EAU Guidelines on

Neuro-Urology

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Neuro-Urology Guidelines aim 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 represent a state-of-the-art reference for all clinicians, as of the publication date.

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) [1-3]. Readers are advised to consult other EAU Guidelines that may address different aspects of the topics discussed in this document.

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 Panel composition

The EAU Neuro-Urology Guidelines panel consists of an international multidisciplinary group of neuro-urological experts. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/neuro-urology/

1.3 Available publications

A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Neuro-Urology Guidelines. These versions are abridged and therefore may require consultation with the full text version. An updated summary has also been published in European Urology [4]. All are available through the EAU website: http://www.uroweb.org/guideline/neuro-urology/.

1.4 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014, and 2015. For this 2016 print updates were made to:

- Chapter 3.1: The summary table on epidemiology of neuro-urological disorders has been revised. (Table 1);
- Chapter 3.2: The Definitions useful in clinical practice table has been updated (Table 2), as well as Table 3 Definitions useful when interpreting urodynamic studies;
- Chapter 3.3: Diagnostic evaluation, new figures have been included, as well as a new table (Table 4) presenting an overview of available patient questionnaires;
- Chapter 3.4: Non-invasive conservative treatment – inclusion of the systematic review results (Tibial nerve stimulation for treating neuro-urological patients: a systematic review and meta-analysis [5]).

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that coordinates the activity of the urinary bladder and bladder outlet. The part of the nervous system that regulates LUT function is disseminated from the peripheral nerves in the pelvis to highly specialised cortical areas. Any disturbance of the nervous system involved, can result in neuro-urological symptoms. The extent and location of the disturbance will determine the type of LUT dysfunctions, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. Since symptoms and long-term complications do not correlate [6], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high-risk of subsequent complications. The risk of developing upper urinary tract damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida [7]. In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

2.1 Introduction

For the 2016 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

Specific sections were updated by way of systematic reviews based on topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Systematic review results included in the 2016 Neuro-Urology Guidelines update are:

1. Tibial nerve stimulation for treating neurogenic lower urinary tract dysfunction: a systematic review and meta-analysis [5].
2. Transcutaneous electrical nerve stimulation for treating neurogenic lower urinary tract dysfunction: a systematic review [8].
3. Which measures are available to evaluate sexual function/dysfunction in adult neuro-urological patients and which are the most appropriate [9]?

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [10]. Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.
A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications ensuing from the systematic reviews have all been peer-reviewed. The decision for re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Neuro-Urology Guidelines. Ongoing systematic reviews include:

- What is the long-term effectiveness and complication rate for bladder reconstructions/substitution and incontinent urinary diversions in neuro-urological patients?
- In neuro-urological patients, is the long-term use of repetitive intra-detrusor injection of botulinum toxin A clinically and urodynamically effective?
- What are the definitions of urinary tract infections in neurogenic bladder dysfunction?
- What are the benefits and harms of continent catheterisable stomas/tubes to treat bladder emptying difficulties in neuro-urological adult patients?
- What is the prognostic value of urodynamic findings in predicting upper urinary tract damage?
- Alpha-blockers in the treatment of voiding dysfunction in neuro-urological patients.

3. THE GUIDELINE

3.1 Epidemiology, aetiology and pathophysiology

3.1.1 Introduction

Neuro-urological symptoms may be caused by a variety of diseases and events affecting the nervous systems controlling the LUT. The resulting neuro-urological symptoms depend predominantly on the location and the extent of the neurological lesion. There are no exact 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 these for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence. This reflects the variability in the cohort (e.g. early or late stage disease) and frequently small sample sizes, resulting in low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

Suprapontine and pontine lesions and diseases		
Neurological Disease	**Frequency in General Population**	**Type and Frequency of Neuro-Urological Symptoms**
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [11] (10% of cardiovascular mortality).	Nocturia - overactive bladder (OAB) - urgency urinary incontinence (UUI) - detrusor overactivity (DO), (other patterns less frequent) [12]. 57-83% of neuro-urological symptoms at 1 month post stroke, 71-80% of spontaneous recovery at 6 months [13]. Persistence of urinary incontinence (UI) correlates with poor prognosis [14].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%).	6.4% of adults > 65 yrs [15].	OAB - UUI - DO 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [16]. Incontinence 3 times more frequent in geriatric patients with dementia than without [17].
Parkinsonian syndrome Idiopathic Parkinson's disease (IPD): 75-80% of Parkinsonian Syndrome. Non-IPD: Parkinson's-plus (18%): - Multiple system atrophy (MSA), - Progressive supranuclear palsy, - Corticobasal degeneration, - Dementia with Lewy bodies. Secondary Parkinson's (2%)	2nd most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [18]. MSA is the most frequent non-IPD PS.	LUTS frequency 30% at onset, 70% after 5 yrs. Storage phase symptoms: Nocturia (78%) OAB - UUI - DO [19]. OAB and DO at the initial phase, intrinsic sphincter deficiency and impaired contractility appear as the disease progress. Complications of neuro-urological symptoms (infections) account for a major cause of mortality in MSA [20]. Impaired detrusor contractility seems to be the urodynamic finding distinguishing MSA from IPD [21, 22].
Brain tumours	26.8/100,000/yr in adults (> 19 yrs), (17.9 benign, 8.9 malignant) [23].	Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [24].
Cerebral palsy	Cerebral palsy: 3.1-3.6/1,000 in children aged 8 yrs [25].	62% of women and 58% of men with cerebral palsy suffer from UI [26] 70% detrusor overactivity. Recurrent UTI and radiologic abnormalities in > 10% of cases [25, 26].
Lesions and diseases between caudal brainstem and sacral spinal cord		
Spinal cord injury (SCI)	Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million [27].	NDO and DSD (up to 95%) and detrusor underactivity (up to 83%) depending on the level of the lesion [28].
Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [29].	Bladder function is impaired in up to 96% of SB patients [30].

Lesions and diseases of the peripheral nervous system		
Lumbar spine Degenerative disease Disk prolapse Lumbar canal stenosis	Male (5%) and female (3%) > 35 yr have had a lumboscitic episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [31]. Detrusor underactivity up to (83%) [28].
Iatrogenic pelvic nerve lesions	Rectal cancer. Cervical cancer (multimodal therapy, radiotherapy and surgery). Endometriosis surgery.	After abdomino-perineal resection (APR): 50% urinary retention. After total mesorectal excision (TME): 10-30% voiding dysfunction [32].
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy causing neuro-urological symptoms: alcohol abuse, lumbosacral zona and genital herpes, Guillain Barré syndrome, porphyria, sarcoidosis.	Worldwide, prevalence of pharmacologically treated diabetes 8.3% [33].	Urgency/frequency +/- incontinence [34]. Hyposensitive and detrusor underactivity at later phase [34].
Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [35].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [36]. DO: 86% [36]. DSD: 35% [36]. Detrusor underactivity: 25% [36].

3.2 Classification systems

3.2.1 Introduction

Relevant definitions are found in the general ICS standardisation report [1, 2]. Section 3.2.2 lists the definitions from these references, partly adapted, and other definitions considered useful for clinical practice (Tables 2 and 3).

3.2.2 Definitions

Table 2: Definitions useful in clinical practice

Autonomic dysreflexia	Autonomic dysreflexia is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction at or above level T6. It is defined as an increase in SBP ≥ 20mmHg from baseline [37]. Autonomic dysreflexia may be symptomatic (headache, blurred vision, stuffy nose, piloerection, flushing, sweating above the lesion level (vasodilatation), pale and cold skin (vasoconstriction) below the lesion level or asymptomatic (silent).
Bladder expression	Various manoeuvres aimed at increasing intravesical pressure in order to facilitate bladder emptying (abdominal straining, Valsalva's manoeuvre and Crede´s manoeuvre) [3].
Bladder reflex triggering	Various manoeuvres performed by the patient or the therapist in order to elicit reflex detrusor contraction by exteroceptive stimuli (suprapubic tapping, thigh scratching and anal/rectal manipulation) [3].

