

# Guidelines on Neuro-Urology

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# 1. BACKGROUND

## 1.1 Aims and objectives

The purpose of these clinical guidelines is to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These guidelines reflect the current opinion of experts in this specific pathology and thus represent a state-of-the-art reference for all clinicians, as of the date of its presentation to the European Association of Urology (EAU).

The EAU Guidelines panel consists of an international multidisciplinary group of experts, including urologists specialised in the care of spinal cord injured (SCI) patients, as well as two specialists in the field of urodynamic technologies.

The terminology used and the diagnostic procedures advised throughout these guidelines follow the recommendations for investigations on the lower urinary tract (LUT) as published by the International Continence Society (ICS) (1-4). Readers are advised to consult the other EAU guidelines which may address different aspects of the topics discussed in this document.

## 1.2 Methodology

### 1.2.1 Data identification

Literature searches were carried out for all sections of the Neuro-Urology Guidelines. Focus of all searches was identification of all level 1 scientific papers (systematic reviews and metaanalyses of randomised controlled trials) in accordance with EAU methodology. In case sufficient data was identified to answer the clinical question, the search was not expanded to include lower level literature.

### 1.2.2 Evidence sources

Searches were carried out in Medline and Embase on the Ovid platform. The searches used the controlled terminology of the respective databases.

### 1.2.3 Level of evidence and grade of recommendation

References used in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (5). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

**Table 1: Level of evidence (LE)\***

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

\* Modified from. (5).

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (6-8).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the panel will include the information.

**Table 2: Grade of recommendation (GR)\***

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

\*Modified from (4).

#### 1.2.4 **Publication history**

The current guidelines present an extensive update of the 2013 publication. The EAU published the first guidelines on Neurogenic LUTD in 2003 with updates in 2008 and 2013. A review paper was published in the scientific journal of the association, *European Urology*, in 2009 (9).

A quick reference document presenting the main findings of the Neuro-Urology Guidelines is available. All texts can be viewed and downloaded for personal use at the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

There is a need for ongoing re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

#### 1.2.5 **Summary of updated information**

The literature was assessed for most of the content of this 2014 print. Structured searches were carried out for:

- Chapter 4. Treatment; for sections 4.1 through 4.2.1 (Non-invasive treatment), covering a minimum time of 2008 through October 2013. No time limitations applied for some subsections. A total of 301 unique records were identified.
- Chapter 5. Urinary Tract infections; Embase and Medline were searched, without time limits, but with a limitation for adults. A total of 383 unique records were identified.
- For Chapter 7. Sexual (dys)function; Medline, Embase, and the Cochrane databases of controlled trials and systematic reviews were searched, without time limits, including all adult patient groups with neurological disorders. A total of 1500 unique papers were identified.
- For Chapter 9. Follow-up; Medline, Embase, and the Cochrane databases of controlled trials and systematic reviews were searched, covering the time frame between July 2005 and August 2013. Only data on adults were considered.

For this 2014 print changes were made in:

- Chapter 4: Non-invasive treatment was revised and the literature was updated for the sections on drug treatment and surgical treatment.
- Chapter 5: Urinary tract infection has been completely revised.
- Chapter 7: Sexual (dys)function and fertility has been completely revised.
- Chapter 9: Follow-up has been revised.

#### 1.2.6 **Future goals**

For 2015 the Expert panel aim to present the results of systematic reviews addressing video-urodynamics, electrical stimulation and surgical treatment in stress urinary incontinence in this patient group.

The use of clinical quality indicators is also another aspect which will be explored. Some examples of quality parameters identified as of particular importance to this patient group are:

1. Diagnosis - Risk assessment of the upper urinary tract must be standardized as defined by video-urodynamic variables, such as maximum detrusor pressure in the storage phase < 40 cm H<sub>2</sub>O; Compliance > 20 mL/cmH<sub>2</sub>O, vesico-ureteric reflux.
2. Diagnosis - The number of febrile urinary tract infections per patient per year should not exceed more than 2.

### 1.2.7 **Potential conflict of interest statement**

The expert panel have submitted potential conflict of interest statements, which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/>.

## 1.3 **Introduction**

The function of the lower urinary tract (LUT) is mainly storage and voiding of urine, which is regulated by a neural control system in the brain and spinal cord that coordinates the activity of the urinary bladder and bladder outlet. Therefore, any disturbance of the nervous systems that control the LUT, including the peripheral nerves in the pelvis, can result in neuro-urological symptoms. Depending on the extent and location of the disturbance, a variety of different neuro-urological symptoms might occur, which can be symptomatic or asymptomatic. Moreover, neuro-urological symptoms can cause a variety of long-term complications; the most dangerous being damage of renal function. As symptoms and long-term complications do not correlate (10), it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high risk of subsequent complications.

According to current knowledge, elevated storage pressure in the bladder, either alone or combined with vesicoureteric reflux (VUR), is the most important risk factor for renal damage (11). Sustained elevated storage pressure in the bladder is mainly due to a combination of increased detrusor activity during the storage phase (detrusor overactivity [DO] or low compliance), combined with detrusor-sphincter dyssynergia (DSD). The combination of these two findings is mainly caused by suprasacral infrapontine spinal lesions. Furthermore, elevated detrusor leak point pressure has been demonstrated to be a risk factor for renal deterioration in patients with meningocele (12). Therefore, renal failure has been the leading cause of death in patients with spinal cord injury for a long time (13). Even today, 26% of patients with meningocele who do not undergo urological treatment develop renal damage. Detrusor leak point pressure > 40 cm H<sub>2</sub>O and low bladder compliance are the main risk factors for renal damage (14).

In recent years, adequate diagnosis and treatment of neuro-urological symptoms in patients with spinal cord lesions have improved the situation of these patients. Nowadays, respiratory diseases are the most frequent (21%) cause of death in patients with SCI (15).

In all other patients with neuro-urological symptoms, the risk of renal damage is significantly lower. However, in Multiple Sclerosis (MS), urodynamics and clinical symptoms do not correlate, which means that asymptomatic patients can present with abnormal urodynamic findings (16). LUT symptoms do not always lead to urological evaluation in patients with MS, even if the symptoms are troublesome (17). Therefore, urological assessment is important in MS patients (18); although respiratory diseases are currently the leading cause of death for patients with MS (19).

In Parkinson disease (PD), neuro-urological disorders have not been mentioned as a significant cause of death. Moreover, patients with PD commonly suffer from overactive bladder without DSD (20), which does not seem to be as threatening to the upper urinary tract as DO with DSD. In patients with PD, urodynamic diagnosis of DO correlates well with diagnosis made by questionnaires (21). For these reasons, regular urodynamic follow-up might be less important in PD patients compared with patients suffering from MS or SCI. The same is true for type 2 diabetes, which frequently leads to neuro-urological symptoms (22), but cardiovascular diseases are the main cause of death in these patients (23).

In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

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## 2. RISK FACTORS AND EPIDEMIOLOGY

### 2.1 Introduction

Neurogenic lower urinary tract dysfunction may be caused by various diseases and events affecting the nervous systems controlling the LUT. The resulting LUTD depends grossly on the location and the extent of the neurological lesion (see also Section 2.3).

There are no figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of those for the development of neuro-urological symptoms. It is important to realise that most of these data show a very wide range of prevalence figures because of the low level of evidence in most published data and smaller sample sizes.

#### 2.1.1 Brain tumours

Brain tumours can cause LUTD in 24% of patients (1). More recently, mostly case reports to small series have been published (2-3). In a series of patients with brain tumours, voiding difficulty was reported in 46/152 (30%) of patients with tumours in the posterior fossa, while urinary incontinence occurred in only three (1.9%) patients (4). Urinary retention was found in 12/17 (71%) children with pontine glioma (5).

#### 2.1.2 Dementia

It is not easy to distinguish dementia-associated LUTD from LUTD caused by age-related changes of the bladder and other concomitant diseases. Therefore, the true incidence of incontinence caused by dementia is unknown. However, it has been shown that incontinence is much more frequent in geriatric patients with dementia than in patients without dementia (6,7).

Alzheimer, Lewy body dementia, Binswanger, Nasu-Hakola and Pick diseases frequently cause neuro-urological symptoms (8-13). The occurrence of incontinence is reported to be between 23% and 48% (14,15) in patients with Alzheimer's disease. In Lewy body dementia, 92% of neuro-urological symptoms is attributed to DO and 53% to incontinence (16). The onset of incontinence usually correlates with disease progression (17). A male-to-female ratio of dementia-related incontinence was found to be 1:15.

#### 2.1.3 Mental retardation

In mental retardation, depending on the grade of the disorder, 12-65% of LUTD has been described (18,19).

#### 2.1.4 Cerebral palsy

Lower urinary tract dysfunction has been described in about 30-40% (20,21).

#### 2.1.5 Normal pressure hydrocephalus

There have only been case reports of LUTD (22-24).

#### 2.1.6 Basal ganglia pathology (Parkinson disease, Huntington's disease, Shy-Drager syndrome, etc.)

Parkinson disease is accompanied by neuro-urological symptoms in 37.9-70% (25-27).

In the rare Shy-Drager syndrome, almost all patients have neuro-urological symptoms (27), with incontinence found in 73% (28).

Hattori et al. (29) reported that 60% of PD patients had urinary symptoms. However, Gray et al. (30) reported that functional disturbances of the LUT in PD were not disease-specific and were correlated only with age. Control-based studies have given the prevalence of LUT symptoms as 27-63.9% using validated questionnaires (31-33), or 53% in men and 63.9% in women using a validated questionnaire, which included a urinary incontinence category (33), with all these values being significantly higher than in healthy controls. Ransmayr reported a prevalence of urge episodes and urge incontinence in 53% Lewy body patients, whereas this was observed in 27% of the PD study population, of which 46% were also diagnosed with DO (34). In most patients, the onset of the bladder dysfunction occurred after the motor disorder had appeared.

#### 2.1.7 Cerebrovascular pathology

Cerebrovascular (CVA) pathology causes hemiplegia with remnant incontinence neuro-urological symptoms in 20-50% of patients (35,36), with decreasing prevalence in the post-insult period (37). In 1996, 53% of patients with CVA pathology had significant urinary complaints at 3 months (38). Without proper treatment, at 6 months after the CVA, 20-30% of patients still suffered from urinary incontinence (39). The commonest cystometric finding was DO (40-45).

In 39 patients who had brainstem strokes, urinary symptoms were present in almost 50%, nocturia and voiding difficulty in 28%, urinary retention in 21%, and urinary incontinence in 8%. Several case histories have been published presenting difficulties with micturition in the presence of various brainstem pathologies (46-48).

