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Review Article

Clinical guidelines for the diagnosis and management of neurogenic lower urinary tract dysfunction

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ABSTRACT

This article reports the current evidence and expert opinions on the diagnosis and management of neurogenic lower urinary tract dysfunction (NLUTD) in Taiwan. The main problems of NLUTD are failure to store, failure to empty, and a combination of these two. Priorities in the management of NLUTD, in order of importance, should be the following: (1) preservation of renal function; (2) freedom from urinary tract infection; (3) efficient bladder emptying; (4) freedom from indwelling catheters; (5) patient agreement with the management modality; and (6) avoidance of medication after proper management. Management of the urinary tract in patients with spinal cord injuries or multiple sclerosis must be based on urodynamic findings rather than on inferences from the neurological evaluation. Identification of high-risk patients is important to prevent renal functional impairment in those with chronic NLUTD. The lower urinary tract function of patients with NLUTD should be regularly followed up by urodynamic study, and any urological complication should be treated adequately. Avoiding a chronic indwelling catheter can reduce the incidence of developing a low compliant bladder. Intravesical instillation of vanilloids and injecting botulinum toxin-A are alternative treatments for refractory detrusor overactivity or a low compliant bladder, and can replace the need for bladder augmentation. When surgical intervention is necessary, less invasive types of surgery and reversible procedures should be considered first, and any unnecessary surgery in the lower urinary tract should be avoided. Keeping the bladder and urethra in good condition without the interference of neuromuscular continuity provides patients with NLUTD the opportunity to use new technologies in the future. Improving the quality of life in patients with neurogenic voiding dysfunction is the most important aspect of treatment.

Conflicts of interest: none.

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1. Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) includes dysfunction of the urinary bladder and urethra due to lesions of the central nervous system or peripheral neurogenic lesions. Cerebrovascular accidents (CVAs), intracranial lesions, Parkinson's disease (PD), cerebral palsy, multiple sclerosis (MS), transverse myelitis, and spinal cord lesions can result in NLUTD [1]. Spinal cord injury (SCI) and MS remain the most difficult to manage disorders causing NLUTD.

Frequency, urgency, and urinary incontinence are all commonly reported in patients with neurogenic detrusor overactivity (NDO). Approximately 10% of patients with stroke develop neurogenic disease [2]. Up to 75% of MS patients report some form of urinary incontinence [3]. One in 10 patients presents with bladder symptoms at the time of MS diagnosis [4]. The vast majority of SCI patients have bladder dysfunction [5].

NLUTD presents a great disease burden on patients, affecting not only their prognosis but also their quality of life (QoL), self-esteem, and relationship with their families. It is commonly associated with urinary incontinence, voiding problems, reduction in bladder compliance, and upper urinary tract damage [6].

Priorities in the management NLUTD, in order of importance, should be the following: (1) preservation of renal function; (2) freedom from urinary tract infection (UTI); (3) efficient bladder emptying; (4) freedom from indwelling catheters; (5) patient agreement with the management modality; and (6) avoidance of medication after proper management. As the diagnosis and management of NLUTD are complex, guidelines for clinical practice in the treatment of patients with NLUTD are mandatory.

2. Purpose

The purpose of these clinical guidelines is to provide information on the incidence, definitions, diagnosis, therapy, and follow-up observation of patients with NLUTD. These guidelines may be useful for physicians and patients in the management of NLUTD.

3. Terminology

The following abbreviations are used throughout these guidelines: AD, autonomic dysreflexia; DA, detrusor areflexia; DSD, detrusor sphincter dyssynergia; DU, detrusor underactivity; NDO, neurogenic detrusor overactivity; NLUTD, neurogenic lower urinary tract dysfunction; NVD, neurogenic voiding dysfunction; SCI, spinal cord injury.

Other terminology follows the recommendations of the International Continence Society [7,8].

4. Etiology of NLUTD

NLUTD may be caused by various diseases and events affecting the nervous systems controlling the lower urinary tract. NLUTD should be considered in patients with sudden onset of lower urinary tract symptoms (LUTSs) such as acute urinary retention or urge urinary incontinence (UUI). The following are possible etiologies of NLUTD. (1) Peripheral neuropathy: diabetes [9], alcohol abuse [10], and herpes zoster [11]. (2) Latrogenic: abdominoperineal resection of the rectum or uterus [12,13]. (3) Demyelinization: MS [14–16]. (4) Dementia: Alzheimer, Binswanger, Nasu, and Pick diseases [17–19]. (5) Basal ganglia pathology: PD, Huntington disease, and Shy–Drager syndrome [20,21]. (6) Cerebrovascular pathology [22,23]. (7) Frontal brain tumors [24]. (8) Spinal cord lesions: traumatic, vascular, medical, or congenital [25–27]. (9) Disc disease [28,29]. (10) Regional spinal anesthesia [30].

5. Epidemiology of SCI in Taiwan

The incidence of SCI worldwide, as reported in the literature, ranges from 12.1 per million to 57.8 per million [31]. Bladder dysfunction occurs depending on the level and location of the SCI [32]. The most common etiologies of SCI are motor vehicle crash injuries in patients under 60 years of age and falls in those older than 61 years [33].