Bladder sensation, absent	*During history taking*, the patient reports no sensation of bladder filling or desire to void [3]. *During filling cystometry*, the patient has no bladder sensation [3].
Bladder sensation, normal	*During history taking*, the patient is aware of bladder filling and increasing sensation up to a strong desire to void [3].
First sensation of bladder filling	The feeling, during filling cystometry, when the patient first becomes aware of the bladder filling [3]. *During filling cystometry*, can be judged by the three following defined points and evaluated in relation to the bladder volume at that moment and in relation to the patient's symptomatic complaints [3].
First desire to void	The feeling, during filling cystometry, that would lead the patient to pass urine at the next convenient moment, but voiding can be delayed if necessary [3].
Strong desire to void	Persistent desire to void, during filling cystometry, without the fear of leakage [3].
Bladder sensation, increased	*During history taking*, the patient feels an early and persistent desire to void [3]. *During filling cystometry*, an early first sensation of bladder filling (or an early desire to void) and/or an early strong desire to void, which occurs at low bladder volume and which persists. It is a subjective assessment, not possible to quantify [3].
Bladder sensation, non-specific	*During history taking*, the patient reports no specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity [3]. *During filling cystometry*, may make the patient aware of bladder filling, for example, abdominal fullness or vegetative symptoms [3].
Bladder sensation, reduced	*During history taking*, the patient is aware of bladder filling but does not feel a definite desire to void [3]. *During filling cystometry*, a diminished sensation throughout bladder filling [3].
Catheterisation	Technique for bladder emptying employing a catheter to drain the bladder or a urinary reservoir [3].
Catheterisation, indwelling	An indwelling catheter remains in the bladder, urinary reservoir or urinary conduit for a period of time longer than one emptying [3].
Catheterisation, intermittent (IC)	Drainage or aspiration of the bladder or a urinary reservoir with subsequent removal of the catheter [3]. When not specified "self", it is performed by an attendant (e.g. doctor, nurse or relative).
Aseptic IC	Use of a sterile technique. This implies genital disinfection and the use of sterile catheters and instruments/gloves [3].
Clean IC	Use of a clean technique. This implies ordinary washing techniques and use of disposable or cleansed reusable catheters [3].
Intermittent self-catheterisation	Performed by the patient him/herself [3].
Daytime frequency, increased	Complaint by the patient who considers that he/she voids too often by day. This term is equivalent to pollakiuria used in many countries [3]. Many population-based studies of OAB have defined frequency as either eight or more voids/day, or eight or more voids/24 h [38].
Diary, bladder	Records the times of micturitions and voided volumes, incontinence episodes, pad usage and other information such as fluid intake, the degree of urgency and the degree of incontinence [3].
Frequency volume chart (FVC)	Records the volumes voided as well as the time of each micturition, day and night, for at least 24 hours [3].
Micturition time chart	Records only the times of micturitions, day and night, for at least 24 hours [3].
Enuresis	Any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective "nocturnal" [3].
Hesitancy	Difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine [3].

Intermittent stream (Intermittency)	Urine flow which stops and starts, on one or more occasions, during micturition [3].
Motor neuron lesion, lower (LMNL)	Lesion resulting from damage to motor neurons of the ventral horns or motor neuron of the cranial nerve nuclei, or resulting from interruption of the final common pathway connecting the neuron via its axon with the muscle fibres it innervates (the motor unit) [3].
Motor neuron lesion, upper (UMNL)	Lesion resulting from damage to cortical neurons that give rise to corticospinal and corticobulbar tracts. It may occur at all levels of the neuraxis from the cerebral cortex to the spinal cord. When rostral to the pyramidal decussation of the caudal medulla, they result in deficits below the lesion, on the contralateral side. When caudal to the pyramidal decussation, they result in deficits below the lesion, on the ipsilateral side [39].
Neurogenic shock	Loss of vascular tone in part of the body deprived of supraspinal control. It commonly occurs during the acute period following spinal cord injury (SCI) and is associated with failure of the sympathetic nervous system. In this condition, systolic blood pressure < 90 mmHg in the supine posture is not the result of low intravascular volume (e.g. blood loss, dehydration, sepsis, cardiac disorders) [37].
Spinal shock	Characterised by marked reductions in spinal reflex activity below the level of injury [37].
Nocturia	The complaint that the individual has to wake at night one or more times to void [3]. Each void is preceded and followed by sleep.
Nocturnal polyuria	It is present when an increased proportion of the 24-hour output occurs at night (normally during the 8 hours whilst the patient is in bed). The night time urine output excludes the last void before sleep but includes the first void of the morning [3].
Neurogenic lower urinary tract dysfunction (NLUTD)	Lower urinary tract dysfunction (LUTD) secondary to confirmed pathology of the nervous supply.
Orthostatic hypotension	Symptomatic (dizziness, headache or neck ache, fatigue) or asymptomatic decrease in blood pressure defined as a drop of at least 20mmHg systolic or 10mmHg diastolic within 3 minutes of moving from the supine to an upright position [3, 38].
Overactive bladder syndrome (also urge syndrome or urgency-frequency syndrome)	Urgency, with or without urge incontinence, usually with frequency and nocturia [3].
Pain, genital and lower urinary tract	Abnormal sensations felt by the individual as pain, discomfort and pressure. Should be characterised by type, frequency, duration, precipitating and relieving factors and by location.
Bladder pain	*During history taking*, pain that is felt suprapubically or retropubically, and usually increases with bladder filling, it may persist after voiding [3]. *During filling cystometry*, is an abnormal finding [3].
Pelvic pain	Is less well defined than, for example, bladder, urethral or perineal pain and is less clearly related to the micturition cycle or to bowel function and is not localised to any single pelvic organ [3].
Perineal pain	In females, between the posterior fourchette (posterior lip of the introitus) and the anus. In males, between the scrotum and the anus [3].
Scrotal pain	May or may not be localised, for example to the testis, epididymis, cord structures or scrotal skin [3].
Urethral pain	Pain that is felt in the urethra and the individual indicates the urethra as the site [3].
Vaginal pain	Is felt internally, above the introitus [3].
Vulvar pain	Is felt in and around the external genitalia [3].
Pelvic organ prolapse	Descent of one or more of the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Absence of prolapse is defined as stage 0 support; prolapse can be staged from stage I to stage IV [3].

Slow stream	Perception of reduced urine flow, usually compared to previous performance or in comparison to others [3].
Spinal cord injury	Incomplete: if partial preservation of sensory and/or motor functions is found below the neurological level and includes the lowest sacral segment. Complete: when there is an absence of sensory and motor function in the lowest sacral segment [40].
Cauda equina	Injuries affecting the cauda equina and generally causing an acontractile or lower motor neuron picture affecting LUT, distal bowel and sexual function [37].
Conal	Injuries affecting the conus medullaris of the spinal cord and often causing a mixed lesion to LUT, distal bowel and sexual functions with a resultant either overactive or acontractile picture [37].
Supraconal	Injuries occurring above the conus medullaris. In general, supraconal injuries cause an overactive or upper motor neuron pattern of damage affecting LUT, distal bowel and sexual functions [37].
Straining to void	Muscular effort used to either initiate, maintain or improve the urinary stream [3].
Terminal dribble	Prolonged final part of micturition, when the flow has slowed to a trickle/ dribble [3].
Urgency	The complaint of a sudden compelling desire to pass urine which is difficult to defer [3].
Urinary incontinence (UI)	Complaint of any involuntary leakage of urine [3].
Stress urinary incontinence	Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [3].
Urge urinary incontinence	Complaint of involuntary leakage accompanied by or immediately preceded by urgency [3].
Mixed urinary incontinence	Complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing [3].
Continuous urinary incontinence	Complaint of continuous leakage [3].
Voided volume, maximum	The largest volume of urine voided during a single micturition which is determined either from the frequency/volume chart or bladder diary [3].

