Evaluation, treatment, and surveillance of neurogenic detrusor overactivity in spinal cord injury patients

Ali Alsulihem1,2, Jacques Corcos1

1Department of Urology, Jewish General Hospital, McGill University, 3755 Côte-Sainte-Catherine Road, Pavillion E, Montreal, QC, H3G 0C7, Canada
2Department of Urology, Prince Sultan Military Medical City, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

Correspondence to: Prof. Jacques Corcos, Department of Urology, Jewish General Hospital, McGill University, 3755 Côte-Sainte-Catherine Road, Pavillion E, Montreal, QC, H3G 0C7, Canada. Email: jcorcos@jgh.mcgill.ca

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Abstract

Neurogenic detrusor overactivity is a common urodynamic finding in patients with supra-sacral spinal cord injury. Early evaluation, stepped management, and close follow-up reduce the risk of upper urinary tract deterioration, renal failure and incontinence. In this article, we aim to outline the modern pathway of the management of this complex disease. Evaluation of patients with history, physical examination, renal function assessment, cystoscopy, and urodynamic study are essential. Management of neurogenic detrusor overactivity with adequate bladder drainage, medical therapy, intradetrusor botulinum injections, and surgery can be offered in a stepwise manner. Follow-up after specific interventions should be done in a timely fashion to detect treatment response and to avoid complications of poorly managed neurogenic detrusor overactivity.

Keywords: Spinal cord injury, neurogenic lower urinary tract dysfunction, neurogenic bladder, neurogenic detrusor overactivity, evaluation, treatment, surveillance

INTRODUCTION

Spinal cord injury (SCI) is one of the most common causes of neurogenic lower urinary tract dysfunction, which affects more than 291,000 individuals in the United States and an annual incidence rate of 17,730 cases1. It is estimated that 70%-84% of SCI patients have neurogenic lower urinary tract dysfunction1.
The effect of SCI on the lower urinary tract is variable and depends on the level and extent of the injury. Neurogenic detrusor overactivity (NDO) is a common urodynamic finding, reported to be present in up to 95% of supra-sacral SCI\(^3\). The ultimate goal of the management of neurogenic lower urinary tract dysfunction is to avoid morbidity and mortality secondary to renal failure and/or infections and to improve quality of life by controlling incontinence. The goal of this review article is to present an up-to-date pathway of the evaluation, treatment, and surveillance of NDO in SCI patients.

**CLASSIFICATION OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION IN PATIENTS WITH SCI**

The lower urinary tract is innervated by the hypogastric nerve, the pelvic nerve, and the pudendal nerve. The hypogastric nerve carries sympathetic innervation from spinal level T10-L1, while pelvic and pudendal nerves carry parasympathetic (pelvic), and motor and sensory innervation (pudendal) from the sacral spinal cord (S2-S4) [Figure 1]\(^4\). Lower urinary tract dysfunction often follows certain patterns, based on the level of the injury, which can be classified into supra-pontine, infra-pontine supra-sacral, sacral, or infra-sacral\(^5\). The supra-sacral injury often results in NDO and infra-pontine supra-sacral lesions often result in detrusor-sphincter dyssynergia [Figure 2]\(^6\). SCI at the vertebral level of T11 may cause sacral nerve damage which may cause underactive detrusor. Injury at the vertebral level of T7 may result in NDO. Injury in vertebral levels between T8 and T10 can generate either hypotonic or overactive detrusor\(^6\). It should be noted that those patterns do not happen in all patients, and further urological evaluation is mandatory to all patients to determine the exact neurogenic lower urinary tract dysfunction regardless of the level of SCI.
THE SEQUELAE OF UNTREATED LOWER URINARY TRACT DYSFUNCTION

The primary functions of the lower urinary tract are: (1) storage of urine under low vesical pressure without leakage; and (2) periodic complete expulsion of urine in socially acceptable time and location. Intact central and peripheral nervous systems are required to achieve these functions\(^\text{[7]}\). SCI and other neurologic disorders frequently affect the functions of the lower urinary tract. Untreated or poorly managed neurogenic lower urinary tract dysfunction may result in: (1) upper urinary tract deterioration resulting in end-stage renal disease; (2) urinary incontinence and urethral damage; (3) recurrent urinary tract infections and urolithiasis; and (4) autonomic dysreflexia\(^\text{[8]}\). In the last half-century, advancement in the management of neurogenic lower urinary tract dysfunction has led to decreased mortality caused by chronic kidney disease, from 50% in the 1950s and 1960s to less than 0.5% in the 1980s\(^\text{[9,10]}\). This emphasized the importance of prompt management of the neurogenic lower urinary tract dysfunction to prevent its sequelae. The 2019 report of the national SCI statistical center has reported a 2.9% mortality rate secondary to genitourinary diseases in SCI patients\(^\text{[11]}\).