A study of the prevalence and incidence of NDO from SCI in Taiwan during 2006–2008 revealed an overall 3-year prevalence rate of 855 per million and an incidence rate of 241 per million person-years, which were similar to a previous study (246 per million person-years) and much higher than those in Japan (124 per million person-years), Canada (53 per million person-years), and the USA (40 per million person-years, 59 per million person-years) [34]. The frequency of NDO was around 16.9% in SCI patients with transient urinary incontinence and 17.5% in those with permanent NDO. Among all SCI patients, 82% with SCI and NDO used catheterization with (46%) or without (36%) pharmacological treatment. Patients with SCI and NDO have more expenses for hospitalization than those without NDO. This has a great impact on the financial burden of health insurance.

6. Clinical symptoms and urodynamic findings in NLUTD patients

6.1. Cerebral vascular diseases

The clinical symptoms of NLUTD depend on the levels of lesions [35]. With lesions above the brain stem, involuntary bladder contractions with sphincter synergy and preserved bladder sensation can occur, and NDO is likely to develop. Urinary incontinence is the most common problem in the acute phase (within 3 months post CVA). The degree of incontinence declines over time. However, other voiding issues might appear. LUTSs, especially storage symptoms such as frequency and urgency with or without UUI, commonly present in the chronic phase (3 months post CVA) [23,36,37].

Because most men with CVAs are elderly, other pathophysiology that causes male LUTSs, such as bladder outlet obstruction, might confuse the diagnosis and treatment of voiding dysfunction in them [38,39]. However, patients with chronic CVAs may have both detrusor overactivity (DO) and uninhibited relaxation of the urethral sphincter causing urinary incontinence [40,41]. Detrusor underactivity (DU) and detrusor hyperactivity with impaired detrusor contractility might be other problematic issues in elderly patients with multiple CVAs or those in the acute phase [42,43].

Urethral sphincter pseudodyssynergia may develop in about 10% of patients during the recovery phase (4–10 months post CVA) [42,43]. Urethral sphincter pseudodyssynergia is characterized by voluntary contraction of the external sphincter during involuntary detrusor contractions [44]. Patients might have LUTSs such as difficult urination, slow stream, and incomplete bladder emptying.

6.2. Parkinson's disease

PD is the second most common neurodegenerative disease after Alzheimer's disease [45], affecting 1 million people each year in the United States [46]. More than 270,000 people in Taiwan have Parkinson's syndrome, and among them 40,000 have PD [47]. PD is a multisystem disorder involving the dopaminergic, noradrenergic,

serotoninergic, and cholinergic systems, and is characterized by motor and nonmotor symptoms [48].

A large proportion of patients with PD present with urinary dysfunction including urgency, increased frequency, or incontinence as predominant symptoms [49]. Urinary symptoms are statistically correlated with the severity of the disease but not with the duration of illness, and no sexual differences have been noted [50]. The presence of voiding dysfunction in parkinsonian patients has been reported in several studies, with an incidence of 37–71% [19]. Voiding dysfunction occurs when the extrapyramidal system is damaged, such as in PD.

A previous investigation showed that 40–70% of parkinsonian patients have some degree of voiding dysfunction, and nearly 70% of them have irritative symptoms [51]. DO was the predominant urodynamic finding, which may explain the LUTSs in patients with PD. Pseudodyssynergia occurs in 25–60% of parkinsonian patients [51]. Patients with PD and a hyperactive urethral sphincter may not be able to adequately relax their urethral sphincter during volitional or reflexic micturition, resulting in inadequate detrusor contractility and an increased postvoid residual (PVR) [52].

6.3. Spinal cord injury

Spinal cord lesions can be traumatic, vascular, medical, or congenital. The incidence in the USA is 30–40 new cases per million of the population. Most patients develop NLUTD [53]. A high correlation exists between the clinical neurological findings and NLUTD in single-level traumatic spinal cord lesions, but not in myelomeningocele and combined traumatic spinal cord lesions [54,55]. In SCI lesions above T6, patients may have smooth muscle dyssynergia and autonomic dysreflexia (AD) in addition to detrusor sphincter dyssynergia (DSD).

SCI patients may have LUTSs such as urgency and UUI. Some patients with bladder neck dysfunction and DSD may also experience difficulty in bladder emptying and urinary retention [56–58]. Usually in patients with a complete spinal cord lesion at the T6–S2 levels, involuntary bladder contractions without sensation and DSD develop [59]. In most patients with spinal cord lesions below S2, detrusor areflexia (DA) with retained residual urethral sphincter tone not under voluntary control will cause difficult urination. Patients have to urinate by abdominal straining, the Crede maneuver, or clean intermittent catheterization (CIC) to empty the bladder [60]. Patients with low urethral sphincter tone may also have urinary incontinence. Interruption of the peripheral reflex arc will cause DA and low bladder compliance, which results in incomplete bladder emptying and may also endanger the upper urinary tract. Spinal bifida and other congenital nerve tube defects are also prevalent in the 25–29-year age group, and half of these patients have DSD [61,62].

