EAU – ESPU - ERN eUROGEN - ERN ITHACA – ERN ERKNet - IFSBH Guidelines on spinal dysraphism in children and adolescents

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1. INTRODUCTION

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It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/ individual circumstances of children and their caregivers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

2. METHODS

These Guidelines were compiled based on current literature following a structured review. Databases covered by the searches included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

Recommendations within the Guidelines are developed by the Panel to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [1];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2] .

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

The term spinal dysraphism refers to a group of malformations of the spine and/or surrounding structures. Dysraphism originates from the old Greek words for bad suture. The Guideline committee prefers this term over spina bifida.

The most common presentation of spinal dysraphism at birth is myelodysplasia. Lesions include spina bifida aperta and occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Spinal dysraphism can also present at a later age with various voiding symptoms [3].

The incidence of spinal dysraphism in Europe according to the EUROCAT numbers [4] has been stable over the last 15 years, with prevalence of 4 to 5 per 10.000 births. Numbers differ around the world: in the USA and Canada numbers are lower with a prevalence of 2-3 per 10.000 births [5, 6]. This might be related to folate-enrichment of cereal grain products (fortification), which is mandatory in the USA since 1998.

There is limited research about prevalence in the Middle East but it seems to be in the same low range [7]. In South America the prevalence differs per country, between 2 and 10 per 10.000 births [8, 9]. In Asia numbers are in the same range [10-12]. In Africa the prevalence is still much higher and in a wider range, as shown in several meta-analyses: 20-130 per 10.000 births [13-15]. Incidence

and prevalence are influenced by lack of data, especially in low-income countries [16]. Mortality at a young age and stillbirth in children with spinal dysraphism are low in high income countries [17], but are still high in low-income countries [18]. These numbers seem to be influenced by the possibility of elective termination of pregnancy for foetal anomaly (ETOPFA).

Although many studies investigated risk factors for spinal dysraphism, no clear conclusions can be drawn. The same accounts for genes related to spinal dysraphism. However, there is clear evidence that the use of folic acid protects and thus lowers the incidence all over the world [19]. Fortification lowers the incidence of neural tube defects including spinal dysraphism, reduces the severity, leads to lower levels of lesions [20], and lowers still-birth and mortality [21]. Mandatory fortification seems to be more effective than supplementation [22]. Fortification also reduces health costs [23]. Thus, supplementation is recommended worldwide by different organisations, including the World Health Organization [24]. However, implementation is still a challenge due to many reasons including lack of knowledge, lack of availability of supplements, unplanned pregnancies and costs [25]. Fortification of rice and corn may be beneficial for countries where people mostly eat rice or corn instead of wheats [26]. However, most people in these countries grow their own rice or corn for their own consumption without any fortification at all. Salt fortification might be another option [21].

Traumatic and neoplastic spinal lesions of the cord are less frequent in children but can also cause severe urological problems. Other congenital malformations or acquired diseases can cause a neurogenic bladder, such as total or partial sacral agenesis which can be part of the caudal regression syndrome [27]. In any child presenting with anorectal malformation (ARM) and cloacal malformations, the development of a neurogenic bladder is possible [28]. Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting. Finally, “non-neurogenic neurogenic” bladder dysfunction, such as Hinman or Ochoa syndrome, have been described. Often no neurogenic anomaly can be found, but severe bladder dysfunction comparable to neurogenic bladders is present [29, 30].

Detrusor-sphincter dyssynergia (DSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of lower urinary tract dysfunction (LUTD), which may lead to incontinence, urinary tract infections (UTIs), vesico-ureteral reflux (VUR), and ultimately to renal scarring and renal failure requiring dialysis and/or transplantation. The main goals of treatment concerning the urinary tract are prevention of UTIs, upper urinary tract deterioration, achievement of continence at an appropriate age and promoting as good as possible Quality of Life (QoL) [31, 32]. With regard to the associated bowel dysfunction, stool continence, with evacuation at a socially acceptable moment, is another goal as well as education and treatment of disturbance in sexual function. Problems also occur or continue during adulthood and transition of care is of utmost importance. Due to the increased risk of development of latex allergy, latex-free products (e.g., gloves, catheters etc.) should be used from the very beginning whenever possible [33].

