A prospective assessment of the validity of the CUA neurogenic bladder guideline

Haider Abed[1], Magdy Hassouna[2], Nader Aldossary[2], Mary Mckibbon[3], Blayne Welk[1,4]
[1]Department of Surgery, Western University, London, ON, Canada; [2]Department of Surgery, University of Toronto, Toronto, ON, Canada; [3]St. Joseph Hospital, London, ON, Canada; [4]Department of Epidemiology and Biostatistics, Western University, London, ON, Canada

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Corresponding author: Dr. Blayne Welk, Division of Urology and Epidemiology and Biostatistics, Western University, London, ON, Canada; Bkwelk@gmail.com

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ABSTRACT

Introduction: The Canadian Urological Association (CUA) neurogenic bladder guideline surveillance strategy for neurogenic lower urinary tract dysfunction (NLUTD) has not been formally evaluated. Our objective was to evaluate the validity of the risk stratification suggested in these guidelines.
Methods: This was a prospective, observational cohort study of adult NLUTD patients with spinal cord injury, multiple sclerosis, or spina bifida who required urodynamics. Patients with a requirement for immediate bladder surgery (not suitable for surveillance) were excluded. Patients completed standardized medical history/questionnaires, baseline urodynamics, renal imaging, and creatinine tests. The primary outcome was the need for different types of urological management between the high-risk and moderate-risk groups.
Results: We enrolled 68 patients; most commonly, these were spinal cord injury patients, and most people were using intermittent catheters. At baseline, 62% (40/68) were classified as high-risk. In this group, there was a numerically greater proportion who received a recommendation for a new urological medication (48% vs. 25%, p=0.06) or a change to their bladder management (45% vs. 36%, p=0.44). A total of 26 high-risk and 23 medium-risk NLUTD patients had a one-year followup visit. A larger proportion of the high-risk patients had a recommendation for a new bladder medication (15.4% vs. 8.7% p=0.47), intravesical onabotulinum toxin (34.6% vs. 13% p=0.08), or an alternate method of bladder management (15.4% vs. 4.3%, p=0.2). Mean creatinine change was slightly greater in the high-risk group (+6.1 vs. +0.4 umol/L, p=0.05).

Approximately 1/3 of both high-risk and moderate-risk patients didn't accept the recommended interventions.
Conclusions: A higher proportion of high-risk NLUTD patients had urology-relevant interventions recommended, both at baseline and at their one-year followup visit. This supports the general concept of risk stratification and the variables used to define high-risk in the CUA's neurogenic bladder guideline.

INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) is a common consequence of conditions such as spinal cord injury (SCI), multiple sclerosis (MS) and spina bifida (SB).[1] There can be significant urologic complications in these patients, such as renal failure, urinary infections, and urolithiasis, all of which can lead to meaningful morbidity.[2] In an attempt to minimise illness in this patient population, numerous medical societies have proposed guidelines for follow-up and screening medical tests among people living with NLUTD.[3] Prior to 2019, the most recognised guidelines in urology tended to recommend frequent routine investigations for all patients. This was based on an overly "sensitive" approach whereby it was assumed to be better to over-investigate a wide group of patients to avoid missing the few with a potentially treatable finding. A significant limitation of these guidelines for this specific aspect of NLUTD management is that there are no large-scale screening studies that address this topic. While some studies have identified, for example, the proportion of people after SCI with asymptomatic urodynamic findings[4,5], this does not fully address the question of screening, which must consider the relative likelihood of downstream patient-relevant outcomes, the sensitivity/specificity of the screening test, the possibility that patients would eventually present clinically and have an unchanged clinical outcome, and the risks of invasive testing like urodynamics (such urinary tract infection[6]).

To address some of this uncertainty, the CUA Neurogenic Bladder guidelines (published in 2019[7]) created a risk stratification system to resolve the issue of previous NLUTD guidelines being written only for high-risk patients (which therefore emphasized aggressive screening), and the fact that many "high-risk" patients reach urologic stability and do not need repeated, invasive monitoring. As part of this process, the available evidence, and the expert opinion of the guideline authors was used to identify high risk patients (table 1[7]). Distinctions between the follow-up of high-risk patients and moderate risk patients are shown in figure 1; the primary difference is the recommendation for frequency of urodynamics (yearly for high risk, periodic (2-5 years) for moderate risk).[7] However, the authors recognised that this system was not evidence-based, and further assessment of the need for this intensity of screening tests, and the validity of the high-risk/moderate-risk stratification would be necessary. The objective of this study was to assess the validity of the CUA neurogenic bladder guideline risk stratification in a prospective cohort study of patients with SCI, MS or SB.