A survey indicated that improving bladder dysfunction, bowel dysfunction, and AD were among the seven highest priorities of SCI patients with paraplegia and tetraplegia [63]. As patients with SCI consider urinary incontinence inevitable after injury, many patients self-manage by decreasing fluid intake, voiding frequently, and wearing pads. Patients can be symptomatic for years prior to seeking treatment [64]. A physician's assessment of the disease burden can be inaccurate and nonreproducible [65]. When the problem is reported, many physicians fail to evaluate the condition [66]. Most physicians would like to treat more complicated physical conditions rather than urinary incontinence.

Neurogenic conditions are associated with a significant reduction in QoL, and urinary incontinence can further reduce it [67]. Bladder symptoms are a leading disability in some neurogenic patients, and are often the cause of reduced participation in work and social activities [68]. Urinary incontinence poses a major limitation to sexuality in SCI patients [69]. The frequency of incontinence has a strong influence on health-related QoL. In one study, among all patients with SCI who had CIC by an attendant, those with indwelling transurethral catheters and suprapubic catheters had the worst mental status [70].

SCI patients have higher rates of depression than the healthy population, and this is closely related to gender and the ability to perform self-catheterization [71]. It has been estimated that <50% of SCI patients have good knowledge about bladder management and pressure ulcers after being discharged from the hospital. They also are reluctant to discuss bladder symptoms with physicians and other patients. Many clinicians believe that NDO does not affect mortality/morbidity. In addition, SCI patients do not know where or how to avail of Medicare benefits [72]. Therefore, there is a need to increase patient awareness of the urological complications of NLUTD and to educate physicians about treatment strategies for NLUTD.

6.4. Multiple sclerosis

MS is a major cause of nontraumatic disability in young adults. The total estimated prevalence is 83/100,000. It is most commonly seen in the 35–64-years age group, with a male to female ratio of incidence of 1:2 [73–76]. Urodynamically, DO occurs in about 44–81%, DSD in about 25%, and DU in 19–40% of patients with MS. Up to 10% of patients have bladder dysfunction at the initial MS diagnosis. Urodynamic studies were found to be abnormal in 50% of asymptomatic MS patients and in 100% of symptomatic patients.

Urgency (32–86%), nocturia (25–82%), and UUI (19–80%) are highly prevalent in MS patients; however, they may also have dysuria (6–79.5%) and urinary retention (8.3–73.8%), depending on the involvement of the central nervous system and chronicity of the disease [77]. Sudden onset of LUTSs and DO or DSD, as found in urodynamic studies, should alert the physician to MS, especially in young adults. MS patients' attitude toward voiding management should be respected. Patients may be bothered more by emptying dysfunction than by bladder storage symptoms.

DO and DSD commonly occur in patients with suprasacral cord lesions, such as those with SCI, MS, or transverse myelitis. The presence of DSD is associated with complete injuries, elevated intravesical pressures, and upper tract complications [55]. Patients with DSD usually have urinary incontinence and a large PVR requiring CIC or an indwelling Foley catheter. These urological complications usually result in a low QoL and may cause more serious complications such as AD, UTI, and upper urinary tract deterioration [78].

7. Classification of NLUTD

A perfect classification system is not yet available. Most of the currently used classifications of NLUTD are based on bladder and urethral dysfunctions. Previous classifications of NLUTD included Bors and Comarr's [79] neurourological classification, Bradley et al's [80] four loops neurological classification, and Lapides' [81] and Krane and Siroky's [82] urodynamic classification of detrusor and urethral sphincter dyscoordination. Wein [83] and Fall et al [84] classified NLUTD as failure to store and failure to empty, based on detrusor and urethral dysfunction. The International Continence Society also separates NLUTD into detrusor and urethral dysfunction in the storage and voiding phases [8].

A clinically useful classification of NLUTD should help physicians manage patients. Early diagnosis and treatment are essential, as irreversible changes may occur, in particular in children with myelomeningocele. Individual variations exist in neurogenic voiding dysfunction (NVD) caused by a specific neurological lesion.

Neurological classification systems cannot describe lower urinary tract disease (LUTD) completely. Therefore, in any particular patient, the description of NLUTD should be individualized.

The main problems of NLUTD are as follows: (1) failure to store due to DO or urethral incompetence; (2) failure to empty due to DA, bladder neck dysfunction, or DSD; and (3) combined failure to store and empty due to DSD or DO and detrusor hyperactivity with impaired detrusor contractility.

8. Classification of SCI severity

Clinicians have long used a clinical scale to grade the severity of neurological loss. First devised at Stoke Mandeville Hospital, Buckinghamshire, Great Britain prior to World War II and popularized by Frankel in the 1970s, the original scoring approach segregated patients into five categories as follows: no function (A), sensory only (B), some sensory and motor preservation (C), useful motor function (D), and normal (E) [85].

The American Spinal Injury Association (ASIA) Impairment Scale follows the Frankel Scale but differs from the older scale in several important respects. First, instead of no function below the injury level, ASIA-A indicates no motor or sensory function preserved in the sacral segments S4–5. ASIA-B is essentially identical to Frankel B but adds the requirement of preserved sacral S4–5 function. It should be noted that the ASIA-A and ASIA-B classifications depend entirely on a single observation, i.e., the preservation of motor and sensory function of S4–5.