Table 3: Definitions useful when interpreting urodynamic studies.

Bladder compliance	Relationship between change in bladder volume and change in detrusor pressure. Compliance is calculated by dividing the volume change (ΔV) by the change in detrusor pressure (Δpdet) during the change in bladder volume (C=V. Δpdet). It is expressed in mL/cm H_2O [3].
Bladder filling, artificial	Filling the bladder, via a catheter, with a specified liquid at a specified rate [3].
Bladder filling, natural	The bladder is filled by the production of urine rather than by an artificial medium [3].
Bladder outlet obstruction	Generic term for obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure [39].
Cystometric capacity	The bladder volume at the end of the filling cystometrogram, when "permission to void" is usually given. The volume voided together with any residual urine [3].
Maximum anaesthetic bladder capacity	The volume to which the bladder can be filled under deep general or spinal anaesthetic and should be qualified according to the type of anaesthesia used, the speed, the length of time, and the pressure at which the bladder is filled.
Maximum cystometric capacity	In patients with normal sensation, is the volume at which the patient feels they can no longer delay micturition (has a strong desire to void) [3].

Detrusor function, normal	Allows bladder filling with little or no change in pressure. No involuntary phasic contractions occur despite provocation [39]. Normal voiding is achieved by a voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span, and in the absence of obstruction. For a given detrusor contraction, the magnitude of the recorded pressure rise will depend on the degree of outlet resistance [3].
Detrusor overactivity	Urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [3].
Detrusor overactivity incontinence	Incontinence due to an involuntary detrusor contraction [3].
Idiopathic detrusor overactivity	When there is no defined cause [3].
Phasic detrusor overactivity	Is defined by a characteristic wave form and may or may not lead to UI [3].
Neurogenic detrusor overactivity	When there is a relevant neurological condition is present [3].
Terminal detrusor overactivity	A single, involuntary detrusor contraction, occurring at cystometric capacity, which cannot be suppressed and results in incontinence usually resulting in bladder emptying (voiding) [3].
Detrusor sphincter dyssynergia (DSD)	A detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. Occasionally, flow may be prevented altogether [3]. This term is specific to patients with a neurologic diagnosis.
Detrusor underactivity	Contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span [3].
Acontractile detrusor	Detrusor that cannot be demonstrated to contract during urodynamic studies [3].
Dysfunctional voiding	Intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated muscle during voiding in neurologically normal individuals [3].
Filling cystometry	Method by which the pressure/volume relationship of the bladder is measured during bladder filling [3].
Filling rate, physiological	Filling rate less than the predicted maximum - body weight (kg) /4 in mL/min [3, 41].
Filling rate, non-physiological	Filling rate greater than the predicted maximum filling rate [3, 41].
Leak point pressure, abdominal (ALPP)	The intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction [3].
Leak point pressure, detrusor (DLPP)	The lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure [3].
Non-relaxing urethral sphincter obstruction	Characterised by a non-relaxing, obstructing urethra resulting in reduced urine flow. Usually occurs in individuals with a neurological lesion [3].
Post void residual (PVR)	The volume of urine left in the bladder at the end of micturition [3].
Pressure flow study	Method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying [3].
Provocative manoeuvres	Techniques used during urodynamics in an effort to provoke detrusor overactivity, for example, rapid filling, use of cooled or acid medium, postural changes and hand washing [3].
Urethral closure mechanism, incompetent	Allows leakage of urine in the absence of a detrusor contraction [3].
Urethral relaxation incontinence	Leakage due to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity [3].
Urethral closure mechanism, normal	Maintains a positive urethral closure pressure during bladder filling even in the presence of increased abdominal pressure, although it may be overcome by detrusor overactivity.
Urethral pressure	The fluid pressure needed to just open a closed urethra [3].
Urethral pressure, maximum	The maximum pressure of the measured profile [3].

Urethral pressure profile	A graph indicating the intraluminal pressure along the length of the urethra [3].
Urethral closure pressure profile	Is given by the subtraction of intravesical pressure from urethral pressure [3].
Urethral closure pressure, maximum (MUCP)	The maximum difference between the urethral pressure and the intravesical pressure [3].
Urethral functional profile length	The length of the urethra along which the urethral pressure exceeds intravesical pressure in women [3].
Urethral pressure “transmission” ratio	The increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure [3].
Urodynamic stress incontinence	The involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction [3].
Urodynamic study, ambulatory	Functional test of the lower urinary tract, utilising natural filling, and reproducing the subject’s every day activities [3].
Urodynamic study, conventional	Normally takes place in the urodynamic laboratory and usually involve artificial bladder filling [3].

