Canadian Urological Association guideline for the diagnosis, management, and surveillance of neurogenic lower urinary tract dysfunction

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1.0 Introduction

1.1 Definitions/Purpose

The term 'neurogenic bladder' describes lower urinary tract dysfunction that has occurred likely as a result of a neurological injury or disease[1]. The International Continence Society (ICS) defines 'neurogenic lower urinary tract dysfunction' (NLUTD) as 'lower urinary tract dysfunction due to disturbance of the neurologic control mechanism.' This broad definition is used to describe a multitude of conditions of varying severity.

Common causes of NLUTD include: spinal cord injury (SCI), multiple sclerosis (MS) and myelomeningocele (MMC). Other causes of NLUTD include: Parkinson's disease, cerebrovascular accidents, traumatic brain injury, brain or spinal cord tumor, cauda equina syndrome, transverse myelitis, multisystem atrophy, pelvic nerve injury and diabetes.

It is well described that neurological disorders can lead to urologic complications including: urinary incontinence, UTIs, urolithiasis, sepsis, ureteric obstruction, vesicoureteric reflux (VUR) and renal failure[2]. Due to the potential morbidity, and even mortality, initial investigation, ongoing management and surveillance is warranted in this patient population. Despite the frequency and potential severity of NLUTD, there are few high-quality studies in the literature to guide urological practices.

Prior neurogenic guidelines vary in their clinical assessment, investigations utilized and surveillance strategies[2-6]. The primary reason is that there is limited evidence to support a common strategy. The purpose of this guideline is to help urologists to identify high-risk patients with NLUTD and to provide an approach to the management and surveillance of patients with NLUTD.

1.2 Classification
The etiology of a NLUTD is often classified based on whether the primary lesion is suprapontine, suprasacral, sacral or infrasacral[7]. A complementary system was developed by Madersbacher et al. based on the function of the detrusor muscle and of the external sphincter[8]. These systems allow a physician to have a general idea of how the lower urinary tract is likely to behave in SCI patients with more complete injuries. (Figure 1). Newer systems using MR urography in combination with urodynamics (UDS) have also been proposed.[9]

2.0 Methodology
This review was performed according to the methodology recommended by the Canadian Urologic Association[10]. EmBASE and Medline databases were used to identify literature relevant to the early urological care of NLUTD patients. Recommendations were developed by consensus and graded using a modified Oxford system which identifies level of evidence (LOE) and grade of recommendation (GOR). This complete version includes the full text of the guidelines (including the sections in the executive summary).

3.0 Canadian epidemiology of neurogenic bladder
There are 3.7 million Canadians living with a neurologic condition,[11, 12] three common types of neurologic conditions are Multiple Sclerosis (MS), Spina Bifida (SB) and Spinal Cord Injury (SCI). In Canada there are 100,000 individuals living with a diagnosis of MS, making it the highest prevalence rate of MS in the world[13]. There are also 35,000 Canadian's living with SB, which is the leading cause of disabling birth defect within the country[11, 12, 14]. In Canada 86,000 persons are living with SCI and 4300 new cases of SCI occur each year.[15] These numbers are projected to increase to 121 000 individuals, with 5800 new cases a year by 2030.[15] Trauma is the most frequent cause of SCI in Canada and most commonly affects men in the 20-29 year age group.[15] Compared to international etiology where the majority of SCI is the result of motor vehicle accidents, in Canada, traumatic spinal cord injury is most commonly caused by falls.[15-17]. Relevant to our aging population statistics, research also demonstrates that a large proportion of traumatic SCI resulting from falls occurs in the senior population.[16, 17] These traumatic SCI cases more frequently result in tetraplegia. Non-traumatic SCI result from disease processes such as MS, SB, tumors and infections. Of Canadians living with both traumatic and non-traumatic SCI, 30,000 experience paraplegia and 13,000 experience tetraplegia.[15, 17] The incidence rate of non-traumatic SCI increases concurrently with age.[17, 18] NLUTD presents a common and

important complication following neurologic disease. In our aging Canadian population, the amount of traumatic and non-traumatic SCI is expected to increase, along with secondary health complications that accompany SCI, such as neurogenic bladder. Research from the U.S. reports frequency of neurogenic bladder to be 40-90% in MS, 40-61% in SB and 70-84% in SCI.[19] A recent Canadian study looking at the impact of bladder, bowel and sexual dysfunction in 51 community dwelling individuals with traumatic SCI reported that 59% of these individuals had bladder dysfunction.[20]

Neurological conditions often result in physical disability requiring the need for assistance with activities of daily living, including assistance with or requiring devices to manage NLUTD. Giesbrecht et al. reported that of Canadians living at home with a physical disability, 51% of individuals using a mobility device required assistance with personal care needs and 36% of these individuals also required assistance with basic medical care.[21] Additionally it was noted that of individuals requiring assistance with care needs at home, those with physical disabilities received an average of 25 hours of care/week versus an 13 hours of care/work given to those without a physical disability.[21] Furthermore, for those individuals with physical disability receiving 25hours of care/week, this reportedly only partially met all the care needs they required.[21]

Neurogenic disease also places an increased demand for health professional services within our health care system and from this a resulting increase in health care costs. For example, a hospital admission for SCI individuals experiencing even uncomplicated urinary tract infections costs the Canadian healthcare system an average of $8, 000.[22] Along with requiring more support with care needs at home, individuals with traumatic and non-traumatic SCI are 2.7 times more likely to contact a physician to address health care needs and also 2.6 times more likely to be hospitalized for health complications.[15] One of the most common health complications causing specifically traumatic SCI individuals to require these additional health care services are urinary tract infections,[23] often experienced as a direct result of neurogenic bladder.

4.0 The diagnosis of NLUTD

To diagnose someone with NLUTD, a defined neurologic condition, or a strong suspicion of an undiagnosed neurologic disease must be present. Potential symptoms which may be suggestive of an undiagnosed acquired neurologic disease include those that precede a diagnosis of MS, cauda equina syndrome, and occult neural tube defect.[7] In these situations, referral to a neurologist for an evaluation may be warranted.

4.1 History and physical exam

In the setting of a diagnosed or probable neurologic disease, a careful evaluation must be carried out to identify symptoms and signs associated with neurogenic bladder dysfunction, with an emphasis on identifying common and potentially serious complications. In most cases, investigations followed by appropriate management can minimize this morbidity. The general

approach to the clinical history specifically relevant to a patient with NLUTD is shown in Table 1.

The timing of this initial evaluation is variable, and dependent on the severity of symptoms, underlying risk of serious urologic complications and the etiology of the neurogenic bladder. Spina bifida[24] and SCI[25] have a significant risk of renal dysfunction, and are acquired at birth (Spina bifida) or often as young adults (SCI); this makes them particularly susceptible to renal dysfunction in their lifetime. This contrasts with slowly progressive diseases such as relapsing-remitting MS, or the predominately elderly population with Parkinsons disease or dementia.

The urologic evaluation of a patient with a newly acquired SCI should occur within 3 to 6 months of the SCI. Efforts should made to assess patients with urologic complications or concerns as soon as possible after the acute SCI. Recent evidence has demonstrated that significant bladder dysfunction can appear early after SCI[26]. Even ambulatory patients who have experienced a SCI can exhibit significant, and often asymptomatic bladder dysfunction when evaluated with UDS.[27] Many patients with MS do not need specialized investigation of their bladder during the initial years after diagnosis. With progression of MS, the risk of bladder dysfunction increases as mobility and functional status decreases, and urologic assessment may become more relevant.[28, 29] When children with spina bifida transition to adulthood, they should be followed by an adult urologist as soon as it is practical to transition them.[30] Ideally, transition to an adult care provider should involve more than a referral; a summary of childhood procedures, up-to-date baseline investigations, and a period of overlapping care may be beneficial[31].

Voiding diaries should be considered for all patients.[32] They allow the patient to self-reflect on their urinary habits, and the physician to measure changes over time in a non-invasive manner and interpret urodynamic findings in the context of the patient's day to day urinary patterns. Validated questionnaires are an optional adjunct to the assessment of NLUTD patients; they are generally used for research purposes in this population.[33]

The specific physical exam to be carried out on patients with NLUTD should include an assessment of body habitus with an abdominal, genital, and rectal exam.[7] It may, in certain circumstances include a focused screening neurologic exam (such as lower limb sensory, motor and reflex function), especially when there is a suspicion of NLUTD without a confirmed neurologic disease. In some of these cases, referral to a neurologist may be appropriate.

