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REVIEW ARTICLE

EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment

Raimund Stein[1] | **Guy Bogaert**[2] | **Hasan S. Dogan**[3] | **Lisette Hoen**[4] | **Radim Kocvara**[5] | **Rien J. M. Nijman**[6] | **Josine S. L. T. Quadackers**[6] | **Yazan F. Rawashdeh**[7] | **Mesrur S. Silay**[8] | **Serdar Tekgul**[3] | **Christian Radmayr**[9]

[1]Department of Pediatric, Adolescent and Reconstructive Urology, Medical Faculty Mannheim, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany

[2]Department of Urology, University of Leuven, Belgium

[3]Division of Pediatric Urology, Department of Urology, Hacettepe University, Ankara, Turkey

[4]Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands

[5]Department of Urology, 1st Faculty of Medicine in Praha, General Teaching Hospital, Charles University, Prague, Czech Republic

[6]Department of Urology and Pediatric Urology, University Medical Centre Groningen, Rijks Universiteit Groningen, Groningen, The Netherlands

[7]Department of Urology, Aarhus University Hospital, Aarhus, Denmark

[8]Division of Pediatric Urology, Department of Urology, Istanbul Medeniyet University, Istanbul, Turkey

[9]Department of Urology, Medical University of Innsbruck, Austria

Correspondence
Raimund Stein, Department of Pediatric, Adolescent and Reconstructive Urology, Medical Faculty Mannheim, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany, Theodor-Kutzer Ufer 1-3, D 68167 Mannheim, Germany.
Email: Raimund.stein@umm.de

Abstract

Background: In childhood, the most common reason for a neurogenic bladder is related to spinal dysraphism, mostly myelodysplasia.

Aims: Herein, we present the EAU/ESPU guidelines in respect to the diagnostics, timetable for investigations and conservative management including clean intermittent catheterization (CIC).

Material and Methods: After a systematic literature review covering the period 2000 to 2017, the ESPU/EUAU guideline for neurogenic bladder underwent an update.

Results: The EAU/ESPU guideline panel advocates a proactive approach. In newborns with spina bifida, CIC should be started as soon as possible after birth. In those with intrauterine closure of the defect, urodynamic studies are recommended be performed before the patient leaves the hospital. In those with closure after birth urodynamics should be done within the next 3 months. Anticholinergic medication (oxybutynin is the only well-investigated drug in this age group—dosage 0.2-0.4 mg/kg weight per day) should be applied, if the urodynamic study confirmed detrusor overactivity. Close follow-up including ultrasound, bladder diary, urinalysis, and urodynamics are necessary within the first 6 years and after that the time intervals can be prolonged, depending on the individual risk and clinical course. In all other children with the suspicion of a neurogenic bladder due to various reasons as tethered cord, inflammation, tumors, trauma, or other reasons as well as those with anorectal malformations, urodynamics—preferable video-urodynamics, should be carried out as soon as there is a suspicion of a neurogenic bladder and conservative treatment should be started soon after confirmation of the diagnosis of neurogenic bladder. With conservative treatment the upper urinary tract is preserved in up to 90%, urinary tract infections are common, but not severe, complications of CIC are quite rare and continence can be achieved at adolescence in up to 80% without further treatment.

Discussion and Conclusions: The transition into adulthood is a complicated time for both patients, their caregivers and doctors, as the patient wants to become independent from caregivers and treatment compliance is reduced. Also, transition to adult clinics for patients with neurogenic bladders is often not well-established.

KEYWORDS
anticholinegics, conservative treatment, EAU/ESPU guidelinie, neurogenic bladder, spinal dysraphism

