of lower urinary tract symptoms and its impact on health-related quality of life in patients with parkinson disease: A randomized controlled trial. *J Wound Ostomy Continence Nurs* 2015; **42**: 94.
297. Monteiro ES, de Carvalho LB, Fukujima MM et al: Electrical stimulation of the posterior tibialis nerve improves symptoms of poststroke neurogenic overactive bladder in men: A randomized controlled trial. *Urology* 2014; **84**: 509.
298. Chen G, Liao L and Li Y: The possible role of percutaneous tibial nerve stimulation using adhesive skin surface electrodes in patients with neurogenic detrusor overactivity secondary to spinal cord injury. *Int Urol Nephrol* 2015; **47**: 451.
299. Tudor KI, Seth JH, Liechti MD et al: Outcomes following percutaneous tibial nerve stimulation (ptns) treatment for neurogenic and idiopathic overactive bladder. *Clin Auton Res* 2020; **30**: 61.
300. Schneider MP, Gross T, Bachmann LM et al: Tibial nerve stimulation for treating neurogenic lower urinary tract dysfunction: A systematic review. *Eur Urol* 2015; **68**: 859.
301. Marinkovic SP and Gillen LM: Sacral neuromodulation for multiple sclerosis patients with urinary retention and clean intermittent catheterization. *Int Urogynecol J* 2010; **21**: 223.
302. Minardi D and Muzzonigro G: Sacral neuromodulation in patients with multiple sclerosis. *World J Urol* 2012; **30**: 123.
303. Andretta E, Simeone C, Ostardo E et al: Usefulness of sacral nerve modulation in a series of multiple sclerosis patients with bladder dysfunction. *J Neurol Sci* 2014; **347**: 257.
304. Engeler DS, Meyer D, Abt D et al: Sacral neuromodulation for the treatment of neurogenic lower urinary tract dysfunction caused by multiple sclerosis: A single-centre prospective series. *BMC Urol* 2015; **15**: 105.
305. Kessler TM, La Framboise D, Trelle S et al: Sacral neuromodulation for neurogenic lower urinary tract dysfunction: Systematic review and meta-analysis. *Eur Urol* 2010; **58**: 865.
306. Zhang P, Wang JY, Zhang Y et al: Results of sacral neuromodulation therapy for urinary voiding dysfunction: Five-year experience of a retrospective, multicenter study in china. *Neuromodulation* 2019; **22**: 730.
307. Chaabane W, Guillotreau J, Castel-Lacanal E et al: Sacral neuromodulation for treating neurogenic bladder dysfunction: Clinical and urodynamic study. *Neurourol Urodyn* 2011; **30**: 547.
308. Chartier-Kastler EJ, Ruud Bosch JL, Perrigot M et al: Long-term results of sacral nerve stimulation (s3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia. *J Urol* 2000; **164**: 1476.
309. Peters KM, Kandagatla P, Killinger KA et al: Clinical outcomes of sacral neuromodulation in patients with neurologic conditions. *Urology* 2013; **81**: 738.
310. Wallace PA, Lane FL and Noblett KL: Sacral nerve neuromodulation in patients with underlying neurologic disease. *Am J Obstet Gynecol* 2007; **197**: 96 e1.
311. Wollner J, Krebs J and Pannek J: Sacral neuromodulation in patients with neurogenic lower urinary tract dysfunction. *Spinal Cord* 2016; **54**: 137.
312. Lombardi G and Del Popolo G: Clinical outcome of sacral neuromodulation in incomplete spinal cord injured patients suffering from neurogenic lower urinary tract symptoms. *Spinal Cord* 2009; **47**: 486.
313. Lombardi G, Musco S, Celso M et al: Sacral neuromodulation for neurogenic non-obstructive urinary retention in incomplete