4.2 Investigations

Office-based
The initial investigations that should be performed for all NLUTD patients include urine dip (to investigate for infection, microscopic hematuria, and unexpected pyuria or proteinuria), and post void residual (PVR) volume measurement. Urine dip may need to be followed by a urine microscopy, and must be interpreted in the context of catheter usage. In patients who are voiding

spontaneously, using reflexive voiding/crede emptying, or using a condom catheter, the detection of an elevated PVR is important to address potential UTI risk and overflow incontinence and may prompt screening for upper tract deterioration. It is important to recognize that a PVR at the time of renal ultrasound may be artificially elevated secondary to the hydration protocol resulting in bladder over-distension; an elevated PVR from a renal ultrasound should be confirmed in a more normal setting.

PVR is not clearly defined as a factor associated with increased risk of complications among patients with NLUTD [34]. In the non-NLUDT population, a value >300mL is used to define chronic urinary retention[35]. In NLUTD patients with a PVR >300mL it is reasonable to follow them for a period of time to determine the stability of their PVR and bladder symptoms. PVR needs to be interpreted based on the proportion of urine voided and method of bladder emptying. The need to treat PVR should be based on patient symptoms rather than an absolute number.

Specific patient populations require further investigation due to a higher risk of serious sequela from bladder dysfunction. The first evaluation of a patient with spina bifida, SCI, or a patient with more advanced MS should include UDS, renal-bladder imaging, and a measurement of renal function.

Urodynamics

They are the gold standard for evaluating NLUTD and are necessary due to the absence of normal LUT sensation, and the poor ability of symptoms to predict high risk features. VideoUDS are preferred as the additional correlation with imaging allows assessment of vesico-ureteral reflex, abnormal bladder morphology, and the behavior of the urinary sphincters during voiding. The availability of videoUDS is not universal, and a voiding cystogram is an acceptable alternative in some cases. Urodynamic diagnoses such as neurogenic detrusor overactivity (NDO), impaired compliance, reduced bladder capacity, or a high detrusor leak point pressure (DLPP, defined as the lowest vesical pressure at which urine leaks from the bladder in the absence of a detrusor contraction or increased abdominal straining) can identify a patient with potentially higher risk of urologic complications (such as renal dysfunction, urinary infections and incontinence)[36-39]. Other potential urodynamic characteristics, such as the duration of the NDO contraction may also predict renal deterioration[40]. A detrusor leak point pressures (DLPP) of >40cmH2O has traditionally been cited as the cut-off above which a patient has a high risk of renal deterioration, however this is based on a historical study of children with spina bifida, and may not be applicable to adult NLUTD. As DLPP increases, so too does the risk of renal dysfunction due to an increased resting pressure in the bladder being transmitted to the kidneys. If a high DLPP only occurs at a volume greater than the usual capacity during the normal daily voiding pattern, then this DLPP may not be physiologically relevant. A low DLPP maintains low pressure drainage from the kidneys, however this often results in urinary incontinence.

Imaging

Renal and bladder imaging is necessary to identify hydronephrosis (a late but potentially reversible sign of bladder dysfunction in NLUTD), renal/bladder stone disease, abnormal bladder morphology (for example thickened bladder wall, diverticula) and both renal atrophy and degree of scarring; both SCI and spina bifida patients are at an increased risk of renal stone disease, and this may present with atypical symptoms (such as nausea or decreased appetite).[41-43] Often bladder stones are asymptomatic and early treatment while they are amendable to endoscopic management is preferable.

Renal function
Patients with SCI and spina bifida are at increased risk of renal dysfunction; a serum creatinine can be used to assess renal function, however it may not accurately reflect renal function in these two populations.[16] Evaluating the creatinine in the context of previous readings is potentially useful, although it is important to note that changes within the normal range may still be significant. Either a nuclear medicine GFR, or a 24hr urine collection for creatinine clearance will better reflect renal function, and allow the identification of early renal dysfunction. While renal dysfunction secondary to bladder dysfunction can occur with MS, it is quite uncommon (estimated at 0.5%)[44].

Cystoscopy
This should be reserved for situations where there is a clinical indication to assess either the urethra or bladder (such as suspicion of urethral strictures or false passages, bladder stones, or bladder cancer). Screening cystoscopy has historically been recommended among patients with indwelling catheters or after SCI, however there is no evidence that screening programs are effective.[45] Cystoscopy has a poor sensitivity for bladder cancer in SCI patients, the higher risk cancers after SCI are rarely detected at an early enough stage which would affect their natural history, and there is very low real-world compliance with cystoscopy screening programs. However, there does seem to be an increased risk of bladder cancer in patients after SCI, potentially as a result of indwelling catheter usage, and cystoscopy should be used when there is suspicion of a bladder tumor[45]. Patients with NLUTD and bladder cancer may present late due to hematuria being attributed to catheter usage, and atypical presentations such as frequent UTIs, urethral discharge or abdominal mass. A recent systematic review suggests that urine cytology outperforms cystoscopy in select populations[46].

Summary
The initial history, physical exam, and investigations serve to identify high risk features in patients with SCI, spina bifida, or more advanced MS patients (Table 2). Assignment of risk is based on relevant abnormalities within one of 5 domains; two are determined from the patient history (etiology of NLUTD and bladder management) and three are determined based on the initial investigations (UDS, renal imaging, and renal function).

Amongst patients with NLUTD due to other etiologies (or early stage MS), the majority can be managed with history, physical exam, urinalysis, and PVR (Figure 2). The subset of these patients with a clinically significant PVR, bothersome incontinence, frequent UTIs, need for catheters as part of their bladder management, known high risk features on UDS, renal imaging and renal function testing or those considering more invasive management options may require UDS, renal-bladder imaging, and renal function measurement.

Recommendations

1. When referred a new patient with neurogenic bladder, a focused history and physical exam, relevant to the neurogenic condition, should be performed. (GOR A, LOE Expert Opinion)

2. All patients with NLUTD should have a urinalysis and PVR as part of their initial evaluation. (GOR B, LOE III)

3. After a SCI, patients should have a baseline urologic assessment within 6 months of SCI, or earlier if clinical concerns exist. (GOR A, LOE II)

4. Patients with SCI, spina bifida, or advanced MS should have a baseline urodynamic study, renal ultrasound, and measurement of renal function. Selected patients with NLUTDdue to other diagnoses may undergo these investigations when referred for specific urologic concerns. (GOR A, LOE III)

5. The treating clinician should identify patients as either being high, moderate or low risk, and offer the patient appropriate initial therapy, and consider a urologic surveillance program as outlined in section 7. (GOR B, LOE III)

5.0 Genitourinary sequelae of NLUTD

5.1 Risk of upper urinary tract deterioration

Upper urinary tract preservation is a priority when managing patients with NLUTD. Remarkable progress has been made in urological prevention and management to improve renal prognosis in the last decades. Historically, the mortality rate due to renal insufficiency in SCI patients was as high as 50% in the 1960s and dropped to less than 3% currently. In contemporary series, reported rates of chronic kidney disease (CKD) vary between 0.6-3.3%[44, 47] for MS, 1.3-5.6%[47, 48] for SCI and up to 8%[49] for MMC patients, which is higher than that of the general population[50, 51].

In terms or risk factors for CKD, several studies have investigated the prognostic value of urodynamic parameters on renal function deterioration. In 1981, McGuire *et al.* studied 42 myelodysplastic children followed for a mean of 7.1 years and reported that higher intravesical pressure (DLPP>40 cmH$_2$O) was associated with vesicoureteral reflux (VUR) and ureteral dilatation[52]. In 1989, another groundbreaking study from Ghoniem e*t al.* studied 32 children with MMC and noted that low bladder compliance on UDS predicted risk of upper urinary tract deterioration (UUTD)[53].

Weld *et al.* studied 316 SCI patients over 18.3 years and observed that low bladder compliance (<12.5 mL/cmH$_2$O) was associated with VUR, radiographic upper tract abnormality,

pyelonephritis and upper tract stones[33]. In a retrospective study of 73 patients with traumatic SCI followed for a median of 41 years after injury, Elmelund *et al.* found that the duration of detrusor contractions (DO/cystometry ratio) was associated with renal deterioration. Indeed, patients with and without renal deterioration had the same maximum detrusor filling pressure (DLPP) (60 cmH$_2$O)[40].