### 2.1.8 **Demyelination**

Multiple sclerosis causes neuro-urological symptoms in 50-90% of the patients (49-51). The reported incidence of voiding dysfunction in multiple sclerosis is 33-52% in patients sampled consecutively, regardless of urinary symptoms. This incidence is related to the disability status of the patient (52). There is almost a 100% chance of having LUTD once these patients experience difficulties with walking. Two to twelve percent of patients present with neuro-urological symptoms, with this finding being as high as 34% in some studies (53). LUTD appears mostly during the 10 years following the diagnosis (54).

### 2.1.9 **Spinal cord lesions**

Spinal cord lesions can be traumatic, vascular, medical or congenital. An incidence of 30-40 new cases per million population is the accepted average for the USA. Most of these patients will develop neuro-urological symptoms (55). The prevalence of spina bifida and other congenital nerve tube defects in the UK is 8-9 per 10,000 aged 10-69 years, with the greatest prevalence in the age group 25-29 years (56), and in the USA 1 per 1,000 births (57). The incidence of urethrovesical dysfunction in myelomeningocele is not completely known, but most studies suggest it is very high at 90-97% (58). About 50% of these children will have DSD (59,60).

In a large review specific data were presented for intradural metastasis from renal carcinoma with 22% of patients presenting with neuro-urological symptoms (61).

Central cord syndrome is an incomplete SCI. A case series (n = 50) presented neuro-urological symptoms in 42% of patients at admission, 12% had residual disturbance during follow-up, but most of the 12% related to patients > 70 years old (60% of that age bracket) (62).

In a hereditary spastic paraplegia series, 38 (77.6%) out of 49 patients presented with neuro-urological symptoms (63).

Caudal Regression Syndrome (CRS): In a case series 61% of patients diagnosed with CRS presented with neuro-urological symptoms (n = 69). 20% of these CRS patients presented with one kidney (64).

Special attention is to be paid to the combination of traumatic SCI and brain injuries: the incidence of traumatic SCI with clinical concomitant brain injury has increased over the past 50 years. These findings have consequences for the diagnosis and treatment of neuro-urological symptoms (65).

In 25% of children with high anorectal malformations, innate neuro-urological disorders are present (66).

### 2.1.10 **Disc disease**

This is reported to cause neuro-urological symptoms in 28-87% of the patients (< 20%) (67,68). The incidence of cauda equine syndrome due to central lumbar disc prolapse is relatively rare and is about 1-5% of all prolapsed lumbar discs (68-75). There have been case reports of neuro-urological disorders without cauda equine syndrome (76) and small series with 90% cure of incontinence (77).

### 2.1.11 **Spinal stenosis and spine surgery**

About 50% of patients seeking help for intractable leg pain due to spinal stenosis report symptoms of LUTD, such as a sense of incomplete bladder emptying, urinary hesitancy, incontinence, nocturia or urinary tract infections (UTIs) (78). These symptoms may be overlooked or attributed to primary urological disorders, with 61-62% affected by LUTD (79,80). The prevalence of neurological bladder is more significantly associated with the anteroposterior diameter of the dural sac than with its cross-sectional area. Spinal surgery is related to LUTD in 38-60% of patients (81,82). In a series with sacrectomy for sacral chordoma's neuro-urological symptoms were found in 74% (83).

### 2.1.12 **Peripheral neuropathy**

**Diabetes:** This common metabolic disorder has a prevalence of about 2.5% in the American population, but the disease may be subclinical for many years. No specific criteria exist for secondary neuropathy in this condition, but it is generally accepted that 50% of patients will develop somatic neuropathy, with 75-100% of these patients developing neuro-urological symptoms (84,85). Diabetic patients suffer from various polyneuropathies, with 'diabetic cystopathy' reported in 43-87% of insulin-dependent diabetics without gender or age differences. It is also described in about 25% of type 2 diabetic patients on oral hypoglycaemic treatment (86).

The prevalence of neuro-urological symptoms in type 2 diabetes gets higher with increasing severity of cardiac autonomic neuropathy (87).

*Alcohol abuse* will eventually cause peripheral neuropathy. This has a reported prevalence that varies widely

from 5-15% (88) to 64% (89). Neuro-urological symptoms are probably more likely to be present in patients with liver cirrhosis. The parasympathetic nervous system is attacked more than the sympathetic nervous system (89).

*Less prevalent peripheral neuropathies* include the following:

- Porphyria: bladder dilatation occurs in up to 12% of patients (90).
- Sarcoidosis: neuro-urological symptoms are rare (91).
- Lumbosacral zone and genital herpes: incidence of LUT dysfunction is as high as 28% when only lumbosacral dermatome-involved patients are considered. The overall incidence is 4% (92,93). Neuro-urological symptoms are transient in most patients.
- Guillain Barré syndrome: the prevalence of micturition disorders varies from 25% to more than 80% (94,95), but is regressive in most cases (96). The true incidence is uncertain because, during the acute phase, patients are usually managed by indwelling catheter.

#### **2.1.13 Other conditions (systemic lupus erythaematosus)**

Nervous system involvement occurs in about half of patients with systemic lupus erythaematosus. Neuro-urological symptoms can occur, but data on prevalence are rare and give an incidence of 1% (97,98). In familial amyloidotic polyneuropathy (FAP) approx. 50% of patients present with neuro-urological symptoms (99).

#### **2.1.14 Human immunodeficiency virus**

Voiding problems have been described in 12% of HIV-infected patients, mostly in advanced stages of the disease (100,101).

#### **2.1.15 Regional spinal anaesthesia**

This may cause neuro-urological symptoms but no prevalence figures have been found (102,103). Neuro-urological symptoms have been described after image-guided transforaminal lumbar spine epidural steroid injection (104), and intrathecal methotrexate injection (105).

#### **2.1.16 Iatrogenic**

Abdominoperineal resection of the rectum has been described as causing neuro-urological symptoms in up to 50% of patients (106,107). One study reported that these symptoms remain a long-term problem in only 10% (108); however, the study was not clear whether this was because the neurological lesion was cured or bladder rehabilitation was successful. Surgical prevention with nerve preservation was shown to be important (109,110).

Neuro-urological symptoms have been reported following simple hysterectomy (111) and in 8-57% of patients following radical hysterectomy or pelvic irradiation for cervical cancer (112-115). Surgical prevention can be used (116). Neurological dysfunction of the pelvic floor has been demonstrated following radical prostatectomy (117).

## **2.2 Standardisation of terminology**

### **2.2.1 Introduction**

Several national or international guidelines have already been published for the care of patients with neuro-urological disorders (118-121). The ICS neuro-urological standardisation report (119) deals specifically with the standardisation of terminology and urodynamic investigation in neuro-urological patients. Other relevant definitions are found in the general ICS standardisation report (122).

Section 2.2.2 lists the definitions from these references, partly adapted, and other definitions considered useful for clinical practice (Tables 3 and 4). For specific definitions relating to urodynamic investigation, the reader is referred to the appropriate ICS report (119).

## 2.2.2 Definitions

**Table 3: Definitions useful in clinical practice**

Acontractility, detrusor	See below under voiding phase (table 4)
Acontractility, urethral sphincter	See below under storage phase (table 4)
Autonomic dysreflexia	Increase of sympathetic reflex due to noxious stimuli with symptoms or signs of headache, hypertension, flushing face and perspiration
Capacity	See below under storage phase
Catheterisation, indwelling	Emptying of the bladder by a catheter that is introduced (semi-)permanently
Catheterisation, intermittent (IC)	Emptying of the bladder by a catheter that is removed after the procedure, mostly at regular intervals
• Aseptic IC	The catheters remain sterile, the genitals are disinfected, and disinfecting lubricant is used
• Clean IC	Disposable or cleansed re-usable catheters, genitals washed
• Sterile IC	Complete sterile setting, including sterile gloves, forceps, gown and mask
• Intermittent self-catheterisation	IC performed by the patient
Compliance, bladder	See below under storage phase
Condition	Evidence of relevant pathological processes
Diary, bladder	Record of times of micturitions and voided volumes, incontinence episodes, pad usage, and other relevant information
• Frequency volume chart (FVC)	Times of micturitions and voided volumes only
• Micturition time chart	Times of micturitions only
Filling rate, physiological	Below the predicted maximum: body weight (kg) / 4 in mL/s (122,123)
Hesitancy	Difficulty in initiating micturition; delay in the onset of micturition after the individual is ready to pass urine
Intermittency	Urine flow stops and starts on one or more occasions during voiding
Leak point pressure	See below under storage phase
Lower motor neuron lesion (LMNL)	Lesion at or below the S1-S2 spinal cord level
Neurogenic lower urinary tract dysfunction (NLUTD)	Lower urinary tract dysfunction secondary to confirmed pathology of the nervous supply
Observation, specific	Observation made during specific diagnostic procedure
Overactivity, bladder	See below under symptom syndrome (table 4)
Overactivity, detrusor	See below under storage phase
Rehabilitation, LUT	Non-surgical non-pharmacological treatment for LUT dysfunction
Sign	To verify symptoms and classify them
Sphincter, urethral, non-relaxing	See below under voiding phase
Symptom	Subjective indicator of a disease or change in condition, as perceived by the patient, carer, or partner that may lead the patient to seek help from healthcare professionals
Upper motor neuron lesion (UMNL)	Lesion above the S1-S2 spinal cord level
Voiding, balanced: In patients with neuro-urological disorders	Voiding with physiological detrusor pressure and low residual (< 80 mL or < 20% of bladder volume)

Voiding, triggered	Voiding initiated by manoeuvres to elicit reflex detrusor contraction by exteroceptive stimuli
Volume, overactivity	<i>See below under storage phase</i>

