Neurogenic Lower Urinary Tract Dysfunction

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Outline

1. Introduction

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.[1] Several classification systems exist for NLUTD. Classifications have been based on descriptions of events during components of the micturition cycle and urodynamic findings.[2] Wein has popularized the Functional System for classification which describes the dysfunction in terms of occurring in the filling/storage or emptying/voiding phase of micturition.[3] This classification, generally divided into "Failure to Store" and "Failure to Empty", has been expanded to include etiology of the voiding dysfunction as well as specific urodynamic findings.

Classifications have also been described based specifically on urodynamic findings. The most widely adopted urodynamic classification is that of Krane and Siroky.[4] In this classification, the activity of the detrusor is noted either hyperreflexic, normoreflexic, or areflexic and activity of the outlet including smooth and striated sphincters is also described. Some of these classifications have been superseded by terminology adapted by the International Continence Society.[5] In this classification,

storage phase and voiding phases of micturition are described separately, and bladder and urethral function is described under each. In the storage phase bladder sensation is also described.

2. Bladder Physiology

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 (**Table 1**).

Table 1: Neurological Conditions Associated with Neurogenic Lower Urinary Tract Dysfunction
Suprapontine causes
Traumatic brain injury
Stroke/Vascular events
Degenerative neurologic conditions - Parkinson's disease - Multiple System Atrophy - Alzheimer's disease
Hydrocephalus
Cerebral palsy
Neoplasms
Infrapontine-suprasacral causes
Trauma/Spinal Cord Injury
Vascular events - Arteriovenous malformations - Spinal cord infarction
Demyelination - Multiple Sclerosis - Transverse Myelitis
Neoplasm
Hereditary spastic paraparesis
Tropical spastic paraparesis (HTLV-I)

Spina bifida

Infrasacral causes

Diabetes mellitus

Cauda equine syndrome

Hereditary motor sensory neuropathy

Pelvic surgery

Pelvic Fracture/Trauma

2.1 Bladder Signaling

Regulation of urine storage and emptying requires delicate and complex interactions between the bladder mucosal layer, detrusor, and both autonomic and somatic nervous systems.

2.1.1 Mucosal Layer

The mucosal layer in the bladder consists of urothelium, a basement membrane, and the lamina propria. The urothelium is a consistent stratified epithelial layer of varying thickness. Umbrella cells comprise the most superficial layer, followed by intermediate and basal layers. **Umbrella cells can secrete mucus and appear to have microvilli which allow the cells to stretch and flatten as the bladder distends.**[6,7]

Neuroendocrine paraneurons and receptors have also been identified in the urothelium which may augment secretion and sensation, although their exact function has not yet been determined. It has been postulated that bladder provokes the urothelium to release chemical mediators (ATP, ACh, and NO), which initiate the micturition signaling pathway. [8,9]

Beneath the urothelial basal layer and basement membrane there exists a rich supply of lymphatics and blood vessels in communication with the lamina propria. Within the lamina propria, there are nerve junctions, fibroblasts, and signaling cells termed interstitial cells of Cajal (ICC). **It is postulated that the ICC cells form a functional network, through gap junctions, which facilitate communication from the urothelium to other regions in bladder and to the afferent nervous system.**[10] **ICC cells may also play a role in facilitating detrusor function.**[11,12] Conditions such as chronic obstruction, spinal cord injury (SCI), and chronic irritation are associated with changes in the urothelium through mechanisms such as fibrosis, hypoperfusion, and cellular hypertrophy. Each different mechanism may contribute to NLUTD in a different way.[13]

2.1.2 Detrusor

The detrusor consists of randomly oriented smooth muscle which has no insertion or origin points providing the ability to maintain continuous tension at different muscle lengths. Potassium channels within the detrusor muscles have been demonstrated to mediate contraction and relaxation through control of intracellular calcium concentrations. [14] Gap junctions have also been located between detrusor cells.[15] An extracellular matrix surrounds the detrusor muscle and acts a scaffold of support. The matrix is constantly remodeled and consists of collagen (type 1 and 3), elastic fibers, adhesive proteins, glycans, and glycoproteins. [16,17] **Strain from chronic obstruction or injury to the bladder can cause a stiffening of the matrix and lead to reduced storage capacity.** In pathologic conditions, such as low bladder compliance, the extracellular matrix becomes less elastic with a concomitant increase in type 3 collagen.[18,19]

2.2 Pharmacology of Bladder Storage and Emptying

Bladder storage requires stimulation of the sympathetic nervous system via adrenergic receptors. Alpha-adrenergic receptors are classified as α1 (post-synaptic) and α2 (pre-synaptic),

although α2 receptors have also been found in postsynaptic locations. There are three subtypes of α1 receptors (α1a, α1b, α1d). **The α1a subtype is the primary subtype in the prostate and urethra, and it is primarily responsible for contraction of the bladder outlet to maintain continence.**[20,21] There is also a contribution of beta-adrenergic receptors with three subtypes identified in the bladder (β1, β2 and β3). β2 and β3 receptors are located in the supratrigonal detrusor with stimulation of these receptors facilitating smooth muscle relaxation. [22,23]

Bladder emptying is enabled by parasympathetic stimulation of the cholinergic receptors, specifically the muscarinic receptors. Five subtypes of muscarinic receptors (M1-M5) have been identified, with M2 and M3 having the highest concentrations within the bladder.[24,25] **Current data suggests that M3 muscarinic receptor is primarily responsible for detrusor contraction,**[26] however in NLUTD it has been noted that the percentage of M2 receptors increase indicating a possible role for these receptors in this population.[27] A higher muscarinic receptor density is present in the supratrigonal region of the bladder compared to the trigone. Medications with anticholinergic properties, bind M2 and M3 receptors to reduce detrusor contractility. OnabotulinumtoxinA reduces bladder contractility by inhibiting presynaptic release of acetylcholine from nerve terminals through binding of SNAP-25, thus reducing stimulation of muscarinic receptors. [28]

Additional non-adrenergic/non-cholinergic (NANC) neurotransmitters and receptors play a role in aberrant bladder storage and emptying. Refractory neurogenic overactive bladder symptoms have been linked to increased detrusor contractility through a P2X receptor pathway [29] and vanilloid receptors.[30] Interactions between phosphodiesterase enzymes (PDE) and their targets cAMP/cGMP likewise are known to influence micturition.[31,32]

2.3 Bladder/Peripheral Nervous System/Spinal Cord Communication

During bladder filling, afferent nerves embedded in the urothelium, lamina propria, and detrusor muscle are stimulated. Bladder neck and proximal urethra have the greatest concentration of afferent nerve bundles with the bladder dome demonstrating the lowest concentration.[3] Two types of afferent nerves, **myelinated A-delta and unmyelinated C fibers carry sensory information** from the bladder to the spinal cord through the pelvic and pudendal nerves**. A-delta fibers, located mostly in the detrusor muscle, are activated during bladder stretching. C fibers are in closer proximity to the urothelium and respond only at higher thresholds of activation, such as those seen with pain and temperature stimuli.**[33,34] It is postulated that refractory urinary frequency and urgency, often present in neurogenic overactive bladder, may result from chronic stimulation of C fibers.

Afferent sensory fibers enter the spinal cord through dorsal roots at S2-S4. Sensory information is carried cephalad through the spinal cord via the myelin coated lateral column of the spinothalamic tract.[35] Motor neurons in the spinal cord appear as grey matter and exit through ventral nerve roots. Of specific interest to urologists, Onuf's nucleus is a collection of motor neurons located in the ventral horn of S1-S3 which innervates the external urethral sphincter.[36,37] Consequently, injury to the sacral spinal cord may result in loss of bladder sensation and sphincteric dysfunction resulting in stress

urinary incontinence.

2.4 Urinary Control in the Brain

The first relay point for bladder sensation traveling through the spinothalamic tract is the periaqueductal grey (PAG) region. Located in the midbrain, the PAG demonstrates activation on positron emission testing during bladder filling.[38] When activated, the PAG inhibits the pontine micturition complex (PMC) in the brain stem to facilitate bladder storage**. Although the PMC coordinates detrusor and urethral sphincter activity, current data suggests that bladder afferents do not directly connect to the PMC. Instead, the PMC is maintained in a state of inhibition by the PAG throughout bladder filling.**[39] During PMC inhibition, the sympathetic nervous stimulation increases bladder relaxation. Exiting the spinal cord at T10-L2, preganglionic sympathetic efferent nerves travel through the hypogastric nerve and stimulate β3 receptors in the detrusor and a-1 receptors in the bladder neck to relax the bladder and close the outlet. (see **Figure 1**)

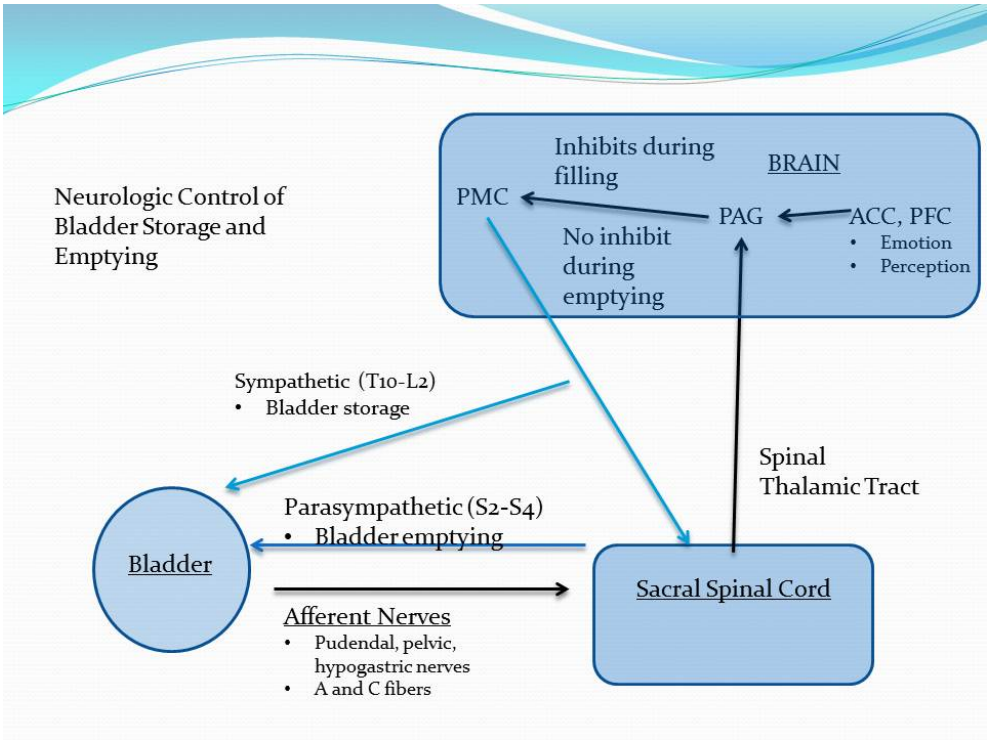

Figure 1: Neurologic Control of Bladder Storage and Emptying

During urine storage, additional higher cerebral regions are activated. Input from the medial prefrontal cortex and the hypothalamus modulate PAG activity and generate consciousness regarding appropriateness of voiding.[39] Sensations of bladder fullness are further processed in the lateral prefrontal cortex and the anterior cingulate cortex, which also generate sensations of pleasantness (or lack thereof) and emotion.[40]

Once a conscious decision is made to empty the bladder, the PAG region removes inhibition from the PMC. The parasympathetic nervous system is then activated and preganglionic parasympathetic efferent nerves exiting from the sacral spinal cord at S2-4 stimulate the

pelvic nerve. The pelvic nerve activates the pelvic plexus ganglia, located adjacent to the bladder. When the parasympathetic system is activated, the spinal cord inhibits sympathetic relaxation of the detrusor and decreases stimulation of the bladder outlet.[41] The pelvic plexus ganglia then stimulate the detrusor muscarinic receptors and urine is expelled.