1 | INTRODUCTION

In childhood, the most common reason for a neurogenic bladder is related to spinal dysraphism, mostly myelodysplasia. Other congenital malformations or acquired diseases that may cause the neurogenic bladder to include total or partial sacral agenesis, which can be part of the caudal regression syndrome, traumatic or neoplastic spinal lesions, and anorectal or cloacal malformations.[1,2] Furthermore, there are forms of neurogenic bladder in which no clear neurogenic abnormality can be found, for example in patients with cerebral palsy and Hinman or Ochoa syndrome.[3,4] Patients with a neurogenic bladder can present with various patterns of detrusor-sphincter dyssynergia,[5] which may lead to urine and/or stool incontinence, urinary tract infections (UTI's), vesicoureteral reflux (VUR), and ultimately renal scarring and renal failure requiring dialysis and/or transplantation. About 12% of neonates with myelodysplasia have no signs of neurourological dysfunction at birth,[6] but bladder dysfunction will occur later in life, especially in first years due to changes in the innervation as well as the development of a tethered cord and other neurological changes. Without treatment, up to 60% to 80% may develop urological problems within the first years of life and less than 5% become continent.[7-10]

A recent survey in 291 patients from three countries with a mean age of 13.9 ± 12.2 years, demonstrated that medication was taken by 78% of patients (64% anticholinergics) and complete dryness rates for urine and stool were 24% and 47%, respectively.[11] A recent systematic review concerning the outcome of adult meningomyelocele patients demonstrated that around 37% (8-85%) were continent, 25% had some degree of renal damage and 1.3% end-stage renal failure.[12] The term "continence" is used differently in the reports, and the definition of "always dry" was used in only 25% of the reports.[13] The main goals of treatment concerning the urinary tract are preservation/improvement of renal function, prevention of UTI's and urinary tract deterioration. Later in childhood, urine and stool continence plays an important role. During adolescence and later on, sexual function and fertility were described as more important to improve the quality of life as much as possible.

Today there are two treatment options used (a) proactive treatment to achieve a low-pressure reservoir and prevent UTIs, with clean intermittent catheterization (CIC) ±anticholinergic medication starting in the first months of life and (b) reactive management, only starting such interventions if problems or changes occur.

2 | MATERIALS AND METHODS

For the update of the guideline, a literature search was performed for all relevant publications published from January 2000 until June 2018, using the following databases: Embase, MEDLINE, Cochrane SRs, Cochrane Central, Cochrane HTA, Clinicaltrial.gov, and WHO International Clinical Trials Registry Platform Search Portal. The string terms Neurogenic Bladder AND children or synonyms of this were used. All English abstracts were screened and relevant original articles and reviews concerning the epidemiology, pathophysiology, diagnostics, treatment and long-term outcome of children and adolescents with neurogenic bladder were investigated concerning their relevance. Relevant papers have been included in the final guideline after the agreement of panel members. A summary of evidence and recommendations were made according to the current requirements of the EAU guidelines office.

2.1 | Classification

The etiology, type, and spinal level of the neurological lesion correlate poorly with the severity of detrusor-sphincter dysfunction. Therefore, urodynamic and functional classifications are much more practical for defining the lower urinary tract (LUT)-pathology and planning treatment in children.

Both detrusor and sphincter may be either overactive or underactive, resulting in four different combinations. This classification system is based on urodynamic findings.[14-16]

Overactive sphincter // overactive detrusor
Overactive sphincter // underactive detrusor
Underactive sphincter // overactive detrusor
Underactive sphincter // underactive detrusor

2.2 | Diagnostic evaluation

2.2.1 | History and clinical evaluation

In neonates, history may include an estimation of voiding frequency and straining. Physical examination should include a thorough inspection of the external genitalia, back, and reflexes. During follow-up, history should include questions on voiding or CIC frequency, urine leakage, bladder capacity, UTI, medication, bowel function, as well as, changes in neurological status. A 2-day diary, recording drinking volume and time as well as CIC intervals, bladder volume and leakage can provide additional information about the efficacy of the treatment.

2.2.2 | Laboratory and urinalysis

After the first week of life, renal function should be tested, for example, by plasma creatinine levels; cystatin C can be a useful marker.[17,18] In patients with impaired renal function, treatment should be optimized as much as possible.

Urine samples can be easily obtained by catheterization as most patients perform CIC. Only in patients with asymptomatic/febrile proven UTI, antibiotic treatment should be started. In most patient's asymptomatic bacteriuria can be detected, which requires no treatment.