Interestingly, increased maximum detrusor pressure during voiding (75-115 cmH2O) has been reported as a risk indicator of renal deterioration in SCI patients with NDO[54, 55].

Despite the lack of strong evidence identifying risk factors for UUTD, causes for UUTD in NGB include bladder outlet obstruction, ureteral obstruction, urinary tract infections, stones and most importantly, persistent high intravesical pressures[56]. High pressures could be from neurogenic detrusor overactivity, poor bladder compliance, detrusor-sphincter dyssynergia (DSD) (simultaneous detrusor and urinary sphincter contractions) or a combination.

The pathophysiology of CKD in NGB is not well understood. In some cases, it appears that a sustained high storage pressure results in prolonged compression of the ureteric orifices, leading to obstructed urine outlet during a prolonged period and, consequently, renal damage[57]. In other situations, high intravesical pressure causes a defective overwhelmed ureterovesical junction with subsequent vesicoureteral reflux (VUR) and UUTD.

Such secondary VUR may appear as hydroureteronephrosis (HUN) on imaging. Since VUR and HUN may be manifestations of high bladder pressures in NGB, treatment should focus first on ensuring low storage pressure. Anti-reflux surgery or double J ureteral stenting should be avoided in these cases.

Most agree that some bladder methods (reflex triggering and Valsalva or Credé manoeuvres) should be strongly discouraged due their threat for the upper tract (GOR B, LOE III). In some cases, carefully monitored patients may be able to use these methods successfully. Clean intermittent catheterization (CIC) is a superior method for preserving bladder compliance compared to chronic suprapubic or urethral catheterization[2, 33].

Symptoms of high intravesical pressure are rarely present (eg. leakage between CIC) and UDS are required to properly identify it. Compliance must be assessed over the range typically seen by the bladder[58]. Despite the fact that patients with a chronic indwelling catheter have an empty bladder most the time, they still warrant follow-up for urologic complications and hydronephrosis.

Overall, patients at higher risk of UUTD are MMC, suprasacral SCI, and men with MS[2]. Clinically stable MS patients have lower rates of UUTD compared to those with SCI and MMC, even in the setting of DSD[44].

Serum creatinine (sCr) has been criticized as a reliable early marker of renal function in patients with NLUTD as they often have muscle atrophy from disuse and denervation. Renography and twenty-four-hour urine creatinine clearance may be preferred to sequentially assess renal function in NGB patients[59]. Another marker of renal damage is the presence of

proteinuria, which can be screened for and warrants a nephrology referral as it is potentially a prognostic risk factor for mortality due to renal insufficiency.

Renal function decline can occur up to 45 years after injury, making lifelong upper tract surveillance of utmost importance.[60]

5.2 Incontinence and urethral damage

Urinary incontinence (UI) is unfortunately commonly observed in patients with NGB, with 20-70% of adult patients being incontinent to some degree[2]. Incontinence highly impacts not only patients' quality of life, causing depression and social isolation[61], but can also have other significant consequences.

Freedom from indwelling catheters is a priority in the management of NGB. Although long-term indwelling catheters should be avoided, they may be inevitable in some patients with poor manual dexterity, mental deficits or patients non-compliant with self-catheterization[62].

Reports on urethral complications from indwelling catheters (IC) are scarce, but they are definitely more common than for patients on clean intermittent catheterization (CIC)[63]. Urethral complications such as strictures, false passages, urethral diverticuli, periurethral abscesses, urethrocutaneous fistula, iatrogenic traumatic hypospadias may be seen in males with an IC[64].

In females, urethral dilation, erosion and potentially destruction may be observed in patients with a long-term indwelling urethral catheter. This is a devastating and difficult-to-treat complication representing a surgical reconstruction challenge with potentially serious secondary consequences such osteitis pubis or non-healing decubiti ulcers from continued urinary leakage[65].

Prevention of these urethral complications is crucial. Daily surveillance of the catheter position to prevent traction down on the leg, ideally positioning the catheter on the abdomen while avoiding kinking, and vigilance to sacral and perineal wounds, and use of suprapubic catheters are of utmost importance. Urethral urinary leakage (catheter bypassing) should be addressed by ruling out bladder stones and infection, avoiding increasing the catheter size, and aggressively treating with oral medications or onabotulinumtoxinA injections[66]. Patients with indwelling urethral catheters should be offered conversion to a suprapubic catheter in the setting of significant urethral damage (GOR A, LOE III) before the urethra has been irreversibly damaged and there is a risk of stress incontinence[62].

Sexuality is adversely affected for 40-91% of patients with NGB[67], and incontinence is a significant contributing factor due to fear of leakage during intercourse, embarrassment, concerns about odours, dyspareunia from vulvar irritation or dermatitis from chronic leakage[68]. Side effects from medications and surgeries to treat UI may also secondarily cause sexual dysfunction from erectile dysfunction, to inadequate vaginal lubrication or even halitosis from xerostomia[69]. Strategies to help prevent UI during intercourse include urinating before sex, favoring some positions or pre-medication with an antimuscarinic. Slings may help to improve coital incontinence[70] and phosphodiesterase type 5 inhibitors may improve lower urinary tract symptoms[71], but these modalities have been mostly reported for non-NLUTD dysfunction and little is known for neurological patients.

Urge urinary incontinence has been identified as an independent risk factor for recurrent falls in MS patients suggesting that managing "wet" neurogenic detrusor overactivity (NDO) should be included in fall prevention strategies[72].

Flack and Powell underlined the economic impact of NGB for patients and healthcare systems. Aspects to consider include direct costs related to supplies needed to stay dry (pads, diapers, liners) and to empty fully (catheters, drainage supplies, and lubricant), time lost from work from medical appointments and cost of procedural interventions[73]. Choosing a bladder care regimen that is cost effective will help improve patients' compliance to treatment[73].

Patients with NGB may also experience fecal incontinence, fecal urgency and/or chronic obstipation which may cause significant social distress, hence requiring an individualized bowel regimen[74].

In order to achieve continence, different methods of management are available. The key is to individualize treatment and monitor effectiveness and patient acceptability of chosen method taking into consideration activities of daily living, cognition and disability (including hand function) while protecting the upper tract.

5.3 Urinary tract infections

Urinary tract infections (UTIs) are common in patients with NLUTD and unfortunately remain difficult to diagnosis, treat and prevent. The heterogeneity of this patient population and lack of quality evidence continue to impede the development of comprehensive guidelines.

It has been estimated that the overall rate of UTI in patients with NLUTD is 2.5 episodes per patient year and that one in five suffer from recurrent UTIs[75, 76]. In this population, UTIs are one of the leading causes of emergency department visits, hospitalizations, and potentially life-threatening septicemia[47]. In addition to local infectious sequelae, UTIs can lead to acute disease exacerbations (eg. MS) and are associated with decreased health-related QoL[76].

The Enterobacteriaceae family represents the most commonly isolated organism in the NLUTD population with E.coli comprising 50% of all strains.   This is lower than that reported in non-neurogenic UTI and is in part explained by the increased incidence of Pseudomonas, Acinetobacter, Enterococcus and fungi such as Candida[77, 78]. Antimicrobial resistance appears to be on the rise with multi-drug resistance found in greater than 50% of uropathogens isolated from SCI patients[77].

Accurate diagnosis of UTI in persons with NLUTD is of paramount importance but is often clouded by the high rate of lower urinary tract colonization and difference in clinical presentation.   Presently, the accepted definition of UTI in persons with NLUTD requires the presence of leukocyturia, bacteriuria, and clinical symptoms (GOR A, LOE III)[79]. There are no evidence-based cut-off values for bacteriuria but the following are generally accepted guidelines:
- >104 cfu/ml (clean voided)
- >102 cfu/ml (clean catheterized sample)
- Any detectable concentration for suprapubic aspirate.

The consensus cut-off value used for leukocyturia is 100 leukocytes/mL or any leukocyte esterase activity on dipstick. Depending on the underlying pathology or level and degree of

injury, persons with NLUTD may exhibit vastly different UTI signs and symptoms.   The International Spinal Cord Injury Society has developed a UTI data set which outlines these signs and symptoms and includes fever, urinary incontinence/failure of control or leaking around catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine, malodorous urine, back pain, bladder pain, dysuria and autonomic dysreflexia[80].

