Neuro-Urology in Spinal Cord Injury

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Abstract

Storage and evacuation of urine is regulated by a neural control system that precisely coordinates the reciprocal activity of these two functional phases of the lower urinary tract (LUT) to achieve continence and to ensure a periodic, controlled voiding. This complex control system includes the sympathetic, parasympathetic, and somatic nervous system, with close interaction of cortical, subcortical, spinal cord neural networks and peripheral nerves. Damage to spinal cord structures results in a dysfunction of storage and evacuation, which can lead to incontinence, incomplete bladder drainage, and deterioration of the upper urinary tract. A straightforward categorization of neurogenic lower urinary tract dysfunction (NLUTD) is almost impossible due to the heterogeneity of spinal cord injuries (SCI) in terms of segmental levels of injury and completeness. An individual diagnostic and therapeutic approach is mandatory for successful treatment of NLUTD. This chapter summarizes the physiological and pathophysiological aspects of a SCI and the diagnostic and therapeutic approaches in different phases after the SCI. The diagnostic assessment includes noninvasive procedures like clinical examinations and determination of post-voiding residual volume by ultrasound and invasive procedures such as urodynamic investigation and cystoscopy. The therapeutic interventions contain conservative therapies like drugs and percutaneous electrical stimulation and minimal invasive therapies such as injections of onabotulinumtoxin in the detrusor and sacral neuromodulation. In cases of failure of conservative treatment, invasive treatments among them bladder augmentation and implantation of an artificial sphincter might be necessary. A lifelong surveillance of the neuro-urological function of individuals with SCI is highly recommended to avoid complications and irreversible alterations of the lower urinary tract.

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15.1 Introduction

The integrity of the pelvic organs with non-impaired bladder, bowel, and sexual function is crucial for achieving a high quality of life and is an important issue in the rehabilitation process of individuals with spinal cord injury (SCI). Regaining sexual function and bladder and bowel control were rated with high priority in individuals with SCI [3]. Therefore an examination and treatment of a pelvic organ dysfunction as a consequence of SCI is crucial for a high quality of life in these patients and furthermore, to achieve urinary continence and to maintain the integrity of upper urinary tract function. To reach this goal, regular follow-up examinations are recommended to preserve lower urinary tract function and to avoid a deterioration of renal function. Diagnosis of neurogenic lower urinary tract dysfunction and sexual dysfunction and therapeutic procedures are already initiated during primary rehabilitation. Based on the lesion level, completeness of the injury, the age and general constitution of the patient, and her or his hand dexterity, an individualized treatment concept is set up. A lifelong care with, e.g., annual control exams of these patients is mandatory to avoid long-term complications.

15.2 Physiology and Pathophysiology of the Lower Urinary Tract

The task of the lower urinary tract (LUT) is mainly to store and voluntarily evacuate urine. To fulfill these tasks, a complex cascade of regulation mechanisms at different levels of the central nervous system (CNS) is involved. Supraspinal centers such as the frontal cortex, the pontine micturition center, and the insula are responsible for the voluntary control of micturition [17, 66]. The spinal cord is essential for the transmission of sensory information originating from the LUT to allow for processing of afferent input by supraspinal neural networks. Together with the afferent fibers and the supraspinal centers, descending inhibitory and excitatory efferent fibers from the cortical micturition centers to the lowest sacral segments form a fine-tuned closed loop system to control storage and evacuation of urine.

For the coordinated storage and evacuation of urine, a complex interaction of sympathetic, parasympathetic, and somatic neural networks is required, and the integrity of the connections between cortical, supraspinal centers, and spinal neurons must be preserved. During the storage phase, sympathetic activity is mediated via the hypogastric nerve to inhibit contraction of the detrusor. Furthermore, simultaneous activation of pudendal nerve fibers causes contractions of the internal and external urinary sphincters, thereby achieving continence. The transmission of activity of the pontine micturition center via the spinal cord to suppress detrusor activity is crucial during storage phase (Fig. 15.1a). SCI may destroy these descending inhibitory nerve fibers with the consequence of unsuppressed detrusor overactivity.

In contrast, during the voiding phase, relaxation of the external and internal urethral sphincters is mediated via suppression of the pudendal nerve and inhibition of

the sympathetic activity. The pontine micturition center enables activity of the sacral micturition center to induce a similar detrusor contraction mediated by muscarinic receptors (M2, M3) (Fig. 15.1b).

SCI also affects the efferent and afferent fibers of the LUT, resulting in a disturbed function of it, which is called neurogenic lower urinary tract dysfunction (NLUTD) [54]. Depending on the level and completeness of the lesion, different clinical manifestations (Fig. 15.2) of NLUTD can occur [111]. Neurogenic detrusor overactivity (NDO) is an involuntary contraction of the detrusor muscle which is associated with increasing pressure in the bladder during the storage phase and may result in urinary incontinence. More importantly, in case of a spastic sphincter muscle, elevated intravesical pressures may cause ureter and renal reflux and may have detrimental effects on the integrity of the upper urinary tract. If this condition is over looked and not be treated, it may lead to renal failure [49, 54]. Furthermore, the coordination between detrusor muscle and urethral sphincter can be affected, which can result in detrusor-sphincter dyssynergia (DSD). DSD is a simultaneous contraction of the bladder and urethral sphincter during the voiding phase, which causes a functional obstruction. Consequences are renal damage by either reflux or obstruction of the upper urinary tract. In addition, it can provoke incomplete drainage and elevated post-void residual urine, often leading to recurrent urinary tract infections (UTI).

Lesions of the lumbar or sacral spinal cord are mainly peripheral nerve lesions resulting in an acontractile bladder with insufficient or incomplete drainage. In addition, a flaccid urethral sphincter can cause urinary incontinence. The type of NLUTD is not unambiguously related to a specific lesion level. Furthermore, the type of NLUTD may change within the course of SCI in particular within the first 6 months after SCI. To apply the appropriate conservative or medical therapy, clinical examinations at regular intervals are recommended with shorter intervals within the first year after SCI [54–120].

The schema from Madersbacher (Fig. 15.3) represents an attempt to categorize the different types of NLUTD. Nevertheless, the clinical manifestation and type of the NLUTD are different in each individual patient. Due to the complex interaction between the supraspinal and cortical centers mediating LUT function via the spinal cord, the same lesion level and degree of sensory or motor completeness may not result in the same NLUTD. Differences may be apparent, e.g., in the characteristics of detrusor overactivity (peak vs. plateau), maximum detrusor pressure during storage phase, or overall bladder compliance. The identification of these differences in NLUTD in each individual with SCI is done by a video-urodynamic (VUD) investigation.

Clinical symptoms may be misleading, because even in patients with incomplete lesions and comparable neurological status, symptoms may vary to a large degree from “unaffected, normal” voiding to complete urinary retention. Unfortunately, these symptoms do not correlate with the type and severity of dysfunction, and up to 70 % of the SCI patients presenting with worsening of the pattern of the NLUTD requiring medical treatment do not show additional symptoms [109]. Therefore an exact diagnosis of NLUTD after SCI by video-urodynamic exam is essential.

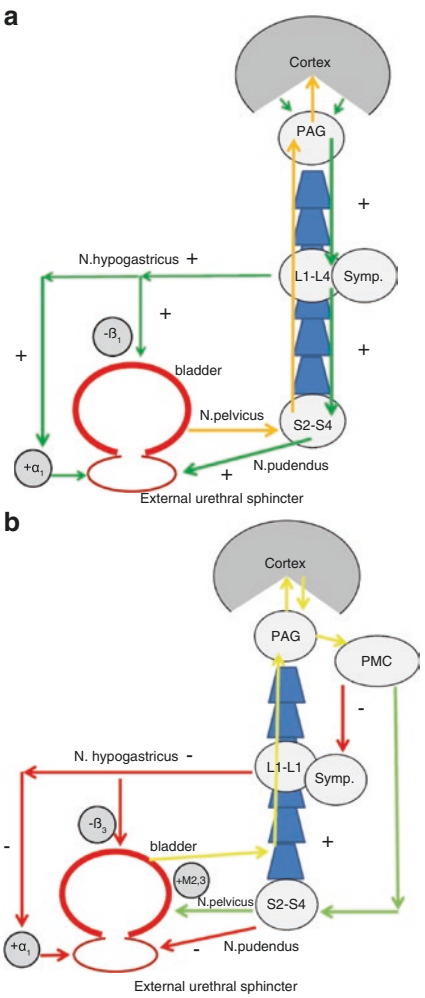

Fig. 15.1 (**a**) Innervation and neural control of the LUT during the storage phase (*Abbreviations*: *N*. nerve, *PAG* periaqueductal gray, *symp*. sympathetic, *L.* lumbar, *S* sacral, $-\beta 3$ beta3-adrenoreceptor inhibition, $+\alpha 1$ −adrenoreceptor 1 activation). (**b**) Neural control of the LUT during the micturition phase (*Abbreviations*: *N.* nerve, *PAG* periaqueductal gray, *symp.* sympathetic, *PMC* pontine micturition center, *L.* lumbar, *S* sacral, *M* muscarinic receptors, $-\beta 3$ beta3-adrenoreceptor inhibition, $+\alpha 1$ − adrenoreceptor 1 activation)

In particular during the first year after trauma, where changes in the neurological status occur, the pattern of the NLUTD can change, and therefore an estimation of the final type and extent of NLUTD is challenging. In the management of NLUTD, the general status, motor impairment, patients' compliance, social circumstance, and patient care after the primary rehabilitation should be taken into account.