2.2.3 | Ultrasound

At birth, ultrasound of the kidneys and bladder should be performed and then repeated (see Figure 1). Dilatation of the upper urinary tract should be recorded according to the classification system of the Society of Fetal Urology[19] including the measurement of caliceal dilatation and anterior-posterior diameter of the renal pelvis. Bladder wall thickness has been shown not to be predictive of high pressures in the bladder,[20] but may be mentioned in the ultrasound report.

2.2.4 | Urodynamic studies

Urodynamic studies (UDS) are one of the most important diagnostic tools in patients with a neurogenic bladder. In patients with postnatal closure of the spina bifida, the first UDS should be performed after the phase of the spinal shock, usually between the second and third months of life.[21] In those patients with prenatal closure, UDS are recommended to be performed before the child is discharged from hospital, because the phase of spinal shock occurred already intrauterine—mostly 2 to 3 months before. In all other patients (see above) UDS should be performed as soon as there is a strong suspicion of a neurogenic bladder (eg, voiding pattern, changes of the upper or LUT). Especially in the newborn age, interpretation of UDS may be difficult, and normal values do not exist. During and after puberty there should be increased attention to bladder and sphincter behavior as bladder capacity, maximum detrusor pressure and detrusor leak point pressure may increase significantly during this time period.[22]

The standards of the International Children's Continence Society should be applied and accordingly reported.[14,23] Natural filling UDS in children with a neurogenic bladder can detect more overactivity compared with conventional UDS.[24,25] It may be an option in cases, where the findings in conventional UDS are inconsistent with symptoms and other clinical findings.[25]

DMSA (^{99}technetium dimercaptosuccinic acid renal) scan is still the gold standard to detect renal scars, which can be seen in up to 46% of older patients with neurogenic bladders.[26-28] Contrarily, ultrasound has a poor correlation with renal scars.[28] A scar on DMSA-scan correlates well with hypertension in adulthood.[28] Therefore, a DMSA scan—as a baseline evaluation in the first year of life—is recommended and could be repeated after recurrent febrile UTIs to define children who have scars and are at risk.

After reviewing and discussing several available guidelines and timetables for children with spinal dysraphism,[29-31] the guideline panel agreed on proactive management with a detailed timetable for the diagnostic evaluations and re-evaluations (Figure 1). In patients with a safe bladder during the first urodynamic investigation, the next UDS can be delayed until 1 year of age.

2.3 | Conservative management

There is controversy about the initial management of a potentially neurogenic bladder, with regard to proactive vs expectant management.[32-34] However, even close expectant management may not be able to prevent