**Table 4: Further definitions useful in clinical practice**

<b>Storage phase</b>	
Maximum anaesthetic bladder capacity	Maximum bladder filling volume under deep general or spinal anaesthesia
Increased daytime frequency	Self-explanatory; the normal frequency can be estimated at about 8 times per day (124)
Nocturia	Waking at night one or more times to void
Urgency	The symptom of a sudden compelling desire to pass urine that is difficult to defer
Urinary incontinence	Any involuntary leakage of urine
• Stress urinary incontinence	On effort or exertion, or on sneezing or coughing
• Urgency urinary incontinence	Accompanied by or immediately preceded by urgency
• Mixed urinary incontinence	Associated with urgency but also exertion, effort, sneezing, or coughing
• Continuous urinary incontinence	
Bladder sensation	
<i>Normal</i>	
• Symptom and history	Awareness of bladder filling and increasing sensation up to a strong desire to void
• Urodynamics	First sensation of bladder filling, first desire to void, and strong desire to void at realistic bladder volumes
<i>Increased</i>	
• Symptom and history	An early and persistent desire to void
• Urodynamics	Any of the three urodynamic parameters mentioned under 'normal' persistently at low bladder volume
<i>Reduced</i>	
• Symptom and history	Awareness of bladder filling but no definite desire to void
• Urodynamics	Diminished sensation throughout bladder filling
<i>Absent</i>	
Non-specific	Perception of bladder filling as abdominal fullness, vegetative symptoms, or spasticity
<i>Definitions valid after urodynamic confirmation only</i>	
Cystometric capacity	Bladder volume at the end of the filling cystometry
• Maximum cystometric capacity	Bladder volume at strong desire to void
• High-capacity bladder	Bladder volume at cystometric capacity far over the mean voided volume, estimated from the bladder diary, with no significant increase in detrusor pressure under non-anaesthetised condition
Normal detrusor function	Little or no pressure increase during filling: no involuntary phasic contractions despite provocation
Detrusor overactivity	Involuntary detrusor contractions during filling; spontaneous or provoked
• Phasic DO	Characteristic phasic contraction
• Terminal DO	A single contraction at cystometric capacity
• High pressure DO	Maximal detrusor pressure > 40 cm H <sub>2</sub> O (119,125)

• Overactivity volume	Bladder volume at first occurrence of DO
• Detrusor overactivity incontinence	Self-explanatory
Leak point pressure	
• Detrusor leak point pressure (DLPP)	Lowest value of detrusor pressure at which leakage is observed in the absence of abdominal strain or detrusor contraction
• Abdominal leak point pressure	Lowest value of intentionally increased intravesical pressure that provokes leakage in the absence of a detrusor contraction
Bladder compliance	Relationship between change in bladder volume ( $\Delta V$ ) and change in detrusor pressure ( $\Delta p_{det}$ ): $C = \Delta V / \Delta p_{det}$ (mL/cmH <sub>2</sub> O)
• Low bladder compliance	compliance $C = \Delta V / \Delta p_{det} < 20$ mL/cm H <sub>2</sub> O (106)
Break volume	Bladder volume after which a sudden significant decrease in bladder compliance is observed
Urethral sphincter acontractility	No evidence of sphincter contraction during filling, particularly at higher bladder volumes, or during abdominal pressure increase
<b>Voiding phase</b>	
• Slow stream	Reduced urine flow rate
• Intermittent stream (intermittency)	Stopping and starting of urine flow during micturition
• Hesitancy	Difficulty in initiating micturition
• Straining	Muscular effort to initiate, maintain, or improve urinary stream
• Terminal dribble	Prolonged final part of micturition when the flow has slowed to a trickle/dribble
<i>Definitions valid after urodynamic confirmation only</i>	
Normal detrusor function	Voluntarily initiated detrusor contraction that causes complete bladder emptying within a normal time span
Detrusor underactivity	Contraction of reduced strength/duration
Acontractile detrusor	Absent contraction
Non-relaxing urethral sphincter	Self-explanatory
Detrusor sphincter dyssynergia (DSD)	Detrusor contraction concurrent with an involuntary contraction of the urethra and/or periurethral striated musculature
<b>Post-micturition phase</b>	
Feeling of incomplete emptying (symptom only)	
Post-micturition dribble: involuntary leakage of urine shortly after finishing the micturition	
Pain, discomfort or pressure sensation in the LUT and genitalia that may be related to bladder filling or voiding, may be felt after micturition, or be continuous	
Symptom syndrome: combination of symptoms	
<ul style="list-style-type: none"> <li>• Overactive bladder syndrome: urgency with or without urge incontinence, usually with frequency and nocturia</li> <li>• Synonyms: urgency syndrome, urgency-frequency syndrome</li> <li>• This syndrome is suggestive for LUTD</li> </ul>	

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## 3. DIAGNOSIS

### 3.1 Introduction

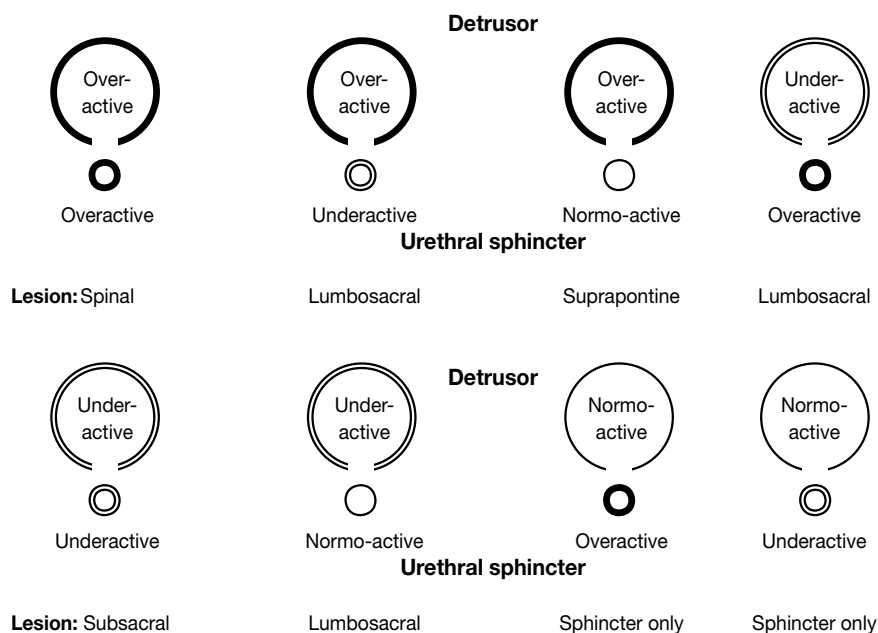
The normal physiological function of the lower urinary tract (LUT) depends on an intricate interplay between the sensory and motor nervous systems, with the autonomous nervous system also having an important role. When diagnosing LUT dysfunction in patients with neurological pathology, the aim is to describe the type of dysfunction involved, as this may not be obvious from the neurological lesion and the patient's symptoms.

A thorough medical history and physical examination is mandatory before any additional diagnostic investigations can be planned. Clinical assessment of patients with neuro-urological symptoms includes a detailed history, a patient voiding diary and systematic physical examination. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

### 3.2 Classification

Several classification systems for neuro-urological symptoms have been proposed. The most useful is a simple classification developed by Madersbacher (1) (LE: 4). It describes neuro-urological function in terms of the contraction state of the bladder and external urethral sphincter during filling and voiding phases, which is then used to decide the appropriate therapeutic approach (1,2) (Figure 1).

**Figure 1 Madersbacher classification system [1] showing typical neurogenic lesions**



### 3.3 The timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders (3). This may help to prevent irreversible changes within LUT, even in the presence of normal neurological reflexes (4,5) (LE: 3). Furthermore, neuro-urological symptoms can be the presenting feature of neurological pathology (6,7) (LE: 3). Thus, early intervention, e.g. intermittent catheterization (IC), can prevent irreversible deterioration of the lower and upper urinary tract (8,9) (LE: 3).

### 3.4 Patient history

History taking is the cornerstone of evaluation and should include past and present symptoms and disorders (Table 3.1). Taking a detailed past history is important because the answers will help to decide diagnostic investigations and treatment options.

- In non-traumatic neurological bladder dysfunction with a slow insidious onset, a careful history may occasionally find that the condition started in childhood or adolescence (10) (LE: 4).
- Urinary history consists of symptoms associated with both storage and evacuation functions of the LUT.
- Bowel history is important because patients with neuro-urological symptoms may also have a related neurogenic condition of the lower gastrointestinal tract, which may reflect the neurological condition of the urinary bladder (11) (LE: 4).
- Sexual function may be impaired because of the neurogenic condition.
- Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) requiring further investigation.
- Remember that patients with spinal cord injury (SCI) usually find it difficult to report UTI-related symptoms accurately (12-14) (LE: 3).

<b>Table 3.1 History taking in patients with suspected neuro-urological disorders*</b>	
<b>Past history</b>	
	Childhood through to adolescence and in adulthood
	Hereditary or familial risk factors
	Menarche (age); this may suggest a metabolic disorder
	Obstetric history
	History of diabetes; in some cases, correction will resolve the neurological problem
	Diseases, e.g. syphilis, parkinsonism, multiple sclerosis, encephalitis
	Accidents and operations, especially those involving the spine and central nervous system
<b>Present history</b>	
	Present medication
	Lifestyle (smoking, alcohol and drugs); may influence bowel and urinary function



	Quality of life
	Life expectancy
<b>Specific urinary history</b>	
	Onset of urological history
	Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy
	Bladder sensation
	Initiation of micturition (normal, precipitate, reflex, strain, Credé)
	Interruption of micturition (normal, paradoxical, passive)
	Enuresis
	Mode and type of voiding (catheterization)
	Urinary bladder diary; (semi-) objective information about the number of voids, day-time and night-time voiding
	Frequency, volumes voided, incontinence, urge episodes
<b>Bowel history</b>	
	Frequency and faecal incontinence
	Desire to defecate
	Defecation pattern
	Rectal sensation
	Initiation of defecation (digital rectal stimulation)
<b>Sexual history</b>	
	Genital or sexual dysfunction symptoms
	Sensation in genital area
	Specific male: erection, (lack of) orgasm, ejaculation
	Specific female: dyspareunia, (lack of) orgasm
<b>Neurological history</b>	
	Acquired or congenital neurological condition
	Mental status and comprehension
	Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
	Spasticity or autonomic dysreflexia (lesion above level Th 6)
	Mobility and hand function

\* Adapted from Bors and Turner (10) (LE: 4; GR: C) and Stöhrer et al. (14) (LE: 4; GR: C).

### 3.4.1 Bladder diaries

Bladder diaries provide data on the number of voids, volume voided, incontinence and urge episodes. Although a 24-hour bladder diary (recording should be done for three consecutive days) is reliable in women with urinary incontinence (15,16) (LE: 3) and helpful in intermittent catheterization (14) (LE: 4), no research has been done on bladder diaries in neurological incontinence. Nevertheless, bladder diaries are considered a valuable diagnostic tool in neuro-urological patients.