The ASIA Scale also added quantitative criteria for C and D categories. ASIA-C was diagnosed if more than half of the muscles evaluated had a grade of less than 3/5. If not, the classification was ASIA-D. ASIA-E implies an SCI without any neurological deficits detectable on a neurological examination of this type.

The new ASIA-A categorization has been more predictive of prognosis than the previous definition, where the presence of function several segments below the injury site but the absence of the function below a given level can be interpreted as an "incomplete" SCI.

The ASIA committee also classified incomplete SCIs into five types. A central cord syndrome is associated with a greater loss of upper limb function compared with the lower limbs. Brown–Sequard syndrome results from a hemisection lesion of the spinal cord. Anterior cord syndrome occurs when the injury affects the anterior spinal tracts, including the vestibulospinal tract. Conus medullaris and cauda equina syndromes occur when the conus or spinal roots of the cord are damaged (Table 1).

9. Diagnosis of NLUTD

Diagnosis of NLUTD should be based on neurological lesions and somatic and visceral dysfunction. Medical comorbidity may alter the LUTSs [25]. The diagnostic procedures should include the following. (1) General history: neurological and systemic diseases. (2) Specific history: urinary history, bowel history, sexual history, and neurological history. (3) Physical examination: general physical examination and neurourological examination. (4) Specific neurourological examination: evaluation of sensation from S2 to S5 bilaterally, reflexes, anal sphincter tone, and volitional contraction of the anal sphincter and pelvic floor. (5) Laboratory tests. (6) Urodynamic study.

10. Urological surveillance

The goal of urological surveillance is functional (F) and anatomical (A) assessment of the urinary tract after NLUTD. The assessments should include the following steps. (1) Laboratory tests (F): These include urinalysis, urine culture, renal function tests, and glomerular filtration rate. (2) Intravenous pyelography (F, A): This is useful for assessing upper tract function and anatomical changes. (3) Renal ultrasound (A): It is used to detect hydronephrosis or renal scarring. (4) Renal scan (F): Both dimercaptosuccinic acid (DMSA) and diethylene triamine pentaacetic acid (DTPA) scans are necessary. (5) Voiding cystourethrography (A) is required. (6) Cystoscopy (A): For the detection of bladder trabeculation and determination of urethral condition, cystoscopy is performed. (6) Urodynamic studies (F): Urodynamic investigation is necessary to document the function or dysfunction of the lower urinary tract. The recording of a bladder diary is highly advisable. Free uroflowmetry and assessment of the PVR are mandatory prior to invasive urodynamics is planned. The detrusor leak point pressure (DLPP) is an important investigation in patients with endangered upper tracts. Specific uroneurophysiological tests such as electromyography of pelvic floor muscles and the urethral sphincter, pudendal nerve conduction velocity, and the bulbocavernous reflex and anal reflex arc latency time are elective procedures. Fast filling cystometry with an ice water test has been presumed to distinguish between upper and lower motor neuron lesions [86]. A positive bethanechol test is considered proof of detrusor denervation [87]. These are optional tests for specific patients with NLUTD. (7) Videourodynamics (F, A): This procedure is performed to determine bladder function and the vesicoureteral reflux (VUR). Videourodynamics is the gold standard for invasive urodynamics in patients with NLUTD. Videourodynamic study can detect bladder and urethral dysfunction, as well as morphological pathology in the lower and upper urinary tract [7,88,89]. If this is not available, a filling cystometry continuing into a pressure flow study should be performed.

Table 1
ASIA Impairment Scale.

A = Complete: No motor or sensory function is preserved in the sacral segments S4–S5.
B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5.
C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade <3.
D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade ≥3.
E = Normal: Motor and sensory functions are normal.

11. Selecting high-risk patients

A significant association between the level of injury and the type of voiding dysfunction has been noted in patients with a single-level SCI. Management of the urinary tract in patients with SCI must be based on urodynamic findings rather than on inferences from the neurological evaluation [57,90].

It is important to screen patients at high risk, including those with complete neurological lesions, cervical spinal cord paraplegia, prolonged indwelling catheter, high DLPP, DSD, AD, a large PVR, and VUR. When the DLPP is >40 cmH_2O, the upper tract is endangered [7,91].

Correction of urological complications and improvement of QoL with respect to urinary incontinence are the two main goals in the management of NVD. In addition, each patient should be evaluated for and managed with an individualized treatment strategy.

12. Treatment of NLUTD

The following should be the primary aims and priorities in the treatment of NLUTD: (1) protection of the upper urinary tract; (2)

improvement of urinary continence; (3) improvement in the patient's QoL; (4) restoration of (parts of) normal lower urinary tract function; and (5) further considerations such as patients' disability, cost effectiveness, technical intricacy, and possible complications.

The first aim of any therapy is protection of the upper urinary tract and reduction of mortality from urological complications in patients with NLUTD [25,56,92–99].

The mainstay of treatment for an overactive detrusor is anticholinergic drug therapy. Rehabilitation and neuromodulation may be effective in selected cases. A condom catheter or pads may reduce incontinence to a socially acceptable level. Any method of assisted bladder emptying should be used with the greatest caution.