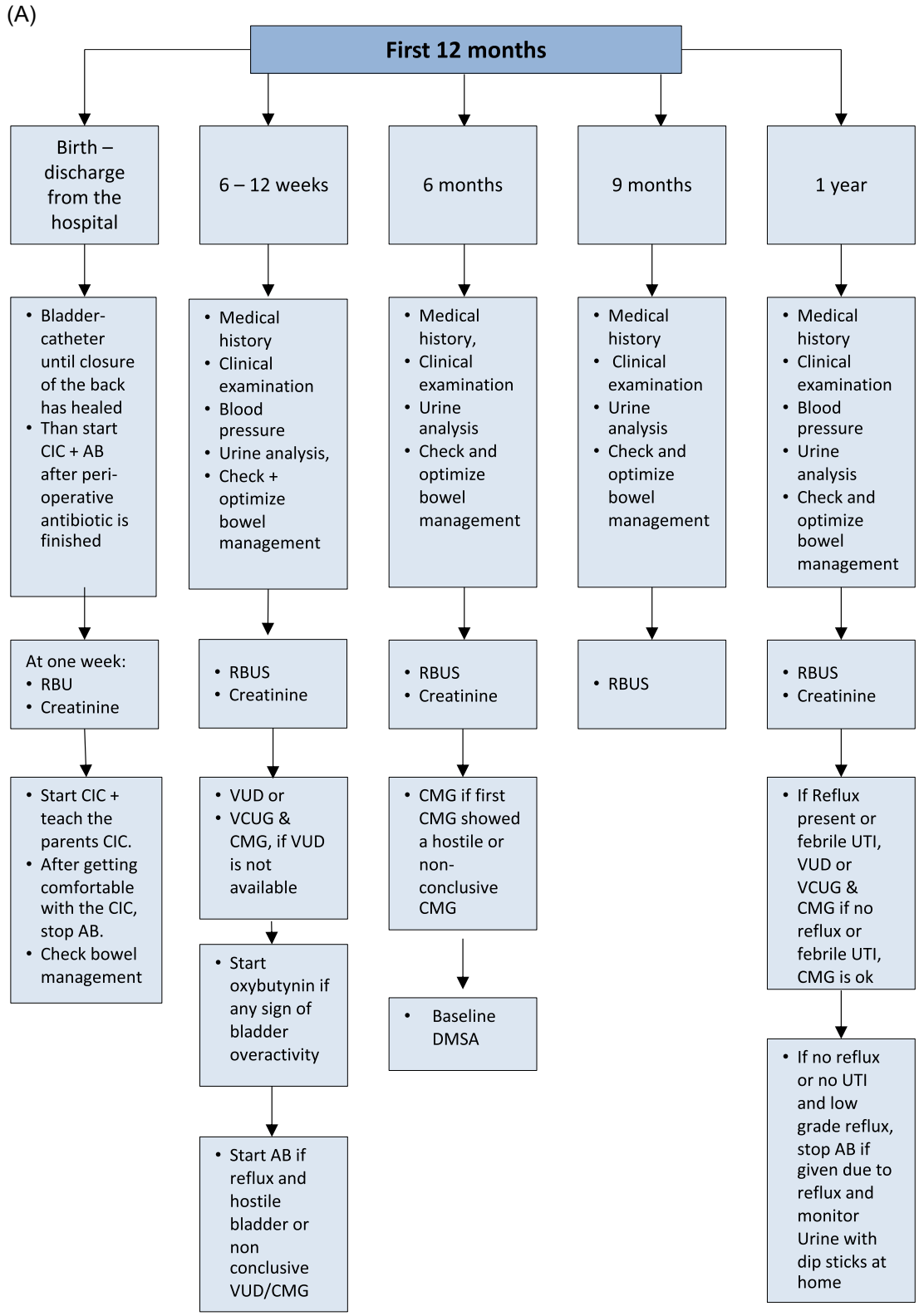

FIGURE 1 Timetable for investigations and interventions. CMG, cystomanometry with electromyogram; DMSA, dimercaptosuccinic acid renal; RBUS, renal and bladder ultrasound; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUD, video urodynamic