Numerous studies clearly demonstrate that screening and treatment of asymptomatic bacteriuria in persons with NLUTD should be avoided (aside from pregnancy and prior to urologic interventions where mucosal bleeding is expected), as it promotes microbe resistance, and can increase the likelihood of symptomatic UTI[75, 81]. (GOR A, LOE II)

Acute UTIs in individuals with NLUTD require judicious antimicrobial therapy in addition to basic primary care and/or sepsis management principles. Urine cultures should always be obtained prior to antimicrobial therapy due to the increased risk of nosocomial and multi-drug resistant microorganisms (GOR A, LOE II). Any catheter in place for > 2 weeks be removed immediately and replaced and that the urine specimen should only be obtained from the new catheter before the initiation of antimicrobial therapy[81].

NLUTD persons with UTI must undergo careful clinical assessment to determine the optimal route, spectrum of coverage and duration of antimicrobial therapy. If UTIs persist then additional investigations such as urodynamic studies or 3-dimensional imaging (ultrasound or CT) should be considered to rule out further complicating factors such as elevated PVRs or bladder stones. Antibiotic stewardship must be observed in NLUTD UTI and, when possible, narrow spectrum antimicrobials should be used for the shortest duration deemed clinically safe. A 7-day course of antimicrobials is recommended for patients with prompt clinical response and 10-14 days for those with significant infection or a delayed response[75] (GOR A, LOE III). Antimicrobial selection following culture collection should be based on local resistance patterns and antibiograms should be consulted when determining empiric therapy if required.

Prevention of UTI by method of bladder management
Bladder evacuation method is the main predictor of NLUTD UTI and as such must be optimized. When possible, clean intermittent catheterization (CIC) should be utilized over other methods. (GOR A, LOE II) Transurethral indwelling catheterization (IC) carries > 5-fold increase risk of recurrent UTIs when compared to suprapubic catheterization (SPC) and clean intermittent catheterization (CIC)[82].   While UTI risk between SPC and CIC appears comparable there is a significantly increased risk of bladder calculi with SPC[83]. Condom catheters are effective and safe in select NLUTD patients (low PVRs and bladder storage pressures) but are significantly associated with Pseudomonas and Klebsiella bacteriuria and an incidence of UTI comparable to CIC.

In those patients with SPC and IC, frequent violation of the closed drainage system increases the risk of UTI and as such should be avoided. In addition, the drainage bag and tubing should always be situated below the level of the bladder to avoid retrograde contamination from

the urinary bag[81, 84]. Catheter placement with a pre-connected urinary bag junction does decrease the risk of colonization and should be utilized when possible[85].   It is generally recommended that indwelling catheters be changed every 2 to 4 weeks, with monthly being the most common interval. These practices are not evidence-based and insufficient evidence exists for guideline recommendations.

Antibiotic and silver-coated catheters have been shown to reduce bacteriuria and UTI but only in the very short term. In addition, concern exists regarding antimicrobial resistance and silver toxicity with long-term use[86].   Routine use is therefore not recommended.

Strong evidence exists against the use of antimicrobials or antiseptics in urinary drainage bags, enhanced meatal care and routine catheter irrigation normal saline. Recent evidence supports the use of daily gentamicin bladder irrigation in NLUTD patients performing CIC with recurrent UTI. A 75% reduction in symptomatic UTI recurrence was noted along with decreased systemic antimicrobial use and subsequent antimicrobial resistance[87].

Antimicrobial prophylaxis
A meta-analysis of 15 RCTs did not support the use of oral antibiotic prophylaxis for NLUTD UTI. Three of the included studies reported an approximately twofold increase in antimicrobial resistance with oral antimicrobial prophylaxis[88].   Therefore, at this time, routine antimicrobial prophylaxis for NLUTD UTI is not recommended for most patients. (GOR A, LOE I)

Currently, evidence is insufficient to recommend routine use of any non-antimicrobial prophylaxis measure including phytotherapy (eg. Cranberry), probiotics, methenamine salts, urine acidification, D-Mannose, oral immunostimulation, or bacterial interference.

5.4 Autonomic dysreflexia
Autonomic dysreflexia (AD) a well known clinical emergency in subjects who have had an SCI. It typically occurs in patients with an injury at level T6 or above. Physiologically, AD is caused by a massive sympathetic discharge triggered by either a noxious or nonnoxious stimulus originating below the level of the SCI. Strategies for acute treatment of emergent AD events have been thoroughly addressed elsewhere[89]. Recent data suggests that intravesical injection of Onabotulin toxinA decreases the frequency and severity of AD episodes[90].

6.0 Treatment of NLUTD

6.1 Assisted bladder drainage
NLUTD can result in impaired bladder emptying. Over 75% of SCI patients are unable to void on their own.[91] The best method of bladder emptying which preserves renal function and minimizes the risks of urinary tract complications such as UTIs and renal or bladder stones must be balanced against quality of life implications such as comfort, convenience and continence.[92] Quality of life (QOL) cannot be ignored as highlighted in a review by McIntyre where SCI patients who could void normally had the highest QOL ratings followed by those who could micturate with assistance or perform CIC themselves, while the worst QOL came when an

indwelling catheter (IC or SP) or CIC by an attendant was required.[93] This is an important reminder to continuously re-evaluate a NLUTD patients' selected drainage method and balance the risks and benefits of their choice.

6.1.1 Non-catheter mechanisms
The non-catheter mechanisms rely on involuntary emptying that is either induced or spontaneous. The Crede manoeuver (external pressure on the bladder) and Valsalva voiding induces bladder drainage via an increase in abdominal pressure that can overcome the external urethral sphincter. It can be inefficient and risk high pressures[5] and cause hemorrhoids, hernias and vesicoureteral reflux (VUR).[94] Spontaneous reflex voiding can occur with stimulation of the sacral or lumbar dermatomes by suprapubic tapping in some patients with upper motor neuron lesions. Condom catheter drainage is often used to collect urine in these non-catheter methods and therefore are more common in male patients. Additionally, males with cervical level lesions without the dexterity for CIC may select condom drainage. For patients using these non-catheter methods, regular screening with ultrasound and urodynamics should be done to avoid complications such as incomplete emptying causing UTIs or stones as well as dangerous elevated detrusor pressures.[5, 95]

6.1.2 Catheter mechanisms
The options for catheter mechanisms to provide bladder drainage include: clean intermittent catheterization (CIC), indwelling urethral catheterization (IC) and suprapubic catheterization (SP). While every attempt should be made to utilize the Gold Standard of CIC introduced by Lapides[96] in 1972, practitioners must understand the limitations of CIC outlined by Elliot [91] which include: a. limited upper extremity motor function, b. anatomic limitations (female or obese), c. limited functional bladder capacity (poor compliance or detrusor overactivity). In a review by Binard, the ideal person for CIC has a low Pdet at capacity, a minimum volume of 350-400 cc, an unobstructed urethra and is compliant, understanding, continent and cooperative with adequate hand function.[97] Practitioners may need to utilize medical means such as anticholinergics, beta 3 agonists or onabotulinum toxin A or surgical means such as augmentation cystoplasty or catheterizable stoma to facilitate successful CIC. While CIC is the Gold Standard, it isn't without complications such as pain for those with sensation, UTI[94] and stricture formation estimated at 4 – 13% from recent reports despite using hydrophilic catheters.[98]

The debate regarding the ideal catheter for those performing CIC does not have a clear winner. Options for patients include: single use disposable catheters that may be non-hydrophilic (uncoated), hydrophilic (coated) or include a gel reservoir. Alternatively, due to financial limitations, many patients still reuse uncoated catheters by various unstudied cleaning protocols (such as washing with warm soapy water and allowing to air dry, and replacing the catheter after a week or when there is visible wear). A recent Cochrane review from 2014 on the issue of catheter reuse was withdrawn after Christison et al. identified several flaws in the data

extraction and conclusions; their revised analysis found that hydrophilic catheters offered a small but significantly lower incidence of UTI and they reported a trend that favours single use catheters over repeated multiple use. The authors clearly state that "until evidence can confidently demonstrate that multiple use is as safe as single use catheters, healthcare providers should advocate a single use of catheters in individuals with SCI."[99] There may be other benefits of hydrophilic catheters such as lower risk of hematuria, stricture rates and improved urinary quality of life. Unfortunately, current evidence is generally of a low quality, and likely particular patient characteristics such as hand function and coverage options will play a large role in dictated how CIC is carried out.

While guidelines promote the use of CIC, many switch to indwelling catheters (IC or SP) as reported by Pannek with many predictors of likelihood: female gender (2.5x), age > 45 (3x), and both severity (AIS A-C tetraplegia) and duration from injury (4X).11 Indwelling catheters allow for some bladder independence but often functional, physical, mental or social factors trigger this decision.