Neurogenic bladder in children with spinal dysraphism presents with various patterns of detrusor-sphincter-dyssynergia with a wide range of severity [34]. About 12% of neonates with spinal dysraphism have no signs of neuro-urological dysfunction at birth [35]. Newborns with spinal dysraphism who initially have normal urodynamic studies are at risk for neurological deterioration secondary to spinal cord tethering, especially during the first six years of life. Close follow-up of these children is important for the early diagnosis and timely surgical correction of tethered spinal cord, and for the prevention of progressive urinary tract deterioration. At birth, the majority of patients have normal upper urinary tracts (UUTs), but up to 60% develop upper tract deterioration due to bladder changes, UTI and/or VUR, if not treated properly [36]. During adulthood around 50% of the patients are incontinent and 15% have an impaired renal function [37]. A systematic review concerning the outcome of adult myelomeningocele patients demonstrated that around 37% (8-85%) are continent, 25% have some degree of renal damage, and 1.3% are in end stage renal failure [38]. The term “continence” is used differently in the reports, and the definition of “always dry” was used in only a quarter of the reports [39]. A recent nationwide survey in the USA showed that less than 50% of the adult spina population reported being continent [40], which demonstrates the need for better counselling and lifelong support.

4. CLASSIFICATION SYSTEMS

To date there are still no validated classification systems that predict outcome for spinal dysraphism. The Orphanet codings do try to classify differences of rare diseases but do not cover the outcome perspectives. Currently an Orphanet classification update is underway to develop a better classification and description of differences between specific patients [41].

As bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion, urodynamic and functional classifications are much more practical for defining who is at risk and for planning treatment in children.

The bladder and sphincter are two units working in harmony to act as a single functional unit. In patients with a neurogenic disorder, the storage and emptying phases of bladder function can be disturbed. The bladder and sphincter may be either overactive or

underactive and present in four different combinations. This classification system is based on urodynamic findings [42, 43]:

- Overactive sphincter and overactive bladder.
- Overactive sphincter and underactive bladder.
- Underactive sphincter and overactive bladder.
- Underactive sphincter and underactive bladder.

5. HISTORY AND CLINICAL EVALUATION

History should include questions on antenatal diagnosis and management, urethral voiding, clean intermittent catheterisation (CIC) frequency, urine leakage, UTI, and bowel function as well as changes in neurological status. History should include review of any medical and surgical intervention. A two-day diary recording fluid intake, CIC intervals, volumes drained, and leakage can provide additional information about the nature of LUTD and efficacy of the treatment. A thorough clinical evaluation is mandatory including examination of the abdomen, external genitalia and the back including a basic neurological examination such as anal tone etc. and should include weight, height and blood pressure measurements due to the higher incidence of obesity and hypertension in this group of patients [44, 45].

5.1 Laboratory – kidney function

Kidney function in children with neurogenic bladder should be evaluated periodically due to the risk of the development of CKD (chronic kidney diseases) [46, 47]. Formal evaluation of kidney function relies on an estimated glomerular filtration rate (eGFR), but formulas based on serum creatinine may overestimate eGFR due to decreased muscle mass in children with neurogenic bladder [48]. Formulas based on cystatin C may be more accurate [49]. Albuminuria is an early marker of renal disease in children with neurogenic bladder [50].

5.2 Laboratory – Urinary tract infections

A catheter urine sample can be obtained in patients who are on CIC. A dipstick analysis can be performed at home to screen for UTI if there are symptoms suggestive of UTI. Pyuria may be assessed by dipstick, microscopy and flow imaging analysis technology [51]. The presence of pyuria on its own is not diagnostic for UTI in children on CIC, but the absence of pyuria in a symptomatic patient suggests a diagnosis other than UTI. Positive urine culture cannot be utilised as a solitary measure for the diagnosis of UTI due to the high incidence of asymptomatic bacteriuria in children with neurogenic bladder on CIC [52]. Pyuria in a symptomatic patient when associated with positive urine culture supports the diagnosis of UTI.

5.3 Urinary tract infection – diagnosis

Urinary tract infections are common in children with neurogenic bladders. However, there is no consensus in most European centres on prevention, diagnosing and treating UTIs in children with neurogenic bladders performing CIC [53]. A combination of symptoms and laboratory measures is recommended for diagnosis. This combination includes: ≥ 2 symptoms (fever ≥ 38°C, abdominal pain, new back pain, new or worse incontinence, pain with catheterisation or urination, or malodorous/cloudy urine) and ≥ 100 000 CFU/mL of a single organism and ≥ 10 WBC/HPF on urine microscopy or equivalent method [54, 55].