3.3 Diagnostic evaluation

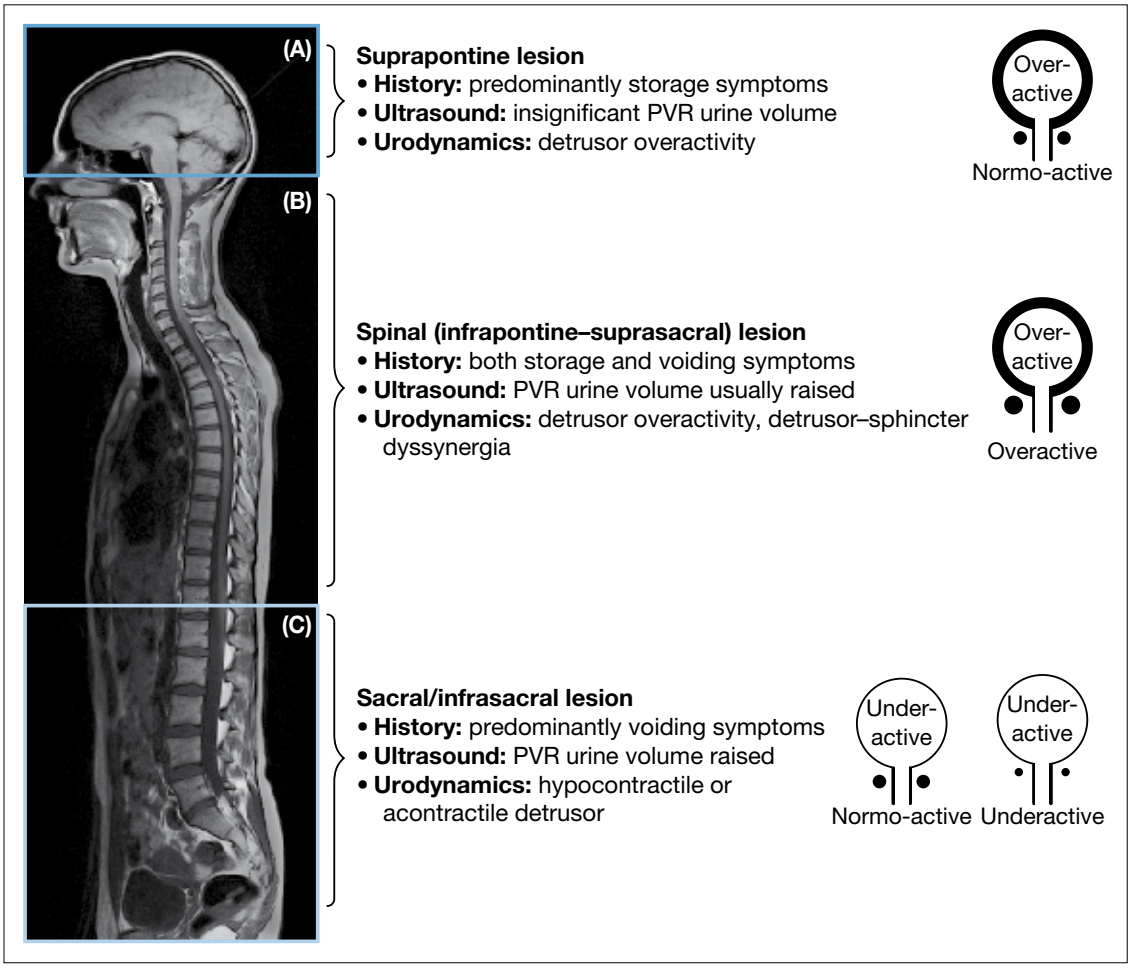
*3.3.1 **Introduction***

The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient’s long-term treatment and follow-up.

*3.3.2 **Classification systems***

The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system for use in daily clinical practice to decide on the appropriate therapeutic approach is provided in Figure 1 [7].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease [7]



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel A denotes the region above the pons, panel B the region between the pons and the sacral cord and panel C the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor–sphincter system. Figure adapted from Panicker et al. [7] with permission from Elsevier. PVR=post-void residual.

3.3.3 Timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders [42]. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [43, 44]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [45, 46]. Early intervention can prevent irreversible deterioration of the LUT and UUT [47].

3.3.4 Patient history

History taking should include past and present symptoms and disorders (Table 4). It is the cornerstone of evaluation, as the answers will aid in diagnostic investigations and treatment options.

- In non-traumatic neuro-urological patients with an insidious onset, a detailed history may find that the condition started in childhood or adolescence [48].
- Urinary history consists of symptoms associated with both urine storage and emptying.
- Bowel history is important because patients with neuro-urological symptoms may also have related neurogenic bowel dysfunction [49].
- Sexual function may be impaired because of the neuro-urological condition [50].
- Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) requiring further investigation.
- Patients with SCI usually find it difficult to report UTI-related symptoms accurately [51, 52].
- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive for an underlying neurological disease or condition.

Table 4: History taking in patients with suspected neuro-urological disorder

Past history
Childhood through to adolescence and into adulthood
Hereditary or familial risk factors
Specific female: Menarche (age); this may suggest a metabolic disorder
Obstetric history
History of diabetes
Diseases, e.g. multiple sclerosis, parkinsonism, encephalitis, syphilis
Accidents and operations, especially those involving the spine and central nervous system
Present history
Present medication
Lifestyle (smoking, alcohol and drugs); may influence urinary, sexual and bowel function
Quality of life
Specific urinary history
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 (catheterisation)
Frequency, voided volume, incontinence, urgency episodes
Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area
Specific male: erection, (lack of) orgasm, ejaculation
Specific female: dyspareunia, (lack of) orgasm
Bowel history
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digitation)
Neurological history
Acquired or congenital neurological condition
Mental status and comprehension
Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
Spasticity or autonomic dysreflexia (especially in lesions at or above level Th 6)
Mobility and hand function

3.3.4.1 Bladder diaries

Bladder diaries provide data on the number of voids, voided volume, pad weight, incontinence and urgency episodes. Although a 24-hour bladder diary (recording should be done for three consecutive days) is reliable in women with UI [53, 54], no research has been done on bladder diaries in neuro-urological patients. Nevertheless, bladder diaries are considered a valuable diagnostic tool.

3.3.5 ***Patient quality of life questionnaires***

An assessment of the patient's present and expected future quality of life (QoL) is important to evaluate the effect of any therapy. QoL is an essential aspect of the overall management of neuro-urological patients, for example when evaluating treatment related changes on a patient's QoL [55]. The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI [56]. Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neuro-urological patient in determining patient QoL [57].

In recent years a proliferation in the number of questionnaires to evaluate symptoms and QoL has been seen. Condition-specific questionnaires can be used to assess symptom severity and the impact of symptoms

on QoL. A patient's overall QoL can be assessed using generic questionnaires. It is important that the questionnaire of choice has been validated in the neuro-urological population, and in the language that it is to be used in.

3.3.5.1 Questions

- Which validated patient questionnaires are available for neuro-urological patients?
- Which questionnaires are the most appropriate for use in neuro-urological patients?

3.3.5.2 Evidence

Three condition-specific questionnaires for urinary or bowel dysfunction and QoL have been developed specifically for adult neuro-urological patients [58]. In MS and SCI patients the Qualiveen [59, 60] is validated and can be used for urinary symptoms. A short form of the Qualiveen is available [59, 60] and it has been translated into various languages [61-64]. The Neurogenic Bladder Symptom Score (NBSS) has been validated in neurological patients to measure urinary symptoms and their consequences [65]. The Quality of Life scoring tool related to Bowel Management (QoL-BM) [66] can be used to assess bowel dysfunction in MS and SCI patients.

In addition, sixteen validated questionnaires evaluating QoL, that also assess urinary symptoms as a subscale or question in neuro-urological patients have been identified [67] (Table 5). The condition-specific Incontinence-Quality of Life (I-QoL) questionnaire which was initially developed for the non-neurological population has now also been validated for neuro-urological patients [68].

A patient's overall QoL can be assessed by generic HRQoL questionnaires, the most commonly used being the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12) [58]. In addition, the quality-adjusted life year (QALY) quantifies outcomes by weighing years of life spent in a specified health state, adjusted by a factor representing the value placed by society or patients on the specific health state [69].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for the validated questionnaires have been assessed.

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [70]	MS	X		X
FILMS [71]	MS	X	X	
HAQUAMS [72]	MS	X	X	X
IQOL [68]	MS, SCI	X		X
MDS [73]	MS	X	X	
MSISQ-15 / MSISQ-19 [74, 75]	MS	X	X	X
MSQLI [76]	MS	X	X	X
MSQoL-54 [77]	MS	X	X	X
MSWDQ [78]	MS	X	X	
NBSS [79]	MS, SCI, Congenital neurogenic bladder	X		
QoL-BM [66]	SCI		X	
Qualiveen/SF-Qualiveen [60, 80]	MS, SCI	X		X
RAYS [81]	MS	X		X
RHSCIR [82]	SCI	X	X	X
Fransceschini [81]	SCI	X	X	X