## 3.5 Quality of life

An assessment of the patient's present and expected future quality of life (QoL) is important because of the effect on QoL of any therapy used (or that is refrained from using). Despite the limitations associated with neurological pathology, adequate treatment is possible in most patients and should not interfere with social independence. The aim of treatment is to manage symptoms, improve urodynamic parameters, functional abilities and QoL, and avoid secondary complications (17,18).

QoL is a very important aspect of the overall management of neuro-urological patients and treatment-related changes in neuro-urological symptoms can have a major impact on patient QoL (19,20) (LE: 2a). The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI (21). Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neurogenic bladder in determining patient QoL (22).

Quality of life is related to an individual's ability to cope with a new life situation (23). QoL can be influenced by several factors, including family support, adjustment and coping ability, productivity, self-esteem, financial stability, education, and the physical and social environment (24) (LE: 3). Age, sex, ethnicity and the patient's acceptance of the condition also need to be considered when assessing QoL (25) (LE: 3).

Although several questionnaires have been developed to assess QoL, there are no specific QoL questionnaires for the general neurogenic bladder dysfunction or the neuro-urological patient population. There is, however, the validated generic tool known as Visual Analogue Scale (VAS) for symptom bother. In addition, a validated

specific tool for QoL in spinal cord lesion and multiple sclerosis patients (Qualiveen®) appears to be a discriminative evaluation instrument (22,26-28). A short form is available (29) and various validated translations (30-33).

A patient's QoL can be assessed secondarily by generic HRQoL questionnaires, including the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), Short Form 36 Health Survey Questionnaire (SF-36), Euro Quality of Life-5 Domains (EQ-5D), Short Form 6D Health Survey Questionnaire (SF-6D), or the Health Utilities Index (HUI).

In addition, the quality-adjusted life year (QALY) quantifies outcomes by weighing years of life spent in a specified health state by a factor representing the value placed by society or patients on the specific health state (34) (LE: 3).

### 3.5.1 Recommendations

	GR
Quality of life should be assessed when evaluating LUT symptoms in neurological patients and when treating neurogenic bowel dysfunction.	B
The available validated tools are Qualiveen®, a specific long-form and short-form tool for spinal cord lesion and multiple sclerosis patients and VAS for symptom bother. In addition, generic (SF-36) or specific tools for incontinence (I-QOL) questionnaires can be used.	B

LUT = lower urinary tract; Vas = Visual Analogue Scale

## 3.6 Physical examination

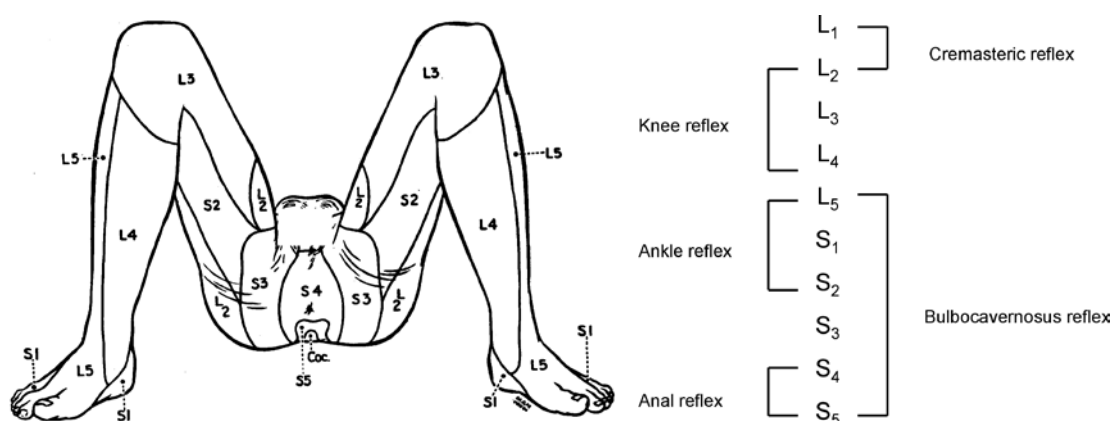
In addition to a detailed patient history and general examination, attention should be paid to possible physical and mental handicaps with respect to the planned investigation.

Neurological status should be described as completely as possible (Figure 1). Patients with very high neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2). It is essential to have this clinical information to reliably interpret later diagnostic investigations.

### 3.6.1 Autonomic dysreflexia (AD)

Be alert for autonomic dysreflexia (AD), which is a sudden and exaggerated autonomic response to stimuli in patients with SCI or spinal dysfunction above level Th 5–Th 6. Hypertension is a relatively common manifestation of AD and can have life-threatening results if not properly managed (35-37) (LE: 3; GR: C).

**Figure 2: The neurological status of a patient with neuro-urological symptoms must be described as completely as possible: (a) dermatomes of spinal cord levels L2-S4; (b) urogenital and other reflexes in the lower spinal cord.**





<b>Table 3.2: Neurological items to be specified*</b>	
<b>Sensations S2-S5 (both sides)</b>	
	Presence (increased/normal/reduced/absent)
	Type (sharp/blunt)
	Afflicted segments
<b>Reflexes (increased/normal/reduced/absent)</b>	
	Bulbocavernous reflex
	Perianal reflex
	Knee and ankle reflexes
	Plantar responses (Babinski)
<b>Anal sphincter tone</b>	
	Presence (increased/normal/reduced/absent)
	Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
<b>Prostate palpation</b>	
<b>Descensus (prolapse) of pelvic organs</b>	

\*Adapted from Stöhrer et al. (14) (LE: 4; GR: C).

### 3.6.2 Recommendations for history taking and physical examination\*

<b>History taking</b>	<b>GR</b>
An extensive general history is mandatory, concentrating on past and present symptoms and conditions for urinary, bowel, sexual, and neurological functions, and on general conditions that might impair any of these.	A
Special attention should be paid to the possible existence of alarm signs, such as pain, infection, haematuria, fever, etc, that warrant further specific diagnosis.	A
A specific history should be taken for each of the four mentioned functions.	A
<b>Physical examination</b>	
Individual patient handicaps should be acknowledged in planning further investigations.	A
The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.	A
The anal sphincter and pelvic floor functions must be tested extensively.	A
Urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.	A

\* All grade A recommendations are based on panel consensus.

## 3.7 Urodynamics

### 3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the (dys-) function of the LUT. It is essential to describe the LUT status in patients with neuro-urological symptoms. In these patients, particularly when DO might be present, the invasive urodynamic investigation is even more provocative than in other patients. Any technical source of artefacts must be critically considered and it is essential to maintain the quality of the urodynamic recording and its interpretation (38). Same session repeat urodynamic investigations are crucial for clinical decision making, since repeat measurements may yield completely different results (39).

In patients at risk for AD, it is advisable to measure blood pressure during the urodynamic study. In many patients with neuro-urological symptoms, it may be helpful to assess the maximum anaesthetic bladder capacity. The rectal ampulla should be empty of stool before the start of the investigation. Drugs that influence LUT function should be stopped at least 48 hours before the investigation, if feasible, or considered when interpreting the results. All urodynamic findings must be reported in detail and performed, according to ICS technical recommendations and standards (38,40,41).

### 3.7.2 Urodynamic tests

A *bladder diary* is a semi-objective qualification of the LUT. It is a highly advisable diagnostic tool. For reliable interpretation, it should be recorded over at least 2-3 days (40,42). Possible pathological findings include a high voiding frequency, very low or very high voided volumes, nocturnal voidings, urgency and incontinence.

*Free uroflowmetry and assessment of residual urine* provide a first impression of the voiding function. It is compulsory prior to planning any invasive urodynamics. For reliable information, it should be repeated at least

2-3 times (40,41,43,44). Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and residual urine. Care must be taken when assessing the results in patients unable to void in a normal position, as both flow pattern and rate may be modified by inappropriate positions and by any constrictions to divert the flow.

*Filling cystometry* is the only method for quantifying the filling function. The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline, as fast filling and room-temperature saline are provocative (18). Possible pathological findings include DO, low bladder compliance, abnormal bladder and other sensations, incontinence, and an incompetent or relaxing urethra.

*Detrusor leak point pressure (DLPP)* (45) appears to have no use as a diagnostic tool. Some positive findings have been reported (46,47). However, its sensitivity is too low to estimate the risk to the upper urinary tract or for secondary bladder damage (48).

*Pressure flow study* reflects the co-ordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more powerful combined with filling cystometry and with video-urodynamics. LUT function must be recorded during the voiding phase. Possible pathological findings include detrusor underactivity, acontractility, DSD, non-relaxing urethra, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD (49,50), non-relaxing urethra, or non-relaxing bladder neck (40,51,52). Pressure-flow analysis mostly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties and has limited value in patients with neuro-urological disorders.

*Electromyography (EMG)* reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter, and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (bladder filling, hyper-reflexive contractions, onset of voiding, coughing, Valsalva manoeuvre, etc). A more detailed analysis (motor unit potentials, single-fibre EMG) is only possible as part of a neurophysiological investigation.

*Urethral pressure measurement* has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings (53).

*Video-urodynamics* is the combination of filling cystometry and pressure flow study with imaging. It is the gold standard for urodynamic investigation in neuro-urological disorders (40,54,55). Possible pathological findings include all of those described under cystometry and the pressure flow study, as well as any morphological pathology of the LUT and the upper urinary tract.

*Ambulatory urodynamics* is the functional investigation of the urinary tract, which uses the predominantly natural filling of the urinary tract to reproduce the patient's normal activity (56). This type of study should be considered when office urodynamics do not reproduce the patient's symptoms and complaints. Possible pathological findings include those described under cystometry and the pressure flow study, provided the flow is also recorded. Notice that the actual bladder volume is unknown during the study.

*Provocative tests during urodynamics.* The LUT function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') will discriminate between upper motor neurone lesions (UMNL) and lower motor neurone lesions (LMNL) (57,58). Patients with UMNL develop a detrusor contraction if the detrusor muscle is intact, while patients with LMNL do not. However, the test gives false-positive results in young children (59) and does not seem fully discriminative in other types of patient (60-63).

Previously, a positive bethanechol test (63) (detrusor contraction > 25 cm H<sub>2</sub>O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol (64), but there was no published follow-up.

### 3.7.3 **Specialist uro-neurophysiological tests**

The following tests are advised as part of the neurological work-up:

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

Other elective tests for specific conditions may become obvious during the work-up and urodynamic investigations.