METHODS

Overview

This is a prospective multi-center cohort study caried out at Western University and the University of Toronto. Ethics approval was granted at both institutions (#114031 and #19-5927 respectively). Study enrollment was carried out from September 2019 until August 2021, at which point new patient enrollment was stopped based on the predetermined end date and funding restrictions.

Study participants

Patients with the diagnosis of SCI, MS or SB who were attending an appointment with one of two academic urologists with an interest in neuro-urology were eligible for recruitment. The patient inclusion criteria were age >18 years, and attending either an initial or follow-up urologic consultation. Only follow-up patients who were due for screening urodynamics at the time of study enrollment were included. We excluded patients who presented with acute urologic issues that require immediate surgical treatment (for example hydronephrosis and the need for bladder augmentation), those who were unwilling to commit to a continued follow-up program, and those who did not have a strong English language proficiency.

Study design

All participants provided written consent. At enrollment, they underwent standard baseline investigations as per the CUA neurogenic bladder guidelines, and the established care pattern of the treating urologist: urodynamics, renal imaging, and a renal function assessment. Patients who refused urodynamic testing were not offered enrollment in the study. Baseline clinical and demographic variables, and a validated symptom/quality of life score (Neurogenic Bladder Symptom Score-SF, where a higher score represents worse symptoms[8,9]) was completed. Using the initial urologic screening investigations, the patient was classified as moderate or high risk (the patient populations included in this study were all moderate and high risk by definition, therefore no low-risk patients were recruited for this study). Urodynamics were carried out based on International Continence Society standards[10]. Follow-up investigations were planned based on the CUA Neurogenic Bladder guidelines, and patients were observed for a maximum of 2 years after enrollment. All data collection was done through a secure, pre-designed redcap database, and data entry rules were used to maximize completeness and minimize data entry errors.

The primary outcomes were the proportion of patients who: 1) were offered intervention (medication, intravesical onabotulinum toxin, or surgery) or a change in their bladder management, and 2) the total NBSS-SF score at baseline. At the time of the study visit, treating physicians prospectively recorded if a recommendation for a change in bladder management, or need for an intervention was necessary, and whether the patient accepted the change or not. Further secondary outcomes were evaluated in the subset of patients with follow-up visits; this included 1) the change between baseline and year 1 follow-up in the serum creatinine, 2) the number with *new* abnormal ultrasound findings (such as hydronephrosis, parenchymal thinning,

renal scars or renal stones), and 3) number of self-reported urinary tract infections over the past one year (defined as symptomatic with a positive urine culture or UTI symptoms that resolved with antibiotics). Ultrasound findings were based on the original radiologist report. The primary exposure was CUA neurogenic bladder risk group (defined as either moderate or high, see figure 1 for details).

Statistical analysis

Our original sample size was estimated using Fischer's exact test, alpha=0.05 and a beta=0.20. The assumed proportions of our primary outcome (recommendation for an intervention) were estimated at 65% (high-risk group) and 40% (medium risk group), leading to a total sample size of 120 patients. However, the COVID-19 pandemic started 6 months after our study was initiated. This led to repeated institutional-wide shutdowns of research activities, and restrictions on patient-care activities altered our ability to perform screening investigations. Due to the global pandemic, one year surveillance urodynamic results were not completed for patients in the high risk group. Due to these significant constraints, we changed the intention of our study to be a pilot study, and we were not able to meet our recruitment goals. A post-hoc sample size calculation based on our actual recruitment suggests we have a beta of 0.52 with the same assumptions outlined above; this means a lack of statistical differences could be the result of an underpowered analysis. For statistical analysis, all data was analyzed with SPSS using a chi-square or Fischer's exact test, or student's t-test, and a $p<0.05$ was considered significant. Mean and standard deviation is reported.