- spinal cord patients: A ten-year follow-up single-centre experience. *Spinal Cord* 2014; **52**: 241.
314. Lombardi G, Nelli F, Mencarini M et al: Clinical concomitant benefits on pelvic floor dysfunctions after sacral neuromodulation in patients with incomplete spinal cord injury. *Spinal Cord* 2011; **49**: 629.
315. Hoen L, Ecclestone H, Blok BFM et al: Long-term effectiveness and complication rates of bladder augmentation in patients with neurogenic bladder dysfunction: A systematic review. *Neurourol Urodyn* 2017; **36**: 1685.
316. Zhang R, Xu Y, Yang S et al: Onabotulinumtoxin A for neurogenic detrusor overactivity and dose differences: A systematic review. *Int Braz J Urol* 2015; **41**: 207.
317. Reyblat P, Chan KG, Josephson DY et al: Comparison of extraperitoneal and intraperitoneal augmentation enterocystoplasty for neurogenic bladder in spinal cord injury patients. *World J Urol* 2009; **27**: 63.
318. Reid S, Tophill P, Osman N et al: Augmentation cystoplasty in neuropathic bladder. *J Spinal Cord Med* 2020; **43**: 217.
319. Phe V, Leon P, Granger B et al: Stress urinary incontinence in female neurological patients: Long-term functional outcomes after artificial urinary sphincter (ams 800(tm) ) implantation. *Neurourol Urodyn* 2017; **36**: 764.
320. Cheng PJ, Keihani S, Roth JD et al: Contemporary multicenter outcomes of continent cutaneous ileocecostoplasty in the adult population over a 10-year period: A neurogenic bladder research group study. *Neurourol Urodyn* 2020; **39**: 1771.
321. Walsh K, Troxel SA and Stone AR: An assessment of the use of a continent catheterizable stoma in female tetraplegics. *BJU Int* 2004; **94**: 595.
322. Zommick JN, Simoneau AR, Skinner DG et al: Continent lower urinary tract reconstruction in the cervical spinal cord injured population. *J Urol* 2003; **169**: 2184.
323. Hellenthal NJ, Short SS, O'Connor RC et al: Incontinent ileovesicostomy: Long-term outcomes and complications. *Neurourol Urodyn* 2009; **28**: 483.
324. Vanni AJ and Stoffel JT: Ileovesicostomy for the neurogenic bladder patient: Outcome and cost comparison of open and robotic assisted techniques. *Urology* 2011; **77**: 1375.
325. Tan HJ, Stoffel J, Daignault S et al: Ileovesicostomy for adults with neurogenic bladders: Complications and potential risk factors for adverse outcomes. *Neurourol Urodyn* 2008; **27**: 238.
326. Husmann DA and Viers BR: Neurogenic bladder: Management of the severely impaired patient with complete urethral destruction: Ileovesicostomy, suprapubic tube drainage or urinary diversion-is one treatment modality better than another? *Transl Androl Urol* 2020; **9**: 132.
327. Chartier-Kastler EJ, Mozer P, Denys P et al: Neurogenic bladder management and cutaneous non-continent ileal conduit. *Spinal Cord* 2002; **40**: 443.
328. Deboudt C, Perrouin-Verbe MA, Le Normand L et al: Comparison of the morbidity and mortality of cystectomy and ileal conduit urinary diversion for neurogenic lower urinary tract dysfunction according to the approach: Laparotomy, laparoscopy or robotic. *Int J Urol* 2016; **23**: 848.
329. Guillotreau J, Panicker JN, Castel-Lacanal E et al: Prospective evaluation of laparoscopic assisted cystectomy and ileal conduit in advanced multiple sclerosis. *Urology* 2012; **80**: 852.
330. Gobeaux N, Yates DR, Denys P et al: Supratrigonal cystectomy with hautmann pouch as treatment for neurogenic bladder in spinal cord injury patients: Long-term functional results. *Neurourol Urodyn* 2012; **31**: 672.
331. Pazooki D, Edlund C, Karlsson AK et al: Continent cutaneous urinary diversion in patients with spinal cord injury. *Spinal Cord* 2006; **44**: 19.
332. Welk B, Carlson K and Baverstock R: A pilot study of the responsiveness of the neurogenic bladder symptom score (nbss). *Can Urol Assoc J* 2017; **11**: 376.
333. Kato H, Hosaka K, Kobayashi S et al: Fate of tetraplegic patients managed by ileal conduit for urinary control: Long-term follow-up. *Int J Urol* 2002; **9**: 253.