2.5 Pathophysiology

Given the neurologic complexity of urine storage and emptying, diseases and injuries affecting the nervous system will manifest with a vast array of lower urinary tract symptoms (LUTS). **Table 1** provides an overview of various neurologic pathologies associated with NLUTD symptoms. **When attempting to predict the neurologic impact on bladder function, one must primarily understand location of the neurologic pathology.**

3. Evaluation and Diagnosis of NLUTD

3.1 NLUTD Evaluation

Evaluation is dependent on the type and extent of neurologic disease with predominant consideration for potential risk to the upper tracts. Other factors dictating assessment include prevention of urinary tract infection (UTI), calculi, providing the patient with a feasible means of bladder management, and whenever possible, continence. The timing of evaluation and treatment, as well as need for follow up studies will vary with the neurologic cause. Current American Urological Association (AUA) Guideline on Adult NLUTD (AUA NLUTD Guideline) provides guidance on laboratory studies, imaging and urodynamic testing and recommends categorizing patients based on their risk level as depicted in **Figure 2**. **Stratification of risk is crucial to identify those patients at risk of damage to the upper urinary tract and preserve renal function[1] (Clinical Principal).** Risk level is initially classified as low-risk or unknown. Those with unknown risk will require further evaluation to allow for accurate risk stratification.[1]

Low-Risk (Table 2)

Patients classified with Low-Risk are affected from a suprapontine lesion or a lesion distal to the spinal cord, and these lesions are not typically at risk of NLUTD complications. These include:

- Suprapontine lesions: Cerebrovascular accident/stroke (CVA), Parkinson's disease (PD), brain tumor, traumatic brain injury, cerebral palsy.
- Lesions distal to the spinal cord (neuropathy): disk disease, pelvic surgery, diabetes mellitus.

Patients to be classified as low risk must have with low-risk neurological conditions and spontaneously void, have stable LUTS and have a low post-void residual (PVR) and have no other identified urological complications such as hydronephrosis or dilation of the ureters, bladder stones, elevated PVR, recurrent UTIs. When obtained, the renal function is normal and/or stable and in those scenarios where multichannel urodynamics (UDS) are available, parameters show safe bladder parameters with synergistic voiding. Upper tract imaging (if assessed) is normal and/or stable. [1]

Unknown-Risk (Table 2)

Patients with suprasacral SCI, multiple sclerosis (MS), transverse myelitis, spinal dysraphism or other neurological conditions known to potentially cause urological complications are categorized with unknown risk and need a complete workup. Other neurologic lesions with identified worsening LUTS, or with identified genitourinary (GU) complications potentially related to NLUTD such as hydronphrosis and/or ureteral dilation, bladder stones, elevated PVR, recurrent UTI is classified as unknown risk. All patients in this category should undergo complete evaluation with renal function, upper tract imaging and urodynamics to stratify them into low, moderate or High-Risk.

	Low-Risk	Moderate-Risk	High-Risk
Renal Function	Normal/stable	Normal/stable	Abnormal/unstable
PVR (voiding patients):	Low	Elevated	N/A
Urinary Tract Imaging	Normal/stable (if assessed)	Normal findings	Hydronephrosis, new renal scaring, loss of renal parenchyma, or staghorn/ large stone burden
Urodynamics	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

Table 2. NLUTD Risk Stratification

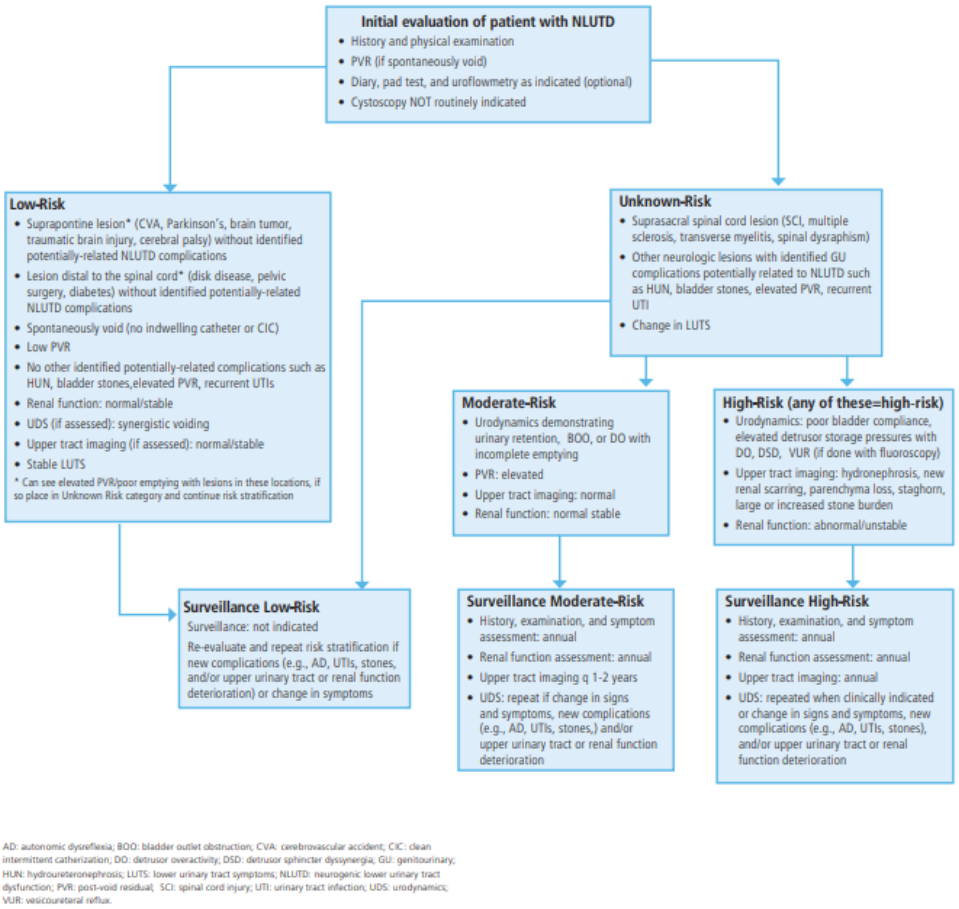

Figure 2: AUA NLUTD Guideline Risk Stratification Flow Chart

3.1.1 History and Physical Examination

See Reference 1

The fundamental history should focus on current and prior urinary symptoms and bladder management. NLUTD may be associated with urinary retention or may be only incomplete bladder emptying with other LUTS depending on the type of the neurologic ailment. Bladder management is aimed to improve quality of life and decrease bothersome urinary symptoms as well as preserve renal function and prevent any deleterious event to the upper tract.

Characterization of the neurological condition resulting in NLUTD and identify all providers (physiatry, physical therapy, neurologist, mental health care provider, etc.) and resources available is key. Understanding the time of onset, severity, progression, prognosis, potential for recovery, disability, presence of ventriculoperitoneal shunt as well as presence of autonomic dysreflexia is important to complete evaluation and necessary counseling of all potential factors to improve symptoms and prevent damage to the upper tracts. [1]

One should inquire about prior and current bladder management (voluntary voiding, CIC, indwelling catheter), characterize prior and current LUTS (frequency, urgency, hesitancy, straining, nocturia, nocturnal enuresis, pad use/diapers, pain). Patients should describe type and frequency of catheterization management if utilized. History can evaluate for different types of urinary incontinence such as stress, urgency or insensate. Patients should be asked about sexual function and desire, as well as fertility function and desire (gynecologic/reproductive history).

Understanding patient level of independence, motor neurologic function (neurological history), lifestyle and quality of life parameters (social history) will help determine realistic expectations for the patient and allow the urologic provider to guide individualized specific therapeutic management. History should include special attention to gastrointestinal review of systems (bowel function and management), gynecologic and obstetric history. Prior surgical urologic surgeries (prior or current presence of urinary stones, transurethral procedure, or urinary diversion, augmentation or utilization of indwelling catheter) and interventions including oral drug therapy, office based and ambulatory procedures (indwelling catheter, onabotulinumtoxinA therapy) to treat urinary symptoms or manage NLUTD need to be investigated.

Physical exam of the patient with NLUTD will vary dependent on the type of neurologic disease. Examination of the back and evaluating for sacral dimple, hair tuft, skin appendages, or an asymmetrical gluteal cleft is required in the patient with a suspected (but not yet diagnosed) neurologic etiology for their voiding dysfunction. Lower extremity neurologic exam for muscle strength, asymmetry, reflexes, and foot abnormalities is also indicated in this situation. GU examination including digital rectal exam (assess for rectal tone, prostate mass/nodule and reflexes) should be performed, with particular focus on urethral damage related to chronic catheterization. Men can develop a urethral erosion, and in women complete bladder neck incompetence may result from a chronic indwelling urethral catheter (figure below). The skin must be examined for decubitus

ulcers and irritation due to urine leakage. Women should be assessed for prolapse and both men and women assessed for rectal prolapse/intussusception particularly in patients with spina bifida who may be voiding with Valsalva rather than CIC. The rate of de novo development of vaginal or rectal prolapse in these groups are upwards of 33% and 32% respectively over 5-6 years of follow up. [42]

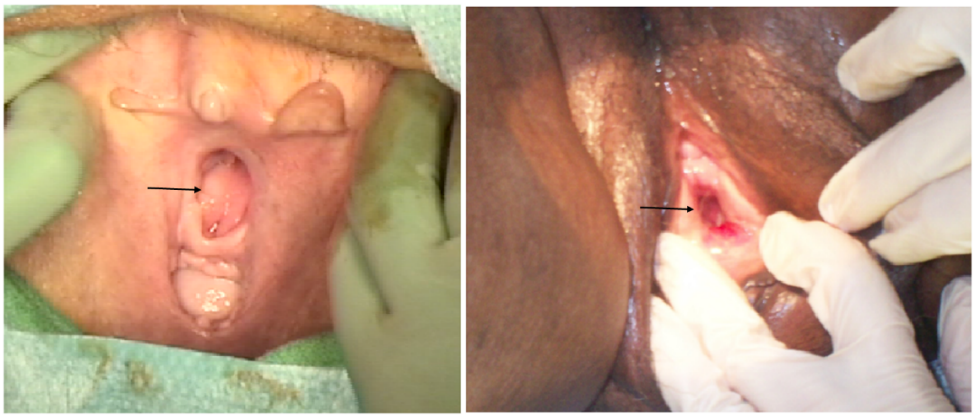

Figure 3: Genitourinary physical exam: external genitalia with urethral erosion associated to chronic indwelling urethral catheter in female patient

3.1.2. Initial Evaluation and Risk Stratification

Initial evaluation includes a comprehensive history, physical exam and urine analysis (UA) (Clinical Principal). When able to void, PVR should be obtained (Clinical Principal). PVR is defined as the volume of urine left in the bladder at the end of micturition[43] and there is no universally agreed upon definition for an elevated PVR.[44,45] In non-neurogenic chronic urinary retention a volume greater than 300ml has been suggested as a definition for elevated PVR.[46] Although non-invasive ultrasound techniques are available to estimate PVR, it is recommended to confirm this with urethral catheterization which could provide a sterile sample if needed and also treat urinary retention. This represents a unique opportunity for patients to be introduced to the concepts of clean intermittent catheterization (CIC) and indwelling catheter. A single episode of elevated PVR is not always indicative of neurogenic dysfunction and could be attributed to other multiple factors (sedentarism, drug adverse event, rapid diuresis, constipation, etc.). An elevated PVR is considered abnormal and could be associated to potential elevated risk and for this reason is recommended to perform multichannel UDS when this is associated to a neurologic condition. [44]

At initial evaluation, optional studies in patients with NLUTD include a voiding/catheterization diary, pad test, and non-invasive uroflow (Expert Opinion). Cystoscopy is not considered standard and should not be performed during initial evaluation of the NLUTD patient (Clinical Principle).[1] It is important to utilize validated questionnaires including symptom assessment instruments (e.g. OAB-q, NBSS) to understand and record baseline symptoms and assess for changes over time to evaluate response to interventions. [1]

A) Further Urine Work-Up

Urinalysis and urine culture should be collected in cases when patient is undergoing a lower urinary tract procedure or if there are symptoms of UTI.[47,48] However, **both patients and caregivers must be extensively counseled that only symptomatic infection should be treated in patients managing with clean intermittent catheterization or indwelling catheter as these patients are chronically colonized** .[49] Indiscriminate treatment of asymptomatic cultures exposes patients to unnecessary antibiotics and increases the risk of bacterial resistance. Discussion of the importance of not over treating asymptomatic bacteriuria is beyond the scope of this article and I refer the reader to the recent 2019 Guideline by the Infectious Disease Society of America that clearly state that patients with catheters or with SCI should not be screened for bacteriuria and nor should it be treated unless they have a planned urological procedure. [50]

Asymptomatic NLUTD patients, clinicians should not perform surveillance/screening urine testing, including urine culture. (Moderate Recommendation; Evidence Level: Grade C). Clinicians should not treat asymptomatic bacteriuria in patients with NLUTD. (Moderate Recommendation; Evidence Level: Grade C) However, when there are signs and symptoms suggestive of a UTI, clinicians should obtain a urinalysis and urine culture allowing for optimal diagnosis and the ability to use culture-specific antibiotics. (Moderate Recommendation; Evidence Level: Grade C)[1] Diagnosis of UTI in patients with altered sensation or impaired cognitive or significant central nervous system deficit is challenging. 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.