Depending on the type of NLUTD, an adequate therapy is essential to maintain a lifelong integrity of the LUT in individuals with SCI. Protection of the upper urinary tract, preservation of renal function, and being continent are crucial for patients' quality of life and participation in daily activities. Therefore, regular and meticulous urologic examinations play a key role in the treatment of patients with chronic SCI.

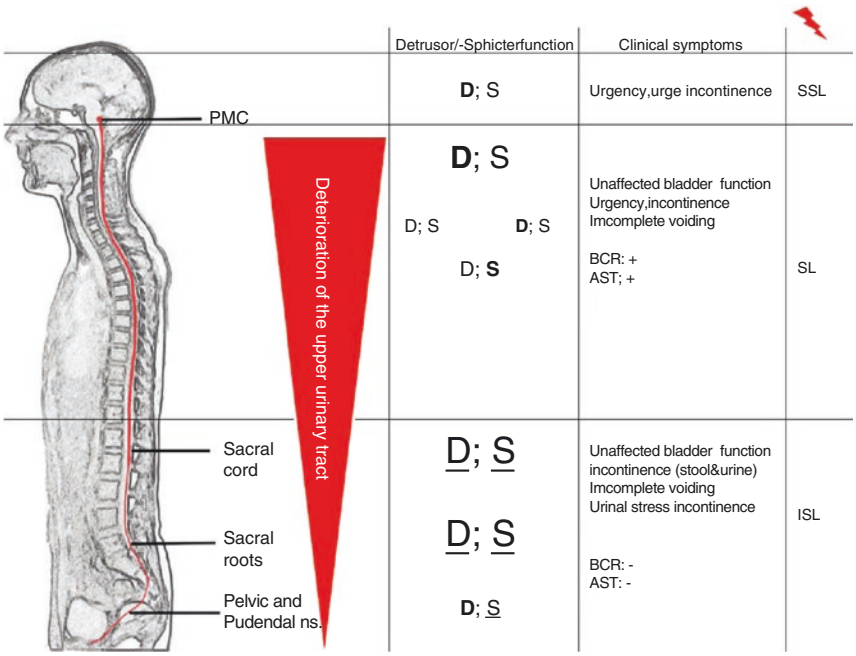

Fig. 15.2 Overview of the pathophysiology of the LUT in SCI (*D* detrusor, *S* sphincter, *SSL* supraspinal lesion, *SL* spinal lesion, *ISL* infraspinal lesion, *BCR* bulbocavernosus reflex, *AST* anal sphincter tone, + positive, – absent). *Underlined letters* stand for "underactive," *normal letters* for "normoactive," and *bold letters* for "overactive." The size of the "D; S" corresponds to the frequency of occurrence

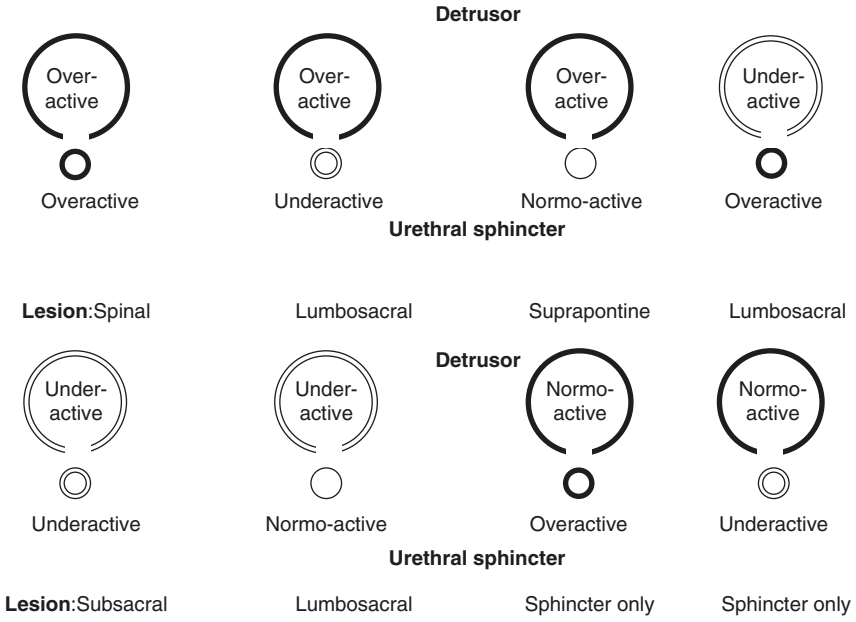

Fig. 15.3 Madersbacher classification of different manifestations of NLUTD

15.3 Diagnostic Procedures

The basic diagnostic approach includes a detailed and complete medical history including the current and previous status of the voiding function (infections, incontinence, hematuria) and surgical interventions at the lower urinary tract, sexual and bowel function, comorbidities, current and previous medication, general health condition, and mental state. Furthermore, the patients' expectations and the aims of the therapy should be discussed.

The physical examination includes palpation of the pelvic region, palpation of the external genital region, prostate exam (men), and testing of sacral reflexes and perianal as well as genital sensations.

Ultrasound of the kidneys and bladder should be a standard procedure to assess renal parenchyma, stone formation, dilatation of the collecting system, and abscess formation. Bladder ultrasound can be used for screening for tumors, stones, and secondary morphologic changes such as a thickened detrusor wall or diverticula. The measurement of detrusor wall thickness represents a useful adjunct tool for the assessment of detrusor function and may evolve to a standard examination in the future [118].

Urine analysis is necessary to indicate UTI. An additional urine culture including the identification of any antibiotic resistance is mandatory in patients with NLUTD, as specific antibiotic treatment is recommended in these patients in order to prevent microbiological resistance [54–120].

Urodynamic investigation is the current "gold standard" to evaluate the LUT function [54–120]. During this investigation, a thin indwelling catheter is used to fill the bladder with saline solution at body temperature with a slow filling speed (<30 ml/min) until the maximum bladder capacity is reached. Simultaneously, the intravesical and the intraabdominal pressures are measured continuously. In addition, the electromyographic activity of the external sphincter muscle is measured via surface electrodes. The procedure of the examination should follow the current guidelines for good urodynamic practices [142]. By using contrast media for bladder filling during the urodynamics together with fluoroscopy (video-urodynamic (VUD) investigation), synchronous, dynamic imaging of the LUT is possible. This procedure allows the detection of secondary changes of the LUT morphology (e.g., bladder stones, diverticula, prostatic influx), vesicoureteral reflux, or detrusor-sphincter/bladder neck dyssynergia. In addition, morphological alterations (e.g., vesicorenal reflux) can be related to functional changes (e.g., detrusor overactivity). The combination of morphologic and functional evaluations is mandatory for treatment stratification and for identification of risk factors for upper urinary tract damage such as low compliance and/or high pressure during the storage phase above 40 cm H_2O [54–120].

Additional examinations such as fluoroscopy of the male urethra, cystoscopy, or other imaging procedures, e.g., transrectal ultrasound, retrograde ureterography, computed tomography (CT), or magnetic resonance imaging (MRI), may be necessary for a thorough diagnosis of unusual clinical presentations. In particular in patients with autonomic dysreflexia, anesthesia may be required for cystoscopy. In

any case, a flexible cystoscope should be used whenever possible to avoid harm to any anatomical structure.

15.3.1 Timing of Diagnostic Procedures During the Acute Phase

During the primary rehabilitation phase, an initial urological evaluation should be established as soon as possible, preferably within the first 2 weeks. After acute care, i.e., after decompression surgery of the spinal cord and stabilization of spine structures, when the patient is in a general condition that allows removal of an indwelling catheter, the bladder management for the first rehabilitation phase needs to be set up. Therefore, a review of the medical history and an ultrasound examination of the lower as well as the upper urinary tract are recommended to exclude any pathological findings on a structural level that may preclude certain treatment options. The initial bladder management regime should be defined based on the results of these evaluations, the general health status of the patient, and associated comorbidities [54].