Indwelling catheter methods (IC or SP) are often felt to be the last choice. Practitioners should advise patients of the risks and benefits; however, the data regarding whether indwelling catheters are dangerous is not clear. Authors have promoted the safety of both IC [92, 100, 101] and SP[102] with no renal deterioration and a low incidence of incontinence. For example, provided an indwelling catheter is draining all the time it seems less likely that high storage pressures or low compliance would matter.[103] SP tubes allow patients to engage in sexual activities and may carry less of a risk of epididymitis over IC[92]. Additionally, patients should be investigated for bladder cancer or bladder stones when appropriate.[103] Those patients living with IC or SP do colonize with polymicrobial and dynamic bacteria at a rapid rate of 5 – 10% per day[104] and is often the cause of stones and symptomatic UTIs. This remains an ongoing frustration for patients and care providers alike.

Selection of an assisted bladder drainage method (CIC, urethral or suprapubic catheter) should be individualized to the patient's motor functions, anatomic limitations, bladder characteristics, prior urologic complications, and quality of life (GOR A, LOE III).

6.2 Oral and transcutaneous medical therapy
Treatment of NLUTD aims to lower detrusor storage pressure and increase bladder capacity in order to protect upper tract function and to decrease urinary incontinence.

Anticholinergics
A meta-analysis in neurogenic detrusor overactivity (NDO) reviewed all RCTs between 1966 and 2011 (total 960 patients). They demonstrated that anticholinergic administration in this population was associated with statistically significant differences in patient-reported cure/improvement, bladder capacity and detrusor pressure compared to placebo. Studies that compared one medication to another (usually oxybutynin IR), did not reveal statistically significant differences. The optimal drug dosage was not identified. [105] Madersbacher et al.

extended their review to include other non-RCT studies, and found an approximate decrease of 30-40% in maximal detrusor pressures and an increase of maximum cystometric bladder capacity of 30–40% for oxybutynin IR, propiverine IR, propiverine ER and trospium chloride IR, compared to placebo.[106] Antimuscarinics should therefore be offered to people with urodynamic findings of neurogenic detrusor overactivity or those with SCI and symptoms of overactive bladder (GOR A, LOE Ia). The preferential drug of choice should be individualized, but evidence for efficacy exists for oxybutynin IR and ER, tolterodine IR and ER, propiverine IR, darifenacin and solifenacin. Antimuscarinic dosage should be escalated to optimize improvement of symptoms or urodynamic parameters, as tolerated by the patient, with the possibility of increasing adverse events. Supratherapeutic dosages may be considered according to tolerability, but should be used cautiously. [107] Combining antimuscarinics may be beneficial for patients who are refractory to dose escalation antimuscarinic monotherapy [108, 109], and is suggested by the EAU guidelines [110]

The administration of antimuscarinics should be considered whether or not patients are using assisted bladder drainage (GOR C, LOE IV). The absence of its usage has been shown to be a risk factor for upper tract deterioration. [111] If the bladder is being drained, there is less of a concern of elevated post-void residual. In patients with indwelling catheters, oxybutynin use was associated with less risk of hydronephrosis, and should be considered. [112]

B3 adrenergic agonist therapy
There is limited evidence for the use of mirabegron for the treatment of NDO or NLUTD. A retrospective review found an improvement in urodynamic parameters in fifteen patients with NDO on mirabegron. [113] There are currently trials underway to assess its efficacy in this patient population. [114] Mirabegron may be a useful alternative to anticholinergics for patients with symptoms of OAB and NLUTD, but further evidence of urodynamic changes are needed in this population (GOR C, LOE IV).

Recommendations:
1. Oral antimuscarinics with dose-escalation are the first-line pharmacological treatment for patients with NLUTD in order to improve OAB symptoms and NDO, decrease urgency urinary incontinence and lower detrusor pressures. (GOR A, LOE Ia)
2.
3. There is very limited data supporting the use of transdermal oxybutynin or mirabegron in NLUTD (GOR C, LOE IV).

6.3 Intravesical therapy
Onabotulinum toxin-A (Botox®) intradetrusor injection has been proven to be an effective and safe long-term therapy for the management of NLUTD secondary to SCI or MS. Results of powered, placebo-controlled, multicenter, phase III RCTs and meta-analysis demonstrated clinically significant outcomes and sustained efficacy in terms of reduced incontinence episodes,

enhanced bladder function, as well as substantial improvements in key urodynamic parameters and quality of life[115-119](GOR A, LOE Ia). Achieved therapeutic effects are comparable between both onabotulinumtoxin-A doses (200 units and 300 units) in terms of efficacy and durability, but catheter initiation rates were dose-dependent[116, 120] (GOR B, LOE Ib). 200 units is the standard recommended dose by Health Canada with more favorable safety profile[121]. Safety assessments identified UTIs and large urine residual or urinary retention as the most frequent adverse events. These findings are more predominant among 300 units groups and patients not using CIC at baseline. Therefore, the likelihood of future need of CIC is increased[116, 118, 120] (GOR A, LOE Ib). Muscle weakness and respiratory problems is another serious complication that is rarely reported [116, 120, 122].

6.4 Intravesical oxybutnin by CIC

Intravesical oxybutynin treatment has been shown to be safe and effective short-term therapy in patients suffering from NDO, who remain incontinent or are intolerant of oral anticholinergic medication[123-127](GOR C, LOE III) A recent multicenter, open-label RCT confirmed the efficacy and safety of intravesical administration of 0.1% oxybutynin hydrochloride with a significant increase in bladder capacity and fewer adverse drug reaction rate[123](GOR B, LOE II). In general, this approach avoids systemic side effects as the drug bypassed first pass metabolism[126], and is mainly suitable in patients already using clean intermittent catheterization (CIC)[125].

Intravesical vanilloids such as capsaicin and resiniferatoxin, reduce NDO by reversible desensitization of the afferent C-fibers, and thereby increase bladder capacity. Their positive clinical and urodynamic benefits last for a period of a few months without systemic side effects[128-130]. Resiniferatoxin is an ultrapotent analogue of capsaicin, with the advantage of less pain during initial administration and superior clinical efficacy[131]. Results of RCT have demonstrated that Botulinum-A toxin intradetrusor injection achieved superior clinical outcomes compared to those of resiniferatoxin instillation[132]. Recently, meta-analyses of relevant RCTs showed poor overall quality of evidence with unfavorable safety profile and no existing licensed substance [130] (GOR C, LOE III).

Recommendations:
1. OnabotulinumtoxinA injection (200 units) in the detrusor is an effective, minimally invasive, treatment that can achieve continence, improve bladder function, and diminish neurogenic detrusor overactivity in individuals with SCI or MS who have an inadequate response to or are intolerant of an anticholinergic medication (GOR A, LOE 1).
2. AbobotulinumtoxinA is also efficacious in NLUTD, with the optimal dose of 750 units. (GOR B, LOE 1b) Intravesical oxybutynin is a safe alternative approach to managing NDO and NLUTD in patients who are doing CIC (GOR B, LOE 2).

6.4 Neural stimulation & neuromodulation therapy

Neuromodulation represents a promising tertiary treatment option for managing patients with refractory neurogenic lower urinary tract dysfunction. It appears to involve modulation of spinal cord reflexes and brain centers via peripheral afferents (genital, tibial and sacral afferents).[133] A recent review on the use of this modality reports that it can be successful in certain carefully selected neurological populations. However, no definitive conclusions can be drawn from the available evidence at this point. Current data supporting the use of sacral neuromodulation (SNM) and peripheral tibial nerve stimulation (PTNS) in this cohort are limited by observational nature, small sample sizes, heterogeneous populations with differing symptom profiles and outcomes measured.