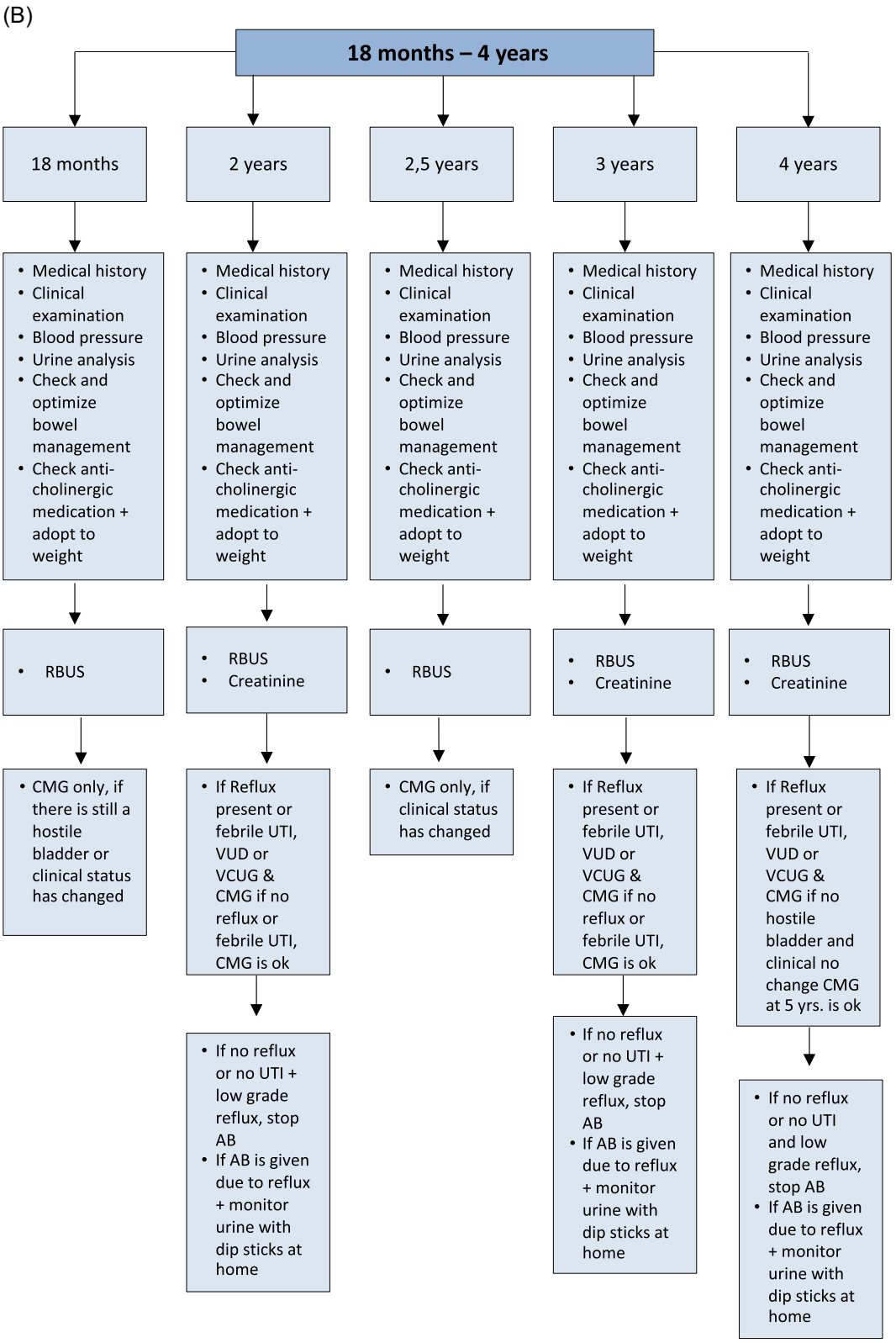

FIGURE 1 Continued

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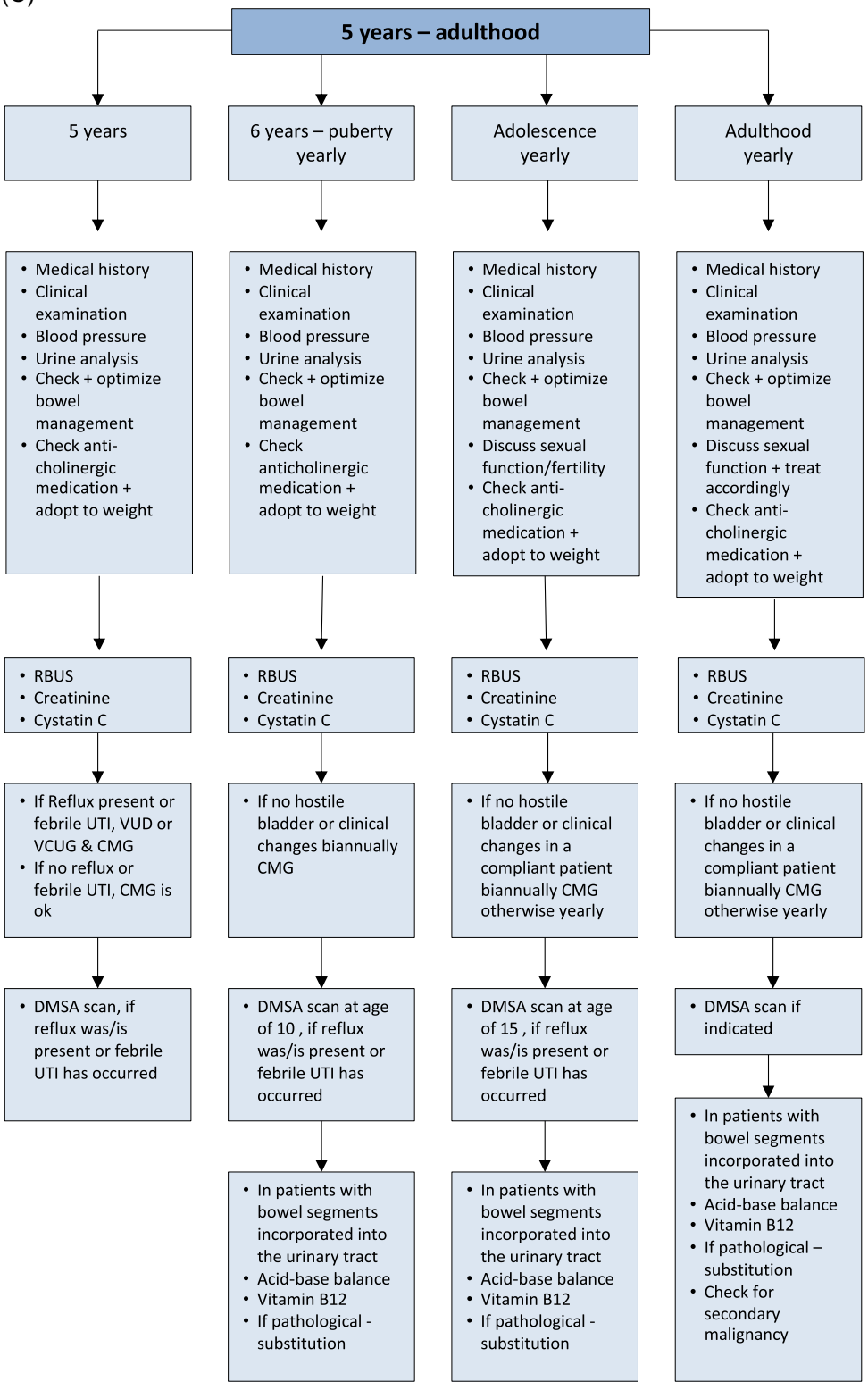