### 3.7.4 **Recommendations for urodynamics and uro-neurophysiology**

Recommendations	GR
The recording of a bladder diary is advisable.	B
Non-invasive testing is mandatory before invasive urodynamics is planned.	A
Urodynamic investigation is necessary to document LUT (dys-) function and same session repeat measurement is crucial for clinical decision making.	A
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.	A
A physiological filling rate and body-warm saline must be used.	A
Specific uro-neurophysiological tests are elective procedures.	C

LUT = lower urinary tract

### 3.7.5 **Typical manifestations of neuro-urological disorders**

Table 3.3 lists typical signs indicating further neurological evaluation, as neuro-urological symptoms may be the presenting symptom (65-69).

**Table 3.3: Typical findings in neuro-urological disorders**

<b>Filling phase</b>	
	Hyposensitivity or hypersensitivity
	Vegetative sensations
	Low compliance
	High-capacity bladder
	Detrusor overactivity, spontaneous or provoked
	Sphincter underactivity
<b>Voiding phase</b>	
	Detrusor underactivity or acontractility
	Detrusor sphincter dyssynergia
	Non-relaxing urethra
	Non-relaxing bladder neck

## 3.8 **Renal function**

In many patients with neuro-urological disorders, the upper urinary tract is at risk, particularly in patients who develop high detrusor pressure during either the filling or the voiding phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity (4,70).

Caregivers must be informed of this condition and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. If necessary, the renal function should be checked; the details for this procedure are beyond the scope of these guidelines.

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## 4. TREATMENT

### 4.1 Introduction

The primary aims for treatment of neuro-urological symptoms and their priorities are (1-4):

1. Protection of the upper urinary tract
2. Improvement of urinary continence
3. Restoration of (parts of) the LUT function
4. Improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity, and possible complications (4).

Preservation of upper urinary tract function is of paramount importance (1-7). Renal failure is the main mortality factor in SCI patients that survive the trauma (5-7). This has led to the golden rule in treatment of neuro-urological symptoms: ensure that the detrusor pressure remains within safe limits during both the filling phase and the voiding phase (1-4). This approach has indeed significantly reduced the mortality from urological causes in this patient group (8).

Therapy of urinary incontinence is important for social rehabilitation of the patient and thus contributes

substantially to QoL. It is also pivotal in preventing UTI (6,7). If complete continence cannot be achieved, methods to attain socially acceptable control of incontinence can be used. The patient's QoL is an essential part of any treatment decision.

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance) or during the voiding phase (DSD, other causes of bladder outlet obstruction), treatment is aimed primarily at "conversion of an active, aggressive high-pressure bladder into a passive low-pressure reservoir" despite the resulting residual urine (1).

## 4.2 Non-invasive conservative treatment

### 4.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure during the filling phase, and incontinence. Therefore, methods to improve the voiding process are practiced in patients with neuro-urological symptoms.

*Bladder expression (Credé manoeuvre):* Regretfully, this method is still applied, foremost in infants and young children with myelomeningocele (9), and those with tetraplegia (10-14). The suprapubic downwards compression of the lower abdomen leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction (9,15). This functional obstruction may increase an already existing high bladder outlet resistance and lead to inefficient emptying. The high pressures created during this procedure are hazardous for the urinary tract (16,17), thus, its use should be discouraged unless urodynamics show that the intravesical pressure remains within a safe range (9,17-20).

*Voiding by abdominal straining (Valsalva manoeuvre):* The same considerations as mentioned above for the Credé manoeuvre also hold for the Valsalva manoeuvre. Most patients are unable to regulate the pressure that they exert on the bladder during the Valsalva manoeuvre, thus, there is a substantial risk of renal damage.

For both methods of bladder emptying, long-term complications are unavoidable (15). The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence (17).

*Triggered reflex voiding:* Stimulation of the sacral or lumbar dermatomes in patients with UMNL can elicit reflex contraction of the detrusor (17). Strict urodynamic control is required (1,21). Interventions to decrease outlet resistance may be necessary for effective reflex voiding (22). Patients should be aware that triggering can induce autonomic dysreflexia in patients with high level SCI (above Th 6) (23) and that reflex incontinence may coexist. For triggered reflex voiding, the risk of high pressure voiding is also present. The morbidity appears to be less for patients with a longer history of this type of bladder emptying (24).

All assisted bladder emptying techniques require low outlet resistance. In most cases this is achieved by surgical (sphincterotomy, botulinum toxin injection, or sphincter stent) or medical ( $\alpha$ -blocking agents) intervention. Even then, high detrusor pressures that endanger the upper tract may still be present. Patients applying any of these techniques hence need dedicated education and close urodynamic and urological surveillance for early detection of any complications (17,18,20,25).

*Note: In the literature the concept "reflex voiding" is used sometimes to cover all three assisted voiding techniques described in this section. This holds also true for some of the references cited here.*

*External appliances:* As an ultimate remedy, social continence may be achieved by collecting urine during incontinence (1,21). Condom catheters with urine collection devices are a practical method for men (26). Otherwise, incontinence pads may offer a reliable solution. In both cases, the infection risk must be closely observed (21). The penile clamp is absolutely contraindicated in case of DO or low bladder compliance because of the risk of developing high intravesical pressure, and in case of significant reflux.

### 4.2.2 Lower urinary tract rehabilitation

#### 4.2.2.1 Bladder rehabilitation including electrical stimulation

##### 4.2.2.1.1 Introduction

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. Regaining voluntary control over LUTD has been described in individuals with non-neurogenic bladder dysfunction, using behavioural treatment in patients with urge incontinence and biofeedback training for stress urinary incontinence. However, evidence for bladder



rehabilitation using electrical stimulation in neurological patients is lacking and mainly based on pilot studies with small patient numbers.

Strong contraction of the urethral sphincter and/or pelvic floor, as well as anal dilatation, manipulation of the genital region, and physical activity inhibit micturition in a reflex manner (21,27). The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres (28). Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction (29). This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level (21,30,31). It might also imply that patients with incomplete lesions benefit (21,31,32), but patients with complete lesions do not (33). However, comparable urodynamic improvements in patients with complete and incomplete lesions using semiconditional electrical stimulation have been reported in the acute phase (34).

#### 4.2.2.1.2 Peripheral temporary electrostimulation

Percutaneous tibial nerve stimulation and external temporary electrical stimulation (e.g. penile/clitoral or intracavitary) suppress neurogenic DO during acute stimulation (35,36). Both techniques have also demonstrated sustained prolonged effects (3 months and 1 year, respectively) in patients with neurogenic bladder dysfunction due to MS (37-39). LUT function remained improved 2 years after transcutaneous electrical stimulation of the bladder in patients with SCI (40). Electrostimulation may also improve continence for at least 3 months in children with MMC (41).

In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and electromyography biofeedback can achieve a substantial reduction of LUTD (42). Furthermore, this treatment combination is significantly superior to electrostimulation alone.

*Biofeedback:* This method can be used for supporting the alleviation of the symptoms of LUTD (43,44).

#### 4.2.2.1.3 Intravesical electrostimulation

Intravesical electrostimulation can increase bladder capacity and improve bladder compliance as well as the sensation of bladder filling in patients with incomplete SCI or meningomyelocele (45). In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual urine volume (46,47).

#### 4.2.2.1.4 Chronic peripheral pudendal stimulation

The results of a pilot study showed that chronic peripheral pudendal stimulation (defined as 15 min, twice daily, during a period of 2 weeks) in patients with incomplete SCI may produce neuromodulatory effects in the brain. These effects are correlated with clinical improvement (48). Semiconditional electrical stimulation of the dorsal penile nerve during 14-28 days improves bladder storage function in patients with SCI (49).

#### 4.2.2.1.5 Repetitive transcranial magnetic stimulation

Although repetitive transcranial magnetic stimulation improves voiding symptoms in patients with PD and detrusor overactivity, and in patients with MS and an underactive detrusor, the duration of the effect, stimulation parameters, and the appropriate patient selection are still under investigation (50,51).

#### 4.2.2.1.6 Summary

To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation. However, there is a lack of well-designed studies for all techniques. The different techniques of external temporary electrostimulation, possibly combined with biofeedback training, may be useful, especially in patients with MS or incomplete spinal cord injury. Further studies are necessary to evaluate the usefulness of these techniques.

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#### 4.2.4 **Drug treatment**

A single, optimal, medical therapy for neuro-urological symptoms is not yet available. Commonly, a combination of different therapies (e.g., intermittent catheterization and pharmacological treatment) is the best way to maximize outcomes, particularly in patients with spinal cord injury with a suprasacral lesion or MS (1-11).

##### 4.2.4.1 *Antimuscarinic drugs*

Muscarinic receptor antagonists are the first-line choice for treating neuro-urological symptoms. They are the most useful drugs available for neuro-urological symptoms and provide an established approach for managing neurogenic detrusor overactivity (NDO), increasing bladder capacity, and delaying the initial urge to void, even when combined with intermittent catheterization (1-3,12-17). Antimuscarinic drugs are used to reduce NDO and make it moderately refractory to parasympathetic stimulation via motor and sensory pathways (18,19). This results in improved bladder storage and reduced symptoms of neurogenic OAB (3,13-15), which in turn helps to prevent urinary tract damage and potentially improve long-term outcomes (17,20).

Although antimuscarinic drugs have been used for many years to treat patients with NDO, the evidence is still limited (14,17,21), and the responses of individual patients to antimuscarinic treatment are variable. A recent meta-analysis has confirmed the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO. No difference in effectiveness or withdrawal due to adverse events has been documented between the different antimuscarinic drugs or different doses (17).

Neurological patients may often need a higher dose of antimuscarinic agents or a combination of them, compared with patients with idiopathic detrusor overactivity (3,8,10,22-25) (LE: 3). However, antimuscarinic drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy (17,23,25).

#### 4.2.4.1.1 Choice of antimuscarinic agent

Oxybutynin (3,8,10,12-15,17,20,22,25-27), trospium (3,17,23,28), tolterodine (29-31) and propiverine (3,15,17,26,32-35) are established, effective, medical treatments (LE: 1a). These antimuscarinic agents are known to be well tolerated and safe, even during long-term treatment. They have diverse tolerance profiles, so that a different antimuscarinic agent may be prescribed if a patient experiences adverse effects or if the therapeutic effect is not sufficient (23). Darifenacin and solifenacin have recently been evaluated in neurogenic OAB secondary to spinal cord injury and MS (17,36-39), with results similar to other antimuscarinic drugs. A study using solifenacin in NDO due to Parkinson's disease is currently suspended (40). The relatively new fesoterodine, an active metabolite of tolterodine, has also been introduced, even though to date there has been no published clinical evidence of its use in the treatment of neuro-urological disorders.