As a general rule, during the very first days to weeks after SCI – the so-called spinal shock phase – the detrusor is reflexive. Therefore, no risk for detrusor pressure related damage of the upper urinary tract exists. Bladder management procedures in the early phase consist mainly of complete evacuation of the bladder to prevent overdistention and renal damage by obstruction.

After the spinal shock phase, detrusor activity might recur, with the associated risk for incontinence and pressure-related renal damage. Therefore, an initial VUD examination should be performed usually within the first 8 weeks after injury to check for the presence of potential risk factors causing damage to the upper urinary tract.

Depending on the type of NLUTD and the initiated therapy regime, a second urodynamic examination is recommended 8–12 weeks later. This examination is important to evaluate treatment effectiveness if urologic treatment has been established or to detect early signs of a clinically asymptomatic neurogenic detrusor overactivity (NDO).

Depending on the findings of the second VUD, the course of SCI, and the bladder management regime, an additional VUD might be useful at the end of the primary rehabilitation phase at 6 months. In case of unexpected complications or an unfavorable outcome (e.g., recurrent, symptomatic UTIs, new onset of urinary incontinence, increasing post-void residual urine, or autonomic dysreflexia), further examinations are necessary to optimize the bladder management (Fig. 15.4).

15.4 Bladder Management During the Acute Phase

In general, the main focus of NLUTD therapy at any time point after SCI is to protect the integrity of the upper urinary tract namely renal function. Further important aims are achieving continence, avoiding recurrent UTI enabling patients to manage their bladder independently, and adapting the bladder management to the general

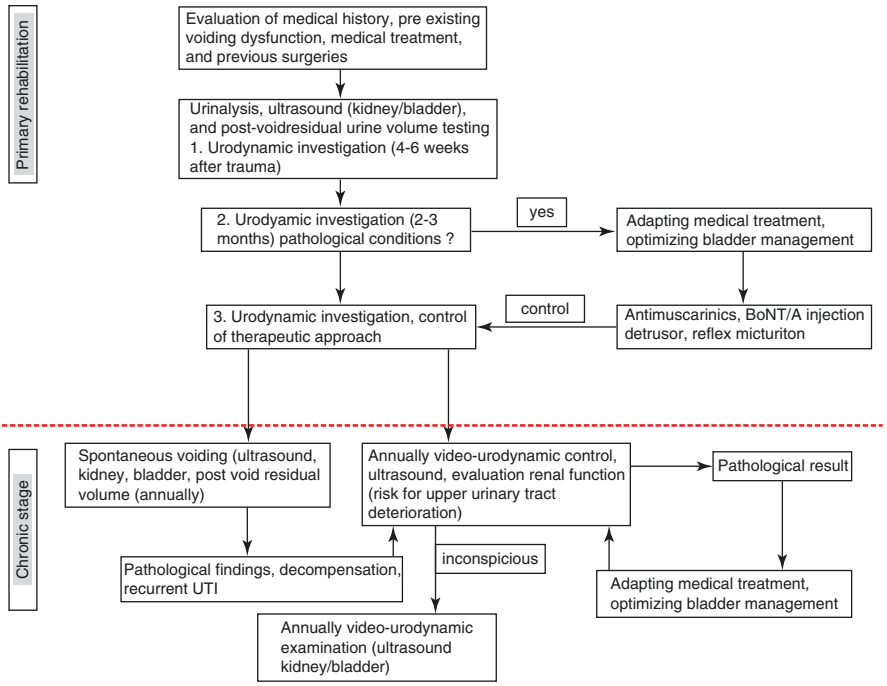

Fig. 15.4 Flowchart of diagnostic procedures in different phases after SCI

condition of the patient. To fulfill these goals, an appropriate bladder management in the acute phase and during the whole primary rehabilitation is crucial.

The primary goal of the bladder management during the acute phase is to ensure a low-pressure urinary drainage without significant residual urine, that is, less than 20 % of the maximum bladder capacity. Initial bladder management immediately after the onset of SCI is commonly an indwelling catheter-either transurethral or suprapubic. To avoid secondary complications, e.g., urethral strictures or recurrent UTI transurethral catheters should be removed and replaced by alternative drainage systems as soon as possible. The intermittent self-catheterization (ISC) is regarded as the optimal bladder evacuation method in cases of insufficient capability to void voluntarily [54–120]. In patients with the inability to perform ISC, either due to comorbidities or due to the extent of motor impairment, assisted catheterization is an alternative. Especially in tetraplegic patients with a lesion level of C4 and above and very limited hand function, ISC is hardly a realistic option. To avoid a permanent suprapubic catheter, the establishment of the reflex voiding with a condom sheet represents an alternative. Patients with motor incomplete lesions (ASIA Impairment Scale (AIS) C and D) may at least partially recover from NLUTD and might regain the ability for spontaneous/voluntary micturition.

The aim of the neuro-urological treatment during primary rehabilitation is to set up and establish procedures for a proper bladder management in each individual patient that reliably protects renal function. Ideally, this treatment should also be convenient, non-invasive, and not time consuming. Due to the probability of neurological recovery during the primary rehabilitation, irreversible surgical interventions should be avoided at this early time point.

Depending on the level and completeness of the lesion, several types of NLUTD occur. Initially, after the onset of SCI, during the so-called spinal shock phase, an acontractile bladder is present. After days to a few weeks, various types of NLUTD may occur, and it has been demonstrated that it is not possible to predict the type of NLUTD. Although in theory, there should be a difference between suprasacral lesions with intact lower motor neurons and lesions of sacral segments with the associated loss of peripheral nerve fibers [29]. Therefore, urodynamic examinations are mandatory for selection of appropriate treatments. An acontractile bladder requires generally no other treatment than evacuation at regular intervals, e.g., by self- or assisted intermittent catheterization (IC). Patients with detrusor overactivity usually need treatment to reduce the elevated detrusor pressure during storage, which will enlarge bladder capacity, lead to continence, and protect renal function. Treatment options may be physical, pharmacological, minimally invasive, or surgical and are discussed in detail in the following paragraphs.

Symptomatic UTI can affect the patients during primary rehabilitation. Especially infections with negative effects on the general health condition may delay the rehabilitation process. In addition, the number of nosocomial infections caused by multi resistant bacteria is constantly increasing [164]. Therefore, meticulous care should be taken to prevent UTI, especially by performing IC under strictly aseptic conditions.

15.4.1 Holistic Rehabilitation Approach

SCI may result in an impairment of motor, sensory, and autonomous functions below the level of lesion. Therefore, SCI does not only lead to NLUTD, but results in limitations of a broad spectrum of activities including mobility and self-care. These functional limitations may represent a barrier for participation in a professional work environment, maintaining social relationships, participating in leisure activities, and being active members of the community. Participation restrictions are highly influenced by environmental factors, e.g. accessibility and availability of adaptive equipment and support [128]. Thus, SCI rehabilitation should comprise all the mentioned aspects. The International Classification of Functioning, Disability and Health (ICF) serves as a comprehensive and universally accepted framework to classify and describe functioning, disability, and health in people with SCI [127]. The ICF comprises four components: body functions, body structures, activities and participation, and environmental factors [128]. Because dedicated SCI care achieves better outcomes than general, nonspecialized care [37, 148], integrative and comprehensive care involving multidisciplinary teams under the supervision of a

physiatrist or a specialist in physical medicine and rehabilitation should be established. The bladder management for an individual with SCI must not be chosen based on the urodynamic data alone, but the aforementioned biopsychosocial factors have to be included in every decision. For example, assisted IC may not be suitable for a tetraplegic male patient returning to work, thus reflex voiding is a more feasible alternative. In patients with brain injuries, antimuscarinic medication may aggravate cognitive dys function; thus onabotulinumtoxin injections may be more appropriate. Surgical interventions during the initial rehabilitation may delay the primary rehabilitation process and should therefore be postponed if other alternatives can still be applied.

15.5 Bladder Management in the Chronic Phase

The ultimate goal of a urologic long-term management of NLUTD is the protection of renal function. An elevated detrusor pressure during storage phase, either due to low bladder compliance or because of detrusor overactivity combined with DSD, is the major risk factor for degradation of renal function [49]. Therefore, the primary goal of the bladder management in these patients is to keep the detrusor pressure low during urine storage and emptying of the bladder [122]. In addition, prevention of secondary morphologic alterations of the lower urinary tract, voluntary bladder emptying at physiologic intervals, continence, and the best possible preservation of quality of life are other important goals of NLUTD treatment. Even in chronic patients, the type of NLUTD is likely to change over time, and clinical symptoms may not reflect the presence of risk factors [109]. As a consequence, urodynamic assessment is mandatory for treatment adaption and risk assessment. A treatment should never be initiated or adapted exclusively only on the basis of clinical symptoms.