FIGURE 1 Continued

injury. In one series 11 out of 60 patients with expectant management needed an augmentation and seven had a decrease in total renal function, which was severe in two.[35]

To reduce neurogenic bladder dysfunction, neurological and orthopedic problems, prenatal treatment of the myelomeningocele has been proposed either by open or endoscopic surgery.[36] Despite some promising reports,[37-40] parents need to be aware of the high risk of developing a neurogenic bladder during follow-up, as demonstrated by the Brazilian group.[41] Regular and close follow-up examinations including UDS (starting soon after birth) are indicated in all these patients.

In general, as patients with meningomyelocele have a higher prevalence of latex allergy, the use of all latex products should be avoided.[42]

2.3.1 | Clean intermittent catheterization

In the neonatal period, every bladder is considered to be a potential high-pressure bladder and should be treated accordingly. CIC should be started soon after birth in all infants with spina bifida as it has been shown that early management can decrease renal complications and the need for later augmentation.[43-45] The acceptance of performing CIC is much better if it is introduced early in life. In patients with an underactive sphincter, it can be periodically checked, if there is still no or almost no residual urine. In infants with spinal dysraphism and no sign of outlet obstruction after UDS, the CIC can be delayed, but a very close follow-up in these patients is mandatory.

A Cochrane review, as well as some recent studies, demonstrate that the incidence of UTI is neither affected by the use of the sterile or clean technique; coated or uncoated catheters; single (sterile) or multiple-use (clean) of catheters; self-catheterization or catheterization by others, or by any other strategy.[46-49] Using hydrophilic catheters, there is a trend to reduce potentially pathogenic bacteria with a higher level of satisfaction.[50] On the basis of the current data, no statement can be made, that one catheter type, technique or strategy is better than the other one.