3.3.6 ***Physical examination***

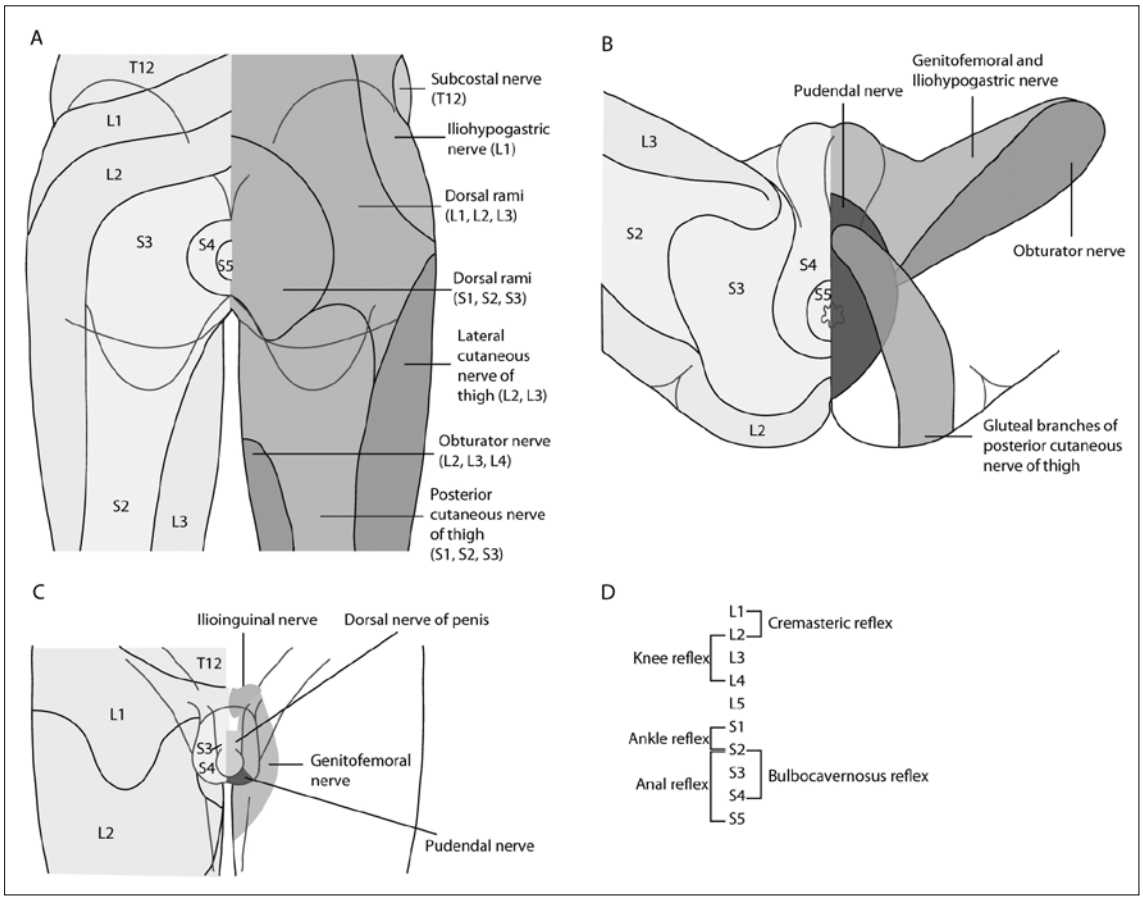
In addition to a detailed patient history, attention should be paid to possible physical and intellectual disabilities with respect to the planned investigations. Neuro-urological status should be described as completely as possible (Figure 2). Patients with a high spinal cord or supraspinal neurological 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.

3.3.6.1 Autonomic dysreflexia

Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction. It generally manifests at or above level T6. The stimulus can be distended bladder or bowel. For example, iatrogenic stimuli during cystoscopy or urodynamics can trigger AD [1]. It can also be secondary to sexual stimulation or a noxious stimulus, e.g. infected toe nail or pressure sore. AD is defined by an increase in systolic blood pressure ≥ 20mmHg from baseline [37] and can have life-threatening consequences if not properly managed [83].

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes [7]



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum [84] (B), male external genitalia [85] (C) and root values of lower spinal cord reflexes (D). Parts A–C adapted from Standring [86], with permission from Elsevier.

Table 6: Neurological items to be specified

Sensation S2-S5 (both sides)
Presence (increased/normal/reduced/absent)
Type (light touch/pin prick)
Affected dermatomes
Reflexes (increased/normal/reduced/absent)
Bulbocavernous reflex
Perianal/anal reflex
Knee and ankle reflexes
Plantar responses (Babinski)

Anal sphincter tone
Presence (increased/normal/reduced/absent)
Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
Prostate palpation
Descensus (prolapse) of pelvic organs

*3.3.6.2 Recommendations for history taking and physical examination**

History taking	LE	GR
An extensive general history is mandatory, concentrating on past and present symptoms including urinary, sexual, bowel, and neurological functions.	4	A
Special attention should be paid to the possible existence of alarm signs, e.g. pain, infection, haematuria, fever, that warrant further specific diagnosis.	4	A
A specific history should be taken for each of the four mentioned functions.	4	A
Quality of life should be assessed when evaluating and treating the neuro-urological patient.	2a	B
The available validated tools are the Qualiveen and I-QoL for urinary symptoms and the QoL-BM for bowel dysfunction for MS and SCI patients. In addition, generic, (SF-36 or KHQ) questionnaires can be used.	1a	A
Physical examination		
Individual patient disabilities should be acknowledged in planning further investigations.	4	A
The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.	4	A
The anal sphincter and pelvic floor functions must be tested.	4	A
Urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.	4	A

** All grade A recommendations are based on panel consensus; I-QoL = incontinence quality of life, MS = multiple sclerosis and SCI = spinal cord injury..*

3.3.7 ***Urodynamics***

3.3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the function and dysfunction of the LUT. In these patients, invasive urodynamic investigation is even more provocative than in general patients. Any technical source of artefacts must be critically considered. It is essential to maintain the quality of the urodynamic recording and its interpretation [1]. Same session repeat urodynamic investigations are crucial in clinical decision making, since repeat measurements may yield completely different results [87].

In patients at risk for AD, it is advisable to measure blood pressure during the urodynamic study [88]. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to ICS technical recommendations and standards [1, 89].

3.3.7.2 Urodynamic tests

Free uroflowmetry and assessment of residual urine: This provides a first impression of the voiding function and is compulsory prior to planning any invasive urodynamics in patients able to void. For reliable information, it should be repeated at least 2-3 times [1]. 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.

Filling cystometry: This is the only method for quantifying the filling function (undertaken at a very slow rate ~20 mL/min). 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 is 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. Possible pathological findings include DO, low bladder compliance, abnormal bladder sensations, incontinence, and an incompetent or relaxing urethra.

Detrusor leak point pressure (DLPP) [90]: This appears to have no use as a diagnostic tool. Some positive findings have been reported [91, 92], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [93, 94].

Pressure flow study: This reflects the co-ordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more powerful if combined with filling cystometry and video-urodynamics. LUT function must be recorded during the voiding phase. Possible pathological findings include detrusor underactivity, BOO, DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [95, 96], non-relaxing urethra, or non-relaxing bladder neck [97, 98]. 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): This 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 (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [99].

Urethral pressure measurement: This has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [100].

Video-urodynamics: This is the combination of filling cystometry and pressure flow study with imaging. It is the gold standard for urodynamic investigation in neuro-urological disorders. Possible pathological findings include all those described in the cystometry and the pressure flow study sections, and any morphological pathology of the LUT and reflux to UUT [101].

Ambulatory urodynamics: This 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. Although this type of study might be considered when conventional urodynamics does not reproduce the patient's symptoms, its role in the neuro-urological patient still needs to be determined [101].

Provocative tests during urodynamics: 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 and lower motor neuron lesions (UMNL/LMNL) [102, 103]. Patients with UMNL develop a detrusor contraction if the detrusor is intact, while patients with LMNL do not. However, the test does not seem to be fully discriminative in other types of patients [104].

Previously, a positive bethanechol test [105] (detrusor contraction > 25 cm H_2O) 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 [106], but there was no published follow-up. Currently, there is no indication for this test.