#### 4.2.4.1.1.1 Adverse effects

Controlled release antimuscarinics have some minor adverse effects; for example, dry mouth. It has been suggested that different routes of administration may help to reduce adverse effects. In a selected group of patients, transdermal oxybutynin was found to be well tolerated and effective (41-43). In contrast, although there are several studies reporting the efficacy and safety of intravesical oxybutynin, there are no standard protocols yet for its use (44-46). Therefore, further research is needed into the use of alternative methods of administration, particularly long-term results (LE: 1b).

#### 4.2.4.2 Other agents

##### 4.2.4.2.1 Phosphodiesterase inhibitors

These drugs have demonstrated significant effects upon OAB in men, through their action on afferent nerves and the urothelium. *In vivo* and pilot studies seem to support that phosphodiesterase inhibitors (PDEis) may become an alternative or adjunct to antimuscarinic and/or  $\alpha$ -blocker treatment of neuro-urological symptoms (47-49).

##### 4.2.4.2.2 $\beta$ -Adrenergic receptor agonist

Beta3-adrenergic receptors have recently been introduced and evaluated in OAB, but there are no current data in the treatment of neuro-urological symptoms. This family of drugs directly inhibit afferent nerve firing independent of the relaxant effects on bladder smooth muscle. In the future, combined therapy with antimuscarinics may be an attractive option, but to date, there is no clinical experience in this patient group (50-52).

##### 4.2.4.3 Adjunctive desmopressin

Additional treatment with desmopressin might improve the clinical efficacy of treatment in patients with nocturnal enuresis (53-56).

#### 4.2.4.4 Drugs for neurogenic voiding dysfunction

##### 4.2.4.4.1 Detrusor underactivity

Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not routinely used in clinical practice. The available studies do not support the use of parasympathomimetic agents, especially when frequent and/or serious possible adverse effects are considered (57). Recently, preclinical studies have documented the potential benefits of cannabinoid agonists on improving detrusor contractility during voiding when administered intravesically (58,59).

##### 4.2.4.4.2 Decreasing bladder outlet resistance

Alpha-Blockers (tamsulosin and naftopidil) seem to be effective for decreasing bladder outlet resistance, post-void residual urine, and autonomic dysreflexia (60). Combination therapy with a cholinergic drug and  $\alpha$ -blocker appears to be more useful than monotherapy with either agent (61,62).

##### 4.2.4.4.3 Increasing bladder outlet resistance

Several drugs have shown efficacy in selected cases of mild stress urinary incontinence, but there are no high-level evidence studies in neurological patients (12).



#### 4.2.4.5 Recommendations for drug treatments

	LE	GR
For NDO, antimuscarinic therapy is the recommended first-line medical treatment.	1a	A
Alternative routes of administration (i.e., transdermal or intravesical) of antimuscarinic agents may be used.	1b	A
Outcomes for NDO may be maximized by considering a combination of antimuscarinic agents.	3	B
To decrease bladder outlet resistance, $\alpha$ -blockers should be prescribed.	1b	A
For underactive detrusor, no parasympathomimetics should be prescribed.	1a	A
In neurogenic stress urinary incontinence, drug treatment should not be prescribed.	4	A

NDO = neurogenic detrusor overactivity

#### 4.2.4.6 References

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### **4.3 Minimal invasive treatment**

#### **4.3.1 Catheterization**

Intermittent self- or third-party catheterization (1,2) is the preferred management of neuro-urological patients who cannot effectively empty their bladders (3,4).

Sterile IC, as originally proposed by Guttmann and Frankel (1), significantly reduces the risk of UTI and/or bacteriuria (3-6) compared with clean IC introduced by Lapedes et al. (2). However, it cannot be considered a routine procedure (4,6).

Aseptic IC is an alternative (3,7) that provides a significant benefit by reducing external contamination of the catheter (8-10). Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients (4,9,11-14). The average frequency of catheterizations per day is 4-6 times (15) and the catheter size most often used are between 12-16 Fr. In aseptic IC, an optimum frequency of 5 times showed a reduction of UTI (15).

Ideally, bladder volume at catheterization should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterization and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk factors for UTI (4,17-27). Both procedures should therefore be avoided when possible.

Silicone catheters are preferred because they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population (28).

#### 4.3.1.1 Recommendations for catheterization

	LE	GR
Intermittent catheterization - whenever possible aseptic technique - should be used as a standard treatment for patients who are unable to empty their bladder	3	A
Patients must be well instructed in the technique and risks of IC	3	A
The catheter size should be 12-16 Fr	4	B
Whenever possible, indwelling transurethral and suprapubic catheterization should be avoided	3	A

IC = intermittent catheterization.

#### 4.3.2 Intravesical drug treatment

To reduce DO, anticholinergics can also be applied intravesically (29-35). This approach may reduce adverse effects because the anticholinergic drug is metabolised differently (33) and a greater amount is sequestered in the bladder, even more than with electromotive administration (34,35).

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres and thereby decrease DO for a period of a few months until the sensation of these fibres has been restored (36-41). The dosage is 1-2 mMol capsaicin in 100 mL 30% alcohol, or 10-100 nMol resiniferatoxin in 100 mL 10% alcohol for 30 minutes. Resiniferatoxin has about a 1,000-fold potency compared to capsaicin, with less pain during the instillation, and is effective in patients refractory to capsaicin. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A injections in the detrusor (41).

#### 4.3.3 Intravesical electrostimulation

Intravesical electrostimulation (42) enhances the sensation for bladder filling and urge to void and may restore the volitional control of the detrusor (43,44). Daily stimulation sessions of 90 minutes with 10 mA pulses of 2 ms duration at a frequency of 20 Hz (44,45) are used for at least 1 week (45). It appears that patients with peripheral lesions are the best candidates, that the detrusor muscle must be intact, and that at least some afferent connection between the detrusor and the brain must still be present (44,45). Also, the positioning of the stimulating electrodes and bladder filling are important parameters (46). With these precautions, the results in the literature are still not unequivocal: both positive (43,45,47,48) and negative (49,50) (LE: 3) results have been reported.

#### 4.3.4 Botulinum toxin injections in the bladder

Botulinum toxin causes a long-lasting but reversible chemical denervation that lasts for about 9 months (51,52). The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in patients with neuro-urological disorders in phase III RCTs randomised placebo-controlled trials (53-55). Repeated injections seem to be possible without loss of efficacy (52,55,56). Generalised muscular weakness is an occasional adverse effect (52,54,56). Histological studies have not found ultrastructural changes after injection (57).

#### 4.3.5 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the upper urinary tract. This can be achieved by surgical interventions (bladder neck or sphincter incision or urethral stent) or by chemical denervation of the sphincter. Incontinence may result and can be managed by external devices (see Section 4.2.1).

*Botulinum toxin sphincter injection* can be used to treat detrusor sphincter dyssynergia effectively by injection in a dosage that depends on the preparation used. The dyssynergia is abolished for a few months, necessitating repeat injections. The efficacy of this treatment is high and there are few adverse effects (58-60).

*Balloon dilatation*: although favourable immediate results were reported (61), no further reports since 1994 have been found. Consequently, this method is no longer recommended.

*Sphincterotomy*: by staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra (53). The laser technique appears to be advantageous (62).

Sphincterotomy also needs to be repeated at regular intervals in a substantial proportion of patients (63), but is efficient and without severe adverse effects (61-64). Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered (65).

**Bladder neck incision:** This is indicated only for secondary changes at the bladder neck (fibrosis) (62,65). When the detrusor is hypertrophied and causes thickening of the bladder neck, this procedure makes no sense.

**Stents:** Implantation of urethral stents causes the continence to be dependent on the adequate closure of the bladder neck only (66). Although the results are comparable with sphincterotomy and the stenting procedure has a shorter surgery time and reduced hospital stay (67,68), the costs and possible complications or re-interventions (67,69,70) are limiting factors in its use.

**Increasing bladder outlet resistance:** This can improve the continence condition. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders (66,71-75).

**Urethral inserts:** Urethral plugs or valves for management of (female) stress incontinence have not been applied in neuro-urological patients. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor was disappointing (76).

#### 4.3.6 **Recommendations for minimal invasive treatment\***

Recommendations	GR
Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity.	A
Sphincterotomy is the standard treatment for detrusor sphincter dyssynergia.	A
Bladder neck incision is effective in a fibrotic bladder neck.	B

\*Recommendations for catheterization are listed separately under Section 4.3.1.

##### 4.3.6.1 **References**

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#### **4.4 Surgical treatment**

##### **4.4.1 Urethral and bladder neck procedures**

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure during filling, which may become even higher during the voiding phase. Procedures to treat sphincteric incontinence are suitable only when the detrusor activity is, or can be, controlled, when no significant reflux is present. Moreover, these procedures require the urethra and bladder neck to be in good condition and mostly result in intermittent catheterization being performed after the procedure (1).

*Urethral sling.* Various materials have been used for this procedure with enduring positive results. The procedure is established in women with the ability to self-catheterize (1-15). In men there are a growing number of reports suggesting that both autologous and synthetic slings may also be an alternative (16).

*Artificial urinary sphincter.* This device has stood the test of time in patients with neuro-urological disorders (1). It was introduced by Light and Scott (17) for this patient group, and the need for revisions (18) has decreased significantly with new generations of devices (8,19-22) allowing one to obtain an acceptable long-term outcome (23,24).

*Functional sphincter augmentation.* By transposing the gracilis muscle to the bladder neck (25) or proximal urethra (26), there is a possibility of creating a functional autologous sphincter by electrical stimulation (25,26). This opens the possibility of restoring control over the urethral closure.

*Bladder neck and urethra reconstruction.* The classical Young-Dees-Leadbetter (27) procedure for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening (28) improved by Salle (29), are established methods to restore continence provided that intermittent catheterization is practiced and/or bladder augmentation is performed (8,18,28-40).

Reduction of bladder-outlet resistance may be necessary to protect the upper urinary tract. This can be achieved by surgical intervention (bladder neck or sphincter incision, or urethral stent) or chemical denervation of the sphincter. Incontinence may result and can be managed by external devices (see Section 4.2.1).

*Botulinum toxin sphincter injection.* This can be used to treat detrusor sphincter dyssynergia effectively by injection at a dose that depends on the preparation used. The dyssynergia is abolished for a few months, necessitating repeat injections. The efficacy of this treatment is high and there are few adverse effects (41-43).

*Balloon dilatation.* Although favourable immediate results have been reported (44), no further reports since 1994 have been found. Consequently, this method is no longer recommended.