2.3.2 | Medical therapy

Detrusor overactivity causes a high-pressure bladder, which is dangerous for the upper urinary tract. Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers the intravesical pressure.[51,52] Early treatment with anticholinergics has long been known to lower the rate of renal deterioration as well as the need for bladder augmentation.[43,45,53] Therefore, anticholinergic treatment should be started if an overactive bladder is demonstrated on UDS, even within the first months of life. The effects and side effects depend on the distribution of the M1 to M5 receptors.[54] Oxybutynin is the most frequently antimuscarinic used in children with a success rate of up to 93%,[55,56] however, it's use is limited by dose-dependent side effects (such as mouth dryness, facial flushing, blurred vision, and heat intolerance, etc,). The dosage is 0.1 to 0.4 per kg per day divided into three doses. Intravesical administration avoids the first-pass effect via the liver, causing less metabolites, less side effects, and has higher bioavailability.[57,58] It can be used in neonates and children suffering from side effects of oral oxybutynin.[59,60] The dosage can be somewhat higher compared with the oral administration: 0.1 to 0.8 mg/kg divided into three doses.[61] There are some concerns about central anticholinergic adverse effects associated with oxybutynin.[62,63] On the other hand, a double-blinded cross-over trial, as well as a case-control study, showed no deleterious effect on children's attention and memory.[64,65] Tolterodine, solifenacin, trospium chloride, and propiverine and their combinations have been used safely in children.[66-72] It should be stated, however, that all antimuscarinic agents are still *off label* use in neonates and young children.

ß3 Agonists like mirabegron may also be an alternative agent and may be effective in patients with neurogenic bladders. However, in children, the experience of mirabegron is limited to case reports,[73] and therefore no recommendation can be made.

α-Adrenergic antagonists may facilitate bladder emptying in children with neurogenic bladder, therefore, causing a lower pressure in the bladder, creating a safer situation for the kidneys.[74] Doxazosin was well tolerated but not effective at least in one study.[75]

2.3.3 | Management of fecal constipation and incontinence

Children with neurogenic bladder usually also have neurogenic bowel dysfunction, most frequently chronic constipation with stool incontinence. This will not only evolve into physical problems but also have an impact on the quality of life. Regular bowel emptying should also be an early goal in children with spinal dysraphism as well as in all other patients with a neurogenic bladder, diagnosed later in life.

In the beginning, the bowel regimen includes mild laxatives (even in toddlers and infants), such as mineral oil, combined with retrograde enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time, rectal suppositories,

as well as digital stimulation by parents or caregivers, can be used. Today, retrograde transanal irrigation is one of the most important treatment options, as regular irrigations significantly reduce the risk for fecal incontinence.[76] Retrograde transanal irrigation can become difficult or impossible due to anatomic or social circumstances and can, therefore, be transformed into an antegrade irrigation fashion, using a Malone antegrade continence enema-stoma.[77,78]

2.3.4 | Urinary tract infection

In children with neurogenic bladders, UTIs are common, but there is no consensus in most European centers, for prevention, diagnosing and treating UTIs in this group of patients.[79] Although asymptomatic bacteriuria is seen in more than half of children on CIC, patients who are asymptomatic do not need treatment.[80-82] Continuous antibiotic prophylaxis (CAP) creates more bacterial resistance as demonstrated by a randomized study.[83] The patients that discontinued prophylaxis had reduced bacterial resistance, however, 38 of 88 started AP again due to recurrent UTIs or parents' requests.[83] A cohort study with 20 patients confirmed these findings. CAP was not protective against the development of symptomatic UTIs and new renal scarring, however, increased the risk of bacterial resistance.[84] A randomized study in 20 children showed that cranberry capsules significantly reduced the UTI-rate as well as the rate of bacteriuria.[85] However, when patients experience recurrent febrile UTIs and VUR is present, prophylactic antibiotics should be started.[86,87]

2.3.5 | Vesicoureteral reflux

VUR is mostly secondary and increases the risk of pyelonephritis. Therefore, the treatment is primarily related to bladder dysfunction.[88] On the other hand, patients with high-grade reflux before augmentation have a higher risk for persistent symptomatic reflux after the enterocystoplasty[89] and simultaneous ureteral reimplantation in high-grade symptomatic reflux especially in those with low-pressure high-grade reflux should be discussed. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years,[90] which is in contrast to the open techniques with a higher success rate,[91] but may have an increased risk of inducing obstruction.