RESULTS

There were 68 total patients enrolled between the two institutions (table 2). NLUTD etiology was SCI (78%, 53/68), MS (17.6%, 12/68), and SB (4.4%, 3/68). The level of injury for most SCI was cervical (47%, 25/53). Most patients utilized CIC (65.1%), followed by voiding (16.7%), and indwelling urethral catheter (7.5%). The majority of the patients lived at home, used a wheelchair (69.1%), and were self-sufficient with respect to urological care (72.1%).

At baseline, 62% (40/68) were classified as high risk and 38% (28/68) as medium risk as per the CUA guidelines (Table 3). Most people in the high risk group were classified as such because of UDS features (75%, 30/40). Classification as medium risk was driven primarily by favorable bladder management (79%, 22/28). Patients often had multiple features accounting for why they were in the high or medium risk group.

Analysis of the baseline data (Table 4) demonstrated that the high-risk group (compared to the medium risk group) had a greater proportion of patients that were recommended new urologic medications (48% vs 25%, p=0.06), intravesical onabotulinum toxin (43% vs 29%, p=0.24), or change in bladder management (45% vs 36%, p=0.44). As ultrasound criteria were part of the classification of high risk versus medium risk, the high risk group also had a higher proportion of patients with abnormal renal ultrasound findings (28% versus 7%). There was no difference in the mean Neurogenic Bladder Symptom Score (SF) between both groups (11.95 vs 12.25, p=0.87).

A total of 26 high risk and 23 medium risk NLUTD patients (Table 5) returned for the one year follow up visit at a mean of 12.1 (± 0.9) months later. Mean NBSS-SF values were again similar between groups at year 1 (high risk group 11.2 vs medium risk group 11.15, p=0.43) and both groups had a similar small improvement from baseline (-0.75 versus -1.1, p=0.67). Mean creatinine change was slightly greater in the high risk group (+6.1 vs +0.4, p=0.05). The number of people with ≥1 UTI during 1 year follow-up was similar between groups (high risk 15.4% vs medium risk 17.5% p=0.85).

Among high-risk patients at 1 year, more high risk patients needed a new bladder-related medication (15.4% vs 8.7% p=0.47), onabotulinum toxin (34.6% vs 13% p=0.08), alternate bladder management (15.4% vs 4.3%, p=0.2) and there was a slightly greater proportion of the high risk patients being recommended surgery (11.5% vs 4.3% p=0.35). The recommended surgeries were bladder augmentation, treatment of bladder stone, or stress incontinence surgery. Approximately 1/3 of both the high risk and the medium risk patients didn't accept recommended NLUTD interventions.

DISCUSSION

The appropriate follow-up and surveillance of patients with NLUTD continues to be a challenging topic given the lack of evidence to inform these decisions. Our objective was to validate the differences in people that are considered moderate risk versus high risk based on the CUA neurogenic bladder guidelines. We conducted a prospective pilot study that enrolled 68 patients. At baseline we found that the high-risk group had a numerically higher proportion of patients who were recommended a new bladder medication, intravesical onabotulinum toxin, or a change in their bladder management; however given our limited sample size, these differences were not statistically significant. Among the 49 patients with one year follow-up data, again the high-risk group had a numerically high proportion who were offered new bladder medications, alternative bladder management options, and a higher numerical increase from their baseline creatinine. The higher proportion of medium risk patients being offered intravesical onabotulinum toxin both at baseline is probably a result of the high portion of high-risk patients who were already using intravesical onabotulinum toxin. Acknowledging that this is a pilot study, these findings support the stratification of patients into medium and high risk groups, and validate the general criteria used by the CUA neurogenic bladder guidelines to assign patients to these groups.

It is important to note that bladder symptoms were similar in both the medium and high risk groups, and did not change significantly in either group at the 1 year mark. This highlights the fact that patient perceived symptoms do not necessarily correlate with the urologic risk and the need for intervention that is apparent to the treating physician. Alternatively, the limited compliance with treatment may also limit the possibility of symptom improvement. Similarly urinary tract infections, which are common, a frequent source of morbidity, and bothersome to patients with NLUTD[11], were similar in both the high risk and medium risk groups. This reinforces the appropriateness of re-evaluating both of these patient groups yearly to see if additional maneuvers could be considered to reduce UTI frequency, to counsel patients on the

difference between asymptomatic bacteriuria and symptomatic infection, and to reoffer patients treatment and interventions (which interestingly about 1 in 3 patients declined).