The main goals of treatment of NLUTD are as follow: (1) correction of urinary tract complications including hydronephrosis, VUR, UTI, and a contracted bladder; (2) lowering storage intravesical pressure, and controlling or alleviating symptoms (including incontinence and difficult urination) [60]; and (3) improving QoL with respect to urinary incontinence, treating urinary incontinence and difficult urination, improving bladder emptying, and avoiding indwelling catheters and UTI [96,97]. It is difficult to estimate the vesicourethral dysfunction based on the level of an SCI. Therefore, a videourodynamic study or pressure flow study combined with voiding cystourethrography is necessary to identify detrusor and sphincter dysfunction. An individual strategy for each NLUTD patient is mandatory.

12.1. Noninvasive conservative management of NLUTD

Conservative management is the mainstay of urological treatment for NVD, if possible. Patients can be instructed to void by abdominal stimulation (triggered reflex voiding), the Crede maneuver, or abdominal straining (Valsalva) [100,101]. If they do not have a balanced bladder after training, CIC, either by themselves or by a caregiver, is necessary [102–104]. Spontaneous voiding with and without triggered voiding and/or bladder expression has been proved to be less safe, except in well-defined patients with regular urological follow-up [105].

In patients with poor hand function and urinary incontinence, use of an external appliance to collect urine is feasible. Long-term indwelling catheters should be avoided, except for patients with tetraplegia and those who are bedbound, in whom an indwelling urethral Foley catheter or suprapubic cystostomy may be an alternative [90,106–109]. In addition, in hospitals with the required facilities, lower urinary tract rehabilitation including behavioral modification, pelvic floor muscle exercises, pelvic floor electrostimulation, or biofeedback may be provided to patients who have incomplete lesions and retained lower urinary tract function, such as those with MS [110–114].

12.2. Intermittent catheterization

Intermittent catheterization (IC) is the standard treatment for patients who are unable to empty the bladder [102,103,115]. Patients should be well instructed regarding the technique and risks of IC. Aseptic IC is the method of choice. The optimal catheter size is 12–14 Fr. The bladder volume must remain below 400 mL, and the post-IC residual should be low. Insufficient patient education and the inherent risk of UTI in patients with NLUTD are contributing factors for poor outcomes [115,116]. The average frequency of catheterizations is four to six times per day. Less frequent catheterization results in higher catheterization volumes and a higher risk of UTI. More frequent catheterizations increase the risk of cross infections and other complications [115,117,118].

Indwelling transurethral and suprapubic catheterization should be performed only exceptionally and under close control, and the catheter should be changed frequently. Silicone catheters are preferred and should be changed every 2–4 weeks. Latex catheters (coated) need to be changed every 1–2 weeks [106,109].

13. Drug treatment of NLUTD

DO can be treated effectively with anticholinergics (oxybutynin, tolterodine, trospium, and propiverine) [119–125]. These drugs have diverse tolerance profiles, and if a patient experiences adverse effects from one drug, another may be prescribed [126]. The long-term efficacy and safety of antimuscarinic therapy for NDO is well documented. A combination of antimuscarinic agents is now used more frequently and is often considered to maximize outcomes for NDO. Alternative methods of administration of antimuscarinic agents, such as transdermally and intravesically, should be considered in refractory cases [127]. In one study in 21 patients with NDO (17 with SCI), the use of tolterodine (4 mg twice daily) and trospium chloride (30 mg 3 times daily) at higher than recommended doses was found to be an effective therapeutic strategy, which improved bladder urodynamic parameters and was not associated with a significant increase in side effects compared with standard dosages [128].

Therapy with drugs to improve detrusor contractility has not been successful. Oral bethanechol can increase intravesical tone and facilitate bladder emptying by abdominal straining in patients who respond to electromotive intravesical bethanechol testing [129].

Alpha-blockers (terazosin and alfulzosin) and skeletal muscle relaxants (baclofen and diazepam) have been partly successful in decreasing bladder outlet resistance [130–133]. A nitric oxide donor has been shown to be effective in reducing bladder outlet resistance in experimental use [134]. There is a lack of prospective, randomized, controlled studies on the medical management of NLUTD. Increased bladder outlet resistance may be achieved by adrenoceptor agonists.

Because patients with NLUTD may have both storage and emptying LUTSs, a combination medication can be used to improve bladder storage and facilitate bladder emptying. To treat incontinence, a combination therapy with anticholinergics and adrenergic agonists (methylephedrine) with CIC is needed. However, careful monitoring of the PVR and any UTIs is necessary. To facilitate voiding, a combination of a cholinergic agent, an alpha-blocker, and a skeletal muscle relaxant can be used. However, urinary incontinence might be exacerbated, and the risk of upper tract deterioration might be increased if the DLPP is high.

NDO is commonly treated by antimuscarinics [135], bladder neck dysfunction by alpha-blockers, and striated sphincter spasticity by skeletal muscle relaxants or nitric oxide donors [134]. Detrusor muscle tone can be increased by cholinergic agents such as bethanechol. These agents are commonly prescribed to achieve better bladder control or efficient emptying [129]. However, NLUTD may not be controlled without combined medications for detrusor dysfunction and bladder outlet resistance. A combination of alpha-adrenergic blockers and antimuscarinic agents is expected to be more beneficial than either of these for the treatment of voiding dysfunction [136]. Addition of desmopressin may improve the efficacy of the treatment [137]. However, adverse effects increase with the use of multiple medications. Therefore, intravesical treatment of NLUTD is a possible future treatment strategy for DO.