Imaging of the upper tracts should be ordered when there is a febrile UTI if the patient does not respond appropiately to antibiotic therapy or in any moderate- or high-risk patients that is not up-to-date with routine upper tract imaging, regardless of their response to therapy (Clinical Principle). Recurrent UTIs in patients with NGLUTD should be evaluated with upper tract imaging and cystoscopy (Clinical Principle). Urodynamic evaluation may be performed in NLUTD patient with recurrent UTI and unremarkable upper and lower tracts (Conditional Recommendation; Evidence Level: Grade C)[1]

B) Urodynamics

Multichannel UDS may be performed when there is a change or worsening in signs or symptoms or new complications, or upper tract or renal function deterioration in patients with moderate- or high-risk NLUTD (Clinical Principle). [1] This topic will be reviewed in more detail in subsequent section 3.2 below.

C) Laboratory

Laboratory evaluation should include assessment of renal function in cases of unknown-risk only. Basic chemistry panel, and yearly PSA should be considered and offered to patients when indicated in selected cases accounting for other medical problems, overall prognosis and accounting for life expectancy (especially when performing prostate cancer screening). [51]

Functional assessment with serum creatinine and calculated GFR is performed yearly in patients with

Moderate and High Risk; however, many of these patients have low muscle mass making these measures less accurate. Indeed, significant functional loss may occur prior to any noted increase in serum creatinine. An alternative assessment is a functional renal scan, which may be used in such instances where the ultrasound reveals a potential anomaly. Twenty-four-hour urine collection for creatinine clearance measurement is cumbersome to perform in the spinal cord population[52] and nuclear medicine studies such as inulin or 51 chromium-ethylene-diamine-tetra-acetate are invasive and expensive. Cystatin C, is a newer and more accurate assessor of renal function and GFR than serum level creatinine, and is not dependent on muscle mass, age, or gender.[53] It is useful in estimating GFR in patients with SCI, but is also cumbersome.[54] If any suspected obstructive anomalies or renal scarring are detected on renal ultrasound, nuclear medicine renal scan is the most sensitive test for decreased function or obstruction.[51]

D) Upper Tracts Imaging Studies

Moderate-Risk patients should undergo imaging studies every 1-2 years, or more frequently if clinically indicated and High risk should be annually. Evaluation for renal and bladder calculi can be best accomplished with ultrasound as well and is more sensitive than abdominal plain film (KUB).[51] However, if a high suspicion for stones is present, CT scan is the preferred imaging evaluation. When clinically indicated, nuclear medicine renal scans are a more sensitive assessment of renal obstruction than serum creatinine, intravenous pyelogram, or voiding cystourethrogram and provide information on renal function.[51]

Patients with low risk NLUTD should not routinely undergo upper tract imaging, renal function assessment, or multichannel UDS. (Moderate Recommendation; Evidence Level: Grade C) However, for those classified with unknown-risk NLUTD, clinician should obtain upper tract imaging, renal function assessment, and multichannel UDS. (Moderate Recommendation; Evidence Level: Grade C). It is important to mention that, **evaluation for risk stratification should be performed once the acute neurological event resulting in NLUTD has stabilized (Clinical Principle).**[1]

3.2. Urodynamics Assessment in the NLUTD

Multichannel UDS are a vital tool in the evaluation and management of NLUTD. Lower urinary tract parameters may be inferred by the level of injury, but correlation is not absolute and formal functional testing is often mandated.[55,56] It should be noted that not all neurologic diseases require urodynamic assessment. However, for any clinical suspicion of bladder dysfunction which could impact the upper urinary tracts, urodynamic becomes essential in the initial and ongoing NLUTD management. Proper performance and interpretation for this complex patient population are imperative.[55]

Multichannel UDS may be performed when there is a change or worsening in signs or symptoms or new complications, or upper tract or renal function deterioration in patients with moderate- or high-risk NLUTD (Clinical Principle).[1] Unsuspected issues such as compliance abnormalities may result in minimal or absent patient symptoms due to sensory loss. It is unclear,

however how often this testing needs to be performed in follow up of patients with neurological disorders. Several clinical practice guidelines exist with varying recommendations ranging from annual testing to testing only those patients with high-risk urinary tracts or with new symptoms. [57] A systematic review of 28 articles addressing this issue found that 49% of NLUTD patients undergoing UDS without new symptoms had findings on testing that prompted a treatment change underlying the importance of routine follow up with UDS. [57]

3.2.1 Storage Problems – Bladder (Compliance)

Due mainly to intrinsic viscoelastic properties, the bladder is normally highly compliant and progresses from empty to full accompanied by a minimal change in pressure. **Bladder compliance is defined as the change in volume over the change in pressure at capacity**. There is no standard or universally agreed upon value of abnormal bladder compliance although calculated values of less than 12.5 ml/cmH_2O (compliance = volume/pressure) have been suggested as abnormal.[58] Low pressure filling is essential to protect upper tract function, as urine delivery from the kidneys is impaired at bladder pressures greater than 40 cm H_2O.[59] (see **Figure 4**).[60] In McGuire's classic evaluation of 209 spina bifida patients, upper tract deterioration was noted with patients who had sustained detrusor pressures of 40cm H_2O or greater before leaking per urethra.[61,62]

Storage problems may additionally result from uninhibited detrusor contractions. Again, urinary incontinence may not always result as the outlet may not relax, or even contract further, particularly in patients with suprasacral lesions, termed detrusor-sphincter dyssynergia. The coordination of the external sphincter and detrusor occurs at the level of the pons, and supra-sacral cord lesions can result in dyssynergia with resultant high detrusor pressures.

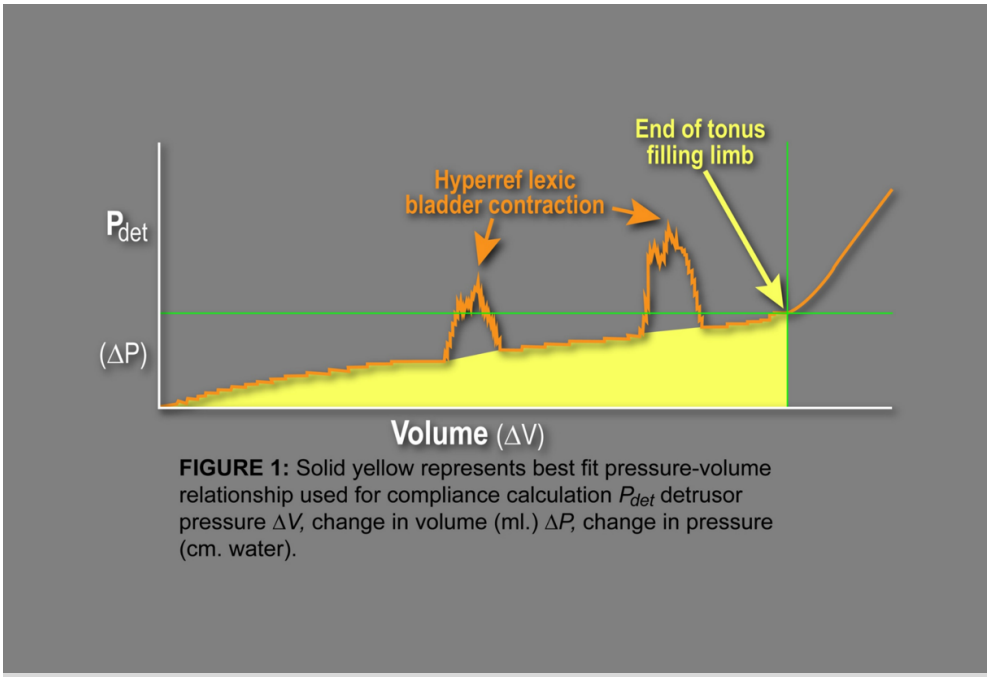

FIGURE 1: Solid yellow represents best fit pressure-volume relationship used for compliance calculation P_{det} detrusor pressure ΔV, change in volume (ml.) ΔP, change in pressure (cm. water).

Figure 4. Hyperreflexic bladder contraction (Neurogenic Detrusor Overactivity/NDO) and poor compliance. [60]

Bladder compliance calculations are obtained during cystometrogram and defined as change in infused volume over change in detrusor pressure.[63] The calculations assume equal distribution of pressure within the bladder and can be artificially low in the setting of VUR, incontinence per urethra/fistula, and bladder diverticulum. Compliance measures may additionally be inaccurate if pressure elevations from detrusor overactivity are included in the calculations hence these should be excluded as in Figure 4.

In a large study of Veterans with SCI, compliance less than 20 ml/cm H_2O was associated with upper tract deterioration, kidney stones and pyelonephritis.[58,] Management strategies for symptomatic low compliance NLUTD patients are likewise heterogeneous. In general, pharmacologic therapy with anticholinergics is first line strategy for improving bladder compliance.[64] Patients with symptoms refractory to anticholinergic therapy may benefit from a combination of alpha blockers, anticholinergics, and tricyclic medications.[60] Additional options include onabotulinumtoxinA and surgical intervention to promote low pressure and/or facilitate diversion may be considered in selected cases and will be discussed in section 4.6.

3.2.2 Storage Problems – Outlet

Urodynamics also involves evaluation of outlet competence. Certain neurologic injuries, such as sacral or peripheral lesions, may result in a fixed and open sphincter. Sphincter damage may also result from chronic catheterization or due to previous surgeries. **The detrusor leak point pressure (DLPP) is defined as the detrusor pressure at which leakage occurs in the absence of a detrusor contraction**. In some, such leakage can be protective of upper tract function. It has been demonstrated for myelomeningocele patients, and extrapolated for other NLUTD patients, that detrusor leak point pressure of greater than 40 cm H2O is associated with upper tract deterioration.[65] Sphincter issues provoked by neurologic insult may also result in stress leakage.

3.2.3 Emptying Problems – Bladder

Some spinal cord patients may maintain the capacity to void spontaneously. However, the majority are unable to generate coordinated contractions for complete emptying and are dependent on alternate means such as catheterization.[66] If storage parameters are safe this may be the only treatment required if patient dexterity or caregivers are available.

3.2.4 Emptying Problems – Outlet

Emptying in the NLUTD patient may be inhibited as previously described by sphincteric dyssynergia. Obstruction may also be due to other pathology such as urethral strictures, BPH, or pelvic organ prolapse. Appropriate GU history and physical, as well as selective utilization of fluoroscopy during UDS, will often aid in the identification of such issues.