Three years after the publication of the CUA neurogenic bladder guidelines, the American Urologic Association (AUA) published the first version of their guideline on adult neurogenic lower urinary tract dysfunction. They included a similar risk stratification system[12]; patients with SCI, MS or SB would generally be considered either high risk (and therefore recommended to receive annual follow-up, renal function and renal imaging, and urodynamics when there was a change in symptoms or complications) or medium risk (and therefore recommended to receive annual follow-up and renal function assessment, with renal imaging every 1-2 years, and urodynamics if there was a symptom change or renal imaging/function change). The level of evidence for this practise was given as "Grade C". However, a systematic review on the topic of surveillance urodynamics found that among people with SCI, annual urodynamics lead to a new intervention in about half of patients, and many of patients did not report new symptoms associated with the urodynamic changes.[4] Studies in patients with MS also show changes to urodynamics that are asymptomatic, however the low risk of renal deterioration makes the importance of these changes less clear. There are few studies in adults with SB to guide surveillance urodynamics. Our findings that the NBSS-SF score was stable, and similar in magnitude in both the high and medium risk groups also support some degree of routine urodynamic assessment.

Our study has several limitations that must be acknowledged. First, the patient population included patients referred to a tertiary care urologists with an interest in neurogenic bladder, and generally included community dwelling people. Second, to achieve our sample size, we included both existing patients (who had been actively managed), and new patients; this likely reflects real world use of these guidelines, but may limit the identification of adverse events (such as utis). Third, the limited sample size precludes any strong statistically significant findings, and these results would be most appropriate to be used to justify and inform a larger study. Fourth, as discussed in the methods, disruptions from the COVID pandemic significantly curtailed some surveillance activities, which accounts in part for the drop in our total cohort analyzed from 68 at baseline to 49 at 1 year, lack of follow-up urodynamic data for the high risk group at 1 year, and why we were unable to meaningfully analyse year 2 data due to significant study dropout. Fifth, we recognise that serum creatinine is a poor marker for renal dysfunction, however it was the most commonly available measure in our study population. Finally, longer-term follow-up is obviously necessary to validate a surveillance strategy which is intended to be life-long. However, we do feel our study contributes to the understanding of the appropriateness of the baseline risk classification for NLUTD patients and highlights the importance of appropriate evaluation and management of these patients to prevent further complications and improve their quality of life.

CONCLUSIONS

Our study evaluated the validity of the baseline risk classification proposed by the CUA neurogenic bladder guidelines. A higher proportion of NLUTD patients who were classified as

high risk (usually due to UDS features) had urology-relevant interventions recommended, both at baseline, and at their 1 year follow-up visit. Further studies are needed to explore the long-term outcomes of NLUTD management strategies.