Dorsal rhizotomy (sacral deafferentation S2-S4/5) and sacral anterior root stimulation (SARS) by an implantable device can achieve safe storage detrusor pressure and voluntary emptying of bladder and bowel in patients with complete SCI. [134-137] Furthermore, it diminishes autonomic dysreflexia.[135, 138-141] This technique has good variable success rates in specialized centers, but comes with long-term complication rate and a very high rate of surgical revisions. (GOR C, LOE III). Although the striated muscle fibers of the urethral sphincter are stimulated, it relaxes sooner than the detrusor smooth muscle, resulting in post-stimulation voiding. This approach can also improve bowel and erectile dysfunction.[139, 142] Alternatives to surgical posterior rhizotomy are investigated in this treatment combination[143-145]. Charcot spinal arthropathy as a potential long-term complication and a possible cause for SARS dysfunction can occur.[146]

There are few studies on PTNS applicability in the NLUTD population, and are limited by their heterogeneity, small sample size and retrospective/prospective non-randomized nature. Results of prospective non-randomized trials and meta-analysis, demonstrated significant improvements on clinical and urodynamic outcomes after a 12-week period, in the MS and Parkinson's disease patient population. PTNS appears to be well tolerated, and effective in small studies with minimal reported adverse events, with mainly mild to moderate pain at the puncture site. (GOR C, LOE IV).[147-150] Recent RCT including 100 patients with NDO following SCI, reported significant improvements in bladder diary variables within 4 weeks after PTNS. However, there was no difference when compared to solifenacin therapy.[151] PTNS therapy is limited by the need for weekly repeated office based procedure, and the need for long term or lifelong maintenance.

Recommendations:

1. SNM could be considered for the treatment of NDO or non-obstructive urinary retention in carefully selected individuals with NLUTD, as it can be a safe and effective option. It should be preceded by an adequate testing phase, and may not be a good alternative to decrease detrusor pressures or improve bladder compliance.
2. PTNS can be efficacious in NLUTD resulting from MS, but requires initial frequent weekly visits. It remains unclear, which subgroups of neurogenic voiding

dysfunction and which underlying neurological disease will respond best to these different therapies.

6.5 Surgical management of lower urinary tract dysfunction

Surgical intervention may be required in a variety of clinical scenarios in managing patients with neurogenic lower urinary tract dysfunction (NLUTD). It is indicated when conservative measures, medical therapy, and minimally invasive interventions alone fail to achieve the objectives of: (1) protecting kidney function and mitigating autonomic dysreflexia by maintaining bladder storage at safely low pressures; (2) ensuring adequate and timely bladder emptying to mitigate the risks of overflow incontinence, recurrent UTIs, bladder stones and kidney damage; (3) preventing the adverse effects of incontinence (eg. dermatitis); and (4) improving quality of life (QoL) by relieving bothersome symptoms of OAB and incontinence.

Bladder augmentation (BA)

BA is indicated in cases of reduced compliance or NDO refractory to all other non-surgical treatments, or reduced bladder capacity necessitating an indwelling catheter or CIC to be done too frequently (Grade B, LOE 2).[6, 152-154] Compliance is increased in 69-100% of cases, continence restored in 75-100%, and QoL improved in >90%.[155-163] Contraindications include bladder malignancy or stones, significant renal dysfunction, bowel disease and/or prior resection, and inability or unwillingness to maintain CIC. Where CIC per urethra is not feasible, patients should be offered continent cutaneous urinary diversion (CCUD).

In cases of thick, fibrous, low capacity bladders, supratrigonal cystectomy is recommended over clam cystoplasty in preparing the bladder for augmentation.[152, 164] The ileum is the recommended segment where possible given a lower risk of complications, good efficacy and ease of use.[155, 162, 163, 165] In cases of grade IV-V reflux ureteric reimplant may be necessary.[152, 166] Long-term risk include adeno- or urothelial carcinoma (1-4.6%), bladder calculi, and perforation (5-13%).[167-172] Careful education and long-term cystoscopic surveillance are therefore recommended; however, the most cost-effective frequency is not established.

Continent cutaneous urinary diversion (CCUD)

In cases where urethral catheterization is precluded, CCUD may be offered after careful consideration and multidisciplinary evaluation.

Most commonly, a simple channel is created from the bladder to the abdominal wall with a valve mechanism to prevent incontinence. Concomitant bladder augmentation is performed only as necessary as indicated above. The most commonly used tube is the appendix (Mitrofanoff appendicovesicostomy)[173, 174] [154] Where the appendix is unavailable or unsatisfactory (must be 8-10 cm in length for adult patients), a segment of terminal ileum can be employed (Yang-Monti or Casale technique), albeit with slightly poorer outcomes.[173, 175, 176]

Where additional length is required, the technique proposed by Casale, or a tapered ileal channel with nipple valve, may be preferred over the "double Monti" procedure.[154, 177]

In cases where it is not prudent to preserve and utilize the native bladder (eg. severely contracted, high grade VUR, concern for malignancy, devastated outlet), a continent catherizable pouch may be preferred. These procedures can be associated with higher risk of metabolic complications, especially if the ileo-cecal junction is utilized.[178-180]

Incontinent urinary diversion (ileovesicostomy and ileal conduit)

Incontinent diversion is a last resort in managing the complications of NLUTD, and indicated in patients who are not candidates for the techniques outlined above, or when expertise is not available. Most commonly, these are offered to a patient at high risk (impaired compliance) who is unable to perform CIC due to upper limb dysfunction.

Ileovesicostomy may be appropriate in select patients. It has the advantages of being technically simple, avoiding the potential complications related to both cystectomy and uretero-ileal anastomoses, obviating the need for indwelling catheters, avoiding any risk for pyocystis, and the maintenance of native anti-reflux mechanism and sexual/reproductive function. It has the disadvantages of preserving the native bladder and outlet with risks of malignancy or ongoing urethral incontinence if this is not also surgically addressed.[152, 181] The technique is described by Schwartz et al and further reviewed by Westney.[62, 182] Few small series are available for review and robust long-term follow-up and QoL data is lacking.[152, 181, 183-187] Complication rates are high (up to 75%), and include impaired emptying, stomal stenosis, parastomal hernia, and renal and bladder stones (up to 25%).[183, 184, 186]

Along with the indications above, ileal conduit may be appropriate in cases of severe incontinence (eg. devastated outlet) with low likelihood of successful reconstruction, end-stage bladder with high-grade VUR, chronic UTIs with impaired compliance, chronic bladder fistulisation, or malignancy. It is the preferred method of incontinent diversion. The bladder should be removed at the time of surgery to reduce the risks of pyocystis (21-61%), chronic symptomatic cystitis, and malignancy.[157, 188-190] Minor complications may develop in 46% and major in 11%, with overall complication rates of 30-70%.[191-194] Upper tract functional preservation is reported in >90% of patients. Significant improvement in urinary-specific QoL but not overall QoL have been reported.[191, 195, 196]

External urethral sphincterotomy

External urethral sphincterotomy aims to allow reflex micturition into a reservoir via condom catheter. Surgery is irreversible and multiple procedures may be required. Patients must be carefully counselled about their options. Long-term follow-up is required given a high rate of recurrent DSD and/or stricture. Patients must be able to retain a condom catheter: A semi-rigid penile prosthesis can be offered to facilitate this; however, there is a 20-30% risk of erosion in this population.[197, 198] Female gender, detrusor underactivity, and desire to preserve fertility are also contraindications. Up to 82% of patients will develop recurrent DSD and require at least one

repeat procedure, thus annual upper tract imaging and urodynamics are recommended.[199-210] Improvements in PVR, hydronephrosis, recurrent UTIs, and AD have been reported in many small series.[152, 199]

Bladder neck closure (BNC)

BNC, combined with some type of diversion, is indicated in cases of severe outlet damage It may be accomplished by a retropubic or transvaginal approach. The former is recommended if augmentation and/or ureteric reimplantation is required, if perineal access is unsatisfactory, or if surgeon expertise dictates. When possible, transvaginal BNC offers satisfactory outcomes with reduced morbidity, operating time, and hospital stay.[211-214] To minimize risk of failure/fistulisation, it is critical that patients are counselled about proper bladder drainage (CIC or continuous depending on their diversion), and that low bladder pressures are maintained.