*Sphincterotomy.* By staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra (45-47). Different techniques are used, and laser treatment appears to be advantageous (45,48,49). Sphincterotomy needs to be repeated at regular intervals in many patients (50), but is efficient and does not cause severe adverse effects (44,45,48,50-52). Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered (45,53).

*Bladder neck incision.* This is indicated only for secondary changes at the bladder neck (fibrosis) (45,48,51,53). This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck (45).

*Stents.* Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck (1,45). The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay (54,55), however, the costs (45), possible complications and re-interventions (54,56,57) are limiting factors in its use (58-61).

*Increasing bladder outlet resistance.* This can improve continence. Despite early positive results with urethral bulking agents, a relatively early loss of continence is reported in patients with neuro-urological symptoms (1,62-71).

*Urethral inserts.* Urethral plugs or valves for management of (female) stress incontinence have not been applied in patients with neuro-urological symptoms. Active-pumping urethral prosthesis for treatment of underactive or acontractile detrusor has been disappointing (72).

#### **4.4.2 Denervation, deafferentation, sacral neuromodulation**

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing detrusor overactivity (62,73-77), but nowadays, it is used mostly as an adjuvant to sacral anterior root stimulation (SARS) (78-80). Alternatives to rhizotomy are sought in this treatment combination (90-92).

SARS is aimed at producing detrusor contraction. The technique was developed by Brindley (93) and is only applicable to complete lesions above the implant location, because its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called "post-stimulus voiding" occurs. This approach has been successful in highly selected patients (78-89,94-96). By changing the stimulation parameters, this method can also induce defecation or erection.

##### **4.4.2.1 Sacral neuromodulation**

Although sacral neuromodulation (SNM) (97) was originally not considered an option for neurogenic lower urinary tract dysfunction, in a systematic review and meta-analysis (98), a pooled success rate of 68% (95% credibility interval (CrI) 50-85%) and 92% (95% CrI 81-98%) was found for the SNM test phase and permanent SNM, respectively. However, there is a lack of RCTs and it is unclear which neurological patient is most suitable for SNM (98).

##### **4.4.3 Bladder covering by striated muscle**

When the bladder is covered by striated muscle that can be stimulated electrically, or ideally that can be contracted voluntarily, voiding function can be restored to an acontractile bladder. The rectus abdominis (99) and latissimus dorsi (100) have been used successfully in patients with neuro-urological symptoms (101).

##### **4.4.4 Bladder augmentation**

The aim of auto-augmentation (detrusor myectomy) is to reduce detrusor overactivity or improve low bladder

compliance. Its advantages are its low surgical burden, low rate of long-term adverse effects, positive effect on patient quality of life, and that it does not preclude further interventions (1,45,102-121).

Replacing or expanding the bladder by intestine or other passive expandable coverage will reduce bladder compliance and at least reduce the pressure effect of detrusor overactivity (122). The inherent complications associated with these procedures include recurrent infection, stone formation, perforation or diverticula, possible malignant changes, and for intestine metabolic abnormality, mucus production and impaired bowel function (1,123-125). The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed.

Bladder augmentation is a valid option to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed. Several different techniques have been published, with comparable and satisfactory results (108,110-112,115-117,124-130). Bladder substitution to create a low-pressure reservoir is indicated in patients with a severely thick and fibrotic bladder wall (131,132).

#### 4.4.5 **Urinary diversion**

When no other therapy is successful, urinary diversion must be considered for the protection of the upper urinary tract and for the patient's quality of life (1,133).

*Continent diversion.* This should be the first choice for urinary diversion. Patients with limited dexterity may prefer a stoma instead of using the urethra for catheterisation (1). A continent stoma is created using various techniques. However, all of them have frequent complications, including leakage or stenosis (1,134). The short-term continence rates are > 80% and good protection of the upper urinary tract is achieved (1,135-148). For cosmetic reasons, the umbilicus is often used for the stoma site (139,141,146,149-154).

*Incontinent diversion.* If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with lower urinary tract destruction, when the upper urinary tract is severely compromised, and in patients who refuse other therapy (1). An ileal segment is used for the deviation in most cases (1,155-159).

*Undiversion.* Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence (1). Also, in young patients, body image may play a role (142). The patient must be carefully counselled and must comply meticulously with the instructions (1). Successful undiversion can then be performed (160).

### 4.5 **Recommendations for surgical treatment**

	LE	GR
In order to treat refractory detrusor overactivity, bladder augmentation is recommended. Detrusor myectomy is an acceptable alternative.	3	A
In female patients with neurogenic stress urinary incontinence who are able to self-catheterise, placement of an autologous urethral sling should be used.	4	B
In male patients with neurogenic stress urinary incontinence, artificial urinary sphincter should be used.	3	A

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## 5. URINARY TRACT INFECTION IN NEURO-UROLOGICAL PATIENTS

### 5.1 Introduction

Urinary tract infection (UTI) is the new onset of sign(s)/symptom(s) accompanied by laboratory findings of a UTI, (bacteriuria, leukocyturia and positive urine culture) (1). There are no evidence-based cutoff values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing intermittent catheterization is present with  $> 10^2$  colony-forming units (cfu)/mL,  $> 10^4$  cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, 10 or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant (1).

Individuals with a neuro-urological symptoms, especially those with SCI, may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. Other problems, such as autonomic dysreflexia, may develop or worsen due to a UTI (2). The most common signs and symptoms suspicious for a UTI in a person with neuro-urological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odor, discomfort or pain over the kidney or bladder, dysuria, or autonomic dysreflexia (2,3).

### 5.2 Diagnosis

Gold standard for the diagnosis is urine culture and urinalysis. A dipstick test may be more useful to exclude than to prove UTI (4,5). As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory (6).

### 5.3 Treatment

Bacteriuria in patients with neuro-urological disorders should not be treated. Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving the outcome (7). UTI in persons with neuro-urological disorders are by definition complicated UTI. Therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment. It depends on the severity of the UTI and the involvement of kidneys and the prostate. Generally, a 5-7 day course of antibiotic treatment



is advised, that can be extended up to 14 days according to the extent of the infection (7). The choice of the antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g. fever, septicaemia, intolerable clinical symptoms, extensive autonomic dysreflexia), the choice of treatment should be based on local and individual resistance profiles (8).

#### 5.4 Recurrent UTI

Recurrent UTI in patients with neuro-urological disorders may indicate a suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, e.g. by treating detrusor overactivity by botulinum toxin type A injection in the detrusor (9), and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory (6).

#### 5.5 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilized. In men performing intermittent catheterization, the use of hydrophilic catheters is associated with a lower rate of UTI; in women this effect could not be demonstrated (10). Bladder irrigation has not been proven effective (11).

Various medical approaches have been tested as UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice for the prevention of UTI could not be demonstrated in randomized controlled trials (12). Methenamine hippurate is not effective in individuals with neuro-urological symptoms (13). There is not sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI (14). There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI, and no evidence that recurrent UTI are reduced (15). Low-dose, long-term, antibiotic prophylaxis cannot reduce UTI frequency, but increases bacterial resistance and is therefore not recommended (7). A newly proposed application scheme of antibiotic substances for antibiotic prophylaxis provided positive results, but the results of this trial need to be confirmed in further studies (16). Another possible future option, the inoculation of apathogenic *E. coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data (17), cannot be recommended as a treatment option. In summary, based on the criteria of evidence-based medicine, there is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations. Therefore, individualized concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine (18). Prophylaxis in patients with neuro-urological disorders is important to pursue, but since there are no data favouring one approach over another, prophylaxis is essentially a trial and error approach.

#### 5.6 Recommendations for the treatment of UTI

	LE	GR
Asymptomatic bacteriuria in patients with neuro-urological disorders should not be treated.	4	A
The use of long-term antibiotics in recurrent UTIs should be avoided.	2a	A
In patients with recurrent UTI, treatment of neuro-urological symptoms should be optimised and foreign bodies (e.g. stones, indwelling catheters) should be removed from the urinary tract.	3	A
In patients with neuro-urological disorders, UTI prophylaxis must be individualized since there is no optimal prophylactic measure available.	4	C

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## 6. TREATMENT OF VESICO-URETERAL REFLUX

### 6.1 Treatment options

The treatment options for vesicoureteral reflux in patients with neuro-urological disorders do not differ essentially from those in patients with other types of reflux. Treatment becomes necessary when the high intravesical pressure during the filling or voiding phase has been treated successfully, but the reflux has not resolved (1-4). Subtrigonal injections with bulking agents or ureteral reimplantation are standard procedures.

*Subtrigonal injections of bulking agents.* This minimally invasive procedure has a relatively good effect with complete success in ~65% of patients (5-12). It can also be easily repeated if not effective and the success rate can be increased to ~75% after the second or third session.

*Ureteral reimplantation.* This technique has immediate and long-lasting results in > 90% of patients (11-13). In deciding which procedure will be offered to patients, the relative risks of more invasive surgery and less-successful therapy should be considered.

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## 7. SEXUAL (DYS)FUNCTION AND FERTILITY

### 7.1 Introduction

Normal sexual function largely depends on the integrity of the nervous system (1). Thus, patients with neurological disease often suffer from sexual dysfunction, which frequently impairs quality of life. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU guidelines (2,3). Here, we specifically focus on patients with neurological disease. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy [4]), provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction.

### 7.2 Male erectile dysfunction (ED)

#### 7.2.1 *Medical treatment using phosphodiesterase type 5 inhibitors*

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in men with erectile dysfunction (ED) and neurological disease (1). All currently available PDE5Is appear to be effective and safe, although there are no high-evidence level studies in patients with neurogenic ED that have investigated efficacy and side effects across different PDE5Is, dosages and formulations. However, a recent network meta-analysis on a mixed ED population has suggested that tadalafil is the most effective agent (5). The most common side effects of PDE5Is are headache, flushing, dyspepsia and nasal congestion, while PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy (6,7).

Several studies including RCTs showed the efficacy and safety of PDE5Is for treating ED in patients with spinal cord injury (SCI) (6,8-11), multiple sclerosis (12-14), Parkinson's disease (15-17), diabetes mellitus (18-21), spina bifida (22) and after radical prostatectomy (23).

Most patients with neurological disease require long-term therapy for ED. However, some patients have a low compliance rate or stop therapy because of side effects (6,7). In addition, it is a prerequisite for successful therapy with PDE5Is that the patient has some residual nerve function to induce the erection.

Since many patients with SCI use on-demand nitrates for the treatment of autonomic dysreflexia, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

#### 7.2.2 *Mechanical devices*

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular (24-28).

