Review Article

Not all neurogenic bladders are the same: a proposal for a new neurogenic bladder classification system

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Abstract: Neurogenic bladder (NGB) has long been defined as a clinical entity that describes a heterogeneous collection of syndromes. The common theme is a bladder disorder concomitant with a neurologic disorder. This definition does not give the clinician much information about the bladder disorder, nor how to treat it, or even what the natural history of the disorder is likely to be. It may be time for a new classification scheme to better define the bladder defect and prognosis, as well as inform treatment. We propose a classification system based on seven categories, each having a neurologic defect in a distinct anatomic location. This is termed SALE (Stratify by Anatomic Location and Etiology). In addition, the presence or absence of bowel dysfunction and autonomic dysreflexia will be reported. In the future, as more definite prognostic information can be gleaned from biomarkers, we anticipate adding urinary nerve growth factor (NGF) and urinary brain-derived neurotrophic factor (BDNF) levels to the definition. We expect the SALE system to efficiently describe a patient suffering from NGB and simultaneously inform the most appropriate treatment, follow-up regimen, and long-term prognosis.

Keywords: Urodynamics; autonomic nervous system (ANS); brain-derived neurotrophic factor (BDNF); nerve growth factor (NGF); urinary bladder; neurogenic

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Introduction

Neurogenic bladder (NGB) is a term used by health care providers to describe dysfunction of the lower urinary tract (LUT) characterized by damage to the central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS). It can remain asymptomatic until in some cases until lower urinary tract symptoms (LUTS) develop. This can decrease quality of life (QoL) and lead to significant long-term costs (1). Some causes include multiple sclerosis (MS), spinal cord injury (SCI), traumatic brain injury (TBI), cerebrovascular accident (CVA), spina bifida, cerebral palsy, transverse myelitis, and diabetes mellitus (DM) (2). Though this clinical definition is commonly used, it lacks enough detail to inform treatment decisions or even assess progress after treatment has begun. This is important because unlike conditions with similar symptoms, such as overactive bladder (OAB), LUTS secondary to NGB can lead to progressive and sometimes life threatening complications such as urinary tract infections (UTIs), urosepsis, and renal failure (2). The location of the neurologic lesion will often determine the type of LUT dysfunction. Typically the diagnosis is made with an initial history and physical exam, but additional investigations such as a post void residual assessment, renal ultrasound, and urodynamic studies are also indicated. After the initial work up, periodic surveillance is recommended (3). This differs from OAB. The recent American Urologic Association (AUA) Guideline on OAB does not advocate this level of workup for the routine patient (4).

The current standard for diagnosis and treatment of NGB, briefly described above and detailed below, is a clinical definition, and does not include imaging or biomarker data, nor does it stratify patients by cause or severity or include information on afferent or efferent

signaling abnormalities. This definition lacks sufficient detail to guide therapy, assess response to therapy, and predict future complications before they occur. Strategies that take into account the specific etiology of the NGB have had a marked impact on QoL and mortality in certain NGB populations, such as SCI and spina bifida, suggesting a need for more specific classification system of these disorders. Despite these gains, QoL and mortality still fall below peers without NGB (5).

The International Continence Society (ICS) has published standards for uniform terminology and urodynamic work up when describing and treating patients with NGB (6). These terms might be incorporated into a more detailed definition that could be used by clinicians to make a more specific work up and treatment plan. For the remainder of this manuscript standardized terminology will be highlighted for the reader.

Prior success in treating neurogenic bladder (NGB)

In 1993 DeVivo and colleagues recognized the death rate from sepsis after a SCI was 82 times higher than expected based on age-matched controls (7). High pressures in the bladder are thought to contribute to damage to the urinary system, renal failure, and incontinence (8). Often the urodynamic combination of "detrusor sphincter dyssynergia (DSD)" and "detrusor overactivity (DO)" can lead to this high pressure situation. Because of advances in the management of the urinary tract after SCI, urologic problems are no longer the leading cause of death after SCI (9). In fact, mortality after the first 2 years has declined by 40%. Despite this success, further improvements in longer term survival remain elusive (5).