3.3.7.3 Specialist uro-neurophysiological tests

The following tests are advised as part of the neurological work-up [107]:

- 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.

3.3.7.4 Recommendations for urodynamics and uro-neurophysiology

Recommendations	LE	GR
The recording of a bladder diary is advisable.	3	A
Non-invasive testing is mandatory before invasive urodynamics is planned.	4	A
Urodynamic investigation is necessary to detect and specify lower urinary tract (dys-) function and same session repeat measurement is crucial in clinical decision making.	1b	A
Video-urodynamics is the gold standard for invasive urodynamics in neuro-urological patients. If this is not available, then a filling cystometry continuing into a pressure flow study should be performed.	4	A
A physiological filling rate and body-warm saline should be used.	4	A
Specific uro-neurophysiological tests are elective procedures.	4	C

3.3.8 ***Renal function***

In many patients with neuro-urological disorders, the UUT is at risk, particularly in patients who develop high detrusor pressure during the filling phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity [108]. Patients with SCI or spina bifida have a substantially higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as multiple sclerosis and Parkinson's disease [109].

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. There are no high level evidence publications available which show the optimal management to preserve renal function [110].

3.4 Disease management

3.4.1 ***Introduction***

The primary aims for treatment of neuro-urological symptoms and their priorities are [111, 112]:

- protection of the UUT;
- achievement (or maintenance) of urinary continence;
- restoration of the LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity and possible complications [112].

Renal failure is the main mortality factor in SCI patients who survive the trauma [113, 114]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [115-117] and has consequently become the golden rule in the treatment of patients with neuro-urological symptoms [111, 112].

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance), treatment is aimed primarily at conversion of an overactive, high-pressure bladder into a low-pressure reservoir despite the resulting residual urine [111]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTI [118, 119]. Complete continence can however not always be obtained.

3.4.2 ***Non-invasive conservative treatment***

3.4.2.1 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. Methods to improve the voiding process are therefore practiced.

Bladder expression (Credé manoeuvre) and voiding by abdominal straining (Valsalva manoeuvre): The downwards movement of the lower abdomen by suprapubic compression (Credé) or by abdominal straining (Valsalva) leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction [120, 121]. The latter may increase bladder outlet resistance and lead to inefficient emptying. The high pressures created during these procedures are hazardous for the urinary tract [122, 123]. Their use should therefore be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [124].

Long-term complications are unavoidable for both methods of bladder emptying [121]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence (SUI) [123].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with UMNL can elicit a reflex detrusor contraction [123]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [125]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [126]. All assisted bladder emptying techniques require low outlet resistance. Even then, high detrusor pressures may still be present. Hence, patients need dedicated education and close urodynamic and urological surveillance [123, 127-129].

Note: In the literature, including some of the references cited here, the concept "reflex voiding" is sometimes used to cover all three assisted voiding techniques described in this section.

External appliances: Social continence may be achieved by collecting urine during incontinence, for instance using pads [112]. Condom catheters with urine collection devices are a practical method for men [112]. The infection risk must be closely observed [112]. The penile clamp is absolutely contraindicated in case of DO or low bladder compliance because of the risk of developing high intravesical pressure and pressure sores/ necrosis in cases of altered/absent sensations.

3.4.2.2 Neuro-urological rehabilitation

3.4.2.2.1 Bladder rehabilitation including electrical stimulation

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. 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 [112, 130]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [93]. Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction [131]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [112, 132, 133]. Evidence for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on small non-comparative studies with high risk of bias.

Peripheral temporary electrostimulation: Early data suggest tibial nerve stimulation and transcutaneous electrical nerve stimulation might be effective and safe for treating neurogenic lower urinary tract dysfunction, but more reliable evidence from well-designed RCTs is required to reach definitive conclusions [5, 134, 135].

Peripheral electrostimulation combined with pelvic floor muscle training/biofeedback: In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [136]. Furthermore, this treatment combination is significantly superior to electrostimulation alone. Biofeedback can be used for supporting the alleviation of neuro-urological symptoms [137].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder compliance and bladder filling sensation in patients with incomplete SCI or MMC [138]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [139, 140].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD and MS patients, this technique is still under investigation [141, 142].

Summary: To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation. However, there is a lack of well-designed studies.

3.4.2.3 Drug treatment

A single, optimal, medical therapy for neuro-urological symptoms is not yet available. Commonly, a combination of different therapies (e.g. intermittent catherisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with SCI with a suprasacral lesion or MS [123, 143-147].

3.4.2.3.1 Drugs for storage symptoms

Antimuscarinic drugs: They are the first-line choice for treating neurogenic detrusor overactivity (NDO), increasing bladder capacity and reducing episodes of UI secondary to NDO by the inhibition of parasympathetic pathways [124, 148-154]. Antimuscarinic drugs have been used for many years to treat patients with NDO [151, 152, 155], and the responses of individual patients to antimuscarinic treatment are variable. Only a recent meta-analysis has confirmed the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO [152].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [143, 145, 153, 154, 156, 157]. However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy [152, 153, 156].

Choice of antimuscarinic agent: Oxybutynin [124, 145, 148, 151-154, 158] trospium [152, 156, 159], tolterodine [160-162] and propiverine [148, 152, 163-166] are established, effective and well tolerated treatments even in long-term use [151, 152, 167, 168]. Darifenacin [168] and solifenacin have been evaluated in NDO secondary to SCI and MS [152, 169-172] with results similar to other antimuscarinic drugs. A study using solifenacin in NDO due to Parkinson's disease has recently been completed [173]. The relatively new drug, 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.

Side effects: Controlled release antimuscarinics have some minor side effects, e.g. dry mouth [174]. It has been suggested that different ways of administration may help to reduce side effects. In a selected group of patients, transdermal oxybutynin was found to be well tolerated and effective [175].

Other agents

Beta-3-adrenergic receptor agonist: Have recently been introduced and evaluated in OAB, but clinical experience in neuro-urological patients is limited [176]. Studies on safety and effectiveness in NDO are ongoing [177]. Depending on the results of this studies, combined therapy with antimuscarinics may be an attractive option [178].

3.4.2.3.2 Drugs for voiding symptoms

Detrusor underactivity: Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not frequently used in clinical practice [179]. Only preclinical studies have documented the potential benefits of cannabinoid agonists on improving detrusor contractility when administered intravesically [180, 181]. Conversely, a randomised controlled study on the use of oromucosal nabixinols (an endocannabinoid modulator), did not report any significant reduction of incontinence episodes in MS patients, although a statistically significant improvement in frequency, urgency and nocturia was documented [182].

Decreasing bladder outlet resistance: α-blockers (e.g. tamsulosin and naftopidil) seem to be effective for decreasing bladder outlet resistance, postvoid residual and autonomic dysreflexia [183].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild stress urinary incontinence (SUI), but there are no high-level evidence studies in neurological patients [124].

3.4.2.4 Recommendations for drug treatments

Recommendations	**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.	2	A
Outcomes for NDO may be maximised by considering a combination of antimuscarinic agents.	3	B
To decrease bladder outlet resistance, alpha-blockers could be prescribed.	1b	A
For underactive detrusor, parasympathomimetics should not be prescribed.	1a	A
In neurogenic stress urinary incontinence, drug treatment should not be prescribed.	4	A

NDO = neurogenic detrusor overactivity

3.4.2.5 Minimally invasive treatment

3.4.2.5.1 Catheterisation

Intermittent self- or third-party catheterisation [184, 185] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [111, 112].