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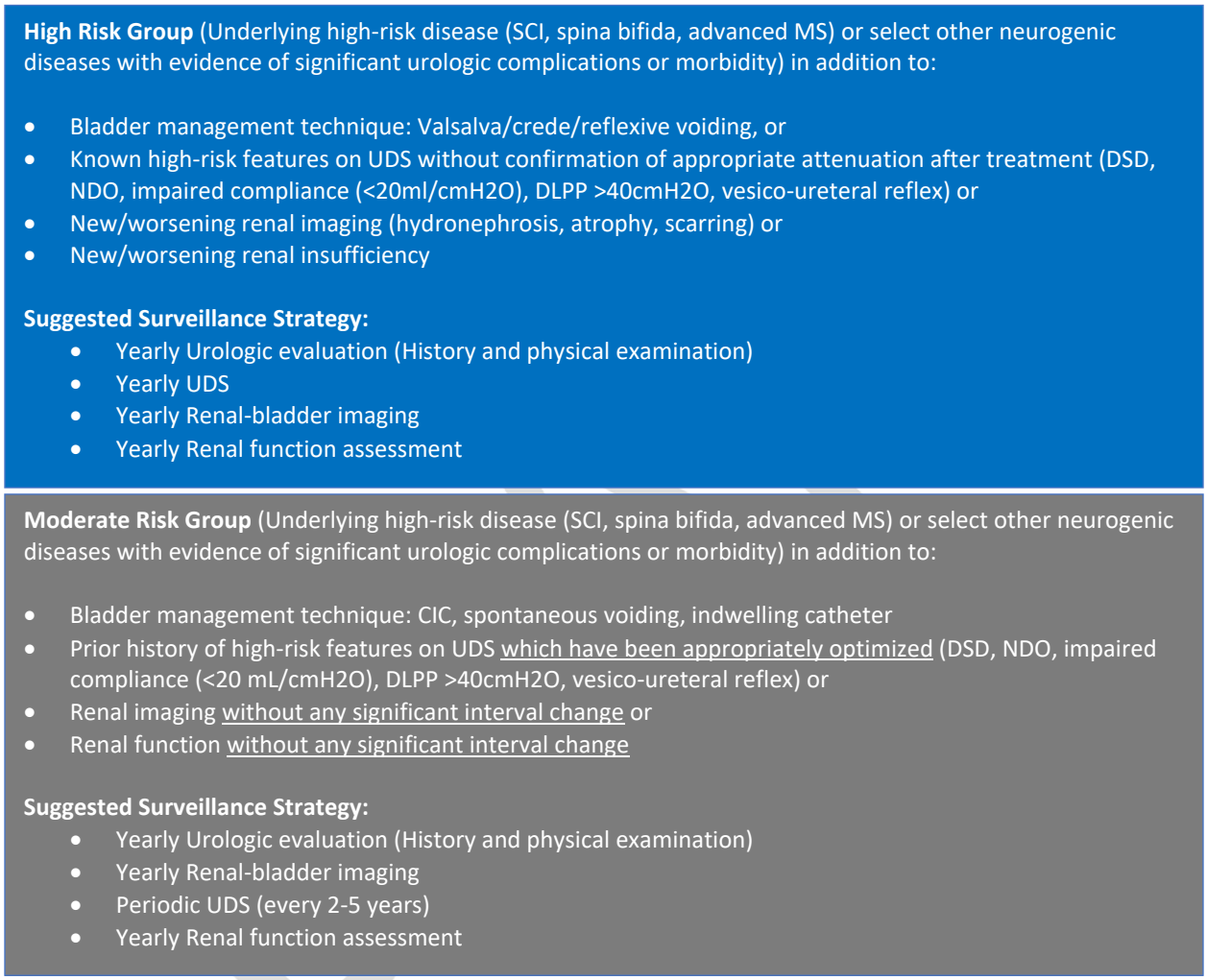
FIGURES AND TABLES

Figure 1. Details of the moderate and high-risk stratification from the CUA neurogenic bladder guideline.



Reproduced from Kavanagh A, et al. *Can Urol Assoc J* 2019;13:E157-76.

Table 1. Indicators of neurogenic bladder patient characteristics potentially at higher risk of urologic morbidity	
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/cm H_2O), DLPP >40 cm H_2O), 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. Reproduced from Kavanagh A, et al. *Can Urol Assoc J* 2019;13:E157-76. DLPP: detrusor leak point pressure; DSD: detrusor sphincter dyssynergia; MS: multiple sclerosis; NDO: neurogenic detrusor overactivity; SCI: spinal cord injury.

Table 2. Baseline demographic data	
Number of patients enrolled	68
Male	50 (73.5%)
Age (years)	47.2±16
BMI (kg/m^2)	26.5±5.3
Living in LTC/rehab	
Yes	0
No	53 (80.3%)
Prefer not to say	13 (19.7%)
Ambulatory status	
Yes, no restrictions	13 (19.1%)
Yes, short distance unaided	3 (4.4%)
Walking aides	5 (7.4%)
Wheelchair	47 (69.1%)
Etiology of NB	
SCI	53 (78%)
SB	12 (17.6%)
MS	3 (4.4%)
SCI patients (n=53)	
SCI level	
Cervical	25 (47.1%)
Thoracic	22 (41.5%)