A clear recommendation for a cutoff value of the storage pressure that effectively prevents renal damage cannot be easily given. McGuire and coworkers demonstrated that patients with a detrusor leak point pressure less than 40 cm H_2O had a lower risk for upper tract damage compared to patients with a detrusor leak point pressure above 40 cm H_2O [100]. More recently, a storage pressure of less than 30 cm H_2O seems to be most beneficial for the protection of renal function [101]. Besides elevated storage pressure, urinary tract infections and their associated complications are the most significant causes for degradation of renal integrity [152].

Today, detrusor relaxation along with IC is recommended as the standard first-line treatment in patients with neurogenic detrusor overactivity [54–120]. Several methods for detrusor relaxation exist including drug treatment, onabotulinumtoxin injections in the detrusor, and surgical interventions. If the storage pressure can be kept in a physiological range, protection of renal function and in many cases continence can be achieved. In a substantial percentage of patients, however, IC cannot be established, mostly due to the lack of manual dexterity (e.g., in tetraplegic patients) or substantial comorbidities. To avoid indwelling catheters, lowering the outlet obstruction is regarded as a second-line treatment option. By establishing reflex voiding with a reduced outlet resistance, less detrusor force is required,

leading to more effective emptying of the bladder. As a result, fewer UTIs occur, upper urinary tract function is preserved, and – if present – episodes of autonomic dysreflexia are reduced [123]. The disadvantage of this method of bladder management is the urinary stress incontinence, which demands an external urine collecting device, normally a condom catheter, and restricts this treatment strategy usually to male patients.

In selected patients with complete SCI, deafferentation combined with the implantation of an anterior root stimulator can reestablish the capability of urine storage and allow for a user-initiated voiding.

15.6 Treatment of NLUTD

15.6.1 Conservative Treatments

15.6.1.1 Temporary Peripheral Electrical Stimulation

Techniques based on electrical stimulation have not been thoroughly assessed in SCI patients. No comparative studies evaluating the influence of stimulation technique (duration, frequency, impulse width), stimulation site (penile nerve, pudendal, sacral, suprapubic, tibial nerve), and application technique (surface electrodes, rectal/vaginal plugs, needle electrodes) have been performed yet. In acute settings, it has been shown that continuous and conditional stimulation can significantly suppress detrusor overactivity resulting in a higher functional bladder capacity [68] and facilitate voiding. The only long-term study using urodynamic assessments and a follow-up period of 2 years demonstrated long-lasting significant and clinically relevant improvements of the bladder capacity (mean increase of 117.7 ml immediately after stimulation and of 101.6 ml 2 years after the treatment). Post-void residual urine decreased by a mean of 81.9 ml immediately after completion of the 3-month treatment and by a mean of 76.9 ml 2 years after the treatment. Intravesical pressure at maximum flow significantly decreased in 68 % of the study participants. The results were accomplished with 30 transcutaneous stimulation sessions of 15 min duration, using pulsed sinusoidal waveforms (50 Hz) with a pulse duration of 200 ms, pulse pause interval of 1000 ms, and a current intensity of 15–20 mA [131]. Therefore, electrical stimulation, temporary or permanent, definitely holds promise for a better rehabilitation of the lower urinary tract in the future [99]. However, the ideal parameter set and patient group (e.g. only incomplete SCI) still have to be identified.

15.6.1.2 Intermittent Catheterization

In patients with significant residual urine or chronic urinary retention, either due to the NLUTD itself or due to treatment of detrusor overactivity, IC is the treatment of choice [54–120]. IC can be performed either by the patient or by a caregiver, if ISC is not possible due to impairments of the upper extremities, comorbidities or lack of compliance. Whenever possible, ISC should be established. In general, IC is well tolerated. As sterile IC is too time-consuming and expensive to be used as a routine

procedure in daily life, the aseptic or non-touch technique is the method of choice, although no high-level evidence exists that it is associated with a fewer complication rate compared to clean catheterization [129]. The use of hydrophilic catheters is associated with fewer complications, especially UTI in male patients [159]. IC frequency should be individually tailored, aiming at catheterization volumes between 300 and 500 ml, continence, and avoidance of autonomic dysreflexia and/or urgency.

The most frequent complication of IC is UTI. As, however, the different studies evaluating UTI differ in definition criteria, it is difficult to estimate incidence and prevalence of this complication [161]. The avoidance of bladder overdistention by performing IC at regular intervals contributes to the prevention of UTI [160]. Besides UTI, urethral strictures are a common complication in men performing IC. The incidence of urethral strictures increases with a longer follow-up with most events occurring after 5 years of IC [124]. In a recent study from Krebs et al., the long-term (median follow-up 5.9 years) occurrence rate of urethral strictures was 25 % in men using IC ($n=415$), which was significantly higher than in men using other bladder evacuation methods ($n=629$). There was no significant effect of tetraplegia or catheter type on the stricture occurrence rate. Approximately one-third of the men suffering from urethral strictures underwent internal urethrotomies [84]. A history of indwelling catheters or urethral lesions is correlated with a higher incidence of urethral strictures in men performing IC [56].

15.6.1.3 Indwelling Catheters

Despite the mentioned risks of IC, it is regarded as the gold standard for bladder evacuation in SCI patients not being able to voluntarily void effectively. Indwelling catheters bare substantial long-term risks such as vesicoureteral reflux, urethral incompetence and leakage, hydronephrosis, severe autonomic dysreflexia, bladder calculi, labial erosion, hypospadias, and carcinoma of the bladder [10]. The risk for septicemia and death was elevated in persons with indwelling catheters [138]. Comparing the long-term complications of suprapubic (SPC) and transurethral (TC) indwelling catheters in SCI patients, no significant differences in complication rates were detected regarding renal function, bladder stones, UTI, and bladder cancer [72]. The risk for bladder stones is about 25 %, whereas the risk for stone recurrence is elevated in patients with TC compared to those with SPC [8]. In TC, urethral and scrotal complication rates were higher, whereas morbidity related to SPC insertion was higher. If SPC are used, the routine use of anticholinergic medication and clamping of the catheter does not seem to be necessary to preserve detrusor compliance and renal function [116].

15.6.2 Pharmacological Treatment

15.6.2.1 Treatment of Detrusor Overactivity

NLUTD affects the majority of patients with SCI. The main concern in these patients is renal damage as a result of high detrusor storage and voiding pressures

[49] which used to be the most common cause of mortality in SCI [136]. High detrusor pressures result from detrusor overactivity or low bladder compliance, often combined with DSD [25]. Antimuscarinic drugs have therefore become the first-line treatment for alleviating NDO [54–120]. The control of storage and voiding detrusor pressures has resulted in lower mortality rates from urological causes in SCI patients [44]. The efficacy and safety of antimuscarinic drugs, such as oxybutynin, trospium chloride, tolterodine, and propiverine, for the long-term treatment of NDO is well established [54–120]. The antimuscarinic treatment of NDO in SCI patients lasts commonly lifelong, and thus compliance with therapy is an important issue. Unfortunately, SCI patients tend to require higher doses of antimuscarinic drugs than those with idiopathic detrusor overactivity, which in turn may lead to a higher number or more severe adverse events [74] and consequently to abortion of treatment [9, 74]. There is no antimuscarinic drug which has been clearly proven to be superior to others in regard to efficacy-side effect ratio; thus individual testing is mandatory [54]. As protection of the upper urinary tract is the main goal of antimuscarinic treatment, lowering detrusor pressures during the storage phase is essential. Evaluation of treatment efficacy therefore has to be based on urodynamic testing instead of symptoms alone [61]. Until today, only few studies are available on the outcome of antimuscarinic treatments of NDO based on urodynamic assessments in patients with SCI. As all studies differ significantly regarding inclusion and exclusion criteria and duration of treatment, merely head-to-head comparisons can reliably compare the efficacy and tolerability of different antimuscarinic drugs. Significant reduction of detrusor overactivity in patients with SCI has been demonstrated for the traditional antimuscarinic drugs, such as oxybutynin, trospium chloride, propiverine, and tolterodine [41, 97]. More recently, the effectiveness of solifenacin has been proven in SCI patients as well [79], whereas no data on darifenacin or fesoterodine are available.

As persons with NDO due to SCI may need high-dose antimuscarinic treatment, it is important to know that high-dose treatment, either as a combination of different drugs or by increasing the dose of a single substance, can increase the efficacy without significantly increasing the side effects [2, 67].

Regarding side effects, dry mouth represents consistently the most common complaint; also gastrointestinal adverse events were frequently reported. Other possible, but less frequent, side effects are blurred vision and cardiac adverse events, particularly the increase of heart rate and prolongation of the QT interval. However, there is no evidence that the currently used antimuscarinics increase the risk of cardiac adverse events in general [74].