334. Spence HM and Allen TD: Vaginal vesicostomy for empyema of the defunctionalized bladder. *J Urol* 1971; **106**: 862.
335. Mazouin C, Hubert J, Tricard T et al: Robot-assisted cystectomy and ileal conduit for neurogenic bladder: Comparison of extracorporeal vs intracorporeal urinary diversion. *J Endourol* 2021;
336. Shimko MS, Tollefson MK, Umbreit EC et al: Long-term complications of conduit urinary diversion. *J Urol* 2011; **185**: 562.
337. Ammirati E, Manassero A, Giammo A et al: Management of male and female neurogenic stress urinary incontinence in spinal cord injured (sci) patients using adjustable continence therapy. *Urologia* 2017; **84**: 165.
338. Sievert KD, Amend B, Gakis G et al: Early sacral neuromodulation prevents urinary incontinence after complete spinal cord injury. *Ann Neurol* 2010; **67**: 74.
339. Redshaw JD, Lenherr SM, Elliott SP et al: Protocol for a randomized clinical trial investigating early sacral nerve stimulation as an adjunct to standard neurogenic bladder management following acute spinal cord injury. *BMC Urol* 2018; **18**: 72.
340. Xiao CG, Du MX, Dai C et al: An artificial somatic-central nervous system-autonomic reflex pathway for controllable micturition after spinal cord injury: Preliminary results in 15 patients. *J Urol* 2003; **170**: 1237.
341. Peters KM, Girdler B, Turzewski C et al: Outcomes of lumbar to sacral nerve rerouting for spina bifida. *J Urol* 2010; **184**: 702.
342. Tuite GF, Homsy Y, Polsky EG et al: Urological outcome of the xiao procedure in children with myelomeningocele and lipomyelomeningocele undergoing spinal cord detethering. *J Urol* 2016; **196**: 1735.
343. Brindley GS, Polkey CE and Rushton DN: Sacral anterior root stimulators for bladder control in paraplegia. *Paraplegia* 1982; **20**: 365.
344. Cardozo L, Krishnan KR, Polkey CE et al: Urodynamic observations on patients with sacral anterior root stimulators. *Paraplegia* 1984; **22**: 201.
345. Castano-Botero JC, Ospina-Galeano IA, Gomez-Illanes R et al: Extradural implantation of sacral anterior root stimulator in spinal cord injury patients. *Neurourol Urodyn* 2016; **35**: 970.
346. Cheng KC, Kan CF, Chu PS et al: Augmentation cystoplasty: Urodynamic and metabolic outcomes at 10-year follow-up. *Int J Urol* 2015; **22**: 1149.
347. Rovner E, Dmochowski R, Chapple C et al: Onabotulinumtoxin improves urodynamic outcomes in patients with neurogenic detrusor overactivity. *Neurourol Urodyn* 2013; **32**: 1109.
348. Liao L, Zhang F and Chen G: Midterm outcomes of protection for upper urinary tract function by augmentation enterocystoplasty in patients with neurogenic bladder. *Int Urol Nephrol* 2014; **46**: 2117.
349. Linsenmeyer TA and Linsenmeyer MA: Impact of annual urodynamic evaluations on guiding bladder management in individuals with spinal cord injuries. *J Spinal Cord Med* 2013; **36**: 420.
350. Schops TF, Schneider MP, Steffen F et al: Neurogenic lower urinary tract dysfunction (nlutd) in patients with spinal cord injury: Long-term urodynamic findings. *BJU Int* 2015; **115** **Suppl 6**: 33.
351. Wu SY, Jiang YH and Kuo HC: Long-term outcomes of augmentation enterocystoplasty in patients with end-stage bladder diseases: A single-institute experience involving 102 patients. *Int Neurourol J* 2017; **21**: 133.
352. Husmann DA: Long-term complications following bladder augmentations in patients with spina bifida: Bladder calculi, perforation of the augmented bladder and upper tract deterioration. *Translational Andrology and Urology* 2016; **5**: 3.
353. Chen JL and Kuo HC: Long-term outcomes of augmentation enterocystoplasty with an ileal segment in patients with spinal cord injury. *J Formos Med Assoc* 2009; **108**: 475.
354. Gurung PM, Attar KH, Abdul-Rahman A et al: Long-term outcomes of augmentation ileocystoplasty in patients with spinal cord injury: A minimum of 10 years of follow-up. *BJU Int* 2012; **109**: 1236.
355. Chancellor MB, Bennett C, Simoneau AR et al: Sphincteric stent versus external