Surveillance

Surveillance of patients with NGB is intended to monitor for the common and/or particularly damaging sequelae of NGB, most notably urinary tract infection, upper tract deterioration, stones, and malignancy. Malignancy in NGB, although rare, is more prevalent than in those with normal bladder function, possibly because of chronic catheterization, frequent UTIs, and stone disease (10).

Recommendations for the care and surveillance of NGB vary based on the cause of the condition as well as how long neurogenic symptoms have been present. Although guidelines do exist for the care and surveillance of patients with NGB (3), an optimal follow-up schedule has not been definitively agreed upon. The 2012 AUA Joint Guideline on Urodynamics makes five recommendations specific to NGB (11). The recommendations are:

(I) A post void residual assessment initially and "as part of ongoing follow-up as appropriate";
(II) An initial cystometrogram (CMG) and "as part of ongoing follow-up as appropriate";
(III) An initial pressure flow study (PFS) and "as part of ongoing follow-up as appropriate";
(IV) Videourodynamics with fluoroscopy "may be performed";
(V) An EMG in combination with CMG.

The European Association of Urology (EAU) has published a guidelines statement on neurogenic lower urinary tract dysfunction (NLUTD) as well (3). The panel has made six recommendations for work up (level of evidence is given as well):

(I) Urodynamic investigation is necessary to document the function of the LUT. Grade A;
(II) The recording of a bladder diary is advisable. Grade B;
(III) Non-invasive testing is mandatory before invasive urodynamics is planned. Grade A;
(IV) Video-urodynamics is the gold standard for invasive urodynamics in patients with NLUTD. If this is not available, then a filling cystometry continuing into a pressure flow study should be performed. Grade A;
(V) A physiological filling rate and body-warm saline must be used. Grade A;
(VI) Specific uro-neurophysiological tests are elective procedures. Grade C.

The specific uro-neurophysiological tests referred to in the 6th recommendation are more commonly done by neurologists and include:

(I) EMG (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
(II) Nerve conduction studies of pudendal nerve;
(III) Reflex latency measurements of bulbocavernosus and anal reflex arcs;
(IV) Evoked responses from clitoris or glans penis;
(V) Sensory testing on bladder and urethra.

These uro-neurophysiological tests have not been incorporated into the mainstream of classification for these disorders and in most cases do not reliably aid the clinician in achieving the major goals of therapy in treating NGB.

The primary aims for treatment of NGB according to the EAU Guidelines should be (3):

(I) Protection of the upper urinary tract;

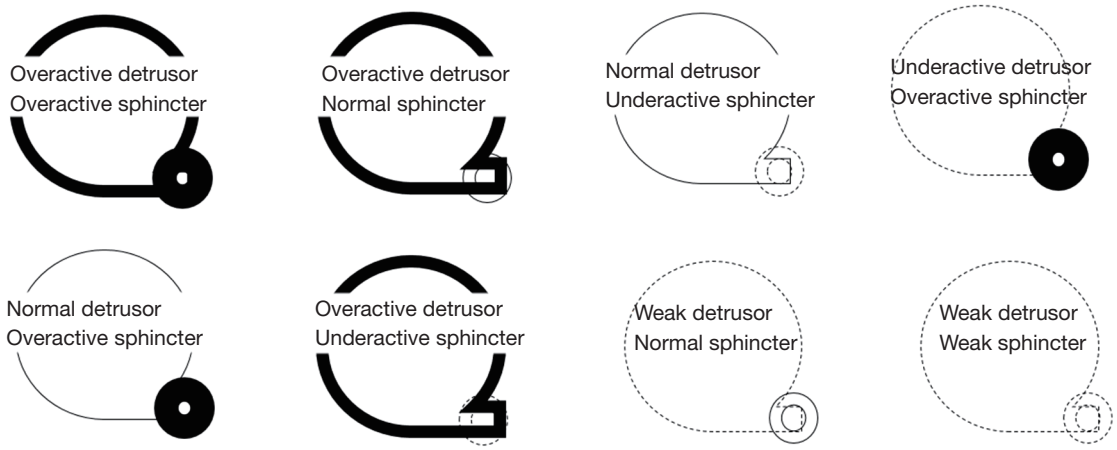

Figure 1 Madersbacher classification system of neurogenic lower urinary tract dysfunction.