3.3 Cystoscopy

Cystoscopy is not recommended for standard screening or surveillance for patients with NLUTD that are managed with or without chronic indwelling catheter (Strong

Recommendation; Evidence Level: Grade B). Patients with SCI are at higher risk than the general population for developing bladder cancer; however, this overall risk is only 0.3% regardless of presence of indwelling catheter.[67] A systematic review of nine studies has shown that cystoscopy and cytology are poor screening tests for bladder cancer in NLUTD patient.[51] Historically, it was recommended that surveillance cystoscopy be performed beginning 5-10 years from the time of catheter placement.[68] However no benefit has been shown from this intervention, even in patients with bladder augmentation, hence routine cystoscopy is not advocated.[51,69,70] **Indications for cystoscopy in this population include hematuria, recurrent UTIs or suspected anatomic anomaly (e.g., false passage, stricture). (Moderate Recommendation; Evidence Level: Grade B).**[1]

3.4 Surveillance of the Patient with NLUTD

Follow up and further evaluation in patients with NLUTD will depend on the level of risk and stability of symptoms and abnormal high risk findings. **Surveillance upper tract imaging renal function assessment, or UDS is not recommended for those with low-risk and stable urinary signs and symptoms (Moderate Recommendation; Evidence Level: Grade C).**[1] **However, any patient with NLUTD with worsening urinary symptoms, complications or new AD should be evaluated and new risk stratification should be performed. Clinician are instructed to educate patients to look for these red flags and avoid waiting until next appointment (Clinical Principle).**[1]

Patients with **stable urinary symptoms, normal renal function and upper tracts stratified with a moderate risk should undergo surveillance with annual focused history, physical exam, and symptom assessment; annual renal function assessment; upper tract imaging every 1-2 years (Moderate Recommendation; Evidence Level: Grade C).**[1]

For those with **high-risk NLUTD and stable urinary signs and symptoms, the clinician should assess the patient with: annual focused history, physical exam, and symptom assessment; annual renal function assessment; annual upper tract imaging; multichannel urodynamic studies, with or without fluoroscopy, which may be repeated when clinically indicated. (Moderate Recommendation; Evidence Level: Grade C).** [1]

4 Management Principles for NLUTD

A variety of neurologic conditions may result in a neurogenic bladder. Consequently, urologic care is many times disease specific. However, there are some common conditions and management strategies which are applicable across disease states.

4.1 Neuro Anatomy Classification

4.1.1 Cortical Lesions

For patients with cortical lesions such as CVA and Alzheimer's, evaluation includes a urinalysis and a PVR measurement along with history and physical exam. These patients typically fall in the category of low risk unless they meet any of the Unknown-Risk factors such as elevated PVR or a history of

urological complications (recurrent UTI, bladder stone etc.) Change in LUTS could also be attributed to other environmental or aging factors and regardless of the etiology.[1]

Symptoms include urinary incontinence from NDO or urinary retention from hypocontractility. Dementia can also present with incontinence from lack of awareness of volitional urinary control.[71] It is critical to remain vigilant and rule out other causes of lower urinary tract dysfunction that are common in an older patient population, such as bladder cancer and BPH. If clinically indicated, evaluation with cystoscopy and/or UDS may be warranted to further assess for alternate causes or clarify treatment options. Cerebral Palsy is usually associated with low rate of urinary symptoms in children but full evaluation with UDS is recommended in those with elevated PVR to rule out the presence of high-risk urodynamic parameters, as urinary retention becomes increasingly common with age.[72]

Cortical lesions typically result in loss of inhibition with coordinated voiding without loss of compliance. Thus, for cortical lesions UDS testing and routine upper tract imaging is not routinely indicated for surveillance but is often needed before any surgical intervention. Certain diseases may impact not just the storage phase (with loss of inhibition and overactivity) but also the emptying phase of voiding. For example, Parkinson's disease has been reported to cause what appeared to be detrusor-sphincter dyssynergia in some studies (further described below in section 8), though it is now thought this represents a manifestation of the skeletal muscle hypertonicity and sphincteric bradykinesia rather than true DSD. [73] Multisystem atrophy can result in an open bladder neck with a fixed internal urethral sphincter[74,] predisposing to stress incontinence and making outlet procedures a high-risk intervention. Normal-pressure hydrocephalus (NPH) is another condition above the brainstem that is characterized by the common triad of dementia, ataxia, and urinary incontinence in the setting of dilated cerebral ventricles and normal cerebrospinal fluid.[75] NPH can occur after CVA or be idiopathic. Treatment with a ventriculoperitoneal (VP) shunt can improve overall status including urinary incontinence.[76]

4.1.2 Spinal Cord Lesions

Spinal cord lesions are categorized according to the American Spinal Injury Association (ASIA).[77] Eighty percent of spinal cord injured patients are male, with motor vehicle accidents being the most common cause (36%), followed by falls (28%), violence (13%) and sports injuries (9%). This demographic is changing with more older individuals and women sustaining spinal cord injuries, particularly from falls.[78,79] As details of SCI are beyond the scope of this outline, please refer to an excellent review of the topic in the AUA Update Series Lesson 25 Volume 27 **Urologic Management of Spinal Cord Injuries**.[80] Following acute spinal cord injury above the sacral level is a period of spinal shock with an acontractile detrusor, loss of sensation, and closed proximal urethra and sphincter. The patient is generally continent with urinary retention. This period lasts from weeks to months and urodynamic assessment during this time is not warranted until reflex function recurs.[81]

4.1.3 Supra-sacral Cord Lesions

Supra-sacral spinal cord lesions include spinal cord injury, spinal cord tumors or infarcts, spina bifida, transverse myelitis, and possibly MS. Supra-sacral SCI is classified as Unknown-Risk and should prompt complete evaluation according to algorithm by AUA NLUTD Guideline already described. Changes in urinary symptoms (NLUTS), or any change in UDS, imaging or renal function should prompt a new evaluation to address and treat etiology to decrease overall risk.[1] This topic will be discussed in a more comprehensive manner in section 5.

Such patients are at risk for impaired compliance and detrusor-sphincter dyssynergia, thus urodynamic evaluation is warranted at baseline assessment in all patients.[82] Upper tract monitoring for hydronephrosis and stone disease is additionally indicated combined with regular assessment of renal function. Management should focus first on protecting upper tract function, providing a socially acceptable means of bladder management, preventing infections, and monitoring for changes in function. Lifetime follow up is typically indicated.

4.1.4 Sacral and Peripheral Lesions

Lesions at or below the sacral cord as well as peripheral lesions (such as damage to the pelvic plexus following radical surgery) can have varying impacts on lower urinary tract function. Damage at this level most often results in normal bladder compliance and detrusor atony, often combined with a fixed external sphincter. Lesions that are distal to the spinal cord are considered low risk. However, any change in LUTS or elevated PVR should prompt complete evaluation with UDS, imaging testing and renal function. Most patients will require intermittent catheterization, and long-term urologic follow up is indicated.

4.2 Treatment of Autonomic Dysreflexia

Autonomic dysreflexia (AD) occurs in approximately 60% of cervical SCI patients and 20% of thoracic SIC patients.[83,84] **The most common trigger for AD is stimulation of the urethra/prostate/internal sphincter region or distention of the bladder or rectum** with the former being a much more potent stimulus.[85] This can be spontaneous or caused by manipulation or instrumentation during activities such as cystoscopy or UDS.[86] Other common causes include plugging of a catheter or clot retention. Understanding and appreciating the pathophysiology of AD is important since it is preventable and failure to recognize it may result in devastating consequences such as seizures, stroke, or even death.

AD is classically characterized by an increase in blood pressure (BP), which can occur suddenly, accompanied by bradycardia. Patients with T6 SCI and above usually have a normal baseline systolic BP of 90-110 mmHg. The International Standards to document remaining Autonomic Function After Spinal Cord Injury (ISAFSCI) recommends a threshold of a rise in systolic blood pressure (SBP) of >20 mmHg from baseline.[87] Systolic BP has been reported to rise up to 300 mmHg and diastolic up to 220 mmHg.[88] An extensive and informative description of the disorder is presented in Blackmer 2003 Rehabilitation Medicine:Autonomic Dysreflexia.

Although reflex bradycardia is traditionally thought to be part of the syndrome of AD, it is only seen in

10% of cases. Tachycardia or no significant change in heart rate is more commonly noted in most patients with AD.[83,86] Patients may experience a variety of symptoms.[88] SCI patients may present with one or more of the following signs or symptoms when experiencing an AD episode. These symptoms may be minimal or even absent, even with significant rises in BP:[88]

- **Pounding headache, usually occipital, bitemporal, and bifrontal in >50% of patients**
- **Flushing and sweating above the level of injury, especially face and neck with cold limbs**
- **Piloerection (goosebumps and shivering) above or below the lesion**
- **Blurred vision with or without the appearance of spots in the visual field**
- **Nasal congestion**
- **Anxiety**
- **Dyspnea**
- **Malaise**
- **Nausea**

Prevention and Treatment

Urologists can play an important role in AD prevention since the primary driver of AD episodes is lower urinary tract stimulation. Educating all patients on the importance of avoiding bladder overdistension either from infrequent catheterizations or from indwelling catheter kinking or clogging. Also ensuring that patients are not using their AD symptoms as a trigger for catheterizing. Patients also need to have a rescue plan in place if they have AD episodes from bladder distention and have difficulty with their catheter. Having a caregiver be able to assist with a Foley change should it get clogged or be able to perform CIC should the patient have acute difficulty is imperative since there are reports of patients suffering fatal strokes after failure to perform CIC. [89] Good bladder management is key since preventing NDO can also prevent AD, either with oral agents or botulinum toxin injections.

Urologists also frequently perform lower urinary tract procedures in the office on this patient population that can trigger AD episodes. Urodynamics, cystoscopy, cystoscopy with botulinum toxin injection and catheter changes are all likely triggers. Urodynamics provokes AD in half to two thirds[90] of patients with lesions above T6. There are certain patients that have been shown in studies to be at higher risk for AD during UDS and these include: NDO at higher pressure, age above 45,[90] higher level of SCI, being >2 years post injury, the presence of DSD and poor bladder compliance[85] and older individuals are more likely to have asymptomatic AD[84] and complete injuries are more likely to have more severe episodes.[91]

Cystoscopy is very stimulating to the urethra/bladder neck/prostate which are potent drivers of AD.[85] Topical lidocaine 2% gel can be applied to the urethra several minutes ahead of the procedure and bladder over distention should be avoided. Cystoscopy with botulinum toxin could also be stimulating to the urethra but also the bladder injections hence both the urethra and bladder require local anesthesia. Pretreatment should be applied such as 30cc of 2% lidocaine left indwelling in the bladder for 20 minutes pre injection. It is a misconception that this analgesia can be skipped because

of lack of pain perception, it is to prevent dysreflexia.

For all office procedures on patients at risk for dysreflexia (SCI T6 and above) regardless of if they have AD episodes or not should be monitored during the procedure with a pre study baseline heart rate and blood pressure and at a minimum blood pressure assessment every three to five minutes during the study. Also inquiring about previous episodes of AD and that patient's specific symptoms is also very helpful since the symptoms tend to be similar between episodes.

The AUA NLUTD Guideline states that clinicians must hemodynamically monitor NLUTD patients at risk for autonomic dysreflexia during urodynamic testing and/or cystoscopic procedures (Clinical Principle). As described below, 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). For those patients with ongoing AD following bladder drainage, clinicians should initiate pharmacologic management and/or escalate care. (Clinical Principle)**[1]

If a patient does have a > 20 mmHg blood pressure rise during a urologic procedure, the procedure should be aborted and the bladder drained quickly with a catheter and all UDS catheters removed and the blood pressure measurement repeated after 3-5 minutes This is typically all that is needed to resolve most AD events. If this is not effective, **sit the patient upright** and ensure they do not have any stimulus below their lesion by removing abdominal binders/compression socks, ensuring all limbs are padded and not compressed and there are no impinging objects. Sitting the patient upright will reduce intracranial pressure during the episode reducing the risk of complications. If this still does not resolve the episode the patient may have impacted stool and lidocaine gel can be instilled into the rectum and the patient gently **disimpacted** after waiting two minutes. If none of these measures are effective and SBP is > 150mmHg **one inch of nitropaste should be applied to the hairless portion of the chest**. If blood pressure is not improved after 10 minutes, then another inch is placed. The advantage of nitropaste is that it can be wiped off as soon as SBP <130 and it is less likely to cause reflex hypotension because of its quick onset and clearance unlike oral agents that take significant time. Nitropaste has an onset of action is typically 9-11 minutes and full clinical effectiveness is in 14-20 minutes. In a study of 260 episodes of AD requiring nitroglycerine ointment with SBP >160 mmHg 77% were controlled without requiring other pharmacotherapy. [92] If the two applications of nitropaste have not relieved the AD then 10mg of oral hydralazine can be given. In the past beta blockers and calcium channel blockers were advocated, but these cause bradycardia and more severe hypotension once the episode is resolved. Any patient who received nitropaste or oral hydralazine should be monitored for several hours for recurrence of the hypertension but also hypotension that does occur in approximately 4% of patients after nitropaste [92] hence, once these therapies are instituted transfer to an emergency facility should be arranged since most clinics cannot accommodate this intensive monitoring.