- sphincterotomy in spinal cord injured men: Prospective randomized multicenter trial. *J Urol* 1999; **161**: 1893.
356. Takahashi R, Kimoto Y and Eto M: Long-term urodynamic follow-up after external sphincterotomy in patients with spinal cord injury. *Neurourol Urodyn* 2018; **37**: 2625.
357. Biardeau X, Chartier-Kastler E, Rouprêt M et al: Risk of malignancy after augmentation cystoplasty: A systematic review. *Neurourol Urodyn* 2016; **35**: 675.
358. Alimi Q, Hascoet J, Manunta A et al: Reliability of urinary cytology and cystoscopy for the screening and diagnosis of bladder cancer in patients with neurogenic bladder: A systematic review. *Neurourology and Urodynamics* 2018; **37**: 916.
359. Hall SA, Curto TM, Onyenwenyi A et al: Characteristics of persons with overactive bladder of presumed neurologic origin: Results from the boston area community health (bach) survey. *Neurourol Urodyn* 2012; **31**: 1149.
360. Welk B, Morrow S, Madarasz W et al: The validity and reliability of the neurogenic bladder symptom score. *J Urol* 2014; **192**: 452.
361. Chen PY, Lee WC, Wang HJ et al: Therapeutic efficacy of onabotulinumtoxin delivered using various approaches in sensory bladder disorder. *Toxins (Basel)* 2020; **12**
362. Parittotokkaporin S, Varghese C, O'Grady G et al: Non-invasive neuromodulation for bowel, bladder and sexual restoration following spinal cord injury: A systematic review. *Clin Neurol Neurosurg* 2020; **194**: 105822.
363. van Ophoven A, Engelberg S, Lilley H et al: Systematic literature review and meta-analysis of sacral neuromodulation (snm) in patients with neurogenic lower urinary tract dysfunction (nlutd): Over 20 years' experience and future directions. *Adv Ther* 2021; **38**: 1987.
364. Gad PN, Kreydin E, Zhong H et al: Non-invasive neuromodulation of spinal cord restores lower urinary tract function after paralysis. *Front Neurosci* 2018; **12**: 432.
365. Keller EE, Patras I, Hutu I et al: Early sacral neuromodulation ameliorates urinary bladder function and structure in complete spinal cord injury minipigs. *Neurourol Urodyn* 2020; **39**: 586.
366. Martens FM, den Hollander PP, Snoek GJ et al: Quality of life in complete spinal cord injury patients with a brindley bladder stimulator compared to a matched control group. *Neurourol Urodyn* 2011; **30**: 551.
367. Hartigan SM and Dmochowski RR: The inflow intraurethral valve-pump for women with detrusor underactivity: A summary of peer-reviewed literature. *J Spinal Cord Med* 2020; **1**.
368. Agatstein E and Aynehchi S: The connected catheter for management of chronic urinary retention (cur) in an adult male with neurogenic bladder - case study. *Urol Case Rep* 2019; **26**: 100947.
369. Joseph DB, Borer JG, De Filippo RE et al: Autologous cell seeded biodegradable scaffold for augmentation cystoplasty: Phase ii study in children and adolescents with spina bifida. *J Urol* 2014; **191**: 1389.
370. Gargollo PC, Ahmed ME, Prieto M et al: Feasibility study of vascularized composite urinary bladder allograft transplantation in a cadaver model. *J Urol* 2021; **206**: 115.
371. Smolar J, Horst M, Sulser T et al: Bladder regeneration through stem cell therapy. *Expert Opin Biol Ther* 2018; **18**: 525.
372. Kim SJ, Cho YS, Park JM et al: Stem cell therapy for neurogenic bladder after spinal cord injury: Clinically possible? *Int Neurourol J* 2020; **24**: S3.
373. Zhou S, Zhang K, Atala A et al: Stem cell therapy for treatment of stress urinary incontinence: The current status and challenges. *Stem Cells Int* 2016; **2016**: 7060975.
374. Levanovich PE, Diokno A, Hasenau DL et al: Intradetrusor injection of adult muscle-derived cells for the treatment of underactive bladder: Pilot study. *Int Urol Nephrol* 2015; **47**: 465.
375. Jorg E, Sartori AM, Hofer AS et al: Deep brain stimulation effects on lower urinary tract function: Systematic review and meta-analysis. *Parkinsonism Relat Disord* 2020; **79**: 65.
376. Sonntag KC, Song B, Lee N et al: Pluripotent stem cell-based therapy for parkinson's



American Urological Association (AUA)/Society of Urodynamics,  
Female Pelvic Medicine & Urogenital Reconstruction (SUFU)

Neurogenic Lower Urinary  
Tract Dysfunction

disease: Current status and future prospects.  
Prog Neurobiol 2018; **168**: 1.