CNS adverse events, especially cognitive impairment, are of particular concern. Until today, however, the incidence of CNS adverse events described in clinical studies is similar to placebo [74]. The mentioned network meta-analysis by Kessler et al. about adverse events of antimuscarinic drugs (though not specifically performed in SCI patients) came to the conclusion that the side effects of most antimuscarinic drugs available do not differ significantly if applied in the recommended dosage. Only oxybutynin immediate release in a dosage above 10 mg/day seemed to lead to more side effects [74].

Mirabegron, a beta-3-agonist, has recently been introduced for the treatment of non-neurogenic overactive bladder. In this patient cohort, based on the limited number of studies currently available, it seems to be a reasonable alternative to antimuscarinic drugs [22]. However, there is no published experience in patients with SCI, and the drug is currently not licensed for treatment of NDO.

In summary, the best antimuscarinic drug has to be determined in each individual patient, based on its tolerability and efficacy obtained by urodynamic assessment. Frequently, several modifications of both the type and the dosage of the drug are necessary.

15.6.2.2 Treatment of Detrusor Underactivity

Currently, no drug with proven efficacy for the treatment of detrusor underactivity exists. It was demonstrated in a cohort of SCI patients with different levels of lesion (cervical, thoracic, and lumbar) that parasympathomimetic drugs do not lead to an improvement of residual urine and/or voiding dysfunction [90]. As this has been proven for other etiologies of detrusor underactivity as well [7], these drugs should not be considered as a treatment option.

15.6.2.3 Infravesical Obstruction

Although urodynamic testing demonstrated a significant reduction of maximum urethral closure pressure, unselective (phenoxybenzamine) and selective (tamsulosin, terazosin) alpha-blockers have only a limited clinical effect on functional bladder obstruction, resulting in a reduction of residual urine and a decrease in maximum detrusor pressure during voiding [1, 59, 93]. Therefore, their use in the treatment of infravesical obstruction has to be individually assessed, as clinical efficacy may vary considerably. However, these drugs may be useful for the treatment of autonomic dysreflexia, especially phenoxybenzamine [59].

15.6.3 Minimal Invasive Treatments

15.6.3.1 Onabotulinumtoxin for the Treatment of Detrusor Overactivity

If the first-line therapy of detrusor overactivity with antimuscarinics is not effective or intolerable due to side effects, the injection of onabotulinumtoxin in the detrusor muscle can increase the bladder capacity and reduce the elevated detrusor pressure [133]. The use of onabotulinumtoxin for treating neurogenic detrusor overactivity was first published in 2000 [143]. The injection caused a significant improvement in bladder capacity and reduced the elevated detrusor pressure. Since this time, intradetrusor injections of onabotulinumtoxin have become a widely used and well-accepted therapy for neurogenic detrusor overactivity. Since 2012, onabotulinumtoxin became licensed for the treatment of neurogenic detrusor overactivity and is currently licensed in the majority of countries worldwide today. Several different products of onabotulinumtoxin are available, in which units of toxin are not comparable to each other. The exact mechanism of action is not yet completely understood, but a direct

efferent effect with inhibition of the presynaptic acetylcholine release is assumed. Furthermore, effects on a variety of different receptors as well as on the afferent nerve fibers are discussed [4]. Depending on the amount of sensitivity preserved, the injection can be performed under local anesthesia. In patients with unaffected sensitivity or risk for autonomic dysreflexia, the procedure should be performed in general anesthesia. Although for neurogenic detrusor overactivity, 200 IU of onabotulinumtoxin is licensed, the dosages used range between 100 and 300 IU, with 300 IU being the most frequently reported dosage for SCI patients performing IC [140]. The effect lasts for a median period between 6 and 12 months; after this period reinjection is necessary [133]. Although a loss of efficacy in up to 25 % of patients during long-term use is reported in single-case series [114], according to current reviews, repeated injections are possible, with no decrease of efficacy [94]. Urinary tract infections in 57–56 %, bleeding in 2–21 %, and urinary retention in 12–42 % are the most frequent side effects, whereas muscle weakness has been reported only very rarely in patients receiving Botox®, and in about 6 % of patients treated with Dysport®, which is not licensed for NDO treatment [94]. Whether antibody formation plays a role as a possible reason for loss of effectiveness still needs to be clarified [94].

In summary, the treatment of neurogenic detrusor overactivity with intradetrusor onabotulinumtoxin injections is a minimally invasive, safe, and effective treatment. Repeated injections are possible.

15.6.3.2 Sacral Neuromodulation

Sacral neuromodulation (SNM) is a minimally invasive approach for the treatment of LUT dysfunction. SNM consists of a two-stage procedure. In the first phase, electrodes are implanted in the S3 or S4 sacral foramina, and a test stimulation phase is initiated. If SNM with temporary electrodes has been successfully applied, impulse generators for permanent neuromodulation are implanted in a second step; otherwise, the electrodes are explanted. Additional interventions to exchange the impulse generators due to a loss of battery charge are required every 4–8 years, depending on stimulation parameters and energy consumption in the individual patient. Currently, no prognostic factors for the success of SNM exist. Thus, a test phase is inevitable.

The mechanism of action has not been completely identified, but a central modulation of afferent and efferent signals in the spinal cord and supraspinal areas seems to play a crucial role [43]. The central modulation is thought to be responsible for the beneficial effects of SNM in both chronic urinary retention and detrusor overactivity, as in both an altered afferent neuronal input seems to be involved in the pathophysiology. SNM is a well-established treatment option for patients with idiopathic LUTS. A systematic review from 2010, however, came to the conclusion that the number of investigated patients with SNM for the treatment of NLUTD was low with high between-study heterogeneity and that there was a lack of randomized, controlled trials [73]. Therefore, SNM should not be used in SCI patients outside clinical studies. In the meantime, some well-documented retrospective case series exist. In a study presenting data from 24 patients with NLUTD due to incomplete SCI, 13 with chronic retention, 11 with

neurogenic NDO, 5 of the 13 patients with chronic retention voided without relevant residual urine and did not require IC anymore. In patients with NDO combined with DSD, neither objective nor subjective SNM success was observed, whereas in patients with pure NDO, a significant decrease in incontinence and a normalization of urodynamic parameters could be observed [95]. In a retrospective case series with 62 patients suffering from NLUTD (majority multiple sclerosis or incomplete SCI (13 patients each), remaining patients with various neurologic disorders), it was shown that SNM also leads to a significant improvement not only of symptoms but also of urodynamic parameters including improvement of DSD in 8 out of 9 patients [27].

Due to the hypothetical mode of action, SNM seems not be effective in complete SCI, as a central modulation is not possible in these patients [144]. In conclusion, SNM should be considered in incomplete SCI patients with NDO or chronic retention, if alternative treatments fail. SNM seems to be effective in both forms of NLUTD present in SCI patients.

15.6.3.3 Minimal Invasive Treatment of Stress Urinary Incontinence

The artificial urinary sphincter is regarded as the treatment of choice for stress urinary incontinence in patients with SCI. However, despite significant success, the complication rates and the invasiveness of the surgical approach stimulated the search for less invasive techniques. The technique, its efficacy, and complication rates are described in detail further below (see paragraph on surgical interventions).

Recently, several minimally invasive treatment options for stress urinary incontinence have been developed. A variety of different bulking agents have been used. Teflon and carbon-coated beads migrate [113]; collagen demonstrated only moderate short-term success and disappointing long-term results [50]. Tension-free tapes are a possible treatment option mainly in females and rarely in male patients, but the clinical experience in patients with SCI is still limited. The published results for alloplastic transobturator suburethral tapes (TOT) in women with SCI are disappointing [117], whereas the short-term results for transvaginal suburethral tapes seem to be more promising [62]. However, experience with both procedures is limited, and especially in the transvaginal suburethral tapes group, the procedure carries the risk of overcorrection by applying too much tension, which may lead to urethral erosion. Therefore, long-term observations are urgently required before these techniques are routinely used. In men, merely two studies exist with small sample sizes.

In summary, the success rate (improvement and cure) is limited to 65 %, and significant complications such as erosion/migration, device infection or failure, implantation site pain, bladder stone formation, and difficult clean ISC were described [55, 102]. Therefore, the technique should be applied with caution in selected patients only.

Lately, new adjustable minimally invasive balloons (ProACT®, Uromedica Inc., Plymouth, USA) have been introduced in SCI patients as well. Only one study with a limited sample size exists, which is not sufficient to recommend the routine use of

this procedure [102]. Autologous myoblasts and fibroblasts for the treatment of stress incontinence are still at an experimental level [91]. Thus, the artificial sphincter still seems to be the method of choice in patients with neurogenic bladder dysfunction.