All clinics that care for these patients should stock lidocaine gel, catheters and at a minimum

nitropaste and have a familiar protocol to all staff (UDS nurse, clinic medical assistants) so they can be familiar with these events. An inpatient nursing driven protocol of the treatment of AD was published by Solinski et al that assessed its effectiveness in 445 AD episodes. When the protocol was followed 97.6% achieved target blood pressure and the only adverse events were hypotension.[93]

4.3 Bladder Management

Goals of urologic management in the NLUTD patient include:

1. Protection of upper tract function.
2. Minimizing complications such as infections and stones.
3. Providing an acceptable and realistic means for urinary drainage.
4. Maintaining urinary continence.

4.3.1 Indwelling Catheter

For select patients, due to dexterity, social situation, progressive disease, or unwillingness or inability to undergo reconstructive procedure, management with a long-term indwelling catheter is chosen. Such patients should be fully informed regarding the risks and benefits of this management strategy. A chronic indwelling catheter always has chronic bacteriuria, and symptomatic infections may also manifest despite meticulous catheter care. Stone formation in both the bladder and kidneys is also a risk. As sensory deficits are common, urethral breakdown in both men and women can occur. This is a particular risk in females and can ultimately result in bladder neck incompetence and leakage around the catheter and resulting skin breakdown (see **Figure 2**). **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).**[1] To prevent urethral loss, suprapubic placement often provides a more feasible option instead of a urethral location. Catheter changes are simpler and do not require transferring the patient out of a wheelchair with supine positioning to change, plus the risk urethral breakdown is eliminated. The risk of stones and symptomatic infections are unchanged with the suprapubic location. The risk of malignancy secondary to indwelling catheters should be discussed prior to committing to this management strategy.[68]

The current AUA NLUTD Guideline recommends clinicians to perform interval physical examination of the catheter and the catheter site (suprapubic or urethral). (Moderate Recommendation; Evidence Level: Grade C) and do not perform screening or surveillance cystoscopy for these patients with indwelling catheters. (Strong Recommendation; Evidence Level: Grade B). However, NLUTD patients with indwelling catheters who are at risk for upper and lower urinary tract calculi (e.g., patients with SCI, recurrent UTI, immobilization, hypercalciuria), clinicians should perform urinary tract imaging every 1-2 years. (Moderate Recommendation; Evidence Level: Grade C).[1]

4.3.2 Clean Intermittent Catheterization (CIC)

Clinicians should recommend clean intermittent catheterization (CIC) rather than indwelling catheters to facilitate bladder emptying in patients with NLUTD. (Strong Recommendation; Evidence Level: Grade C).[1] NLUTD patients frequently use CIC or an indwelling catheter to facilitate bladder emptying though, there are few comparative studies demonstrating superiority of catheterization technique, type, or emptying schedule.[94,95] In a retrospective study of 308 SCI patients followed over 18 years, upper tract changes were more frequent in patients with indwelling catheters (18%) compared to those using intermittent catheterization (6.5%). This dataset also demonstrated intermittent catheterization was associated with fewer long term complications.[95,96] Other studies have supported favorable outcomes for SCI patients performing intermittent catheterization.[97] However, long term follow-up suggests that NLUTD patients frequently change to indwelling catheters after starting with intermittent catheterization.[98] Newer prospective studies have focused more on patient reported bladder symptoms and quality of life in patients requiring bladder management and patients had the fewest bladder symptoms with indwelling catheters or after reconstructive surgery compared to those patients performing intermittent catheterization.[99] This change in primarily focusing on patient satisfaction rather than simply on complications deserves more attention. Indwelling catheter is associated with infections, stones, and deterioration of the upper tract. Suprapubic tube (SPT) is better tolerated and is not associated with urethral injury when compared to urethral catheters. Indwelling urethral catheter is associated with urethral erosion, fistula, epididymitis, and abscess but UTI rate is not different than SPT.[100,101,102]

NLUTD Patients managed with CIC or indwelling catheters often have a colonized urinary tract and **clinicians should not perform surveillance/screening urine testing, including urine culture. (Moderate Recommendation; Evidence Level: Grade C). However, when a UTI is suspected, clinicians should obtain the urine culture specimen after changing the indwelling 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)**[1]

Clinicians may counsel NLUTD patients with recurrent UTI who use various forms of catheter management that cranberry extract has not been demonstrated to reduce the rate of UTIs. (Conditional Recommendation; Evidence Level: Grade B). Daily antibiotic prophylaxis is not recommended for those managed with indwelling catheter to prevent UTI since it is not effective Strong Recommendation; Evidence Level: Grade B). However, in those NLUTD patients who perform CIC with recurrent UTI, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of UTIs following a shared decision-making and discussion regarding increased risk of antibiotic resistance. (Conditional Recommendation; Evidence Level: Grade C). Bladder instillations to reduce the rate of UTIs may be offered for these patients as well.(Expert Opinion).[1] The evidence supporting suppressive therapy with gentamicin irrigation is scarce but was associated with fewer courses of UTI-treatment no apparent low risk for AE's. The dose utilized was 30-60ml which was instilled in the bladder and removed at the next catheterization time.

4.3.3 Other Bladder Management Types

There is limited data on the effect of behavioral and physical therapy in this population. Although, most studies have a small sample, not generalizable, focus mainly on MS and CVA, have non standard interventions, there are no significant adverse events and are based on the concept that strengthen of the pelvic floor musculature was associated with reduction of LUTS and may be correlated with improvements on various QoL questionnaires. **Clinicians may recommend pelvic floor muscle training for appropriately selected patients with NLUTD, particularly those with MS or CVA, to improve urinary symptoms and quality of life measures.** (Conditional Recommendation; Evidence Level: Grade C)

Other less invasive bladder management methods include voiding, condom catheter, reflex voiding and bladder expression with Valsalva. Although these may be categorized as “non-invasive”, these can be associated with deleterious effects to the upper tracts. Voiding should be evaluated in patients with NLUTD and high risk disease such as SCI or spinal dysraphism as recommended in AUA Guideline for UDS.[103] Evaluation and further urologic testing is recommended in cases of neurodevelopmental impairment or when voiding cannot be differentiated from urinary incontinence; cases of incomplete bladder emptying, retention or LUTS in the presence of NLUTD.[104,105] Condom catheter drainage has been associated with several potential complications such as poor bladder emptying, hydronephrosis, upper tract deterioration, UTI, skin, and penile injury. Sphincterotomy is required to be performed to secure an open bladder neck but often requires repeat procedures over time and periodic urodynamic testing is recommended.[106,107]

Reflex voiding is non-physiologic and is associated with a bladder contraction through activation of C-fibers and an intact peripheral reflex arc in the setting of supra-sacral injury or lesion. Bladder reflex triggering can be induced by rhythmic suprapubic percussions. Detrusor contraction could be joined by bladder neck fibers, pelvic floor muscles activation and simultaneous contraction of the external sphincter (DSD). Bladder expression and triggered bladder voiding are also associated with adverse events including upper tract urinary damage, renal deterioration, UTI, lithiasis, autonomic dysreflexia, worsening urinary incontinence, and loss of bladder compliance. Bladder expression may be safe in the setting of lower motor neuron disease when there is confirmed compliant, non-contractile bladder, and urethral sphincter with open bladder neck.[108,109]

4.4 Oral Drug Therapy

Treatment of urinary symptoms of urgency incontinence, urgency and frequency is performed with anticholinergic medication as previously described. **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).**[1] The AUA NLUTD Guideline advocates for a shared decision-making model to inform, discuss the pros and cons and especially describing the potential for cognitive decline from anticholinergics’ adverse event.[110] In selected NLUTD patients, use of alternative agents less likely to cross the blood-brain barrier without demonstrated cognitive risk may be appropriate. The use of recently approved beta-3 agonist in the NLUTD population is currently well accepted despite the limited available data. Beta-3

drugs can be utilized alone or in conjunction with anticholinergic to minimize side effects from the bladder.

Clinicians may recommend alpha-blockers to improve voiding parameters in NLUTD patients who spontaneously void. (Conditional Recommendation; Evidence Level: Grade C).[1] The use of alpha-blockers combined with antimuscarinics to improve symptoms across diverse NLUTD ailments is now a standard, especially when addressing voiding impairment from possible sphincteric dyssynergia and/or treating high detrusor pressure registered during UDS.

There is level one data from systematic reviews supporting the use of anticholinergic drugs with improvement in UDS parameters of maximum cystometric capacity and maximum detrusor pressure.[111,112] The most frequently reported AE was dry mouth and oxybutynin IR was the drug associate with the highest risk for AE. Although high doses were not associated with higher rates of AEs, combination of anticholinergic drugs was associated with higher AE rates.[111] It is important to mention that included studies in these reviews have short follow-up data, high risk or unknown bias, incomplete evidence for particular patient groups or medications. It is particularly noted the lack of standard measurements with limited utilization of validated surveys. [113]

Oral drug therapy can be tailored across NLUTD ailments with the understanding that some specific conditions may display a superior benefit. Specific treatment for most common NLUTD entities will be described in the subsequent sections.

4.5 Surgical Treatment

Urodynamic evaluation to assess storage capacity and emptying ability is crucial for determining options for patients requiring reconstruction. Key considerations including disease type and possibility of progression, manual dexterity (ability to catheterize), reliability, desire for continence, skin issues, and socially acceptable management all weigh into the decision for the type of reconstruction.

4.5.1 Chemodenervation with OnabotulinumtoxinA

Botulinum toxin has revolutionized management of the NLUTD. The most commonly used serotype, onabotulinumtoxinA, is one of the seven serotypes produced by the Clostridium botulinum bacteria. There are four commercially available types, Botox™, Dysport™, Xeomin™ and Prosigne™, and dosage is not interchangeable between the types. [114] Since only Botox™ currently has U.S. approval for use in the lower urinary tract, doses reported in this section will refer to Botox™ only.

OnabotulinumtoxinA injections are performed in the bladder via a transurethral cystoscopic technique. **The mechanism of action for onabotulinumtoxinA includes reducing bladder contractility by inhibiting presynaptic release of acetylcholine from nerve terminals through binding of SNAP-25, thus reducing stimulation of the muscarinic receptors**.[28] There is no consensus recommendation on optimal anatomic injection region or whether intradetrusor versus submucosal injections have greater efficacy.