13.1. Intravesical treatment of NDO

Intravesical instillation of capsaicin or resiniferatoxin can successfully eradicate incontinence due to DO and can be considered a second-line treatment for NVD [138–140]. After a single

intravesical instillation of capsaicin, DO was found to be decreased and urinary continence improved for 3–6 months. Patients treated with intravesical instillation of resiniferatoxin fared better than those treated with capsaicin, mainly because of less irritation and durable effects. For the treatment of high-level SCI and DSD, a dose of 10μM was necessary to achieve good therapeutic results. However, the high concentration of intravesical vanilloid may induce AD during intravesical instillation, which has limited this treatment to the clinical trial stage [141].

13.2. Neurotoxin bladder and urethral injections

The treatment strategy for NLUTD should include less invasive and reversible procedures such as neurotoxin injection into the detrusor or urethral sphincter for bladder control and emptying. Intravesical botulinum toxin-A (BoNT-A; Botox or Dysport) injection has been demonstrated to be effective in restoration of urinary continence and remains durable for up to 9 months [142–144]. Detrusor BoNT-A injection increases bladder capacity and decreases intravesical pressure. Doses of 200 U and 300 U were found to have the same therapeutic effects on NDO, and 200 U has been approved by the US Food and Drug Administration [145]. This treatment is also effective in treating children with myelomeningocele with detrusor hyperreflexia and incontinence [146,147]. Repeat BoNT-A detrusor injections seem to be as effective as the first injection [148]. In one study, BoNT-A was significantly more effective in reducing the maximum pressure of uninhibited detrusor contractions than resiniferatoxin at all follow-up time points [149]. Urethral BoNT-A injection reduces urethral resistance in patients with DSD and DA [150], and an early return of detrusor contractility seems possible in patients with urethral sphincter pseudodyssynergia due to CVAs or PD [151].

In 2011, detrusor injection of 200 U onabotulinumtoxinA was approved by the United States Food and Drug Administration for the treatment of NDO due to SCI and MS. Detrusor injections of 200–300 U of onabotulinumtoxinA can reduce detrusor contractility, improve bladder compliance, and restore urinary continence in patients with NDO [142,152,153]. However, clinically, this treatment usually induces impaired detrusor contractility, a large PVR, or urinary retention in patients with NDO. About 70% of patients require periodic CIC, and subsequent UTI could become a *de novo* problem [154].

BoNT-A toxin treatment of DO due to spinal cord lesion has been reported to provide satisfactory results [155,156]. DU develops after detrusor injection of 300 U of onabotulinumtoxinA, and improvement in the urodynamic and QoL parameters last for 9 months [157]. Seventy-three percent of patients with neurogenic bladder can return to continence after treatment [154]. Recent studies further revealed that an injection of 100 U of onabotulinumtoxinA intradetrusor for MS seems to be effective and safe. Most patients can void voluntarily without compromising voiding efficiency [76,158]. In patients with PD and refractory DO, intradetrusor injection of 100 U of onabotulinumtoxinA also induced clinical and urodynamic improvement in overactive bladder, which lasted for 6 months [159,160].

Recent randomized, double-blind, placebo control trials of BoNT-A on NDO revealed that BoNT-A has benefits in both SCI and MS patients with NDO. BoNT-A significantly reduced urinary incontinence and improved urodynamic parameters and QoL in MS and SCI patients with NDO. Doses of both 200 U and 300 U of onabotulinumtoxinA were well tolerated, with no clinically relevant differences in efficacy or duration of effect [145]. Interestingly, BoNT-A injections for NDO that included the trigone were found to have significant superiority in treating both incontinence episodes and urodynamic parameters compared with injections that spared the trigone [161].

13.3. Urethral or detrusor BoNT-A injections for DSD?

Patients with DSD usually have both storage and emptying symptoms. Some patients with DSD must have CIC performed by themselves or caregivers, in addition to voiding by abdominal tapping. However, some patients with DSD prefer spontaneous voiding without instituting CIC and some might prefer being dry after treatment even if CIC is necessary. Therefore, management of voiding dysfunction and incontinence in patients with SCI and DSD is a challenge for physicians, and should be considered an art.

About 95% of patients with suprasacral lesions demonstrate DO with or without DSD [59]. Hand dexterity, abdominal muscle power, bladder sensation, and the degree of urethral sphincter dyssynergia might affect voiding efficiency and LUTD. Urethral BoNT-A injections can reduce urethral resistance [67,150]. Combined detrusor and urethral BoNT-A injections can achieve the desired goals [155]. Reduction of DO can decrease urinary incontinence, whereas reduction of urethral resistance can decrease the PVR.

Although intradetrusor BoNT-A injections for NDO can increase bladder capacity and achieve urinary continence, CIC is still required. This management is rational but might not be adopted widely in developing countries where public services for CIC are lacking. Patients who do not have facilities or resources for CIC may prefer spontaneous voiding and wearing an external appliance without using CIC. To improve incontinence, decrease urgency episodes, and retain spontaneous voiding function, a lower dose of BoNT-A for detrusor injections may provide satisfactory results for the majority of patients with spinal cord lesions and DSD [162].