15.6.3.4 Minimal Invasive Treatments to Lower Outlet Resistance

Today, detrusor relaxation combined with IC is regarded as standard treatment in patients with NDO due to SCI [109]. However, in a substantial percentage of patients, IC cannot be established, mostly due to lack of manual dexterity. Therefore, lowering the detrusor leak point pressure still is a viable treatment option today, especially in tetraplegic men [123]. As a urine collecting device (condom catheter) is required due to the resulting stress urinary incontinence, these procedures are restricted to male patients. To achieve this goal, external sphincterotomy is regarded as the gold standard today. Long-term follow-up has demonstrated satisfying results in the majority of patients [123]. The indications for external sphincterotomy have been described as hydronephrosis, vesicoureteric reflux, and autonomic dysreflexia or recurrent urinary tract infections due to poor bladder emptying [134]. Today, laser sphincterotomy or incision of the external sphincter with an electric knife in the 12 o'clock position is the most frequently used procedure. The most frequent complications are bleeding, infections, and erectile dysfunction [134]. In long-term follow-up, sphincterotomy failure is not infrequent. Its treatment often consists of either re-sphincterotomy or insertion of a SPC [154]. Re-sphincterotomy rates vary between 32 and 82 % [135, 162]. Furthermore, in long-term follow-up, penile retraction can occur, with subsequent inability to apply a condom catheter.

In patients who are reluctant to undergo irreversible surgery, external urethral stents or onabotulinumtoxin injections in the sphincter provide potentially reversible options for treatment of DSD with success rates comparable to sphincterotomy [28]. Over the recent years, several different stents have been used for the treatment of DSD. Basically, permanent stents with urothelial ingrowth, like the UroLume® (American Medical Systems, Minnetonka, USA), and thermosensitive stents without urothelial ingrowth, like the Memokath® (Pnn Medical, Kvistgaard, Denmark), exist. Thermosensitive stents can easily be removed if necessary. Results of temporary treatments with these stents are favorable [63]. Urothelial ingrowth can be a long-term problem in permanent stents, leading to recurrent endoscopic resections [147, 158]. In addition, removal of these stents can be extremely difficult [158]. Despite encouraging short-term results, the long-term results of Memokath® stents were disappointing. Mehta et al. reported that the overwhelming majority of these stents have to be removed due to encrustation, migration, and unresolved dysreflexia [103]. An average time of 13 months for development of encrustation is described [96]. Therefore, stents are mainly used for evaluation of treatment success. If a temporary stent ensured effective bladder emptying, sphincterotomy can be performed, or a permanent stent can be used [47]. Temporary stents can be used as a long-term solution, but have to be replaced if significant problems occur and are therefore an expensive alternative.

Onabotulinumtoxin injections in the external sphincter are another option for treatment of DSD in patients opting for triggered reflex voiding [125]. However, the results on the outcome of this treatment are contradictory. Whereas one study observed a relevant improvement in comparison to lidocaine injections [34], others were not able to show satisfactory results [86]. In addition, the positive effect is temporary, and repetitive injections are necessary. Thus this technique should be used in carefully selected patients who are not willing to undergo sphincterotomy or stent insertion and who do not complain about repetitive interventions [104].

15.6.4 Surgical Interventions

15.6.4.1 Bladder Augmentation

If conservative or minimally invasive detrusor relaxation fails, augmentation cystoplasty is a frequently used surgical option to obtain adequate bladder capacity and low intravesical pressure. Various augmentation techniques using different materials, most commonly ileum segments, have been described [14]. The reported success rates regarding postoperative urinary continence and patient satisfaction, as well as increased bladder capacity and decreased maximum detrusor storage pressure, are high in patients with NLUTD, with no obvious advantage of one technique over another [16, 53, 58, 75, 130]. The postoperative complications associated with augmentation cystoplasty are the same which may result from any major abdominal surgery including small bowel obstruction. More specifically, formation of urinary tract stones, recurrent urinary tract infections, impaired bowel function, metabolic disturbance, and malignancy are the main inherent long-term complications after augmentation ileocystoplasty [53]

In our own series of 29 SCI patients who underwent bladder augmentation, 20/29 patients (69 %) were continent compared to 2/29 preoperatively. Augmentation cystoplasty resulted in a significant increase in the median bladder capacity (from 240 to 500 ml) and compliance (from 13 to 50 ml/cm H_2O). The median maximum detrusor pressure had decreased significantly from 38 to 15 cm H_2O. Complications were observed in 11/29 (38 %) patients, including paralytic and obstructive ileus, impaired bowel function, bladder stones, dehiscence, metabolic acidosis, and autonomic dysreflexia. Approximately half of the patients affected by complications (6/11) required surgical re-interventions [80].

In summary, protection of renal function, adequate bladder capacity, and low detrusor pressure can be achieved using augmentation ileocystoplasty in patients suffering from refractory NLUTD. The most important caveats in SCI patients are bowel dysfunction, as this complication may aggravate preexisting neurogenic bowel dysfunction. Bowel dysfunction, including malabsorption, diarrhea, flatulence, fecal urgency, and incontinence, has been observed in more than 50 % of patients with NLUTD after augmentation cystoplasty [149]. In addition, as SCI patients undergoing bladder augmentation are often younger than bladder tumor patients, in whom also intestinal segments are incorporated in the lower urinary tract, attention has to be paid to malignancies in the augmented bladder. We start

routine cystoscopic examination of the bladder in asymptomatic patients 3 years after ileocystoplasty [5], based on our experience of short latency periods and the severity of the condition. Metabolic disturbances, such as metabolic acidosis or vitamin B12 depletion, seem to be rare complications of augmentation in SCI patients [150]

In conclusion, augmentation ileocystoplasty represents a valuable surgical option for treatment of low bladder capacity and refractory detrusor overactivity in patients with NLUTD, after conservative and minimal invasive treatment options have failed.

15.6.4.2 Sacral Deafferentation and Sacral Anterior Root Stimulation

Sacral deafferentation and sacral anterior root stimulation by an implantable anterior root stimulator (SDAF/SARS), often referred to as "Brindley procedure," has been developed by G. S. Brindley [24] and D. Sauerwein [141]. The technique has been demonstrated to achieve safe detrusor storage pressures, user-initiated voiding in physiologic intervals, and continence in patients with complete SCI, thus resembling the normal bladder cycle more closely than any other procedure [87, 153]. In addition, positive effects on health-related quality of life [155] and even cost-effectiveness [157] have been demonstrated.

In brief, the technique SDAF/SARS consists of intradural deafferentation of the sacral levels S2 to S5 and implantation of an intradural or extradural anterior root stimulator (Finetech Medical Ltd., Hertfordshire, UK). Resection of the afferent sacral roots leads to detrusor areflexia, whereas stimulation of the efferent roots initiates micturition. As stimulation is initiated by a hand-held control device, micturition is voluntary and catheter-free. In addition, the anterior root stimulator can be used for bowel evacuation in about 80 % of the users.

In our own experience, comprising 137 patients with a mean time between surgery and the most recent follow-up of 14.8 years, the long-term success of SDAF/SARS is remarkable. As a result of decreased detrusor pressure in the storage phase and increased detrusor compliance, SDAF/SARS treatment drastically decreased the number of patients being at risk for upper urinary tract damage by more than 75 %. Mean bladder capacity significantly increased from 272 ml preoperatively to 475 ml at follow-up. Furthermore, the annual UTI rate was significantly decreased by more than 50 %. With renal ultrasound no signs of renal obstruction were detected. At the last follow-up visit, 107 (78.1 %) patients were still using the stimulator [78].

Due to the need of intradural surgery and resecting intact nerves, SDAF/SARS is limited to patients with complete SCI and centers with experience in the procedure. Thus, SDAF/SARS will remain an effective treatment option for refractory NLUTD after failure of conservative and minimally invasive treatment options.

15.6.4.3 Artificial Urinary Sphincter

The most important factor in the treatment of stress urinary incontinence in patients with SCI is the exact diagnosis. If urinary incontinence is not caused by sphincter

insufficiency, but by detrusor overactivity, insertion of an artificial urinary sphincter may well lead to severe upper urinary tract damage. Absence or sufficient suppression of detrusor overactivity is an important prerequisite for the implantation of an artificial sphincter.

The artificial urinary sphincter is regarded as the gold standard for the surgical treatment of stress urinary incontinence in male and female SCI patients. Since its introduction in 1973 [146], it has been continuously improved. In post-prostatectomy incontinence, the bulbar urethra is the preferred cuff implantation site. After SCI, however, patients are mostly wheelchair bound, thus putting their whole body weight on the bulbar urethra. Moreover, fluoroscopy frequently reveals an open bladder neck, especially in patients with infrasacral lesions. Consequently, the prostatic urethra is constantly filled with urine, which may be a possible factor for recurrent infections and prostatic influx in male patients. Therefore, sphincter implantation in patients with SCI is recommended at the bladder neck [11].