In NLUTD patients with SCI or MS 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).[1] Level one data from robust double blind randomized, multicenter, industry sponsored trial, suggested that number of incontinence episodes significantly decreased six weeks after onabotulinumtoxinA. Repeated injections are associated with similar effect even after initial low response rates. The most frequent side effects are UTIs, urinary retention and hematuria. [115] Starting intermittent catheterization may be necessary in patients who void, like those with MS, hence a lower dose of onabotulinumtoxinA (100 U) is recommended in this particular population.[116] **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).** [1]

The AUA NLUTD Guideline recommends the utilization of onabotulinumtoxinA in NLUTD patients, other than those with SCI and MS after lack of improvement with oral medications. It is stated that clinician may offer onabotulinumtoxinA to improve bladder storage parameters, decrease episode of incontinence and improve quality of life measures for those patients who are refractory to oral drugs (Conditional Recommendation; Evidence Level: Grade C). [1]

4.5.2 Neuromodulation techniques

The data on utilization of posterior tibial nerve stimuli is limited and the AUA NLUTD Guideline supports this for selected patients with spontaneous voiding with symptoms of urgency, frequency, and/or urgency incontinence (Conditional Recommendation; Evidence Level: Grade C). Improvement has been demonstrated in patietns with MS, PD, and CVA who have OAB symptoms and continue to be able to void.[1]

Sacral neuromodulation (SNM) has been shown to be effective in select patients with NLUTD including those with NLUTD due to MS, CVA, and PD. **Clinicians may offer sacral neuromodulation to select NLUTD patients with urgency, frequency, and/or urgency incontinence. (Conditional Recommendation; Evidence Level: Grade C).** However, **SNM should not be offered in cases of SCI or spina bifida. (Moderate Recommendation; Evidence Level: Grade C).**[1]

4.5.3 Outlet Procedures

Of note, the outlet must also be assessed prior to any bladder procedure, as increasing bladder capacity without addressing an incompetent outlet will provide suboptimal results. Bulking agents, sling procedures, or in extreme cases, bladder neck closure with catheterizable stoma, may be required.[117,118,]

Urethral bulking agents may be offered 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) [1]

Slings and artificial urinary sphincter should be offered to select NLUTD patients with stress urinary incontinence and acceptable bladder storage parameters. (Moderate Recommendation; Evidence Level: Grade C) [1]

With regards of bladder neck closure, it is **recommended a thorough discussion of risks, benefits, and alternatives, prior to offer bladder neck closure along with concomitant bladder drainage methods to select patients with NLUTD and refractory stress urinary incontinence. (Expert Opinion)**[1]

4.5.4 Urinary Reconstruction

Clinicians may offer augmentation cystoplasty to select NLUTD patients who are refractory to, or intolerant of, less invasive therapies for NDO and/or poor bladder compliance. (Conditional Recommendation; Evidence Level: Grade C) [1]

If after botulinum toxin capacity is inadequate, leakage occurs due to neurogenic detrusor contraction, or if unacceptably poor compliance is present, urinary diversion, augmentation cystoplasty, with or without catheterizable stoma may be recommended.

The decision to proceed with surgical treatment urologic reconstruction in the NLUTD patient should be viewed as a permanent option. Increasing bladder capacity may be accomplished by bladder augmentation. Most neurologic patients requiring augmentation do not have the ability to spontaneously void, but in those that do, augmentation will most frequently result in the need for intermittent catheterization as well as irrigation. If the patient is unable to catheterize per urethra, the addition of a catheterizable channel may be included and this can be created with the appendix (Mitrofanoff), tapered ileum (Monti) or with an ileocecal segment.[119] **This concept is supported by the AUA NLUTD Guideline which states that clinicians may offer continent catheterizable channels, with or without augmentation, to select NLUTD patients to facilitate catheterization. (Conditional Recommendation; Evidence Level: Grade C)**[1]

Augmentation is most commonly performed using ileum or colon. Stomach has been used in the past, though this has fallen out of favor for several reasons, including hematuria/dysuria syndrome and hypochloremic, hypokalemic metabolic alkalosis. The selection of segment to utilize for augmentation depends on surgeon preference, patient anatomy, and metabolic considerations. Long term (25+ years) functional outcomes in spina bifida patients [120] SCI and MS patients[121] are very favorable with high continence rates and very low long-term complications. Patient-reported bladder function and quality of life among SCI patients performing intermittent catheterization with an augmentation cystoplasty was better than those patients receiving botulinum toxin or simply performing intermittent catheterization. [122]

If the outlet is evaluated to be incompetent, simultaneous procedures to improve outlet resistance or even close the urethra may be performed. Pubovaginal slings or artificial urinary sphincters can be performed at the time of augmentation. Closure of the bladder neck should be done with exceptionally careful consideration, as this limits future access to the bladder via a catheterizable

stoma, typically 12-14 Fr in diameter, preventing larger scopes and urologic instrumentation. It is imperative that bladder compliance be fully evaluated and treated if necessary, prior to closing or obstructing the outlet, as severe hydronephrosis and renal functional loss can rapidly occur if bladder storage is unsafe. In some settings of a completely destroyed outlet, however, this may be the only existing option.

Perioperative complications including blood loss, bowel obstruction, bowel leak, urine leak, venous thromboembolism, pneumonia, and even mortality must be explained. Metabolic considerations, particularly in the patient with impaired renal function, may require medical management. Consistent catheterization is required, with a risk of perforation in noncompliance, resulting in a surgical emergency and potential mortality. Stomal stenosis can occur with any channel, with revision and repeat surgery often required. Leakage from the stoma and/or urethra can persist and be problematic. Mucus production in the urine in patients with bowel in continuity of urine occurs, whether from ileal conduit, augmentation, or continent reservoir and therefore a lifelong regimen of irrigation is recommended. In the augmented bladder, stone formation has been reported in up to 50 % of patients. Patients continue to have risk of symptomatic UTIs, and patients should be educated as to the expected presence of chronic bacteriuria. However, in those patients who have persistent NDO causing incontinence despite augmentation can receive botulinum toxin injections into the native portion of the reconstructed bladder with some success rather than proceeding with repeat reconstruction.[123]

Urinary diversion with ileal conduit is an additional options when other reconstruction is not feasible due to risk or unmanageable conditions (fistulas, inability of CIC etc) , with simple cystectomy typically indicated due to the risk of future pyocystis. Simple cystectomy is less morbid than radical cystectomy and in general requires less operative time.[124]

The risks and benefits as well as the long-term maintenance and follow-up required of patients undergoing urinary tract reconstruction should be thoroughly discussed preoperatively. **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)**[1]

Ileovesicostomy is performed in selected cases and constitutes a major surgical reconstruction which includes a urinary diversion method offered to adults. Ideal candidates are characterized by having a small bladder capacity and severe incontinence due to NDO. However it is important to continue surveillance and follow up to confirm leakage at a low pressure given the fact that bladder is left in place and could potentially generate high risk pressure and deleterious effect to the upper tracts. This surgery may be offered to patients who are unable to perform self-CIC or those with condom catheter induced skin breakdown. **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).**[1]

In NLUTD patients who have undergone lower urinary tract reconstruction incorporating a

bowel segment(s), the clinician should assess the patient annually with: (Expert Opinion)

- **focused history, physical exam, and symptom assessment.**
- **basic metabolic panel.**
- **urinary tract imaging.**[1]

4.6 Follow-Up and Post Treatment

Depending on risk stratification from AUA NLUTD Guideline, it is recommended regular visits with primary care physician or physiatrist for those patients with Low-Risk and urologic evaluation should be repeated at any time when there is a change in LUTS, there is elevated PVR. Patients in the Moderate-Risk category should undergo specific surveillance every year for renal function and every 1-2 years with imaging to assess upper tracts. The periodicity of UDS for this Moderate risk category is not well defined. For those patients with high-risk parameters, particularly if elevated bladder storage pressures, impaired compliance it is recommended to treat and evaluate renal function, upper tracts and repeat UDS yearly or even more frequent if necessary, until these parameters are deemed stable. [125,126,127] **The AUA NLUTD Guideline recommends clinicians should repeat UDS at an appropriate interval following treatment in those patients with impaired storage parameters and/or voiding that place their upper tracts at risk (Expert Opinion).** [1]

Escalation of management for those patients who are refractory to oral drug therapy, onabotulinumtoxinA with persistent symptoms and moderate- to high-risk factors should be entertained. **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)**.[1] Depending on patient's neurologic impairment, overall social environment and expectations, comprehensive counseling should be provided to address change in bladder management and offer surgical interventions to promote low bladder pressures by urinary diversion in a prompt manner with indwelling catheter while considering other more permanent options.

It is important to mention that **any patient with symptomatic recurrent UTI or hematuria should undergo cystoscopy and the AUA makes special mention of those patient who have underwent lower urinary tract reconstruction with utilization of bowel (Moderate Recommendation; Evidence Level: Grade C).** None the less the risk of malignancy is very low and this indication controversial it is recommended to perform cystoscopy to rule this out.[1]

5. Spinal Cord Injury

5.1 Pathophysiology and Clinical Manifestations

Spinal cord injury is often due to trauma but may also occur secondary to infections, vascular injuries or surgical interventions. Patients with SCI usually have alterations to the functions of the lower urinary tract (NLUTD) and bowel, in addition to sexual dysfunction.[128] The neurologic deficit and LUTS in SCI is determined by the extent of injury to the spinal column and the level of the injury. Injury to the spinal column may be complete or incomplete, with complete anatomic transection

being rare. Spinal cord injuries are typically categorized by the vertebral level; however, it is important to remember that the vertebral level has a different relationship to the spinal column at different locations. In particular, the sacral spinal cord begins at the T12- L1 vertebral level and the termination of the spinal cord, the cauda equina, begins around the vertebral level of L2. Injury to the spinal cord may extend in a cranial or caudal direction or both from the level of the vertebral injury.[128]

Immediately following a SCI, a period of spinal shock is noted.[128] Spinal shock consists of absent somatic reflex activity and flaccid muscle paralysis below the level of the SCI. **During spinal shock the bladder is acontractile and areflexic**. The smooth sphincter mechanism is intact, and the striated sphincter tone is maintained without voluntary control. A patient with spinal shock will have urinary retention which may be managed with some form of catheterization. Patients are often initially managed with in indwelling Foley as they recover from surgery and other injuries. Clean intermittent catheterization may be started at any time the patient is clinically stable. The duration of spinal shock is highly variable and may last for days to months. Urologists may not be involved in the care of the spinal cord injured patient until after the patient is out of spinal shock or there is a change in urinary signs and symptoms. However, in the patient with an acute neurological event resulting in NLUTD, the clinician should perform risk stratification once the neurological condition has stabilized.[1]

5.1.1 Suprasacral Spinal Cord Injury

A **complete lesion above the sacral spinal cord usually results in NDO, smooth sphincter synergia and striated sphincter dyssynergia**. Striated sphincter dyssynergia will result in an obstruction with high detrusor pressure and poor bladder emptying. These patients require a complete work up to risk stratify and manage their NLUTD.[1]

5.1.2 Sacral Spinal Cord Injury

The patient with a **sacral SCI, typically in addition to having absent sensation and flaccid paralysis below the level of the injury, will demonstrate detrusor areflexia with normal or high compliance** . Over time decreased compliance may develop although the reasons for this change are not well understood. Typical outlet findings consist of a competent smooth sphincter and a striated sphincter that has fixed tone without voluntary control.

5.2 Clinical Evaluation

Suprasacral SCI requires a comprehensive evaluation as detailed in the first section of this chapter based on the AUA NLUTD Guidelines. Recommended tests include PVR for those who are voiding, UDS, upper tract imaging as well as evaluation of renal function. Comprehensive history, physical exam, and urinalysis are recommended as part of the initial evaluation. All patients with SCI are considered unknown risk based on the disease process even if they spontaneously void and should undergo further evaluation Bladder diary, pad test, and non-invasive uroflow are considered optional tests and should be offered based on the clinical scenarios.

Urodynamics are paramount and can be performed with fluoroscopy when available since high

storage and high voiding pressures may result in renal injury even without VUR, hence the importance of preventing these to avoid upper tract dilation and/or renal impairment. The level of injury and the neurologic findings do not always correlate to the urodynamic findings.[56] History and clinical exam have been deemed insufficient in SCI patients to determine a detailed individual diagnosis of their type of NLUTD.[129] Since maintenance of low storage pressure is a critical goal in treating the spinal cord injured patient, UDS should be performed early in the evaluation and repeated to ensure that low pressure storage is achieved and maintained. Once low-pressure storage is achieved, studies can be repeated but the frequency of these tests has not been established with many clinicians reserving this invasive test for worsening urologic symptoms, upper tract deterioration or new recurrent UTIs rather than specified time.[130] Any clinical changes should precipitate an earlier study.