Lumbar	5 (9.4%)
Sacral	0
Missing	1 (1%)
Completeness of SCI	
Complete	17 (32.1%)
Incomplete	28 (52.8%)
Unknown	8 (15.1%)
ASIA score	
A	19 (35.8%)
B	2 (3.8%)
C	2 (3.8%)
D	3 (5.7%)
E	0
Unknown	27 (50.9%)
Autonomic dysreflexia	
Yes	15 (28.3%)
No	38 (71.7%)
Primary bladder management	
Normal voiding	11 (16.7%)
Bladder reflex triggering	2 (3%)
Bladder expression	3 (4.5%)
CIC	43 (65.1%)
Indwelling	5 (7.5%)
Diversion	2 (3%)
Need assistance for bladder management*	7 (10.3%)
Significant	3 (4.4%)
Moderate	9 (13.2%)
Occasional	49 (72.1%)
None	
Baseline UDS	
Capacity (ml)	404 (189)
Compliance (ml/cm H_2O)	50 (95)
NDO	41 (60.3%)
DLPP (ml/cm H_2O)	9.2 (20.2)
VUR	27 (39.7%)

Numbers are mean (SD) or n (%). *Examples of how significant, moderate and occasional were defined: Occasional (change foley catheter 1x/month, flush bladder 1–2/week) moderate (help with positioning for CIC, help with condom catheter at night) significant (perform daily CIC, daily bladder flushes, daily emptying of foley bag or changing of incontinence pads). BMI: body mass index; CIC: clean intermittent catheterization; DLPP: detrusor leak point pressure; LTC: long-term care; MS: multiple sclerosis; NB: neurogenic bladder; NDO: neurogenic detrusor overactivity; SB: spina bifida; SCI: spinal cord injury; UDS: urodynamic studies; VUR: vesicoureteral reflux.

Table 3. CUA risk group stratification and reason based on baseline data	
Low-risk*	0
Medium-risk	28 (38.3%)**
Bladder management	22/28 (78.5%)
UDS features	3/28 (10.7%)
Renal imaging	18/28 (64.2%)
Renal function	19/28 (67.8%)
High-risk	40 (61.7%)**
Bladder management	6/40 (15%)
UDS features	30/40 (75%)
Renal Imaging	5/40 (12.5%)
Renal function	4/40 (10%)

*No patients in our cohort were considered low risk as per the CUA criteria for classification, as we only included MS, SCI, and SC patients in this study. **Patients had overlapping criteria for risk stratification assignment, therefore, the numbers do not add to 100%. CUA: Canadian Urological Association; UDS: urodynamic studies.

Table 4. Baseline characteristics based on risk stratification			
	High-risk group n=40	Medium-risk group n=28	p
Urologic medication recommended	19 (48%)	7 (25%)	0.06
Intravesical onabotulinum toxin recommended	17 (43%)	8 (28.5%)	0.24
Urologic surgery recommended	4 (10%)	5 (17.8%)	0.34
Bladder management recommended	18 (45%)	10 (35.7%)	0.44
Renal US abnormalities	11 (27.5%)	2 (7.1%)	0.035
Patients with ≥1 UTIs in the previous year	3 (7.5%)	2 (7.1%)	0.95
Creatinine (umol/L)	75 (±31)	68.6 (±21.6)	0.36
NBSS-SF total score	11.95 (±5.8)	12.25 (±5.7)	0.87

NBSS-SF: neurogenic bladder-symptom score-short form. US: ultrasound; UTI: urinary tract infection.

Table 5. One-year follow up based on risk stratification			
	High-risk group n=26	**Medium-risk group n=23**	**p**
Urologic medication recommended	4 (15.4%)	2 (8.7%)	0.47
Intravesical onabotulinum toxin recommended	9 (34.6%)	3 (13%)	0.08
Urologic surgery recommended	3 (11.5%)	1 (4.3%)	0.35
Recommended change to bladder management	4 (15.4%)	1 (4.3%)	0.20
New renal US changes	2 (7.7%)	1 (4.3%)	0.62
Patients with ≥1 UTIs in the previous year	4 (15.4%)	4 (17.5%)	0.85
Creatinine (umol/L) (change from baseline)	81.1 (±40) (+6.6)	69 (±19.9) (+0.4)	0.30 0.05
NBSS-SF total score (change from baseline)	11.2 (±5.3) (-0.75)	11.15 (±5.6) (-1.1)	0.43 0.67

NBSS-SF: neurogenic bladder-symptom score-short form. US: ultrasound; UTI: urinary tract infection.