(II) Improvement of urinary continence;
(III) Restoration of (parts of) the LUT function;
(IV) Improvement of the patient's QoL.

For victims of SCI specifically, a 2011 review of recommendations for primary care physicians suggests initial evaluation of these patients should include urinalysis, urine culture and sensitivity, serum blood urea nitrogen/creatinine, creatinine clearance, and urodynamics (12). Follow-up of these patients includes urinalysis and ultrasound every 6 months, urine culture whenever symptoms occur, urologic follow-up yearly, and urodynamic evaluation every 1–2 years (13). For those patients using intermittent self-catheterization, many urologists advocate for regular cystoscopy and random and targeted bladder biopsies in addition to regular urine cytology (14).

Existing classification systems

In addition to the clinical classification system described in the introduction, Madersbacher has proposed a classification system based on the tone of the bladder and urinary sphincter (15). A schematic representation appears in *Figure 1*. One advantage of this system is that it is easy to understand, explains the nature of the dysfunction, and can be accurately characterized using urodynamics. Unfortunately, the tone of these muscles may change over time, depending on the etiology of the injury. A classification system should inform therapy decisions and prognosis, and depending on the etiology of the neurologic injury the function of the bladder and urinary sphincter may change over time. The Madersbacher model does not take etiology into account, nor does it account for the difference between striated and smooth muscle urinary sphincter, which has important implications for treatment, but remains difficult to detect clinically.

Adding to the definition of neurogenic bladder (NGB)

The current definition of NGB is not detailed enough to guide management or inform prognosis. These patients can further be stratified using a few established strategies and possibly some new ones that are being developed. Certain diagnoses carry a higher risk of upper tract deterioration, and even death, such as SCI (7). The general term "NGB" does not distinguish between these diagnoses. One proposal is to begin to define NGB based on the anatomic defect in the nervous system. This is driven by the etiology, such as "neurogenic bladder-SCI" or "neurogenic bladder-MS". One advantage of such a system would be to provide more information on prognosis or response to a specific treatment. One disadvantage is a significant increase in complexity, making adoption of such a system less likely. One compromise would be to group etiologies based on the level of the neurologic insult, creating fewer categories into which most of the common etiologies of neurologic dysfunction could be placed.

For patients with a history of SCI or lesion around the T5-T6 level, the presence or absence of symptoms of autonomic dysreflexia should be noted. This manuscript proposes a new classification system that takes the anatomic location of the defect into account based on the etiology. In other words, Stratify by Anatomic Location and Etiology (SALE). We propose this be called the SALE NGB classification. Each category was chosen because they combine

an etiology with some common clinical and urodynamic findings as outlined below.

Stratify by Anatomic Location and Etiology (SALE classification)

Supra-pontine neurologic disorders

Supra-Pontine neurologic lesions differ from other neurologic insults because they lead to loss of tonic inhibition of the pontine micturition center (PMC). This can lead to spontaneous involuntary DO, which is different than DO that occurs after supra-sacral SCI. In the case of SCI, a period of spinal shock occurs, after which a segmental reflex develops at the level of the sacral spinal cord, mediated by C-fiber afferents, which leads to DO (16,17). This category is characterized by storage dysfunction. Normal uroflow and normal pulmonary vascular resistance (PVR) can generally be expected. In some cases detrusor underactivity (DU) has been reported, as well as detrusor overactivity with impaired contraction (DOIC), so it is important to acknowledge that DO is not the only finding in supra-pontine injury.

Neurogenic bladder—cerebrovascular accident (CVA)

CVA is most commonly associated with "urge urinary incontinence" and "DO". It is thought to be due to loss of the inhibitory function of the frontal cortex on the PMC. Typically the sphincter is coordinated and only DO results from a suprapontine lesion, keeping the upper tracts more safe than an infra-pontine lesion, such as SCI. DO is not the only finding that is possible in CVA, however. In fact one prospective observational series of consecutive post-CVA patients reported 79% of 106 patients were incontinent, with 56% exhibiting DO on urodynamics, 14% with DOIC, and 15% with DU (18). Some investigators have even suggested that anterior distribution infarcts may confer worse bother due to LUTS (based on overactive bladder symptom score) (19).