## **Neurogenic Lower Urinary Tract Dysfunction**

### **Panel, Consultants, and Staff**

#### **Panelists**

David A. Ginsberg, MD (Chair)  
University of Southern California  
Los Angeles, California

Stephen Kraus, MD (Vice Chair)  
UT Health San Antonio  
San Antonio, Texas

Timothy B. Boone, MD, PhD  
Houston Methodist  
Houston, Texas

Anne P. Cameron, MD  
University of Michigan Urology  
Ann Arbor, Michigan

Angelo Gousse, MD  
University of Miami Memorial Hospital Miramar  
Miramar, Florida

Melissa R. Kaufman, MD (PGC Rep)  
Vanderbilt Urologic Surgery  
Nashville, Tennessee

Erick Keays (Patient Advocate)  
Keays Consulting

Michael J. Kennelly, MD  
Carolinas HealthCare System  
Charlotte, North Carolina

Gary E. Lemack, MD  
UT Southwestern  
Dallas, Texas

Eric S. Rovner, MD  
Medical University of South Carolina  
Charleston, North Carolina

Claire C. Yang, MD  
University of Washington  
Seattle, Washington

#### **Consultants**

Lesley Souter, PhD  
Nomadic EBM Methodology  
Smithville, Ontario Canada

#### **Staff**

Marybeth Farquhar, PhD, MSN, RN  
Erin Kirkby, MS  
Leila Rahimi, MHS  
Brooke Bixler, MPH  
Emily Calvert, MSN, RN

### **Conflicts of Interest Disclosures**

All panel members completed COI disclosures. Disclosures listed include both topic- and non-topic-related relationships.

**Consultant or Advisor:** **David A. Ginsberg, MD:** Urovant; **Angelo E. Gousse, MD:** Allergan, Precision Medical Devices; **Melissa R. Kaufman, MD:** Boston Scientific, EBT Inc; **Michael J. Kennelly, MD:** Astellas, Coloplast, Allergan, Boston Scientific, Dignify Therapeutics, Cogentix, Taris, SchwabCare, Craig H. Neilsen Foundation, National Spinal Cord Injury Association; EBT Medical, Urovant; **Stephen R. Kraus, MD:** Allergan, Astellas, InCube, Avation, Urovant; **Gary E. Lemack, MD:** Blue Wind, Contura, Allergan, Urovant, Theranova; **Anne K. Cameron, MD:** Medtronic; **Eric S. Rovner, MD:** Astellas, Allergan, Medtronic, Bluewind, Valencia, Hologix.

**Health Publishing:** **David A. Ginsberg, MD:** Neurology and Urodynamics; **Melissa R. Kaufman, MD:** Journal of Urology.

**Investment Interest:** **Eric S. Rovner, MD:** NextMed

**Leadership Position:** **David A. Ginsberg, MD:** Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction; **Michael J. Kennelly, MD:** Academy of Spinal Cord Injury Professionals, Society of Urodynamics, Female Pelvic Medicine & Reconstruction, American Spinal Injury Association, Academy of Spinal Cord Injury Professionals

**Meeting Participant or Lecturer:** **Michael J. Kennelly, MD:** Axonics; **Anne K. Cameron, MD:** Wellspect.

**Other:** **Stephen R. Kraus:** Laborie; **Melissa R. Kaufman, MD:** Cook Myosite.

**Scientific Study or Trial:** **Timothy B. Boone, MD PhD:** Boston Scientific; **David A. Ginsberg, MD:** Procept, Bioness; **Melissa R. Kaufman, MD:** Valencia Technologies, Medtronic; **Michael J. Kennelly, MD:** Cook Myosite, FemPulse; **Gary E. Lemack, MD:** Stimgard **Eric S. Rovner, MD:** NIH/NIDDK, Urovant; **Claire C. Yang, MD:** National Institutes of Health.

### **Peer Reviewers**

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

**AUA Reviewers (Board of Directors, Science and Quality Council, Practice Guidelines Committee, Journal of Urology)**

Diane Bieri Esq.  
John Denstedt, MD  
David F. Green, MD  
Anthony Y. Smith  
Thomas Stringer  
James A. Eastham, MD  
Sean Elliott  
Henry Lai  
Adam Klausner  
Charles R. Powell  
Elizabeth Takacs  
Sara Lenherr  
Rose Khavari  
Lara Maclachlan  
Colin Goudelocke  
Ayman Mahdy  
Blayne Welk  
Pat Shenot  
Hari Tunuguntla  
Andrew C Peterson  
Ramy Goueli  
Rena Malik  
Thomas Kessler  
Sarah E Mcachran  
David Rapp  
Casey Kowalik

**Public Commenters (via public notice on AUA website)**

Kirill Shiranov  
Divya Ajay  
Kevin Connolly

**Disclaimer**

This document was written by the Neurogenic Lower Urinary Tract Dysfunction Panel of the American Urological Association Education and Research, Inc., which was created in 2016. The PGC of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of neurogenic lower urinary tract dysfunction. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the

support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.