INITIAL EVALUATION AND MANAGEMENT AFTER ACUTE SCI

Early phase after SCI (the spinal shock)

After acute traumatic SCI, a spinal shock phase occurs. The bladder is hypotonic, and urinary retention and overflow incontinence happen in the absence of management. This phase resolves as early as 2 weeks, with an average of 8 weeks, and can be prolonged up to a year\(^\text{[6]}\). The extent and duration of this phase are variable and depend on the extension and the completeness of the spinal injury\(^\text{[12]}\). During this phase,
conducting a urodynamic study had been considered of limited clinical value⁴. Recent evidence has shown the presence of adverse urodynamic findings in those patients in the early phase (within 40 days of the injury)⁴. The best management at this phase is to ensure complete bladder drainage by intermittent catheterization (IC) or an indwelling urethral catheter⁶⁻¹². Once the patient is stabilized medically, a trial of spontaneous voiding along with post-void residual measurement or self-intermittent catheterization, if the patient cannot void spontaneously, should be tried, while admitted in a rehabilitation facility¹².

**Initial urological evaluation**

This will take place at the first consultation and includes: detailed history, physical examination, bladder diary (often catheterization record), post-void residual, urinalysis and culture, renal function assessment, and upper urinary tract imaging⁶⁻¹². Urodynamic assessment and cystoscopy may be indicated at the first evaluation, depending on the stage of evolution of the neurogenic bladder dysfunction.

**History**

Complete medical and surgical history is essential for further evaluation and potential management options and consideration of personalized treatment and follow up. Information about initial trauma and level and completeness of SCI (ASIA score), associated trauma to the urinary tract, and previous lower urinary tract diseases and treatments before spinal cord injury should be documented. The patient's mental and physical capacity should also be noted. History should also include the history of urinary tract infection frequency, symptoms, and treatments. Social history and social support, history of alcoholism or drug abuse are also important for long-term management. History of bowel management, past medical history of acute angle glaucoma, uncontrolled hypertension, and myasthenia gravis should be elicited as it might be a potential contraindication for medications that can be used for the treatment of NDO⁶⁻¹².

**Physical examination**

General physical examination is warranted, including a focused examination of the abdomen and genitalia. The ability to perform self-intermittent catheterization should be noted, along with previous abdominal scars or any contraindications that might complicate the insertion of suprapubic catheter insertion. If the clinician is in doubt regarding the patient's capability of performing IC, a consultation in ergotherapy could be very helpful. A focused neurologic exam is required, including anal tone, perineal sensation, and bulbocavernous reflex¹².

**Bladder diary**

A bladder diary is highly recommended but not well studied¹³. It can add further information about how frequent the patient is urinating or catheterizing, the amount of urine drained, and the post-void residual. It can add further value in the monitoring of the treatment effect. Components of bladder diary recommended by ICS include voiding time, voided volume, incontinence episodes/use of pads, amount of fluids ingested, urgency, and incontinence degree, along with the method of emptying the bladder¹²,¹⁴.

**Urinalysis and culture**

Urinalysis and microscopy are recommended in the initial visit and in follow up⁶⁻¹² to investigate the possibility of UTI in the presence of symptoms with subsequent urine cluture, and it can also detect microscopic hematuria, pyuria, or proteinuria, which might warrant further investigations. The presence of asymptomatic bacteriuria, which is frequent in patients performing IC, is not an indication of antibiotics in the majority of cases.

**Post-void residual**

Post void residual measurement is recommended in patients who void spontaneously, or uses valsalva voiding, reflexive voiding/crede voiding and/or condom catheter. The presence of elevated residual might
trigger further evaluation and different management in those patients, as it increases the risk of UTIs and upper tract deterioration