7.0 Surveillance studies for NLUTD patients in the community setting

After initial assessment and treatment to optimize bladder function, NLUTD patients are followed with regular clinical assessment and in some cases surveillance investigations. NLUTD surveillance is stratified based on the risk of NLUTD sequelae. Although it is suggested that clinical examination alone is not sufficient to determine individual urologic management strategies in patients with NLUTD[215], data demonstrating the value of surveillance investigations in the setting of NLUTD is lacking[216]. Similarly, urodynamic risk stratification has been suggested based on high pressure storage and voiding features, but characterization of overall risk groups for NLUTD sequelae remains largely undefined to date[52, 54, 217]. Typically, surveillance protocols suggest either on-demand or regularly scheduled urodynamic studies, upper tract imaging and cystoscopy but there is little consensus on specific approach[3-5, 218]. Consequently, practice patterns vary with regard to the type and frequency of studies utilized in NLUTD surveillance[48, 218-220]. Our suggested approach for NLUTD stratifies patients based on their urologic risk factors and specific investigations are recommended:

7.1 Surveillance clinical assessment

The primary goal of clinical assessment is to stratify patients based on their risk of NLUTD sequelae. Patients deemed low risk are followed with a simple clinical assessment while those deemed higher risk undergo a more detailed evaluation of the urinary tract function and anatomy. Depending on the specific risk factors involved, this may include urodynamic evaluation, renal-bladder imaging and renal function assessment. The detailed evaluation of the higher-risk groups is intended to address modifiable factors that may allow the patient to be reclassified as a lower risk patient. Relevant findings on history include bladder management technique (particularly high-risk groups including condom drainage, valsalva/crede/reflexive bladder emptying), incontinence pattern, UTI profile, autonomic dysreflexia, most recent urodynamic evaluation and upper tract imaging. ***We recommend regular yearly clinical assessment of all NLUTD patients with their physiatrist, neurologist or general practioner; we recommend that a urologist is***

involved in the assessment of patients who are in the moderate or high-risk categories as described in Figure 3 (for example SCI, SB, advanced MS). (GOR C, LOE IV).

7.1 Surveillance investigations

Imaging
Routine surveillance imaging provides interval evaluation of the anatomy of the urinary tract and characterizes hydronephrosis, renal atrophy, scars, urinary stones, diverticula, trabeculation, large bladder lesions and quantifies post-void residual. A recent systematic review concluded that there is sufficient evidence to recommend yearly US of the kidneys and urinary tract as a useful, cost-effective, noninvasive method for routine long-term follow-up to detect upper urinary tract problems in all individuals with SCI. Although the findings have been applied to other underlying pathologies within NLUTD, the benefit has not been quantified[41]. ***We suggest yearly renal and bladder ultrasound in high and moderate risk NLUTD patients as described in Figure 3 (for example SCI, SB, advanced MS). (GOR C, LOE IV).***

Cystoscopy
While historically utilized for concerns of increased bladder cancer risk, cystoscopy can be a valuable tool in the evaluation of urethral or bladder integrity and can provide an estimate of external sphincter function. The value of surveillance cystoscopy for bladder cancer surveillance in the SCI population was addressed in a recent systematic review by Cameron et al[41]. The investigators believed that the incidence of bladder cancer was too low to be well evaluated in these studies, and screening cystoscopy and biopsy did not fit the criteria for a screening test of the general NLUTD population. Patients with prior augmentation cystoplasty have historically been followed with yearly surveillance cystoscopy due to increased risk of bladder cancer[221]. Recent studies demonstrate no benefit from surveillance cystoscopy in the augmented population[170, 222, 223]. ***We support the utilization of cystoscopy for the assessment of suspected urethral or bladder pathology. We do not support routine surveillance cystoscopy for bladder cancer screening in NLUTD with or without augmentation cystoplasty (GOR C, LOE IV).***

Urodynamics
Attempts at establishing a risk versus benefit ratio for regularly scheduled surveillance urodynamic studies are limited by heterogeneous populations and varying surveillance strategies. Some authors demonstrate benefit of regularly scheduled yearly urodynamic evaluation[224, 225]. Conversely, others establish a safe lower urinary tract with baseline UDS, and subsequently perform annual renal ultrasonography for surveillance. UDS in this strategy is repeated only when patients presented with changing incontinence patterns or alarming radiologic changes[226]. Existing guidelines have little consensus on the specific strategy of implementation and high enrollment studies are not currently available. ***We support the utilization of surveillance UDS in moderate risk patients every 2-5 years and high risk patients every year (GOR C, LOE IV).***

Video UDS or a cystogram should be performed in patients where further knowledge of the urinary tract anatomy is needed.

7.3 Proposed surveillance strategy
There is a lack of evidence to establish any clear strategy of surveillance for NLUTD as evidenced by the varying recommendations of numerous prior guidelines[3-5, 218]. The primary goals of surveillance screening studies are to mitigate NLUTD sequelae and we propose a strategy based on risk stratification. *Our proposed surveillance strategy is included in Figure 3. The integrity of this strategy has not been verified empirically, it represents the consensus opinion of our contributors. (GOR C, LOE IV).*

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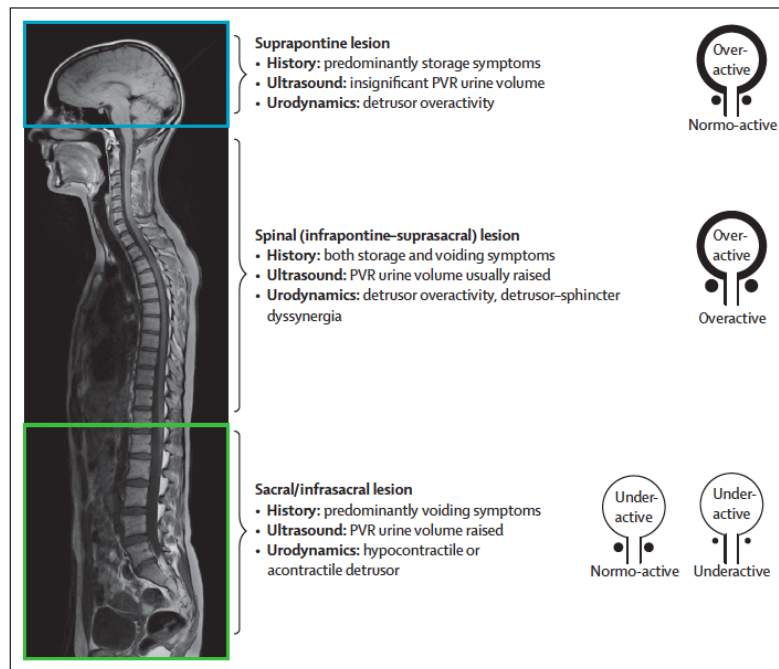
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Figures and Tables

Fig. 1. Classification of lower urinary tract dysfunction based on level of lesion (adapted from Panicker et al[7]).

Suprapontine lesion
- **History:** predominantly storage symptoms
- **Ultrasound:** insignificant PVR urine volume
- **Urodynamics:** detrusor overactivity

Over-active
Normo-active

Spinal (infrapontine–suprasacral) lesion
- **History:** both storage and voiding symptoms
- **Ultrasound:** PVR urine volume usually raised
- **Urodynamics:** detrusor overactivity, detrusor–sphincter dyssynergia

Over-active
Overactive

Sacral/infrasacral lesion
- **History:** predominantly voiding symptoms
- **Ultrasound:** PVR urine volume raised
- **Urodynamics:** hypocontractile or acontractile detrusor