Patients with SCI undergoing artificial sphincter implantation seem to be at a higher risk for failure of the implant compared to patients with post-prostatectomy incontinence. In a retrospective comparative study, patients in the neurogenic group had a higher risk of nonmechanical device failure, requirement for reoperation, and poor overall long-term continence rates compared to men with a post-prostatectomy incontinence [106]. After a follow-up of at least 10 years, a continence rate of 75 % in predominantly neurogenic patients was demonstrated, but 48 of 61 patients required at least one revision [45].

In summary, high short-term and long-term continence rates can be achieved by the artificial urinary sphincter in SCI patients, but the complication and revision rates are much higher than in patients post prostatectomy [69]. In patients emptying their bladders by IC, the pump is not needed, because an active opening and closure of the sphincter cuff – the only function the pump is used for – is not necessary in these patients. Using a modified technique, in which a port system was implanted instead of a pump, in 51 SCI patients performing IC, a satisfying long-term outcome (median follow-up 8 years) with an objective continence rate of 70.6 % and a subjective cure rate of 90.2 % was demonstrated. With 35.3 % long-term reoperation rates are lower than in most of the previously reported studies [11].

A flow chart summarizes the therapeutic options (Fig. 15.5)

15.7 Urinary Tract Infection and Prostatitis

UTI are among the most common complications of NLUTD due to SCI. In up to 60 % of SCI patients, symptomatic UTI occur after primary rehabilitation [151]. UTI are the most frequent reason for septicemia in this group of patients and are associated with a significant increase in mortality [12, 40]. Furthermore, symptomatic UTI impair the quality of life of the affected persons [112].

Unfortunately, there is no definition of UTI that is universally accepted. The currently best accepted definition defines UTI in patients with NLUTD as the new onset of sign(s)/symptom(s) accompanied by laboratory findings of a UTI

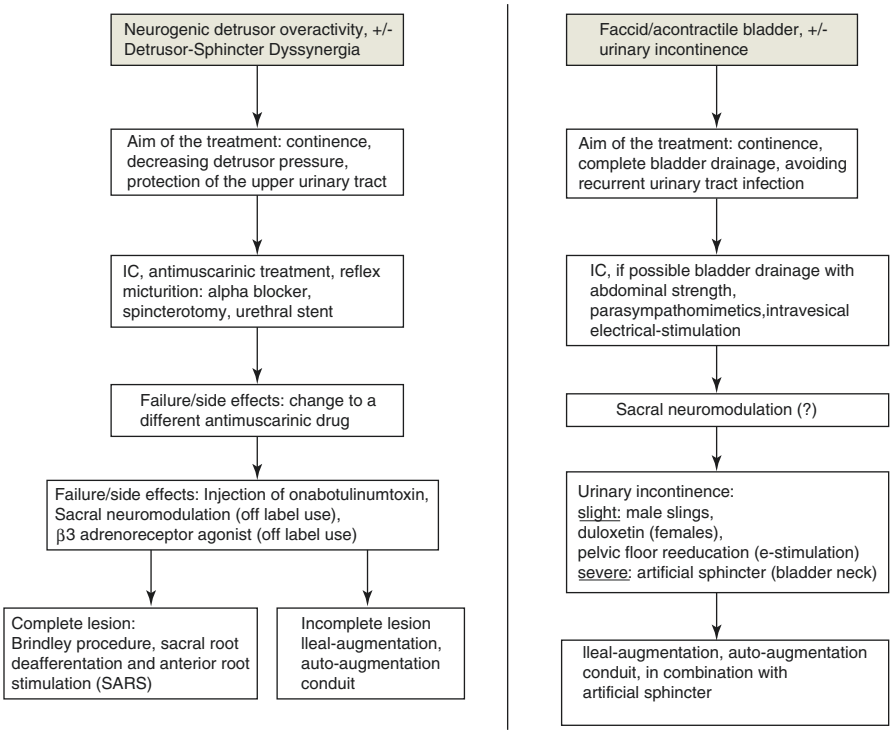

Fig. 15.5 Flowchart of therapeutic procedures of NLUTD

(bacteriuria, leukocyturia, and positive urine culture) [108, 54]. There are no evidence-based cutoff values for the quantification of the laboratory findings.

Individuals 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. The most common signs and symptoms suspicious for a UTI in a person with SCI are fever; new onset or increase in incontinence, including leaking around an indwelling catheter; increased spasticity; malaise; lethargy or sense of unease; cloudy urine with increased urine odor; discomfort or pain over the kidney or bladder; dysuria; or autonomic dysreflexia [51, 112]. As UTIs in patients with SCI are related to the underlying NLUTD, UTIs in this group of patients are by definition complicated UTIs.

The diagnosis is based on symptoms, urine culture, and urine analysis. A dipstick test seems to be more useful to exclude than to prove a UTI [35, 65]. In patients with SCI, resistance patterns and the bacterial strains found may differ from those detected in able-bodied persons; microbiologic testing, including evaluation of the resistance pattern, is strongly advised [13]. As mentioned above, signs and symptoms may differ from those in able-bodied persons. To facilitate symptom-based diagnosis, the International Spinal Cord Society (ISCoS) developed a basic data set in which the most common symptoms are listed [51].

15.7.1 Treatment of UTI

As in able-bodied patients, treatment of asymptomatic bacteriuria should not be performed, as this treatment results in significantly more resistant bacterial strains without influencing the risk for symptomatic UTI [42]. As UTIs in SCI patients are complicated UTIs, a single-dose treatment is not appropriate. The duration of treatment is not well defined. In general, a 5–7-day course of oral treatment with a single substance is advised, if feasible [13]. If urogenital organs (kidney, prostate, testicles) are involved, treatment may be prolonged to 14 days [42]. As the causative bacteria are usually not predictable, urine should be taken for a urine culture prior to antibiotic treatment. If it is mandatory to initiate immediate treatment (e.g., in case of fever, septicemia, intolerable symptoms), antibiotic treatment should be chosen based on individual resistance profiles [36]. As SCI often affects young patients, organ-preserving treatment should be performed if possible. In selected patients with epididymo-orchitis, e.g., testicle, preservation is possible even in the case of intrascrotal abscess formation [120].

15.7.2 Recurrent UTI

Recurrent UTI are frequently defined as more than one episode in the last 6 months or more than two episodes in the last 12 months [6]. In persons with SCI, recurrent UTIs may be related to the underlying NLUTD. Therefore, treatment of NLUTD, e.g., detrusor overactivity, residual urine, or resulting secondary problems like bladder stones, is the first step to avoid recurrent UTI [70]. If possible, indwelling catheters should be avoided.

15.7.3 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilized.

The use of hydrophilic catheters for IC has been demonstrated to be associated with a lower rate of UTI in men, but not in women [26]. Bladder irrigation with various substances, ranging from disinfectants to saline solution, has not been proven effective in the prevention of UTI [156]. However, in patients with ileal pouches, irrigation with tap water had significant impact on bacteriuria [15]. If these results could be replicated in patients with NLUTD, bladder irrigation with tap water may be an alternative technique, especially in patients with indwelling catheters.

The prostate is regarded as a possible source for recurrent UTI in male SCI patients. Recent research could demonstrate that bacteria can be detected in the majority of male SCI patients, but their presence is not related to recurrent UTI [81]. In addition, antibiotic treatment did not lead to bacterial eradication even in SCI patients with bacterial prostatitis [82]. Thus, prevention of recurrent UTI should not comprise treatment of bacteria found in the prostate.

Unfortunately, no evidence-based recommendation for pharmacological prevention of recurrent UTI in SCI patients exists.

The benefit of cranberry juice or cranberry extracts is unclear. Although several small case studies suggested a benefit of cranberry use, the largest randomized controlled trial could not demonstrate a positive effect of cranberry products [88]. As there are huge differences between the different products available (juice, capsules/tablets), especially regarding the concentration of proanthocyanidin, which represents the agent for the antibacterial effect, more studies are needed before a final recommendation can be given. As one of the postulated effects of cranberry products is the reduction of bacterial adhesion to urothelial cells [126], future studies may have to consider also the influence of different bacterial strains on the study results. Other substances frequently used are methenamine hippurate and L-methionine. A Cochrane review came to the conclusion that methenamine hippurate is not effective in individuals with NLUTD [89]. For urine acidification with L-methionine, only a single study with some methodological weaknesses exists, which is not sufficient to support its use [57]. Additionally, the substance may lead to elevated homocysteine blood levels, which is a risk factor for arteriosclerosis [48]. There is one study demonstrating that the bacterial extract OM-89, consisting of immunostimulating components derived from 18 *Escherichia coli* strains, significantly reduces bacteriuria in patients with SCI. However, there was only a nonsignificant trend that the frequency of recurrent UTIs is reduced [60].