**Urodynamic study**

Urodynamic evaluation is the cornerstone in the evaluation of lower urinary tract dysfunction in SCI patients, but its technique and timing are essential. Several urological authorities and guidelines recommend performing the first study 3 to 6 months after the injury, as recent evidence has shown that adverse urodynamic parameters can appear as early as 40 days after SCI. However, in our practice, the first UDS is performed at the first sign of change in the urinary tract. It could be the onset of a UTI, the beginning of leakage between IC, the appearance or worsening of autonomic dysreflexia, etc. If the first study is done during the spinal shock phase, a repeat study is warranted after the resolution of spinal shock. Video Urodynamics, if available, is considered as the gold standard in the evaluation of patients with NLUTD after SCI, as it can detect vesicoureteric reflux and unmask hidden low bladder capacity and low compliance in patients with VUR. Presence of poor prognostic features [Table 1] in the urodynamic study does require appropriate treatment and follow up urodynamics should be done to monitor the treatment effect and the need for further treatment. Repeat urodynamic study should be selectively used based on the patient’s course over time and with any change in clinical course. There is no consensus in which intervals that urodynamics should be repeated in the high-risk population.

**Imaging**

Renal and bladder imaging is recommended in the initial evaluation of neurogenic bladder patients, preferably an ultrasound, to avoid the risk of exposure to radiation, at three months after the injury. The ultrasound can detect complications of neurogenic lower urinary tract dysfunction, such as hydronephrosis, kidney or bladder stones, abnormal bladder morphology such as tumors, thickened bladder wall, or diverticulae, and renal atrophy or scarring. The follow-up surveillance depends on the presence of adverse findings on urodynamics, which mandates more frequent imaging (every 6-12 months). The imaging might be delayed to 2-3 years in the absence of poor prognostic features on urodynamics.

**Renal function assessment**

Serum creatinine and estimated glomerular filtration rate are commonly used to assess renal function. It is less accurate than other methods such as creatinine clearance and nuclear GFR. Monitoring the changes of serum creatinine within the normal range is essential. It should be kept in mind that those patients might have less muscle mass, and GFR reduction might not reflect largely on serum creatinine level. Initial creatinine level and periodic follow-up are recommended, especially with unfavorable features on urodynamics, hydronephrosis, and febrile urinary tract infections.

**Cystoscopy**

Cystoscopy is an important, office-based evaluation of the lower urinary tract. It can detect bladder outlet obstruction due to urethral stricture or prostatic hypertrophy, and bladder abnormalities such as bladder
tumor, trabeculation, bladder tumors, and bladder stones. Although the value of cystoscopy at initial evaluation has been questioned\(^8,12,13,16\), we recommend doing cystoscopy at initial evaluation, and as diagnostic tool for patients who present with difficult catheterization to diagnose urethral stricture and false passage, or when presenting with recurrent urinary tract infection, increased incontinence, bladder spasticity and/or dysreflexia for possibility of finding a bladder stone. It should be noted that cystoscopy is a mandatory investigation for hematuria workup\(^7\). Screening cystoscopy for patients on a chronic indwelling catheter is recommended for early diagnosis of bladder cancer, although the value of such an approach has not been proven\(^\text{[17]}\).

## Treatment of NDO

The goals of NDO treatment are to reduce its risks on the urinary tract by reducing detrusor storage pressures, increasing bladder capacity, improving incontinence, and improving patient's quality of life. Table 2 summarizes management strategies of neurogenic lower urinary tract dysfunction and NDO. Treatment effect monitoring in a timely fashion (2-3 months) is essential to avoid long term complications of the poorly managed bladder\(^\text{[12]}\).

### Adequate bladder drainage using catheterization

It is estimated that around 75% of SCI injury patients cannot void spontaneously\(^\text{[18]}\), which mandate assisted bladder drainage. Types of bladder drainage include: (1) clean intermittent self-catheterization (CISC); (2) indwelling suprapubic catheterization; and (3) indwelling urethral catheterization.

The patient should be aware of risks and benefits of the several methods of bladder drainage and advised to avoid indwelling urethral catheters if possible, to reduce risks of urinary tract infections, bladder stone formation, and urethral erosion\(^\text{[13,20]}\). It is recommended to keep patients, who cannot empty their bladder spontaneously, on CISC\(^\text{[6,12,13]}\). The frequency of CISC depends on many factors, such as fluid intake, bladder volume, and urodynamic parameters, and is recommended to do it 4 to 6 times/day\(^\text{[20]}\). CISC teaching is preferably done early during the rehabilitation phase, to evaluate the patient ability to perform it, and to evaluate for the possibility of spontaneous voiding\(^\text{[12]}\).

CISC, although considered as the gold standard of assisted bladder drainage mechanism, have several limitations [Table 3], that treating physician should carefully assess and adjust those limitations if possible or shift the patient to alternative drainage options\(^\text{[18,21]}\).