Neurogenic bladder—traumatic brain injury (TBI)

TBI can be associated with 47% of all SCI's (20). Due to the complex cognitive and mobility issues that often accompany these patients, it is best to take a team approach and follow the guidelines for SCI when assessing a patient with TBI (20). TBI should be considered in any case of SCI.

Neurogenic bladder—normal pressure hydrocephalus (NPH)

NPH includes the classic symptom triad of gait disturbance, dementia, and urinary incontinence. Patients with NPH exhibit neurogenic urinary dysfunction similar to other suprapontine lesions, with 64% describing urgency and frequency, 57% complaining of incontinence, and 95% exhibiting DO on urodynamics (21). DU is much less frequently seen, with one series exhibiting a 5% prevalence (22). One distinction is that despite normal intracranial pressures with this condition, a ventriculo-peritoneal shunt can often improve the LUTS seen in NPH, in fact, in one series 32 patients underwent a shunt and 90% reported improvement in LUTS (22).

Neurogenic bladder—cerebral palsy (CP)

CP is a supra-pontine neurologic insult that leads to spastic upper motor neuron symptoms. Urgency (42.6%), urge incontinence (40.7%), and enuresis (16.7%) were reported commonly in a series of 54 children. The children with CP who reported LUTS also had a significantly weaker stream (17.2±7.8 *vs.* 22.6±7.5 mL/s, P=0.013) suggesting an element of "detrusor-sphincter dyssynergia (DSD)" (23).

Neurogenic bladder—Parkinson's disease

Parkinson's disease presents with variable urodynamic findings, most commonly "DO" (67%), and variable LUTS, namely nocturia (77%), urgency (36%), and frequency (32%), but can also exhibit DU (12%) (24). LUTS often appear after motor symptoms from Parkinson's disease develop. "DSD" is not commonly seen, which is important since DSD has been associated with upper tract damage in SCI and spina bifida (25). The other basal ganglia disorders have similar variable presentations, with Shy-Drager syndrome exhibiting a classic striated sphincter dyssynergia, classically with a weak striated sphincter and open bladder neck on video urodynamic imaging. This means that procedures to open the bladder neck/outlet, such as trans-urethral resection of the prostate (TURP) should be undertaken with caution in Shy-Drager and multiple systems atrophy, since they have a high likelihood of rendering the patient incontinent. One prospective comparison between 21 patients with Parkinson's disease and 15 with multiple systems atrophy revealed urodynamic evidence of DO in 81% of the Parkinson's group and 54% in the multiple systems atrophy (25). These conditions do not typically lead to deterioration of the upper urinary tract.

Pontine neurologic disorders

These are very rare and can be caused by tumors or ischemic infarcts.

Neurogenic bladder—brain tumor

Brain tumor can cause LUTS in 24% of supra-pontine tumors (26) and pons-based pediatric tumors have been noted to cause urinary retention in 71% of children (27).

Neurogenic bladder—cerebellar ataxia syndromes

Cerebellar ataxia syndromes includes Friedreich's ataxia along with many other autosomal dominant and autosomal recessive motor and cognitive disorders. Slurring dysarthria, gait disturbance, and progressive limb ataxia (including tremor) characterize these disorders. One series sent questionnaires with 158 respondents who reported LUTS (82%). A smaller subset agreed to urodynamics and investigators found DU in the majority, with 14% exhibiting upper tract dilation by ultrasound. The urodynamic study was normal in 14% (28). These genetic disorders have important implications for family members who are at risk as well.

Supra-sacral spinal cord/upper motor neuron disorders

Supra-sacral SCI leads to DO via establishment of new C-fiber mediated segmental reflexes as described above with the additional loss of coordination of the smooth urethral sphincter, known as DSD. This category is characterized by storage and emptying dysfunction. "Urinary urgency/frequency, urge urinary incontinence, and intermittent stream or hesitancy" can be expected. "Urinary retention" is common during the first 6–8 weeks after a SCI, a period known as spinal shock, but not all supra-sacral neurologic disorders are caused by SCI. Urinary retention may persist after spinal shock has resolved.