Low-dose, long-term, antibiotic prophylaxis is frequently performed. However, this regime does not reduce UTI frequency, but increases bacterial resistance and can therefore not be recommended [42]. Recently, a modified application scheme of antibiotic substances for prophylaxis (weekly cycling oral antibiotics (WOCA)) has been introduced with promising initial results concerning both efficacy and side effects, but the results need to be confirmed in future studies [139].

In summary, as no evidence-based preventive measure for recurrent UTI in patients with SCI exists, the existing methods have to be individually assessed. Initial data imply that additional options may be available in the future. Intravesical inoculation of apathogenic *E. coli* strains has provided positive initial results in small studies which need to be confirmed [30]. In a case series, classical homeopathic treatment provided excellent results which have to be confirmed in a randomized study [119]. In addition, treatment options that were proven to be effective in patients with uncomplicated UTI, e.g., phytotherapy or D-mannose treatment, should be systematically assessed in SCI patients [52, 77]. Finally, new concepts for non-antibiotic antibacterial treatment, as, e.g., bacteriophages, have to be further evaluated in the future [76].

15.8 Sexual Dysfunction

15.8.1 Erectile Dysfunction

The etiology of erectile dysfunction in men with SCI is multifactorial. Although erection is physiologically a result of the parasympathetic innervation of the penis, many other factors, including vascular dysfunctions, medication, depression, or

stress, can contribute to erectile dysfunction. After SCI, psychogenic and reflex erections are possible. A psychogenic erection is usually preserved in patients with an SCI below L3. Reflex erections are generally not possible in patients with injuries from S2 to S4 due to the damage of lower motor neuron axons.

First-line treatment usually consists of oral phosphodiesterase inhibitors, which utilize the nitric oxide-cGMP (cyclic guanosine monophosphate) pathway. This pathway relaxes cavernosal smooth muscle allowing for increased blood flow and in turn creating an erection. Sildenafil, tadalafil, and vardenafil have proven to be comparably efficacious and satisfactory in the treatment of erectile dysfunction in men with SCI [137]. Although some head-to-head comparisons indicate that tadalafil is more effective than sildenafil, especially in patients with lower motor lesions [33], until today there are not enough data available to state that one drug is more effective than the others. Usually, higher dosages are required in men with SCI than in able-bodied patients. Contraindications for phosphodiesterase inhibitors do not differ from those in able-bodied men [145]. However, as men with autonomic dysreflexia due to SCI tend to treat this with nitrates, they have to be specifically counseled not to combine these medications to avoid severe complications [46].

Sildenafil, the most studied drug of the three, has also been shown to be more satisfactory than other treatment options, especially intracorporeal injections and vacuum constriction devices, although intracorporeal injections produced a more rigid erection. However, patients using intracorporeal injections were not satisfied with the route of administration [105]. Intraurethral prostaglandins seem to be less effective than the other mentioned treatment options [18].

Penile implants bare the risk of infections [92] and should therefore be only used in cases where all other treatment options failed and the patients' demands for a therapy are high.

Regarding sensory function, recent studies indicate that a surgical approach connecting the dorsal nerve of the penis to the intact ipsilateral ilioinguinal nerve can restore erogenous penile sensation and improve the quality of sexual health in highly selected patients with absent penile but good groin sensation [110].

15.8.2 Fertility in Men

Male infertility after SCI is characterized by erectile and ejaculatory dysfunction as well as inferior semen quality [21]. The deterioration of semen characteristics appears very early after SCI [31, 98] and mainly affects sperm motility and viability [121]. Long-term cryopreservation results in a significant decrease in sperm motility and viability. Progressive motility and total motility were reduced by 91 % and 84 % to 1 % and 2.5 %, respectively [85]. The ejaculate volume and sperm concentration remain within normal limits, however, in the lower range. Thus, routine long-term cryobanking of semen harvested early after SCI cannot be recommended.

The effects of SCI on semen quality are well described in the literature [21]. The etiology of decreased sperm motility and viability after SCI is still under debate. Although it has been reported that 51 % of men with SCI have at least one hormonal

abnormality [107], there does not seem to be a clear association between hormonal alterations and sperm quality [20]. Spermatogenesis and epididymal function are temperature sensitive, and prolonged sitting in a wheelchair may result in elevated scrotal temperature and consequently in dyspermia [23]. However, ambulatory SCI men also show poor sperm quality [20], and thus elevated scrotal temperature is not likely a relevant contributor to dyspermia after SCI. Balanced accessory gland function is crucial for sperm mobility and viability. In males with SCI, there is evidence of vesicular gland and prostate dysfunction [19, 121]. Furthermore, different biochemical alterations of the seminal fluid have been reported [19]. The seminal fluid of males with SCI may even be toxic for sperm, as it is able to inhibit the motility of sperm from fertile men. In addition, abnormal sperm transport and storage, resulting from autonomic nervous system dysfunction (mainly sympathetic) following SCI, may also contribute to dyspermia [121]. Finally, the altered testicular vascular situation (increased vascular resistance resulting from uninhibited sympathetic activity) may play a role in the development of dyspermia after SCI [83].

As a result of ejaculatory dysfunction, assisted ejaculation is required in more than 90 % of SCI men in order to obtain semen samples [21, 71]. Penile vibratory stimulation is the first-line method for assisted ejaculation, followed by transrectal electrical stimulation for nonresponders [19, 32]. The combined success rate of these two methods ranges between 80 and 90 %.

15.8.3 Fertility in Women

A traumatic SCI does not impair fertility in women. Following a phase of amenorrhea, which occurs in about a third of patients after acute SCI, lasts for about 4 months, and is presumed to be due to a temporary rise in prolactin, reoccurrence of ovulation can be demonstrated, reestablishing the possibility of becoming pregnant for women with SCI [132].

Conclusion

As treatment of NLUTD in patients with SCI is not based on symptoms alone [109], regular controls of upper and lower urinary tract function are mandatory. In SCI patients, this should include video-urodynamic or urodynamic evaluation, bladder ultrasound, and assessment of renal function [54]. Whereas urodynamic examination is standardized, the best method for evaluation of renal function is under debate. Renal ultrasound is useful to detect renal scarring, stones, or dilatation of the collecting system. Regarding blood tests, it is evident that serum creatinine alone is not sufficient, as it is dependent on the muscle mass, which is often reduced in SCI patients. Therefore, serum creatinine levels underestimate the degree of renal damage. The advantage of serum cystatin C levels compared to creatinine is under debate, but most authors regard cystatin C as the superior method in SCI patients [39]. Creatinine clearance is basically a reliable tool, but especially in incontinent patients, urine collection is not always easy.

Renal scintigraphy is the method of choice, as it can assess renal function exactly and separately for each renal unit. However, its availability is limited and it is associated to a radioactive exposure.

Thus, the following strategy can be recommended:

- Within the first 2 weeks after SCI: renal and bladder ultrasound to assess pre-existing morphologic alterations
- After the spinal shock phase (>6 weeks after SCI): video-urodynamics, bladder ultrasound, renal function (serum cystatin C, renal ultrasound)
- 5 months after onset of SCI: urodynamic control
- 9–12 months after injury: (video-)urodynamics, bladder ultrasound, renal function (serum cystatin C, renal ultrasound)

If the assessments mentioned above demonstrate favorable urodynamic results (no risk for renal damage, defined as maximum detrusor pressure < 40 cm H_2O and a detrusor compliance ≥ 20 ml/cm H_2O, normal renal function and normal results on renal ultrasound; [115]), annual controls are scheduled for the first 5 years after SCI. If the controls demonstrate a stable state after 5 years, follow-up intervals can be extended (e.g., every 2 years). If the results are unfavorable (maximum detrusor pressure ≥ 40 cm H_2O or a detrusor compliance < 20 ml/cm H_2O or impaired renal function or abnormal findings on renal ultrasound, [115]), treatment should be initiated, and controls should be performed at shorter intervals until a favorable result has been achieved.

If clinical symptoms, such as recurrent UTI, incontinence, autonomic dysreflexia, decreased bladder capacity, or difficulties in catheterization, occur, a neuro-urological evaluation should be performed as soon as possible. Depending on the symptoms, it should include urodynamic assessment, ultrasound, and cystoscopy, if feasible, and treatment should be initiated.

For treatment of a UTI, urine testing should only be performed if a UTI is suspected due to the presence of clinical symptoms. Regular urinalysis without any clinical symptoms of a UTI may result in a too frequent application of antibiotics and should be discouraged to avoid bacterial resistances.

In patients with indwelling catheters and bladder augmentation, we recommend cystoscopy at regular intervals, initially after 5 years. In augmented bladders other authors suggest a less strict follow-up due to a low incidence of malignancies [64]. In patients with indwelling catheters, the identification of bladder tumors is difficult by cystoscopy alone. Therefore, the best follow-up strategy is still under debate [38, 163].

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