If CISC cannot be performed [Table 3], alternative management options include indwelling suprapubic catheterization or indwelling urethral catheterization. Suprapubic catheters are generally preferred over urethral catheters, with some studies supporting that preference. Suprapubic catheters have advantages over urethral catheters, which include the elimination of risks of urethral erosions and iatrogenic hypospadias\(^\text{[22]}\), fewer risks of epididymitis and enable patients to perform sexual activities\(^\text{[22]}\). Some evidence showed a decreased risk of urinary tract infection with suprapubic catheters\(^\text{[24-26]}\). Indwelling catheters (urethral and

### Table 2. Overview of management approach to neurogenic lower urinary tract dysfunction and NDO

<table>
<thead>
<tr>
<th>Management Lines</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assisted bladder drainage</td>
<td>Clean intermittent self-catheterization, indwelling suprapubic catheters, indwelling urethral catheters</td>
</tr>
<tr>
<td>Systemic medications to reduce intravesical pressure</td>
<td>Anticholinergics, beta-3 agonists</td>
</tr>
<tr>
<td>Intra-detrusor botulinum toxin A injection</td>
<td>Onabotulinum toxin A, abobotulinum toxin A</td>
</tr>
<tr>
<td>Sacral nerve stimulation</td>
<td>N/A</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Bladder augmentation, urinary diversion</td>
</tr>
</tbody>
</table>

NDO: neurogenic detrusor overactivity
suprapubic) should be changed every 4-6 weeks, and the use of silicon catheters is recommended\textsuperscript{[22]}. It should be kept in mind that indwelling catheters (urethral and suprapubic) associated with increased risk of bladder cancer (up to 10%) in the long term\textsuperscript{[27,28]}, therefore, screening cystoscopy has been recommended to start 10 years after indwelling catheter insertion. In cases of increased urethral leakage, recurrent urinary tract infection, or increased sediments and frequent catheter blockages, cystoscopy is also recommended to rule out the presence of bladder stones\textsuperscript{[22,28]}.

Therefore, we discourage the utilization of indwelling urethral catheterization and prefer the use of suprapubic catheters as a second-line option if clean IC (first line option) is not a feasible option for SCI patient.

**Systemic medications to treat neurogenic detrusor over-activity**

Systemic medications have been used to reduce detrusor storage pressure, increase bladder capacity, and improve urinary incontinence\textsuperscript{[8,12,13,22]}. The most commonly used medications are anticholinergics (antimuscarinics), and beta-3 agonists. Systemic medications, along with CISC, constitute the first-line management of NDO in SCI patients\textsuperscript{[13,29]}. Follow up after starting the systemic medication is warranted, which includes follow-up of symptoms improvement and urodynamic study in 3 months\textsuperscript{[12]}.

Antimuscarinics (anticholinergics), antimuscarinic receptor antagonists are the most commonly used medications in the treatment of NDO\textsuperscript{[8,12]}. Several medications in this class are available and in multiple forms [Table 4]. It is expected to decrease the maximum detrusor pressure by 30%-40%, and to increase the bladder capacity by 30%-40%\textsuperscript{[36]}. It increases the maximum cystometric capacity by 49.79 mL and lowers detrusor pressure at the strongest contraction by 38.3 cm H\textsubscript{2}O\textsuperscript{[34]}. The possible adverse reactions should be monitored, along with improvement in symptoms and urodynamic parameters. Common adverse reactions include dry mouth, dry eyes, constipation, blurred vision, cognitive impairment (confusion), prolonged Q-T interval, and headache\textsuperscript{[29]}. Anticholinergics should be avoided in patients with glaucoma, myasthenia gravis, gastrointestinal obstruction, and severe ulcerative colitis\textsuperscript{[12]}. Another form of anticholinergic administration includes intravesical administration of 10 mL of 0.1% of oxybutynin three times daily, which shown to be equally effective to oral oxybutynin and with fewer systemic side effects\textsuperscript{[33]}. The choice of specific anticholinergic medication is based on availability, tolerability, and side effect profile [Table 4].