Neurogenic bladder—spinal cord injury (SCI)

Neurogenic bladder-SCI has been associated with upper tract deterioration, unlike more slowly progressive neurologic conditions such as MS (29). "Non-relaxing urethral spincter obstruction" or "DSD" has been associated with elevated voiding pressures and may contribute to damage to the upper urinary tract, and has poor "compliance", whether associated with "vesicoureteral reflux (VUR)" or not (30). Distinguishing SCI from other forms of NGB has therapeutic implications as well. For instance, there is evidence that early sacral neuromodulation during the period of spinal shock may prevent the development of urinary incontinence during the convalescent period (31). This evidence is from small trials and it is possible that the therapeutic benefit in SCI, if found to be durable, may also be seen in NGB from other etiologies, such as MS.

Neurogenic bladder—degenerative disc disease

Degenerative disc disease has been associated with DU in 27% of patients (32). Decompressive spinal surgery is associated with improvement, but not for all affected patients, with some still requiring CIC following surgery (33).

Neurogenic bladder—spina bifida

Spina bifida for many years has been associated with renal deterioration, and in fact, these patients suffer renal failure more often than the general population (29,34,35). This is thought to be due to high storage pressures and high detrusor leak point pressure in the bladder (36). Strategies incorporating early institution of CIC and anticholinergic therapy, with periodic bladder and renal surveillance to guide more invasive therapy, has reduced renal deterioration to negligible levels (37). A recent review of 369 patients with spina bifida managed with bladder augmentation noted only a 0.5% mortality rate over 10.8 years attributed to renal failure. The authors suggest that bladder augmentation has been a key factor in the increased survival (38). One retrospective review of 144 children with spina bifida undergoing urodynamic studies revealed equal distributions of patients with DSD (47%) and DO (42%) and none developed end-stage renal failure, although all had been started on anticholinergics and CIC shortly after birth (37). Another revealed that at a mean age of 6.5 months 43% of spina bifida patients exhibited "acontractile detrusor", 19% with decreased compliance, and 75% with a detrusor leak point pressure of >40 cmH_2O (39). One important prognostic implication for this category is that these patients can develop tethered cord later in life and any change in bladder function should prompt a work up for this, which sets spina bifida apart from most patients with NGB.

Sacral spinal cord disorders

Sacral SCI leads to weak or absent detrusor contraction ("DU or acontractile detrusor") and a tonic contraction of the smooth urinary sphincter ("non-relaxing urethral sphincter obstruction"). Emptying dysfunction predominates. Uroflow can be expected to be absent or diminished. Urodynamics may reveal abdominal straining to empty and elevated post void residual.

Neurogenic bladder—cauda equina syndrome

Cauda equina syndrome classically manifests with saddle anesthesia. Urodynamic findings include reduced or absent bladder sensation and DU, often resulting in urinary retention, sometimes so severe that it causes overflow incontinence. Paradoxically, this patient population can also acquire DO, possibly due to loss of CNS inhibition of post-ganglionic peripheral neurons (40).

Neurogenic bladder—following radical pelvic surgery

Following radical pelvic surgery is characterized by DU, poor sensation to filling, and coordinated or fixed-tone sphincter. Clinically these patients present with urinary

retention or UTIs. It is not thought to be progressive.

Lower motor neuron/neuropathy disorders

Neurogenic bladder—diabetes mellitus (DM)

DM has been associated with up to a 50% rate of "DU" (41) and in the Nurse's Health Study II those with DM exhibited a 20% greater risk of urinary incontinence when compared with controls not affected by DM (42). As might be expected, neuropathy related to poorly controlled DM occurs in multiple organ systems, including NGB, and one 23-year population-based longitudinal study demonstrated significantly decreased DM-related QoL (43). Any treatment plan for NGB-DM should incorporate strategies for improved glucose control, and will usually involve monitoring for urinary retention with a plan to empty the bladder with clean intermittent self catheterization if certain criteria are met, such as recurrent infections or a residual volume above a certain point.

Neurogenic bladder—peripheral neuropathy

Peripheral neuropathy most commonly causes impaired sensation of filling and can be caused by many metabolic disorders. LUTS from neuropathy are found in alcohol abuse (5–15%) (44), porphyria (12%) (45), sarcoidosis (45), herpes zoster (46), herpes simplex 2 (47), and many other conditions.