Under-active
Under-active
Normo-active   Underactive

Fig. 2. Initial investigations and risk stratification for neurogenic lower urinary tract dysfunction (NLUTD) patients. High-risk patients are considered those with spinal cord injury (SCI), spina bifida, advanced multiple sclerosis (MS) or select other neurogenic diseases with evidence of significant urological complications or morbidity in addition to: 1) bladder management technique: Valsalva/crede/reflexive voiding; or 2) known high-risk features on urodynamics (UDS) without confirmation of appropriate attenuation after treatment (detrusor-sphincter dyssynergia [DSD], neurogenic detrusor overactivity [NDO], impaired compliance (<20 ml/cmH$_2$O), detrusor leak point pressure [DLPP] >40cmH$_2$O, vesico-ureteral reflex); or 3) new/worsening renal imaging (hydronephrosis, atrophy, scarring); or 4) new/worsening renal insufficiency. Patients with SCI, spina bifida, or advanced MS without high-risk features are considered moderate risk. More details are provided in Fig. 3. PVR: post-void residual; UA: urinalysis; US: ultrasound; UTI: urinary tract infection.
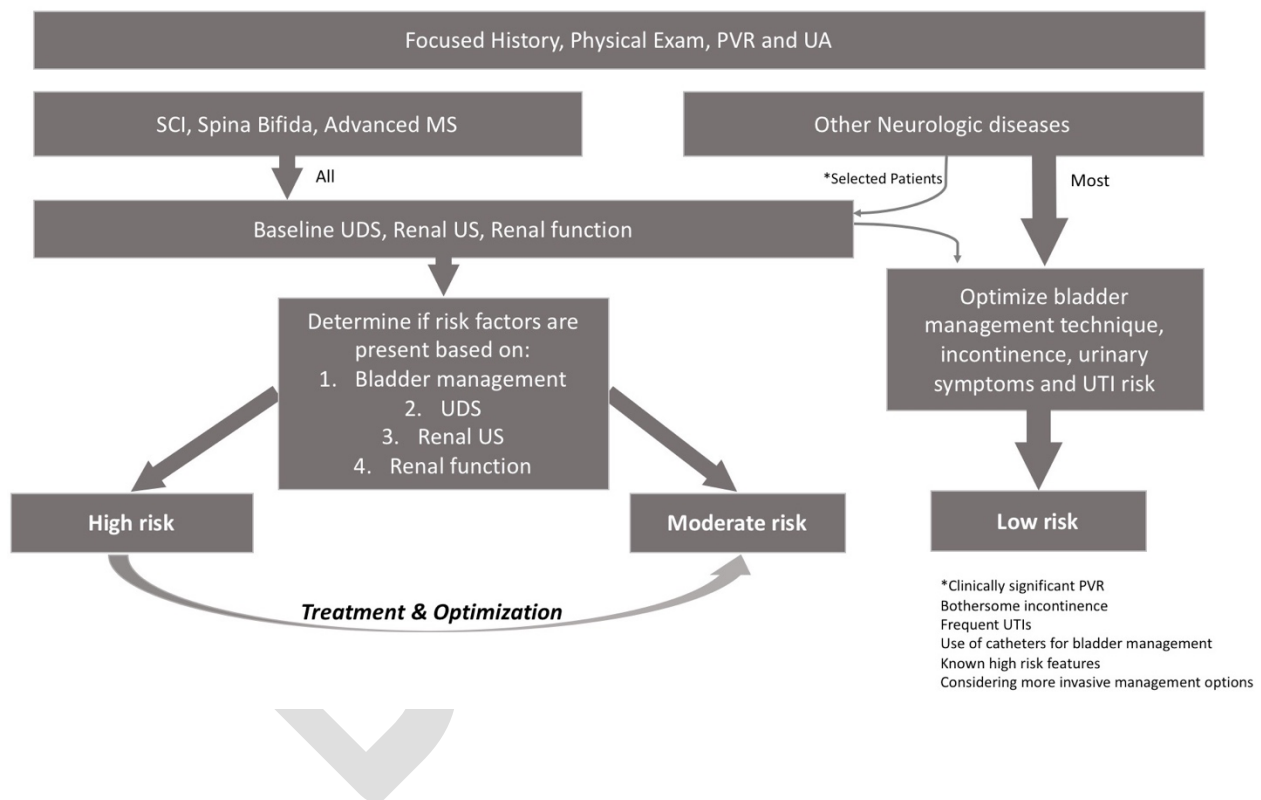
Fig. 3. Surveillance Strategy for neurogenic lower urinary tract dysfunction (NLUTD) based on patient risk stratification. DLPP: detrusor leak point pressure; DSD: detrusor-sphincter dyssynergia; MS: multiple sclerosis; NDO: neurogenic detrusor overactivity; PVR: post-void residual; SCI: spinal cord injury; UDS: urodynamics.

High-risk group (underlying high-risk disease [SCI, spina bifida, advanced MS] or select other neurogenic diseases with evidence of significant urological complications or morbidity) in addition to:
- Bladder management technique: Valsalva/crede/reflexive voiding, or
- Known high-risk features on UDS without confirmation of appropriate attenuation after treatment (DSD, NDO, impaired compliance (<20 ml/cmH$_2$O), DLPP >40 cmH$_2$O, vesico-ureteral reflex) or
- New/worsening renal imaging (hydronephrosis, atrophy, scarring) or
- New/worsening renal insufficiency

Suggested surveillance strategy:
- Yearly urological evaluation (history and physical examination)
- Yearly UDS
- Yearly renal-bladder imaging
- Yearly renal function assessment

Moderate-risk group (underlying high-risk disease [SCI, spina bifida, advanced MS] or select other neurogenic diseases with evidence of significant urological complications or morbidity) in addition to:
- Bladder management technique: CIC, spontaneous voiding, indwelling catheter
- Prior history of high-risk features on UDS which have been appropriately optimized (DSD, NDO, impaired compliance [<20 mL/cmH$_2$O], DLPP >40 cmH$_2$O, vesico-ureteral reflex) or
- Renal imaging without any significant interval change or
- Renal function without any significant interval change

Suggested surveillance strategy:
- Yearly urological evaluation (history and physical examination)
- Yearly renal-bladder imaging
- Periodic UDS (every 2-5 years)
- Yearly renal function assessment

Low-risk group (no evidence of high-risk disease and no features on initial evaluation that would be considered high risk)

Suggested surveillance strategy:
- Yearly evaluation with GP, physiatrist, neurologist, or urologist (history and physical examination with attention to general neuro-urological assessment outlined previously)
- Yearly renal imaging in select cases
- Re-referral for urological evaluation as suggested by:
  - New onset/worsening incontinence, or
  - New frequent urinary infections, or
  - New onset catheter issues (for example, penile/urethral erosions, encrustation, bypassing)
  - Renal-bladder imaging changes suggestive of upper or lower UT deterioration (hydronephrosis, new clinically significant PVR, or significant increase in PVR) or new stone disease

Table 1. Elements of a focused neuro-urological history	
History of the neurologic disease	Tailored to the disease. Examples:
	SCI: Year and level/completeness of lesion (ASIA level), frequency of autonomic dysreflexia, level of spasticity, mobility/transfers
	MS: Year and type of MS (primary progressive, secondary progressive, relapsing remitting), mobility level (or Expanded Disability Status Scale)
	Spinal bifida: Type (i.e., ambulatory lipomyelomeningocele), caregiver, VP shunt, latex allergy, prior reconstructive surgery
Bladder management history	Use of catheters (CIC, indwelling [size and frequency of changes], Condom), crede/straining/reflexive bladder emptying, bladder medications, and prior urologic surgery history
Storage symptoms & voiding symptoms	Frequency, urgency, nocturia, incontinence Weak stream, intermittency, straining, incomplete emptying
General components	Allergies, medications, alcohol/drug use/smoking
NLUTD complications	1. UTIs (symptoms, culture status, associated sepsis/fever, response to antibiotics/antibiotic resistance, triggers, hospital admissions)
	2. Sequela of incontinence (skin breakdown, ulcers, pad usage, bother)
	3. Bladder or renal stone disease
	4. Catheter complications (urethral loss in women; urethral erosion, false passages, strictures in men, encrustation/sediment)
	5. Renal function (imaging results, renal function)
Review of relevant systems	1. Bowel function
	2. Sexual function
	3. Coexisting non-NLUTD dysfunction (prostatic enlargement, stress incontinence)
	4. Gross hematuria
	5. Gynecologic/pregnancy history
	6. Genitourinary/pelvic pain
	7. Motor abilities (hand function, ability to transfer)
	8. Cognitive function
	9. Support systems/care givers

CIC: clean intermittent catheterization; MS: multiple sclerosis; NLUTD: neurogenic lower urinary tract dysfunction; SCI: spinal cord injury; UTI: urinary tract infection.

Table 2. Indicators of NLUTD patient characteristics potentially at higher risk of urologic morbidity

	High-risk diagnoses/features
Etiology of neurogenic bladder	SCI, spina bifida, advanced MS
Bladder management method	Valsalva/crede/reflexive bladder emptying, indwelling catheter SCI patients with autonomic dysreflexia associated with bladder function
Urodynamics	DSD, NDO[*], impaired compliance (<20 mL/cmH$_2$O), DLPP >40 cmH$_2$O), vesico-ureteral reflux
Renal-Bladder imaging	New onset/worsening hydronephrosis, stone disease, renal atrophy/scarring Abnormal bladder morphology
Renal function	New onset/worsening renal insufficiency

[*]The exact characteristics of NDO that are most concerning for renal dysfunction are not clearly defined. High-risk NDO should be interpreted based on the volume at onset, duration, peak pressure, and associated incontinence. These urodynamic findings should be interpreted in the context of the normal voiding habits of the patient. DLPP: detrusor leak point pressure; DSD: detrusor-sphincter dyssynergia; MS: multiple sclerosis; NDO: neurogenic detrusor overactivity; NLUTD: neurogenic lower urinary tract dysfunction; SCI: spinal cord injury.