#### 7.2.3 *Intracavernous injections and intraurethral application*

Patients not responding to oral drugs may be offered intracavernous injections. Intracavernous penile injectable medications (alprostadil, papaverine and phentolamine) have been shown to be effective in a number of neurological conditions, including SCI, multiple sclerosis, and diabetes mellitus (29-34), but their use requires careful dose titration and some precautions. The reported complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

An intracavernous injection of vasoactive medication is the first therapeutic option to consider in patients taking nitrate medications, for whom there are concerns about drug interactions with PDE5Is, or in patients for whom PDE5Is are ineffective.

Intraurethral application of alprostadil is an alternative route of administration, but it was found to be less effective in SCI patients suffering from ED (35).

#### 7.2.4 *Penile prostheses*

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type (36-38).

### 7.2.5 Recommendations

	LE	GR
In neurogenic ED, oral PDE5Is are the recommended first-line medical treatment.	1b	A
In neurogenic ED, intracavernous injections of vasoactive drugs (alone or in combination) are the recommended second-line medical treatment	3	A
In neurogenic ED, mechanical devices such as vacuum devices and rings can be effective and may be offered to patients.	3	B
In neurogenic ED, penile prostheses should be reserved for selected patients.	4	B

### 7.3 Male fertility

Reproductive function in men largely depends on neurological mechanisms so that infertility may be caused by ED, ejaculatory dysfunction, and abnormal semen parameters (39-41). Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, spina bifida, multiple sclerosis and SCI (41). ED is managed as described above. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine (41). If these agents fail, the harvest of semen from the urine may be considered (41). In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval and assisted reproductive technologies may become necessary (39,41).

Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection (ICSI), men with SCI now have a good chance of becoming biological fathers (42-44).

In men with retrograde ejaculation, the use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation (45). More comparative trials are needed to evaluate the impact of intracavernous injections on ejaculation and orgasmic function, their early use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term (6). Prostatic massage is safe and easy to use for obtaining semen in men with lesions above T10 (46).

The two most commonly used methods of sperm retrieval in men with SCI are vibrostimulation and transrectal electroejaculation (47-49). Semen retrieval is more likely with vibrostimulation in men with lesions above T10 (50-52). In men with SCI above T6, autonomic dysreflexia often occurs during sexual activity and ejaculation (53,54) so that patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition.

Midodrine may be combined with vibrostimulation in men not responding to vibrostimulation alone. However, electroejaculation is the second choice for sperm retrieval when repeated tries at vibrostimulation have failed (55).

Surgical procedures, such as microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful (56,57).

#### 7.3.1 Sperm quality and motility

The following has been reported about sperm quality and motility:

- Vibrostimulation produces samples with better sperm motility than electrostimulation (47,58).
- Antegrade samples have better sperm motility than retrograde samples.
- Electroejaculation with interrupted current produces better sperm motility than does continuous current (59).
- Bladder management with clean intermittent catheterization may improve semen quality compared to indwelling catheterization, reflex voiding or bladder expression (60).
- Sperm quality in men with SCI is enhanced by processing in able-bodied seminal plasma (61).
- Freezing of sperm is unlikely to improve fertility rates in men with SCI (39).

### 7.3.2 Recommendations

	LE	GR
In men with SCI, vibrostimulation and transrectal electroejaculation are effective methods of sperm retrieval.	3	B
In men with SCI, MESA, TESE or ICSI may be used after failed vibrostimulation and/or transrectal electroejaculation.	3	B
In men with SCI above T6, it is essential to counsel patients at risk and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	3	A

### 7.4 Female sexuality

Most relevant publications on neurogenic female sexual dysfunction are on women with SCI and multiple sclerosis. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life (62-64). Although sexual dysfunction is very common in women with multiple sclerosis, it is still often overlooked by medical professionals and further research is needed to establish effective therapeutic options (65,66).

Studies show that the greatest physical barrier to sexual activity is urinary incontinence. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimize the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others (63,67-69).

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Sildenafil may partially reverse subjective sexual arousal difficulties, while manual and vibratory clitoral stimulation may increase genital responsiveness (70,71). Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder (72), there is a lack of high-evidence level studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive T11-L2 pinprick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm is more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5), even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions (73-75).

Studies have reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services for women with SCI. Affected women were less likely to receive sexual information than men (75-77).

#### 7.4.1 Recommendation

	LE	GR
There is no effective medical therapy for the treatment of neurogenic sexual dysfunction in women.	4	A

### 7.5 Female fertility

There are few studies on female fertility in neurological patients. More than a third (38%) of women with epilepsy had infertility and the relevant predictors were exposure to multiple (three or more) antiepileptic drugs, older age and lower education (78).

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately 6 months after SCI (79), there are no high-evidence level studies. Further investigations using appropriate research methodology are needed (39). About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury (80).

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, anaemia, and autonomic dysreflexia (81,82). Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies (80).



Epidural anaesthesia is chosen and effective for most patients with autonomic dysreflexia during labour and delivery (83,84).

There is very little published data on women's experience of the menopause following SCI (85).

### 7.5.1 Recommendation

	LE	GR
In women with a neurological disease, the management of fertility, pregnancy and delivery requires a multidisciplinary approach tailored to individual patient's needs and preferences.	4	A

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## 8. QUALITY OF LIFE

### 8.1 Introduction

Quality of life (QoL) is a very important aspect of the overall management of patients with neuro-urological disorders (1). The type of bladder management may influence the health-related QoL (HRQoL) in patients with SCI (2). The effectiveness of urological treatment and the urodynamic functionality of the neurogenic bladder have become increasingly determinant of patient QoL (3). QoL is a reflection of the individual's ability to cope with the new life situation (4). Despite the limitations associated with neurological pathology, adequate treatment is possible in most patients and should not interfere with social independence. QoL can be influenced by several factors including family support, adjustment and coping ability, productivity, self-esteem, financial stability, education, and the physical and social environment (5) (LE: 3). Age, sex, ethnicity, and the patient's acceptance of the condition should also be taken into consideration when assessing QoL (6) (LE: 3).

### 8.2 Quality of life assessment

There are no specific QoL questionnaires for neurogenic bladder dysfunction or neuro-urological symptoms. The only validated tools are a generic Visual Analogue Scale (VAS) for symptom bother, and Qualiveen® which is a specific tool for QoL in spinal cord lesion and multiple sclerosis patients. Qualiveen appears to be a discriminative evaluation instrument (3,7-9) and a short form is now available (10).

More commonly, QoL is assessed secondarily by generic HRQoL questionnaires such as the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), Short Form 36 Health Survey Questionnaire (SF-36), Euro Quality of Life-5 Domains (EQ-5D), Short Form 6D Health Survey Questionnaire (SF-6D), or the Health Utilities Index (HUI).

Furthermore, the quality-adjusted life year (QALY) metric quantifies patient outcomes, by weighting years of life spent in a specified health state by a factor representing the value that society or patients place on that health state (11) (LE: 3).

### 8.3 Therapy influence on quality of life

Appropriate therapies should manage symptoms, improve urodynamic parameters, functional abilities and QoL, and avoid secondary complications (8,12). Changes in neuro-urological symptoms appear to be a major determinant of patient QoL (13,14) (LE: 2a).

### 8.4 Conclusions and recommendations

Conclusions	LE
One of the main aims of therapy is to improve quality of life.	1
There is a lack of disease-specific outcome measures assessing HRQoL in patients with neuro-urological symptoms.	

Recommendations	GR
Quality of life should be assessed when evaluating lower urinary tract symptoms in neurological patients and when treating neurogenic bowel dysfunction.	B
The available validated tools are Qualiveen, a specific long- and short-form tool for spinal cord lesion and multiple sclerosis patients and VAS for symptom bother. In addition, generic (SF-36) or specific tools for incontinence (I-QOL) questionnaires can be used.	B

### 8.5 References

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## 9. FOLLOW-UP

### 9.1 Introduction

Neurogenic lower urinary tract dysfunction is often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary (1-24).

Depending on the type of the underlying neurological pathology and the current stability of the uro-neurological symptoms, the interval between initial investigations and control diagnostics may vary and in many cases should not exceed 1-2 years. In high-risk neuro-urological patients this interval may be much shorter. Urinalysis should be performed regularly; the frequency to be guided by patient symptoms. The upper urinary tract should be checked at regular intervals in high-risk patients; at least once every 6 months. In these patients, physical examination and urine laboratory should take place every year. Any significant clinical change warrants further, specialized, investigation.

## 9.2 Recommendations for follow-up

	LE	GR
In high-risk patients, the upper urinary tract should be assessed at least every six months.	4	A
In high-risk patients, physical examination, and urine laboratory should take place every year.	4	A
Any significant clinical changes should instigate further, specialized, investigation.	4	A
Urodynamic investigation is a mandatory baseline diagnostic and in high-risk patients, should be done at regular intervals.	3	A

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## 10. CONCLUSIONS

Neurogenic lower urinary tract dysfunction is a multi-faceted pathology. It requires an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about his/her future.

The urologist or paediatric urologist can select from a wealth of therapeutical options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, a close surveillance is necessary for the patient's entire life.

With these guidelines, we offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as less invasive as possible.

## 11. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

AD	autonomic dysreflexia
CRS	caudal regression syndrome
CVA	cerebrovascular
DLPP	detrusor leak point pressure
DO	detrusor overactivity
DSD	detrusor sphincter dyssynergia
ED	erectile dysfunction
EMG	electromyography, electromyogram
EQ	euro quality
FAP	familial amyloidotic polyneuropathy
FVC	frequency volume chart
GR	grade of recommendation
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HUI	health utilities index
I-QOL	incontinence quality of life instrument
IC	intermittent catheterisation
ICS	international Continence Society
ICSI	intracytoplasmic sperm injection
KHQ	king's health questionnaire
LE	level of evidence
LPP	leak point pressure
LMNL	lower motor neuron lesion
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
MESA	microsurgical epididymal sperm aspiration
MS	multiple sclerosis
NDO	neurogenic detrusor overactivity
NLUTD	neurogenic lower urinary tract dysfunction
PD	parkinson disease
QALY	quality-adjusted life year
QoL	quality of life
SARS	sacral anterior root stimulation
SCI	spinal cord injury
SF	short form
SNM	sacral neuromodulation
UMNL	upper motor neuron lesion
UTI	urinary tract infection
VAS	visual analogue scale
VUR	vesicoureteric reflux

### **Conflict of interest**

All members of the Neuro-Urology Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.