Neurogenic bladder—Guillain-Barre syndrome

Guillain-Barre syndrome has been associated with LUTS in 27.7% of patients including 9.2% with "urinary retention" (48). Urodynamic findings in a smaller subset from the same series revealed "DO" in 89% and DU in 78%, some of which exhibited both urodynamic findings (48).

Demyelinization disorders

Neurogenic bladder—multiple sclerosis (MS)

MS is characterized by variable symptoms, with 54% exhibiting LUTS in one cross sectional cohort. In some cases LUTS are the first symptom of MS and lead to its diagnosis. Risk factors for development of urinary symptoms include duration of MS greater than 8.5 years and increased symptom severity (49).

Syndromes with no neurologic lesion

Neurogenic bladder—Fowler's syndrome

Fowler's syndrome is characterized by young women with idiopathic spasm of the urethral sphincter. They often suffer from urinary retention and typically come to clinical attention through painful straining to void. It is important to make this distinction because these patients often respond well to sacral neuromodulation (50).

Neurogenic bladder—dementia

Dementia carries unique challenges because some of the urinary symptoms, such as incontinence, might be behavioral in nature. Incontinence can be seen in 23–48% of dementia with Lewy bodies (51). Alzheimer's patients exhibited a 53% rate of urge incontinence , and DO can be seen in up to 93% of patients with dementia associated with Lewy bodies, and 40% of those with Alzheimer's (52). Poor cognition may leave the caregivers with uncooperative patients, and urinary frequency is difficult to assess. This requires a different treatment strategy than the other etiologies for NGB, such as incorporating more social services. Many anticholinergic medications may not be suitable, since they can exacerbate dementia, and dual use of anticholinergic medications (such as oxybutynin or tolterodine) with acetylcholinesterase inhibitors (such as donepezil) has been shown to decrease a patient's ability to perform activities of daily living (53).

Stratify by biomarker

Biomarkers carry the promise to enhance the diagnosis of neurologic disease as well as assess the progress of therapy, and in some cases, predict future course of disease. Many biomarkers have been studied in the context of NGB, both in serum and urine, and two show significant promises and may someday be incorporated into a definition of NGB.

Stratify by biomarker—nerve growth factor (NGF)

NGF is detectable in the urine and has been extensively studied as a diagnostic and prognostic biomarker for OAB (54). It is produced by human urothelium and smooth muscle cells and increased urinary NGF levels are seen after SCI, as well as in denervated bladders, stretch injury, and inflammation (55). NGF levels are low in subjects with normal voiding habits, and do not vary with gender or time of day (56). NGF is not just a biomarker; it has the ability to alter the excitability of afferent C fibers as well as reflex bladder activity (57).

Rising urinary NGF levels have also been correlated with symptoms. NGF levels detected in the urine were noted to be significantly higher in the OAB-wet sub-group (2.13±3.87) compared to the OAB-dry sub-group (0.265±0.59) and control groups (0.07±0.21) (58). NGF levels did not appear to change with age or BMI (P=0.088 and 0.886 respectively). NGF levels in the urine appear to increase in "normal subjects" (without OAB) when the bladder is filled (0.011±0.008) *vs.* NGF levels at bladder volumes full enough to give the urge sensation (0.086±0.022, P=0.005) but do not appear

as responsive in subjects with OAB, where baseline levels are higher. In that investigation 39 subjects with a diagnosis of OAB had elevated baseline NGF levels compared with 35 healthy controls (0.450±0.130 *vs.* 0.011±0.008, P=0.001) but the difference in urinary NGF levels between first sensation of filling and later when urge was sensed failed to reach statistical significance in the OAB group (P=0.064) (59).