Sterile IC, as originally proposed by Guttmann and Frankel [184], significantly reduces the risk of UTI and bacteriuria [112, 186, 187], compared with clean IC introduced by Lapides *et al.* [185]. However, it has not yet been established whether incidence of UTI, other complications, or user satisfaction are affected by sterile or clean technique, coated or uncoated catheters or by any other strategy. Sterile IC cannot be considered a routine procedure [112, 187].

Aseptic IC is an alternative to sterile IC [188].

Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients [112, 189-192]. The average frequency of catheterisations per day is 4-6 times [193] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of 5 times showed a reduction of UTI [193]. Ideally, bladder volume at catheterisation should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI [112, 194-202]. 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 [203].

3.4.2.5.2 Recommendations for catheterisation

Recommendations	**LE**	**GR**
Intermittent catheterisation - 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 catheterisation should be avoided.	3	A

IC = intermittent catheterisation

3.4.2.5.3 Intravesical drug treatment

To reduce DO, antimuscarinics can also be administered intravesically [204-208]. The efficacy, safety and tolerability of intravesical administration of 0.1% oxybutynin hydrochloride compared to its oral administration for treatment of NDO has been demonstrated in a recent randomised controlled study [208]. This approach may reduce adverse effects because the antimuscarinic drug is metabolised differently [205] and a greater amount is sequestered in the bladder, even more than with electromotive administration [204].

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 [209-211]. 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 a patient refractory to capsaicin. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A (BTX-A) injections in the detrusor [210]. Currently, there is no indication for the use of these substances, which are not licensed for intravesical treatment.

3.4.2.5.4 Botulinum toxin injections in the bladder

BTX-A causes a long-lasting but reversible chemical denervation that lasts for about 9 months [212, 213]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. BTX-A has been proven effective in patients with neuro-urological disorders due to MS or SCI in phase III RCTs [214-216] and systematic reviews [217, 218]. Repeated injections seem to be possible without loss of efficacy [212, 216, 219]. The most frequent side effects are UTIs and elevated PVR [215, 216]. IC may become necessary. Rare but severe adverse events include autonomic dysreflexia and respiratory problems. Generalised muscular weakness may occur [212, 215, 219].

3.4.2.5.5 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the UUT. This can be achieved by chemical denervation of the sphincter or by surgical interventions (bladder neck or sphincter incision or urethral stent). Incontinence may result and can be managed by external devices (see Section 3.4.2.1).

BTX-A: 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 has been reported to be high and with few adverse effects [220-222]. However, a recent Cochrane report concluded that because of limited evidence future RCTs assessing the effectiveness of BTX injections also need to address the uncertainty about the optimal dose and mode of injection [223]. In addition, this therapy is not licensed.

Balloon dilatation: Favourable immediate results were reported [224], but there are no further reports since 1994 so 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 [111, 112, 214]. Different techniques are used, and laser treatment appears to be advantageous [225, 226]. Sphincterotomy needs to be repeated at regular intervals in many patients [227], but it is efficient and does not cause severe adverse effects [111, 224]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [228].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [111, 225]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [111].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [112]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [229, 230]. However, the costs [111], possible complications and re-interventions [231, 232] are limiting factors in its use [233-236].

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 [112, 237, 238].

Urethral inserts: Urethral plugs or valves for the 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 were disappointing [239].

3.4.2.5.6 Recommendations for minimal invasive treatment*

Recommendations	LE	GR
Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity in MS or SCI.	1a	A
Bladder neck incision is effective in a fibrotic bladder neck.	4	B

**Recommendations for catheterisation are listed separately under Section 3.4.2.5.2*
MS = multiple sclerosis; SCI = spinal cord injury.

*3.4.3 **Surgical treatment***

3.4.3.1 Bladder neck and urethral procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure. Procedures to treat sphincteric incontinence are therefore suitable only when the detrusor activity can be controlled and when no significant reflux is present. A simultaneous bladder augmentation and IC may be necessary [112].

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-catheterise [112, 240-245]. There is growing evidence that synthetic slings can be used effectively with acceptable medium to long-term results and minimal morbidity in neuropathic patients [246, 247]. In men, both autologous and synthetic slings may also be an alternative [246-250].

Artificial urinary sphincter: This device was introduced by Light and Scott [251] for patients with neuro-urological disorders [112]. It has stood the test of time and acceptable long-term outcomes can be obtained [252-257].

Functional sphincter augmentation: By transposing the gracilis muscle to the bladder neck [258] or proximal urethra [259], there is a possibility to create a functional autologous sphincter by electrical stimulation [258-260]. This opens the possibility of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter procedure [261] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [262] improved by Salle [263], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [112, 264].

Urethral inserts: See section 3.4.2.5.5.

3.4.3.2 Denervation, deafferentation, sacral neuromodulation

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing detrusor overactivity [265-267], but nowadays, it is used mostly as an adjuvant to sacral anterior root stimulation (SARS) [268-272]. Alternatives to rhizotomy are sought in this treatment combination [273-275].

SARS is aimed at producing detrusor contraction. The technique was developed by Brindley [276] 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 [269, 277, 278]. By changing the stimulation parameters, this method can also induce defecation or erection.

Sacral neuromodulation (SNM) [279] might be effective and safe for treating neuro-urological symptoms but there is a lack of RCTs and it is unclear which neurological patient is most suitable [280-282].

3.4.3.3 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 [283] and latissimus dorsi [284] have been used successfully in patients with neuro-urological symptoms [285, 286].

3.4.3.4 Bladder augmentation

The aim of auto-augmentation (detrusor myectomy) is to reduce detrusor overactivity or improve low bladder compliance. The advantages are: low surgical burden, low rate of long-term adverse effects, positive effect on patient QoL, and it does not preclude further interventions [111, 112, 287-293].

Replacing or expanding the bladder by intestine or other passive expandable coverage will improve bladder compliance and at least reduce the pressure effect of detrusor overactivity [294, 295]. Inherent complications associated with these procedures are: recurrent infection, stone formation, perforation or diverticula, possible malignant changes, and for intestine metabolic abnormality, mucus production and impaired bowel function [112, 296-298]. 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 [289, 299-307]. Bladder substitution to create a low-pressure reservoir is indicated in patients with a severely thick and fibrotic bladder wall [112]. IC may become necessary after this procedure.

3.4.3.5 Urinary diversion

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT and for the patient’s QoL [112].

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. A continent stoma can be created using various techniques. However, all of them have frequent complications, including leakage or stenosis. The short-term continence rates are > 80% and good protection of the UUT is achieved [112, 308-320]. For cosmetic reasons,

the umbilicus is often used for the stoma site [315, 318, 319, 321-323].

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 LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [112]. An ileal segment is used for the deviation in most cases [112, 324-327].

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 [112]. The patient must be carefully counselled and must comply meticulously with the instructions [112]. Successful undiversion can then be performed [328].

3.4.3.6 Recommendations for surgical treatment

Recommendations	LE	GR
In order to treat refractory neurogenic detrusor overactivity, bladder augmentation is recommended. Detrusor myectomy is an acceptable alternative in highly selected cases.	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

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection (UTI) is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [321]. There are no evidence-based cut-off values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing IC 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 [321].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [329]. The exact working mechanisms, however, still remain unknown.

The presence of asymptomatic bacteriuria in SCI patients is higher than in the general population, and varies depending on bladder management. Prevalence of bacteriuria in those performing clean IC varies from 23-89% [330]. Sphincterotomy and condom catheter drainage has a 57% prevalence [331]. Asymptomatic bacteria should not be routinely screened for in this population [332].

Individuals with 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 [333]. The most common signs and symptoms suspicious of a UTI in those 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 odour, discomfort or pain over the kidney or bladder, dysuria, or autonomic dysreflexia [333, 334].