2.3.6 | Sexuality and fertility

There is a higher incidence of sexual dysfunction and infertility in patients with spinal dysraphism. These patients usually have a normal desire, however sexual arousal, orgasmic function, and overall satisfaction depend on a variety of factors. The spinal level of spina bifida is important, and in boys with a spinal lesion below thoracic 10, two of three can have psychogenic erections rather than reflex erections. In addition, most patients have a mixed pattern which does not strictly correlate with the level of the spinal neurological lesion.[92] This becomes more important as the patient gets older.[93]

In girls with meningomyelocele, the prevalence of precocious puberty is high compared with the normal population.[94] If precocious puberty is found in children younger than 10 years of age, it is advised to delay pubertal onset and development (eg, with luteinizing hormone-releasing hormone [LH-RH] analog).[95] Females who are sexually active and/or trying to conceive a child, taking folic acid supplementation along with maintaining adequate levels of vitamin B12 may reduce the risk for having a fetus with a neural tube defect.[96-98]

Women seem to be more sexually active than men in some studies from the USA and the Netherlands.[93,99] In an Italian study, men were more active.[100] The level of the lesion was the main predictor of sexual activity.[100,101] Erectile function can be improved by sildenafil in up to 80% of the male patients.[102,103] Neurosurgical anastomosis between the inguinal nerve and the dorsal penile nerve, in patients with a lesion below L3 and disturbing sensation, is still to be considered as an experimental treatment.[104]

Concerning fertility, studies indicate that at least 15% to 20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence. Only 17% to 30% of the patients talk to their doctors about sexuality, 25% to 68% were informed by their doctors about reproductive function.[93,99] Women with spina bifida, have a higher incidence (1-5%) of having a child with spina bifida. If both parents are affected, the risk may increase to 15%. Furthermore, pregnant women with spina bifida are likely to develop uterine prolapse, pelvic deformities, premature labor, and have a higher risk of needing a cesarean section. It is therefore advised that young women with spina bifida be thoroughly counseled before conception.[105] For children and adolescents with other causes of a neurogenic bladder there are almost no data available concerning sexuality and fertility, except for adult patients with a traumatic lesion of the spinal cord. But this is out of the scope of this guideline.

2.4 | Follow-up

Neurogenic bladder patients require lifelong multidisciplinary follow-up, including not only urological aspects but also neurological and orthopedic aspects.

Regular investigation of upper and LUT is mandatory (Figure 1). In patients with changes in the function of the upper urinary tract and/or LUT, a complete neurological reinvestigation should be recommended including a total spine magnetic resonance imaging to exclude a secondary tethered cord or worsening of the hydrocephalus. Also, if some neurological changes are observed, a complete investigation of the urinary tract should always be included.

As the overall prognosis of patients with myelodysplasia and neurogenic bladder dysfunction is good, lifelong follow-up should be well prepared in transition and in close cooperation with the experienced urologist.

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction may result in different forms of LUTD and ultimately result in incontinence, UTIs, VUR, and renal scarring.	2a
In children, the most common cause a neurogenic bladder is myelodysplasia (a group of developmental anomalies that result from defects in neural tube closure).	2
Bladder sphincter dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are more practical in defining the extent of the pathology and in guiding treatment planning.	2a
Children with a neurogenic bladder can have disturbances of bowel function as well as urinary function, which require monitoring and if needed, management.	2a
The main goals of treatment are the prevention of urinary tract deterioration and the achievement of continence at an appropriate age.	2a

Abbreviations: LUTD, lower urinary tract dysfunction; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Recommendations	LE/strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2 Strong
In all newborns, intermittent catheterization (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity starting IC may be delayed. If the IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (ultrasound) and lower tract (urodynamics).	3 Strong
Start anticholinergic medication early in newborns with evidence or a suspicion of an overactive detrusor.	2 Strong
Treatment of fecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital evacuation. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema/antegrade continence enema stoma should be discussed.	3 Strong
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3 Weak
A lifelong follow-up of upper and lower urinary tract function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	3 Weak

Abbreviations: UTI, urinary tract infection.

Summary of evidence and recommendations has been established by the EAU/ESPU guideline panel after reviewing and discussing the current literature.[106]

ORCID

Raimund Stein http://orcid.org/0000-0002-3217-5089
Guy Bogaert http://orcid.org/0000-0002-5989-1253
Hasan S. Dogan http://orcid.org/0000-0002-1145-7343

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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