Treatment of NDO and DSD may also be different between genders. Female patients with SCI and DSD usually have more severe urinary incontinence and need diaper protection. CIC requires more facilities and resources for women, so women with SCI and DSD may prefer to be dry and get rid of diapers. By contrast, male SCI patients can use an external appliance to collect urine and prevent urine soiling. Therefore, the desire to become dry is not as great as that in females. Nevertheless, male SCI patients may not appreciate being completely dry and may need CIC after detrusor BoNT-A injection. In that case, a small dose of BoNT-A, e.g., 200 U of onabotulinumtoxinA, would be adequate to increase bladder capacity and allow patients to void by abdominal tapping [163].

There are several important issues that physician should know prior to performing BoNT-A injections in patients with NDO: (1) behavioral modification should be the first management; (2) BoNT-A injections should be given to patients after antimuscarinics fail or there are intolerable adverse events; (3) CIC is necessary for most patients who respond to BoNT-A; (4) monitoring the PVR and subsequent UTI is necessary; (5) monitoring the upper urinary tract (by renal sonography or glomerular filtration rate) is important; (6) repeated BoNT-A injections are necessary to maintain the desired therapeutic effect; and (7) patients with urethral strictures, those who are unwilling to perform CIC, and those with failure after the first treatment should not receive this therapy.

13.4. Renal function preservation

Renal function is also an important issue in the management of NVD, especially in chronic SCI patients. Patients with DSD, a low compliant bladder, and high intravesical pressure at end-bladder filling may be at high risk of renal failure. The incidence of chronic renal disease in patients with paraplegia and neural tube defects is higher than that in the healthy population [164]. Bladder management affects bladder compliance, and compliance changes

with time. Patients using IC have a significantly higher incidence of normal compliance than those with Foley management. Low bladder compliance is statistically associated with VUR, radiographic upper tract abnormality, pyelonephritis, and upper tract stones. CIC is a superior method for preserving bladder compliance and preventing upper tract complications associated with low compliance [165]. Patients with DSD who are currently using an indwelling catheter, performing CIC, or voiding spontaneously should be monitored annually to prevent renal failure. Oral antimuscarinic agents or intravesical Botox injections might provide a low-pressure bladder and preserve renal function in the long-term management of NLUTD.

13.5. AD and UTI in SCI

AD is a potentially life-threatening condition and occurs most often in individuals with SCI above the T6 level [166]. It is characterized by severe paroxysmal hypertension (episodic high blood pressure) associated with throbbing headaches, profuse sweating, nasal stuffiness, flushing of the skin above the level of the lesion, bradycardia, apprehension, and anxiety, which are sometimes accompanied by cognitive impairment [167]. Patients with chronic SCI may develop AD during bladder overdistention, stool impaction, or UTI.

The most common causes of AD are bladder distention and stool impaction. UTI can also trigger AD regardless of whether there is an indwelling catheter or not. In spinal cord transection, these afferent impulses are unable to travel past the injury, resulting in an enhanced spinal cord reflex to the autonomic nervous system in response to stimuli. It is believed that these afferent stimuli trigger and maintain an increase in blood pressure via sympathetically mediated vasoconstriction in the muscle, skin, and splanchnic vascular beds [168].

The incidence of AD in patients with SCI above T6 ranges from 19% to 70%. Patients with DSD have a higher incidence of AD. Alpha-blockers or detrusor BoNT-A injections have been proved to be able to alleviate AD.

Febrile UTI should be treated with adequate antibiotics, according to the results of urine culture. No treatment is necessary for asymptomatic bacteriuria. Urodynamic study is indicated in patients with recurrent UTI. When high intravesical pressure, large PVR, VUR, contracted bladder, or other lower urinary tract abnormalities are detected, medication or a surgical intervention to lower intravesical pressure or increase bladder capacity, or an antireflux procedure should be instituted.

13.6. Surgical management of NVD

For patients without therapeutic effects after medical treatment or intravesical vanilloid instillation, surgical intervention is mandatory to treat urological complications and preserve renal function.

Transurethral external sphincterotomy provides significant reduction of voiding pressure and AD in male SCI patients. The high systolic and diastolic blood pressure as well as PVR will decrease after sphincterotomy [169]. Transurethral incision of the bladder neck can also reduce AD and facilitate spontaneous voiding in patients with incomplete cervical SCI [170]. In tetraplegic patients, a urethral stent implant can relieve urethral resistance and facilitate spontaneous voiding. However, the patient should be monitored for possible stent migration. The most frequent stent complication is displacement, followed by stenosis, lithiasis, and intraprosthetic calcification. In all, 8.5% of patients require stent removal [171].

Bladder augmentation either by a segment of intestine [94] or autoaugmentation using myomectomy [172] can result in a large-capacity, low-intravesical-pressure, and nonreflux condition. Most patients reported no significant change in bowel function, and nearly all patients expressed extreme satisfaction with urological management [173]. However, long-term complications, such as stone formation, loose stools, metabolic acidosis, and chronic UTI, remain [174]. In patients with cervical SCI or severe urethral sphincter deficiency, continent lower urinary tract reconstruction (such as a Kock pouch) or closure of the bladder neck plus continent ileostomy and bladder augmentation may provide a chance to become continent and evacuate the bladder by CIC from an ileostoma [175].