5.3 Bladder Management and Treatment

Bladder management principles and oral drug therapy is displayed in Figure described in Section 4 apply to SCI population. **In NLUTD patients with SCI or MS 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).**[1] Data from a double-blind, randomized trial of MS and SCI NLUTD patients suggested that number of incontinence episodes significantly decreased (21 for 200 units, 23 for 300 units) 6 weeks after onabotulinumtoxinA injections. Median time for request for retreatment was approximately 250 days. Injections of 200 units proved equally effective as 300 unit injections with a reduced side-effect profile.106 Repeated injections are associated with similar efficacy, even after initial low response rates. The most frequent side effects are UTIs, urinary retention and hematuria. [115] An initial dose of 200U should be tried and if ineffective there is evidence that increasing the dose to 300U is safe and may salvage some patients.[131]

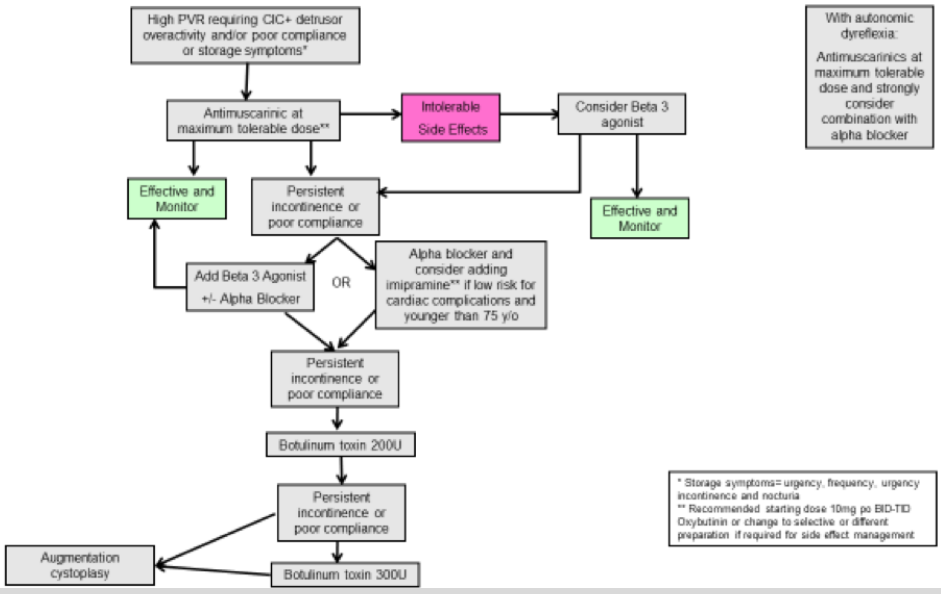

Figure 5. Algorithm for Management of NLUTD in patients with SCI

Urologic Interventions are described earlier in this Chapter to address outlet as well as those major surgical interventions to facilitate catheterization for those select patients with upper extremity and dexterity limitations who may benefit from a continent stoma. Status of renal function and ongoing medical problems are crucial as well, when counseling about continent stoma with/without enterocystoplasty augmentation vs. incontinent urinary diversion, or suprapubic tube.

6. Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder affecting the dopaminergic neurons of the substantia nigra, but also remotely located neurons. In addition to the classic symptoms of rigidity, gait difficulty, tremor and bradykinesia, at least 45% of patients will also suffer from voiding dysfunction. [132,133] The most common symptoms include urgency, frequency, nocturia, and urgency leakage with a typical UDS finding of NDO. [134] Residual urine is typically low in contrast to patients with Multisystem Atrophy (MSA).

Previously, it was assumed that PD was associated with sphincteric dysfunction. Bradykinesia of the external sphincter with uninhibited contractions may be detected, but true dyssynergia has not been demonstrated. Historically, outlet procedures such as TURP were discouraged due to concerns with sphincteric control, however data leading to this conclusion may be inaccurate for PD's patients. Prior to considering a non-reversible intervention with PD's patients, UDS assessment is recommended.

Patients with MSA may present with urinary symptoms of frequency, urgency and urgency incontinence prior to the onset of other neurologic symptoms. The classic urodynamic findings in Multisystem Atrophy are NDO, striated sphincter denervation on EMG and an open bladder neck on UDS with fluoroscopy.[128]

Treatment

Antimuscarinic agents, as available for the idiopathic overactive bladder patient, may be utilized in the PD's patient.[135] Attention should be paid to side effects, as constipation and bowel dysfunction may already be present due to the neurologic disease. Beta -3 agonists may represent a better choice since they do not exacerbate constipation or have any cognitive side effects that may severely affect this patient population. Also, many of these patients have difficulty voiding and these agents do not increase PVR. Nonetheless, the utilization of antimuscarinic drugs is supported and minor AE's have been reported after using solifenacin which also showed decreased 24-hour frequency, nocturia, and incontinence episodes in this particular population. [136] The administration of the alpha-blocker doxazosin has shown to improve maximum flow rate and self-reported urinary symptoms also with mild AEs.[137]

Intradetrusor injections of botulinum toxin for overactive bladder symptoms refractory to medications has been used successfully in PD patients. [138] As noted previously, sphincteric bradykinesia may be present and mimic BPH symptoms in the male patient, and alpha-blockers are recommended first-line treatment in patients with obstructive voiding symptoms. These should be used with caution

as patients may already have orthostatic hypotension due to other medications or PD. Transurethral resection of the prostate should be used in caution in the male PD's patient, with incontinence rates of up to 28% reported,[139] though many authors now suspect those patients may have been misdiagnosed with PD's and potentially were actually suffering from MSA.[14,15]

Sacral neuromodulation or percutaneous tibial nerve stimulation are attractive options in the PD patient as they do not cause urinary retention. If the patient is amenable to intermittent catheterization, botulinum toxin can be beneficial. PD patients have been included in reports of successful sacral neuromodulation in pooled studies in the NLUTD population,[16] though to date no separate study of its use has been published.

7. Multiple Sclerosis

7.1 Epidemiology, Pathophysiology and Classification

Multiple sclerosis (MS) is the most common neuroinflammatory disease of the central nervous system (CNS). The disease is characterized by demyelinating plaques throughout the CNS which are thought to be caused by T cell/macrophage induced inflammatory reactions. MS can be challenging to diagnose because there is no definitive test. Clinicians utilize the McDonald Criteria which requires MRI findings to correlate with 2 neurologic clinical manifestations, separated by time and recovery.[140] A spinal tap showing oligoclonal bands also supports the diagnosis when no neurologic recovery has occurred. The initial onset of neurologic symptoms typically occurs between ages 20-50, and presentation at an age greater than 40 may be associated with a greater risk of more rapid disability.[141] The disease affects approximately 85 cases per 100,000 people, with women two to four times more commonly affected than men.[142,143,144]

Multiple sclerosis can be roughly categorized into three major subtypes:

- Relapsing/Remitting: Neurologic symptoms present and then completely or partially resolve after 2 days to 6 weeks. There is no progression of severity of disease between episodes.
- Secondary Progressive: 50% of the relapsing/remitting patients will develop progressive neurologic symptoms that do not return to baseline, particularly in the lower extremities. Secondary Progressive MS typically occurs more than 10 years after initial diagnosis.
- Primary Progressive: 10% of patients will experience continuous neurologic degradation after initial presentation, characterized by no remission.

Disability is commonly reported in the literature through the Extended Disability Symptom Score which measures disease impact on multiple systems including voluntary muscle control, vision, memory, balance, sensorium, and bowel/bladder function. A single score is given which ranges from 1 (minimal impact) to 10 (death from disease). Patients with scores > 6.5 require constant bilateral assistance to walk 20 meters without resting and have impact on 2 systems.[145]

7.2 Urologic Evaluation

Urologic symptoms are common in patients with MS. In the 2010 North American Research Committee on MS (NARCOMS) cross sectional survey, 65% of responding MS patients reported moderate to severe urinary symptoms.[146] **Urinary urgency is usually the most prevalent reported symptom in MS**. In some studies, up to 21-50% of patients experience frequent episodes of urinary incontinence in addition to hesitancy and 25% of patients report urinary retention.[146,147,148] Although a relatively uncommon presentation, it has been reported that up to 14% of MS patients had urinary complaints as the initial MS symptom.[149] Urinary symptoms usually become prevalent in MS patients between 6-8 years after initial diagnosis.[147,148,149,150]

The Neurogenic Bladder Symptom Score (NBSS) is a second patient reported outcome measure that assesses objective symptoms related to NDO.[151]

Based on **AUA NLUTD Guidelines patients with MS can be categorized as low or Unknown-Risk depending on PVR and presence of other complications. Those at unknown risk need to complete further evaluation with UDS, imaging of the upper tracts and evaluation of renal function.**[1] Meta-analysis of urodynamic data in MS patients (22 studies, 1882 MS patients) demonstrated NDO in 62%, DSD in 25%, hyporeflexia in 20%, and no pathologic findings in 10%.[152] Although UDS are commonly used to differentiate LUTS in MS patients, there are no uniform recommendations defining which MS patients need urodynamic testing or the timing of repeated evaluations. The tests may be most helpful in differentiating MS patients with hypocontractility from those with obstructive DSD.

7.3 Radiologic Findings and Prognosis

Volume growth of an MRI identified lesion appears to modestly correlate with urinary symptom progression within the first 5 years.[153] Location of the lesion is difficult to directly correlate with urinary symptoms, although patients with lesions in the medial frontal lobes, cerebellum, insula, dorsal midbrain, and pons have demonstrated low urinary specific quality of life.[154] MS patients with cervical spinal cord involvement[155] are likely to display some urinary hesitancy and there is some data linking cervical lesions and detrusor-sphincter dyssynergia on UDS.[156]

Risk factors for developing upper urinary tract pathology in MS patients remains unclear. De Seze compiled data from 11 studies consisting of 1200 MS patients and found a rising incidence of upper tract complications over time for symptomatic MS patients. This data suggested that upper tract changes were most likely to occur 6-8 years following diagnosis.[150] Increased patient age and low bladder compliance have also been associated with an increased risk for upper tract change, although the overall risk for upper tract changes in the MS population is low around 3%.[156,157,158]

7.4 Treatment

Guidelines from the AUA for evaluation and management of NLUTD are described in earlier sections of this chapter. Pathways for addressing LUTS in MS patients have additionally been developed for national health care systems[159,160] and non-urologic specialists.[161] In general, treatment recommendations attempt to minimize morbidity and maximize quality of life for the MS patient as

mobility may decrease during disease progression.

7.4.1 Bladder management

Catheterization is frequently utilized by the MS population in the setting of urinary retention. In a large patient registry, 37% of MS patients reported using some type of catheter assistance for bladder emptying. [146] Clean intermittent catheterization is routinely suggested for elevated PVR. However recent data suggests that patients with MS and elevated PVR should be offered CIC based on LUTS and not based on the actual PVR number alone since higher numbers do not necessarily correlate with worse symptoms.[162] In some CIC treatment plans, patients catheterize per a set time schedule, ranging from every 3 to 6 hours. Other CIC programs will instruct the patient with intact bladder sensation to perform CIC when they sense bladder fullness. MS patients utilizing intermittent catheterization remain at risk for UTIs. However, one study demonstrated that while 90% of these patients developed bacteriuria, only 14% developed symptomatic UTIs. [163] If an indwelling catheter is indicated for long term care, the United Kingdom consensus statement recommends offering a suprapubic instead of a urethral catheter.[160]

The authors of this chapter support spontaneous volitional voiding while having elevated PVR on this very unique patient's population as long NLUTD are stable while categorized as Moderate-Risk and periodic surveillance is established as recommended by current AUA NLUTD Guidelines. [1] Treatment of urinary symptoms with oral drugs or onabotulinumtoxinA will increase overall risk of retention and increase frequency of visits is recommended while starting or escalating dosing of these therapies. It is recommended to discuss the specific risks of urinary retention and the potential need for CIC prior to starting this therapy. [1] Catheterization in patients with MS is associated with increase rate of UTIs which can be associated with flare of MS or even progression of overall disease and for this reason we recommend close surveillance when starting any catheterization method as well.