3.5.2 Diagnostic evaluation

The gold standard for diagnosis is urine culture and urinalysis. A dipstick test may be more useful to exclude than to prove UTI [335, 336]. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [337].

3.5.3 Disease management

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 [338]. UTI in persons with neuro-urological disorders are by definition a 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 [338]. 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 [339].

3.5.3.1 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, by treating detrusor overactivity by BTX-A injection in the detrusor [340], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [337].

3.5.3.2 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilised. The use of hydrophilic catheters is associated with a lower rate of UTI in a recent meta-analysis [341]. Bladder irrigation has not been proven effective [342].

Various medical approaches have been tested for UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice for the prevention of UTI could not be demonstrated in RCTs [343]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [344]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI [345]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI, and no evidence that recurrent UTIs are reduced [346]. Low-dose, long-term, antibiotic prophylaxis cannot reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [338].

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 [347]. Another possible future option, the inoculation of apathogenic *Escherichia coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data [348], 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, individualised concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine [349]. 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.

*3.5.4 **Recommendations for the treatment of UTI***

Recommendations	LE	GR
Asymptomatic bacteriuria in patients with neuro-urological disorders should neither be screened for nor be treated.	4	A
The use of long-term antibiotics for recurrent UTI 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 individualised since there is no optimal prophylactic measure available.	4	C

UTI = urinary tract infection.

3.6 Sexual (dys)function and fertility

These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [350]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [351, 352]. In neuro-urological patients sexual problems can be identified at three levels: primary (direct neurological damage), secondary (general physical disabilities) and tertiary (psychosocial and emotional issues) sexual dysfunction [353]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [354], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction.

3.6.1 ***Erectile dysfunction (ED)***

3.6.1.1 Phosphodiesterase type 5 inhibitors (PDE5Is)

Questions:

- What is the effectiveness of the various PDE5Is in the different neuro-urological patient groups?
- What common side-effects are described?

Evidence:

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic erectile dysfunction (ED) [350, 355]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10mg was shown to be more effective than sildenafil 50mg. All currently available PDE5Is appear to be effective and safe, although there are no high-evidence level studies in neuro-urological patients investigating efficacy and side effects across different PDE5Is, dosages and formulations [356].

For MS patients two studies reported significant improvement in ED when using sildenafil and tadalafil. One study, however, showed no improvement in ED with sildenafil.

In Parkinson's disease normal erectile function was described in over half of the patients using sildenafil 100mg and a significant improvement in IIEF score was found compared to placebo. While most neuro-urological patients require long-term therapy for ED some have a low compliance rate or stop therapy because of side effects [357, 358], most commonly headache and flushing [355]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/ high-level paraplegia and multiple system atrophy [357, 358]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce 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.

3.6.1.2 Drug therapy other than PDE5I

Fampridine to treat neurogenic spasticity has been shown to be beneficial in improving ED in two domains of the IIEF-15 in SCI and MS patients, however, with a significant discontinuation rate due to severe adverse events [359]. Sublingual apomorfine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [360]. In Parkinson's disease pergolide mesylate showed a significant improvement in IIEF-15 scores up to 12 months follow-up [361].

3.6.1.3 Mechanical devices

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [362-366].

3.6.1.4 Intracavernous injections and intraurethral application

Patients not responding to oral drugs may be offered intracavernous injections (alprostadil, papaverine and phentolamine) that have been shown to be effective in a number of neurological conditions, including SCI, MS, and diabetes mellitus [367-373] but their use requires careful dose titration and some precautions. Complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first-line therapeutic option in patients taking nitrate medications, as well as those with concerns about drug interactions with PDE5Is, or in whom PDE5Is are ineffective. 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 are unclear [357]. Intraurethral alprostadil application is an alternative but a less effective route of administration [373, 374].

3.6.1.5 Sacral neuromodulation

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence level studies are lacking [355].

3.6.1.6 Penile prostheses

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. At a mean follow-up of seven years 83.7% of patients with SCI were able to have sexual intercourse [355]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [375-377].

3.6.1.7 Recommendations for erectile dysfunction

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

ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.

*3.6.2 **Male fertility***

Male fertility can be compromised in the neurological patient by ED, ejaculation disorder, impaired sperm quality or various combinations of these three disorders. Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, spina bifida, MS and SCI [378]. ED is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [378]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [379]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [380].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [381]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [373, 378, 382, 383]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [384-386]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [387, 388]; patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition. In SCI patients the use of oral midodrine can improve sperm retrieval at vibrostimulation [389].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [390].

Surgical procedures, such as, microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful [391, 392]. 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 [393-395].

3.6.2.1 Sperm quality and motility

The following has been reported on sperm quality and motility;

- Bladder management with clean IC may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression [396].
- In SCI patients sperm quality decreases at the early post traumatic phase demonstrating lower spermatozoid vitality (necrospermia) reduced motility (asthenospermia) and leucospermia [391].
- Long-term valproate treatment for epilepsy negatively influences sperm count and motility [397].
- Vibrostimulation produces samples with better sperm motility than electrostimulation [398, 399].
- Electroejaculation with interrupted current produces better sperm motility than continuous current [400].
- Freezing of sperm is unlikely to improve fertility rates in men with SCI [401].

3.6.2.2 Recommendations for male fertility

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, especially at or above Th 6, it is essential to counsel patients at risk and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	3	A

ICSI = intracytoplasmic sperm injection; MESA = microsurgical epididymal sperm aspiration; SCI = spinal cord injury; TESE = testicular sperm extraction.

3.6.3 ***Female sexuality***

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS. 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 [402-404]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [405, 406].

The greatest physical barrier to sexual activity is UI. A correlation has been found between the urodynamic outcomes of low bladder capacity, compliance and high maximum detrusor pressure and sexual dysfunction in MS patients. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimise 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 [402, 407-409].

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Data on sildenafil for treating female sexual dysfunction are poor and controversial [410]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [411], there is a lack of high-evidence level studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive Th 11-L2 pin-prick 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 [412-414].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [410].

Women with SCI reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services and were less likely to receive sexual information than men [412, 415, 416].

3.6.3.1 Recommendation for female sexuality

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

3.6.4 ***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 [417].

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 [418], there are no high-evidence level studies. 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 [419].

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 AD [420, 421]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [419].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [422, 423].

There is very little published data on women's experience of the menopause following SCI [424].
Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [425]. Clinical management should be individualised to optimize both the mother's reproductive outcomes and MS course [426].

3.6.4.1 Recommendation for female fertility

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

3.7 Follow-up

3.7.1 ***Introduction***

Neuro-urological disorders are often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary [110].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological 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 should be much shorter. Urinalysis should be performed regularly; the frequency to be guided by patient symptoms. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; about once every 6 months. In these patients, physical examination and urine laboratory should take place every year. Any significant clinical change warrants further, specialised, investigation. However, there is a complete lack of high-evidence level studies on this topic and every recommendation must be viewed critically in the individual neuro-urological patient [110].

3.7.2 ***Recommendations for follow-up***

Recommendations	LE	GR
In high-risk patients, the upper urinary tract should be assessed at regular intervals.	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, specialised, investigation.	4	A
Urodynamic investigation is a mandatory baseline diagnostic and in high-risk patients, should be done at regular intervals.	3	A

3.8 Conclusions

Neuro-urological disorders have a multi-faceted pathology. They require 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 their future. The 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.

These Guidelines 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 non-invasive as possible.

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5. CONFLICT OF INTEREST

All members of the EAU Neuro-urology Guidelines 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 EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. 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.