Beta-3 agonists, mirabegron, the commercially available beta-3 agonist to treat detrusor overactivity, has been introduced recently. It acts on beta-3 receptors on the detrusor muscle to induce relaxation of the detrusor muscle\textsuperscript{[29]}. Its use in NDO has been shown to increase the volume at the first detrusor contraction and to improve bladder compliance, with a non-significant increase in bladder capacity when compared to placebo\textsuperscript{[34]}. The usual dose of Mirabegron is 25-50 mg/day, which can be increased to 100 mg/day\textsuperscript{[33]}. The possible adverse reactions include hypertension, urinary tract infection, and headache\textsuperscript{[29]}. The use of mirabegron is currently limited in neurogenic bladder patients, as limited evidence exists to support its use in this population\textsuperscript{[8,31]}. It might be considered as an alternative in patients with contraindication to using anticholinergics, or as an add-on treatment to anticholinergics\textsuperscript{[35,36]}.

<table>
<thead>
<tr>
<th>Table 3. Limitations of CISC\textsuperscript{[18,39]}</th>
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<tr>
<td><strong>Limitations of CISC</strong></td>
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<tr>
<td>Limited upper extremity motor function</td>
</tr>
<tr>
<td>Anatomic limitation</td>
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<tr>
<td>Limited functional bladder capacity (below 300 mL)</td>
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<tr>
<td>Obstructed urethra</td>
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</table>

CISC: continuous intermittent self-catheterization; NDO: neurogenic detrusor overactivity
Intravesical injection of botulinum toxin

Onabotulinumtoxin A (Botox) is a neurotoxin that causes detrusor muscle relaxation by preventing the release of acetylcholine on pre-synaptic parasympathetic nerve ending, resulting in a reduction of NDO, incontinence episodes, and increase of bladder capacity. It has been approved as a treatment of neurogenic detrusor overactivity in SCI patients since 2011. The usual dose is 200 units, injected into detrusor muscle in 20 sites delivered via cystoscope. It increases the bladder capacity by 134.75 mL, volume at first involuntary detrusor contraction with a median difference of 163.42 mL, reduced maximal detrusor pressure at a median of 30.48 cm/H\textsubscript{2}O, and reduced urinary incontinence episodes by 12.45/day, in compression to placebo. It also improved the bladder compliance and reduced incidence of detrusor overactivity when compared to baseline (OR = 64.27; 95%CI: 12.17-339.28; \(P < 0.00001\)).

The possible common adverse effects include urinary tract infections, hematuria, generalized weakness, and urinary retention (which is not a concern in patients using CISC). The effect usually lasts approximately nine months, and repeat injection is indicated after the disappearance of its effect.

Abobotulinum toxin A (750 IU) is another botulinum toxin that has also been used in the management of NDO with similar outcomes to onabotulinum toxin A. Shifting to abobotulinium toxin A (Dysport) after failed onabotulinum toxin A therapy has been found successful in about 52%-57% of cases.

The clinician should evaluate the response of Botulinum Toxin A 2-3 months with symptomatic and
urodynamic evaluation 2-3 months after the first injection and then if there is a change of clinical course and recurrence of symptoms despite recent injection\(^{[12,40]}\).

**Sacral nerve stimulation**

Several retrospective and observational studies have evaluated the role of dorsal rhizotomy (sacral deafferentation S2-S4/5), combined with anterior sacral root stimulation in the treatment of NDO\(^{[42-45]}\). This treatment has been shown to effectively reduce elevated detrusor pressure, improve compliance, increase bladder capacity, improve urinary incontinence, and achieve voluntary bladder and bowel emptying in patients with complete SCI\(^{[41-44]}\). This technique has a variable success rate in specialized centers but is limited by long-term complications and a high rate of surgical revision. It might be offered by experienced centers and in highly selected patients as a third-line option after failure of previous medical and minimally invasive options\(^{[8,13]}\).

**Surgical treatment of NDO**

Surgical treatment options are considered when all medical and minimally invasive treatment options have failed to eliminate poor urodynamic parameters [Table 1]. Surgical options include bladder augmentation and urinary diversion.

Bladder augmentation, using a bowel segment, should be considered in patients who failed all medical and minimally invasive management for reduced bladder capacity and NDO\(^{[8,13]}\). It can eliminate urinary incontinence in 75%-100%, improve bladder compliance in 69%-100%, and improve quality of life in 90% of patients\(^{[4]}\). The addition of a continent catheterizable channel might be considered if the patient cannot catheterize through the urethra\(^{[8,46]}\). Contraindications to performing bladder augmentation include bladder malignancy, Chronic kidney disease (creatinine clearance less than 40 mL/min), bowel disease, previous significant bowel resection, inability to do CISC (such as quadriplegia), or unwillingness to perform CISC\(^{[8,46]}\). Long term complications include bladder stone formation, metabolic complications, intraperitoneal bladder perforation, urosepsis, vesicoureteric reflux, recurrence of NDO and adenocarcinoma or urothelial carcinoma in up to 6%\(^{[8,46-49]}\). Therefore, lifelong surveillance with cystoscopy is recommended. In case of recurrence of incontinence, video urodynamic is recommended, and in the presence of NDO, treatment with Botox injection into the augmented bladder can be tried before surgical revision or urinary diversion\(^{[49]}\).