7.4.2 Behavioral Modification

Sparse studies are available to assess the efficacy of behavioral therapy for NDO related to MS. DeRidder demonstrated improvement in mean functional bladder capacity (178cc to 205cc) and reduction in mean number of urinary frequency episodes (12.7 to 9.1) after one month of pelvic floor muscle training. [164] Combining behavioral therapy modalities may also offer benefit for MS patients. McClurg randomized 30 women with MS into treatment groups of pelvic floor muscle training, EMG biofeedback, and neuromuscular stimulation and found improved efficacy in reducing number of leaking episodes and in volume leaked when all three modalities were utilized compared to a solitary treatment. This data demonstrated an 85% reduction of urinary incontinence episodes with all three modalities combined, compared to a 47% improvement when patients employed only 2 modalities. [165]

As previously described in Section 3 of this chapter, the AUA supports pelvic floor muscle training for appropriately selected patients with NLUTD, particularly in cases of MS or CVA, to improve urinary symptoms and QoL measures. [1]

7.4.3 Oral Drug Therapy

The AUA NLUTD Guideline recommends antimuscarinics, beta-3 adrenergic receptor agonists, or a combination of both, to improve bladder storge parameters in NLUTD patients. Alpha-blockers may be recommended to improve voiding parameters in NLUTD patients who spontaneously void.[1]

Antimuscarinics

Cross-sectional surveys demonstrate MS patients have significant LUTS and are likely undertreated. Indeed, studies have reported that only 43% patients with significant urinary urgency had undergone urologic evaluation and only 51% were treated with an anticholinergic.[146] Under-treatment may be partially due to a dearth of high-quality trials demonstrating efficacy of anticholinergic medications in the MS population. Data published from a dose escalation study of solifenacin in 30 symptomatic MS patients found a decrease in number of micturitions and pad use per day.[166] A meta-analysis of the current literature regarding anticholinergic therapy for MS-related incontinence found only 5 applicable studies, none of which included placebos or long-acting anticholinergic medications. No conclusions suggesting benefit from anticholinergic usage could be drawn from the analysis.[167] Overall, there is sparse level 1 evidence regarding optimal dose or medication for treating overactive bladder symptoms in MS patients. Cognitive side effects should be strongly considered before starting anticholinergic medications in MS patients with disease related changing mental status. It has been shown that MS patients do experience cognitive dysfunction with the use of antimuscarinics.[151] One small study showed great effectiveness of mirabegron combined with desmopressin in the treatment of patients with MS inadequately treated with solifenacin.[168]

Beta-Agonists

The AUA NLUTD Guideline supports the use of beta-3 adrenergic receptor agonists nonetheless the data on these drugs is still limited. A small prospective study showed similar response rates to mirabegron and solifenacin. Authors concluded that improvement in urinary symptom severity was greater with solifenacin, though this potential benefit needs to be weighed against the increased risk of worsening constipation.[169] A multicenter study showed no difference when assessing urinary symptoms in MS patients receiving either mirabegron or anticholinergic therapy and significant improvement was reported in all groups during the 12 week study.[170]

Alpha-Blockers

Although alpha-blockers are commonly used to treat obstructive symptoms and urinary retention in MS patients, little data is available regarding efficacy. Some reports have noted a 41% improvement in flow rate with a 26% reduction of post void reduction in MS patients treated with an alpha blocker for 4 weeks.[171] Additional studies of mixed DSD pathologies, including MS, also found tamsulosin effective in treating obstructive symptoms.[172]

Desmopressin

In contrast to alpha-blockers, multiple studies have been published investigating the efficacy of desmopressin for MS related nocturia. While on desmopressin, MS patients experienced a decrease in nocturia by mean 0.5-1.5 episodes/night and an increase of uninterrupted sleep by a mean of 2

hours. Reduction in urinary frequency was limited to the first 6-8 hours after delivery. Urine sodium and maximal urinary daily output remained relatively stable in a meta-analysis of MS patients on desmopressin. [173,174]

7.4.4 OnabotulinumToxinA

The AUA NLUTD Guideline states that **onabotulinumtoxinA should be recommended** in patients with SCI or MS that are refractory to oral medications to improve bladder storage parameters, decrease episodes of incontinence, and improve QoL measures. **It is also recommended to counsel patients about potential risk for CIC**.[1] **Multiple trials have demonstrated that patients with MS receiving intradetrusor botulinum toxin injections improved cystometric capacity by 50-300%, improved time to first desire by 50%, and significantly reduced daily incontinence episodes**. Patients with recurrent UTIs likewise improved after successive botulinum injections **Table 3**.[114,115,175,176,177,178,179,180,181]

Patients with detrusor-sphincter dyssynergia may also benefit from injections into the external sphincter, although efficacy data for this indication is inconsistent.[182] Botulinum toxin does require retreatment due to its mechanism of action and most studies suggest improvement begins to wane after 6 months. Patients who are currently voiding need to be counseled that risk of urinary retention increases with 200 units, compared to 100-unit injections. Starting CIC may be necessary in patients who void, like those with MS, hence a lower dose of onabotulinumtoxinA (100 U) is recommended in this particular population. [116]

Table 3: Treatment with Botox™

Study	N (%MS)	Dosage	Outcome	Comment
Ginsberg (2012)[114]	416 (54)	100, 200	Dose dependent improvement in incontinence episodes	Randomized, placebo controlled trial, Dose dependent retention
Sussman (2013)[36]	275 (56)	200, 300	Increased MCC - 157cc 200, 300 - 6.5cc placebo	Mixed SCI/MS sample; QOL data presented
Cruz (2011)[115]	154 (56)	200, 300	At 12 weeks, change in UI - 15.5/week placebo - 24/week 200, 300	Randomized, blinded placebo, o difference in 200, 300 efficacy
Wefer (2009)[38]	214 (5)	290	58% reduction in UTI incidence	Cost $830 (617 euro)/year per patient
Game (2008)[39]	30 (50)	300	Decrease in UTI from 1.75/6 months to 0.2/6months	Failures had minimal changes in urodynamics

Ehren (2007)[40]	31 (20)	500	Improvement in capacity, compared to placebo	All patients on tolterodine; Dysport used
Kalsi (2007)[41]	43 (100)	300	300% increase in capacity 45% decrease frequency 77% incontinence episodes	98% performed CIC after
Schulte-Baukloh (2006)[77]	16 (100)	300	58-77% improvement in max capacity. 38-64% pad use reduction	Injection to both external sphincter and detrusor
Popat (2005)[80]	44 (66)	300	53% improvement in max capacity, incontinence	

7.4.5 Neuromodulation

Given the likely neurogenic source of voiding dysfunction in MS patients, neuromodulation offers great potential for alleviating symptoms. Sacral nerve stimulation has been attempted for both non-obstructive urinary retention and NDO in MS patients. In a small series of 14 patients with a mean EDSS of 4, post void residuals decreased from a mean 308 to 50cc over 4- year follow up. [159] Additional studies comprising 33 patients with MS and other neurogenic causes of voiding dysfunction noted a 58% reduction of CIC episodes/24 hours after neuromodulation.

With the new MRI compatible devices, neuromodulation indication has been expanded for the MS population as MRI is often a critical component of continued neurologic assessment. Alternative non-implantable neuromodulation modalities have been investigated for use in MS patients. Percutaneous dorsal penile/clitoral nerve stimulation resulted in a mean 95% increase in bladder capacity [160] and posterior tibial nerve stimulation improved bladder capacity by 50% in a mixed neurogenic bladder cohort. [161] Urodynamic improvement was also demonstrated in additional small MS cohorts.[164] Pudendal nerve stimulation offers some theoretically benefits over sacral nerve stimulation, but no robust data is yet available on outcomes in MS patients.

Although the data supporting sacral neuromodulation for MS is not robust, the AUA NLUTD Guideline states that SNM may be offered to select NLUTD patients with urgency, frequency, and/or urgency incontinence. [1]

7.4.6 Urinary Diversion/Reconstruction/Suprapubic tube

Select MS patients with low bladder capacity/compliance, refractory urinary incontinence, global debilitation, and/or recurrent urosepsis may benefit from augmentation cystoplasty and/or continent catheterizable stomas following failure of conservative treatments. Data are limited regarding outcomes and follow-up for these invasive procedures.

Suprapubic tube placement is also a viable option with much less surgical morbidity and is well tolerated in this population who face increasing disability over time and may lose the ability to perform catheterization of an augmented bladder or continent stoma.

8. Neurospinal Dysraphism

Neurospinal dysraphism is the malformation of the vertebral arches that is likely associated to further malformation of the neural tube. This could be classified depending on the type of defect on spina bifida occulta when there is only a vertebral defect and spina bifida cystica (aperta) when there are both a bony and a neural tube (spinal cord) defect. Myelomeningocele is the most common form of spina bifida cystica (>90%) and about half will affect the lumbosacral region. The level of the lesion does not correlate with urodynamic findings. [183] Myelomeningocele occurs in approximately 1 per 1000 live births.[71,184] Neurologic LUT dysfunction is commonly associated with myelomeningocele with an incidence of more than 90%.[71,184]

8.1 Evaluation

Based on **AUA NLUTD Guidelines patients with spinal dysraphism need to complete further evaluation with PVR, UDS, imaging of the upper tracts and evaluation of renal function.**[1] Initial evaluation, periodic surveillance and complete evaluation is described earlier in this chapter. Goals of therapy include reduction in detrusor pressure and maintenance of bladder compliance and social continence. [185] Understanding renal function and considering nuclear scans to assess for this will aid in preventing deleterious events to upper tracts. Urinary symptoms will persist throughout adulthood, lifelong urologic follow-up is recommended, and it is fundamental to identify barriers and facilitate transition to adult care in a multidisciplinary approach. [186]

The common urodynamic findings are areflexic bladder with an open bladder neck. Urinary incontinence will occur when the resting residual fixed external sphincter pressure threshold is reached. This is independent of NDO or any increase in abdominal pressure and is commonly described as detrusor leak point pressure.[65] Stress incontinence is also common and is influenced by increase in intra-abdominal pressure. Patients without incontinence can be associated with low rate of DSD (10% to 15%). Regardless of the pattern of LUT dysfunction in the adult, the main goal of therapy is the avoidance of high storage pressures.[65,187]

8.2 Treatment

Neurogenic bladder symptoms will rely on the type of bladder management and affected by the presence of prior bladder surgery or status of prior urinary diversion or augmentation, as well as status of upper tract dysfunction. Management principles are previously described in this chapter and apply to this unique category for NLUTD. Spina bifida patients can present with a wide variety of symptoms and these are independent of the type of spine dysraphism and cannot be predicted. The management goal relies on surveillance to make sure patient's remain in the Moderate-Risk category and for this reason it is strongly recommend to do complete periodic evaluation as supported by the AUA. [1] For those patients with urinary retention, CIC is the mainstay management of continent and incontinent patients and this will depend on upper extremity, hand dexterity as well as other scoliosis and body habitus limitations. Continent stoma diversion to facilitate catheterization can be offered in this population and are usually performed along augment enterocystoplasty before adulthood.

LUT dysfunction secondary to occult spinal dysraphism may not manifest in childhood. Patients may be referred with symptoms of urinary incontinence or recurrent UTIs. It is fundamental to offer complete urologic evaluation and consider possible ongoing neurogenic etiology in young adults with inexplicable findings of urinary incontinence. Referral to neurology or spine specialist should be prompted as well as ordering spine imaging. Symptoms of back pain, leg weakness, foot deformity, scoliosis, sensory loss, and bowel or LUT dysfunction[188] are associated to a tethered cord syndrome which can occur in in 3% to 15% of patients with myelomeningocele. Surgical urologic interventions should be delayed after neurosurgery. There is no typical dysfunction in TCS, and treatment must be based on urodynamic evaluation. LUT dysfunction may not be present until the teenage years or later.[189]

Videos

A New Technique for Removal of Chronically Implanted Neuromodulator Leads

Robotic Augmentation Enterocystoplasty and Appendicovesicostomy

Transvaginal Bladder Neck Closure

Presentations

NEUROGENIC BLADDER Presentation 1

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