It also appears to distinguish urge incontinence from stress incontinence. Urinary NGF was measured in 38 women with mixed urinary incontinence, 26 women with urodynamic proven DO only, 21 women with persistent urodynamic proven stress incontinence after continence surgery, 15 women with *de novo* DO after continence surgery, and 31 control subjects. The urinary NGF levels were low in the controls and in women with pure stress incontinence (0.06±0.004 *vs.* 0.056±0.037, P=0.108), and significantly higher in women with *de-novo* DO after stress incontinence surgery (2.39±0.90, P<0.001) and mixed incontinence with DO (1.00±0.244, P<0.001). The women with pure DO had similar elevations (0.587±0.170, P=0.002). An elevated urinary NGF level of >0.05 was found in only 9% of women with stress incontinence, 77% with DO, 81% with mixed incontinence, and 80% with *de-novo* DO after surgery (60). This study indicated that NGF could be a potential biomarker for the presence of DO in women with mixed etiologies and justifies further study in defining NGB in terms of NGF as a biomarker for severity of disease.

NGF levels may decrease with successful therapy for DO. Patients suffering neurologic deficits following CVA also appear to exhibit elevated urinary NGF levels that increase with the severity of the deficit. Investigators in Taiwan noted no increase in urinary NGF levels for patients with no deficit or minimal deficit, and increased with moderate deficits and further increased with severe deficits (61).

Caution should be used, however, since NGF can also be elevated in conditions where the bladder is irritated, such as cancer, stones, and cystitis (62).

NGF levels also appear to decrease after successful response to therapy. Subjects with decreased NGF levels 3 months after treatment with botulinumtoxin A (BoNT-A) generally responded to therapy while those without a decrease in NGF did not respond. The important factor was that both subjects with idiopathic DO as well as neurogenic DO exhibited this decrease in NGF (63). This effect appears to be durable, as NGF levels checked 6–12 months post injects remained low in responders, but not all subjects were included in the extended analysis (63).

In addition to predicting successful BoNT-A treatments, urinary NGF levels may predict response to sacral neuromodulation. One group of investigators demonstrated decreased levels of urinary NGF 5 days after S3 peripheral nerve stimulation (PNS) compared to baseline (64). A total of 23 subjects with urodynamic proven DO and a history of failed treatment with anticholinergics exhibited urinary NGF levels significantly decreased from 17.23 pg/mg to 9.24 J/mg (P<0.02) after PNS. Similar to the studies referenced previously, baseline NGF levels were higher for those with proven DO (19.82 *vs.* 7.88 pg/mg, P<0.002) (64).

Stratify by biomarker—brain derived neurotrophic factor (BDNF)

Similar to NGF, BDNF has been investigated as a biomarker to indicate presence and severity of OAB. It has been noted to increase in a time dependent fashion that correlates with the development of neurogenic DO after acute SCI, and appears to play a role in inhibiting neuronal sprouting in rats (65). In fact, chronic exogenous BDNF inhibited the development of neurogenic DO in rats, while sequestering BDNF after acute SCI allowed for the development of neurogenic DO as well as increased axonal growth in the dorsal horn of the spinal cord following injury (65). In the future it may become a target of therapy. Additionally, it may play an important role in inflammatory conditions and has been noted to heighten sensitivity to pain in mice (66). As a biomarker detectable in the urine, it has been noted to increase in women with a diagnosis of OAB compared to healthy women without OAB (mean 628.1±590.5 *vs.* 110.4±159.5, P<0.001) and decreased after a 3-month trial of lifestyle intervention (mean 628.1±590.5 *vs.* 432.5±589.0, P=0.033). BDNF also decreased after a 3-month trial of oxybutynin extended release, 10 mg (628.1±590.5 *vs.* 146.6±264.9, P<0.001) (56). BDNF may not only serve as a urine biomarker to grade the severity of the damage to the LUT after SCI, but may someday be used as a target for therapy and would be a useful addition to a classification scheme for NGB once prognosis can be tied to rising or decreasing levels of BDNF.

Conclusions

In conclusion, we propose a new scheme to define NGB in adults call the SALE system (Stratify by Anatomic Location and Etiology) that will have seven categories based on the anatomic level of neurologic dysfunction. We hope this will better inform clinicians as to how to work up and treat these patients, as well as how best to monitor progress in the four main goals of treating NGB, namely (I) protection of the upper urinary tract; (II) improvement of

urinary continence; (III) restoration of the LUT function; and (IV) improvement of the patient's QoL. In the future we anticipate including biomarker status as part of the definition. Two promising biomarkers are NGF and BDNF.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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