Other surgical treatments for NLUTD to increase bladder capacity and improve storage function include urethral and bladder neck procedures: urethral sling, artificial urinary sphincter [176], functional sphincter augmentation, bladder neck and urethra reconstruction (Young–Dees–Leadbetter procedure) [177], detrusor myectomy (autoaugmentation), denervation, deafferentation, neurostimulation, neuromodulation: sacral rhizotomy and sacral anterior root stimulation, bladder covering by striated muscle, and urinary diversion [94].

13.7. Treatment of VUR

Ureteral reimplantation has an immediate and long-lasting result in over 90% of patients [178,179]. Subtrigonal injections of bulking agents may be tried first in patients with NLUTD and VUR [180]. Ureteral reimplantation alone or combined with bladder augmentation in patients with contracted bladder are effective procedures in patients with failed initial injection procedures [181]. When treating VUR, the physician should consider lowering the intravesical pressure at the same time [182]. The relative risks of more invasive and less successful therapies should be considered first.

14. QoL issues

QoL is also important in the treatment strategy for NVD. Patients' agreement with the management modality, their hand function and capability for self-care, and social, economic, and family support should be taken into consideration. Intravesical BoNT-A injection provides great satisfaction to patients with neurogenic DO [183]. However, > 70% of patients need CIC to evacuate their bladder [154]. This treatment may not be accepted by patients in Asian countries, as their environment and social support are not as good as those in western countries [162]. When performing BoNT-A injections for patients with DSD, injecting into the detrusor or urethra should be evaluated carefully prior to treatment. An unpublished study comparing SCI patients receiving intravesical BoNT-A with those receiving urethral sphincter BoNT-A showed that the intravesical group had more improvement in QoL than the urethral group. When considering the needs of patients with NLUTD, either a reduced dose of BoNT-A or a combination of detrusor and urethral BoNT-A injections may provide better therapeutic satisfaction in patients who wish to preserve spontaneous voiding and become less incontinent.

15. Rational treatment strategy for NVD

Bladder and urethral dysfunction changes with time in patients with NLUTD. These patients should be followed up regularly for lower urinary tract dysfunction, and any urological complication should be treated adequately. Avoiding a chronic indwelling catheter can reduce the incidence of developing a low compliant bladder. Long-term antimuscarinic therapy can decrease urinary incontinence and lower intravesical pressure. Intravesical

instillation of vanilloids and BoNT-A injections are alternative treatments for refractory DO or a low compliant bladder, and can replace the need for bladder augmentation. When surgical intervention is necessary, less invasive types of surgery and reversible procedures should be considered first, and any unnecessary surgery in the lower urinary tract should be avoided. Keeping the bladder and urethra in good condition without the interference of neuromuscular continuity provides patients with NVD a chance to try new technologies in the future. Improving the QoL in patients with NVD is the most important aspect of treatment.

16. Future technologies

Many novel therapeutic trials of treatments for SCI and NLUTD have been conducted in recent decades. Repair of spinal cord trauma by nerve grafts and stabilization of the grafted area with fibrin glue containing acid fibroblast growth factor have been successful in treating chronic paraplegia [184]. Transplants of fibroblasts expressing brain-derived nerve growth factor and neurotrophin-3 have been applied in an animal SCI model and found to improve both bladder and hindlimb function, which was associated with reorganization of spinal circuitry [185]. Transplantation of immortalized neural stem cells into the injured spinal cord could promote recovery of voiding function in rats [186]. Direct re-establishment of a somatoautonomic reflex pathway to reinnervate the neurogenic bladder has been successful in children with myelodysplasia [187]. Nerve crossover surgery in a neurogenic bladder by cutting the proximal portion of the S2–S3 roots and end-to-end anastomosis to the intercostal nerves can restore central connections to the bladder [188]. Using intermittent electrical stimulation of the pudendal nerve or sacral anterior root stimulation can provide alternative treatments for DA and DSD [189–191]. The use of bladder acellular matrix grafts may be a choice for bladder augmentation to improve bladder capacity in SCI-induced neurogenic bladder [192,193]. All these technical advancements show that NVD could be treated adequately in the future.

17. Guidelines for follow-up

Although patients with LUTD may be properly diagnosed and treated, all patients should receive life-long surveillance to prevent the development of urological complications and undesired LUTSs [60,194,195]. The following procedures are important in long-term follow-up: (1) possible UTI checked by the patient (dipstick); (2) urinalysis every 2nd month; (3) assessment of the upper urinary tract, bladder morphology, and PVR every 6 months (by ultrasound); (4) physical examination, blood chemistry, and urine laboratory tests every year; (5) detailed investigation by a specialist every 1–2 years and on demand when risk factors emerge. The investigation is specified according to the patient's actual risk profile, but should in any case include a videourodynamic investigation and be performed in a leading neurourological center.; and (6) more frequent investigations in high-risk patients or if demanded by the neurological pathology or the NLUTD status.

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