Urinary diversion, is considered as last resort option in the management of NDO if the patient is unfit or not a candidate for bladder augmentation. Urinary diversion options include continent and incontinent diversion\(^{[46]}\).

Continent urinary diversion with continent catheterizable channels is performed when the patient can catheterize but cannot use native bladder due to a severely contracted bladder with severe vesicoureteral reflux or devastated bladder outlet, or bladder malignancy\(^{[8,47]}\). It carries a higher risk of long-term metabolic complications. It is contraindicated in patients with chronic kidney disease (creatinine clearance less than 40 mL/min) and in a patient who are not fit for CISC\(^{[8,48]}\).

Incontinent urinary diversion is a last resort option\(^{[8,13,49]}\), in which urine is diverted to the skin by using bowel segment (usually ileum) in patients who cannot perform CISC and in patients who are unfit or failed other surgical options\(^{[8,13,46]}\). An ileal conduit is a familiar procedure to urologists, the most commonly performed continent urinary diversion procedure, and the preferred incontinent urinary diversion procedure\(^{[8,46,50]}\). It results in renal function preservation in 88% to more than 90% of patients\(^{[8,56]}\). Possible complications include ureteral anastomatic stenosis, stomal or incisional hernia, stomal stenosis, bowel obstruction, urinary tract infections and pyelonephritis, urine leak, urolithiasis, and metabolic complications (acidosis)\(^{[46,51]}\). Overall major complications can reach up to 11%\(^{[8]}\).
Other incontinent urinary diversion includes ileovesicostomy, which avoids ureteric reimplantation and cystectomy and related complications but has the disadvantage of leaving a bladder segment, which can increase the risk of malignancy or urethral incontinence\cite{[8,46,47,52]}. It can be considered in select patients. Robust long-term results and quality of life data are lacking\cite{[8]}. Reported complications include impaired bladder emptying, urethral incontinence, stomal stenosis, parastomal hernia, and urolithiasis\cite{[46,52-56]}. Therefore, monitoring patients postoperatively is essential to detect complications, and surveillance is of paramount importance.

**Monitoring, follow up, and surveillance**

We recommend regular and tight surveillance after initial management, with clinical history, physical examination, and urodynamic evaluation after initiation of any intervention, to monitor response and to determine successful treatment and need for augmentation of medication dose or considering alternative management option. The time between the visit should be within 2-3 months after the initiation of medications or botulinum toxin A injection\cite{[8,12,40]}. After controlling poor urodynamic features, annual follow up of symptoms, renal function, and upper tract ultrasound are recommended\cite{[6,8,13]}. Repeat urodynamic and cystoscopy is recommended after a change in the clinical course, such as new incontinence or recurrent urinary tract infections\cite{[6]}

**Urinary tract related factors impacting the quality of life in SCI patients**

Quality of life (QOL) in SCI was found to be associated with a poorly managed urinary tract. Worse QOL scores were found to be associated with urinary incontinence and recurrent UTIs\cite{[57-59]}. Well managed bladder with surgery and indwelling catheters had better QOL scores than patients who use clean IC\cite{[58]}. Worst QOL scores were associated with SCI patients who do not use catheters and leak on diapers\cite{[58]}. This emphasizes the importance of proper management of urinary incontinence in SCI patients to improve their quality of life.

**CONCLUSION**

NDO secondary to SCI has a significant impact on patient quality of life, morbidity, and mortality. Early detailed evaluation and timely intervention are of paramount importance to avoid its long-term sequelae. Patients should be aware of the possible risks and benefits of each management option, and physicians should keep patients under close monitoring to act early upon any changes in patients’ course of the disease. Research in NDO should continue to address several poorly studies areas in pathophysiology, treatments, and surveillance, as most of the available recommendations in this field are largely based on retrospective studies.

**DECLARATIONS**

**Authors’ contributions**

Wrote the first draft of the manuscript: Alsulihem A
Reviewed and edited the final manuscript: Corcos J

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Conflicts of interest
Both authors declared that there are no conflicts of interest.

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