5.4 Urinary tract infection – management

Management of UTI in patients with neurogenic bladder should follow recent guidelines for UTI treatment in children [56]. The choice of antibiotic should be based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity-testing of the isolated uropathogen. The higher prevalence of UTI causative agents other than *E. Coli* in children with neurogenic bladder should be taken in account during the initial therapy choice. Evaluation of CRP, procalcitonin, blood count, serum electrolytes and kidney function should be performed in children with febrile UTI. Evaluation of kidney function is important before introducing potentially nephrotoxic agents to avoid further kidney damage in children with chronic kidney disease (CKD). In patients not responding to antibiotics, treatment-resistant uropathogens or urinary obstruction should be considered and an US examination is recommended in these cases. Recurrent febrile UTI can have a significant impact on kidney function leading to an eGFR decrease after the fourth episode in almost 30% of children with neurogenic bladder [57].

5.5 Urinary tract infection – prophylaxis

There are conflicting data about use of antibiotic prophylaxis in children with neurogenic bladder who are on CIC. Some studies show a lower risk of UTI with prophylaxis [58]. On the other hand, continuous antibiotic prophylaxis (CAP) creates more bacterial resistance [59]. A cohort study with 22 patients confirmed these findings. A Cochrane review supports the use of cranberry products to reduce the risk of symptomatic UTIs [60].

5.6 Urinary tract infection – Clean intermittent catheterisation

Introduction of CIC reduces the incidence of UTI after 12 months from 60% to 20% independently of antibiotic prophylaxis [61]. In those with recurrent UTI, intravesical instillation of gentamycin or neomycin/polymyxin may be an option [62]. The reuse of catheters may increase bacteriuria but does not increase the risk of symptomatic UTI. A cross-over study in 40 children with neurogenic bladder demonstrated that the reuse of catheters for three weeks compared to one week increased the prevalence of bacteriuria from 34% to 74%. However, during the study period of eighteen weeks, none of the patients developed a febrile UTI [63].

5.7 Imaging

*5.7.1 **Ultrasound***

At birth, ultrasound (US) of the kidneys and bladder should be performed and then repeated at least annually. If there are any clinical changes in between, another US should be performed. Dilatation of the UUT should be reported according to the classification system of the Society for Fetal Urology [64], including the measurement of calyceal dilatation and the antero-posterior diameter of the renal pelvis. Residual urine and bladder wall thickness (BWT) should also be noted. Though BWT has been shown not to be predictive of high pressures in the bladder [65], it is a readily available screening tool for early bladder changes [66]. A dilated ureter behind the bladder should be recorded. The rectal diameter on US can give information on constipation.

Ultrasound scan of the spine can be performed in new-borns and small infants before ossification of arches to provide information about the spinal cord anomaly.

*5.7.2 **Technetium Dimercapto-Succinic Acid scan***

A Technetium Dimercapto-Succinic Acid (DMSA) Renal scan is the gold standard to evaluate renal parenchyma and a baseline evaluation in the first year of life is recommended. In contemporary series, renal scars can be detected in up to 25% of patients after 10 years follow-up. Repeat scans are required to monitor for renal scarring especially if there is recurrent UTI or VUR [67].

*5.7.3 **Magnetic resonance imaging***

An early baseline Magnetic Resonance Imaging (MRI) scan of the head and spine is required in both open and closed spina bifida patients. It is important in identifying ventriculomegaly, Arnold Chiari II malformation; and in defining the extent of spinal abnormality including presence of fatty filum, low lying cord, associated syringomyelia (40% incidence) [68], and any tethering. A fast spine MRI protocol in young patients can be useful to avoid the need for sedation [69]. A follow-up MRI scan may be performed to assess the development of tethered cord, arachnoid cysts, dermoid and epidermoid cysts, and progression of any pre-existing syringomyelia. The timing of an MRI scan depends on clinical symptoms, especially if there is any late onset progressive neurological deficit. The vast majority of children will have radiographic signs of spinal cord tethering [70], but secondary tethered cord syndrome with progressive spinal cord deformity, progressive scoliosis, deteriorating ambulation and deteriorating bladder and/or bowel dysfunction occurs only in 27-30% of these patients [71].

5.8 Urodynamic studies/videourodynamics

Urodynamic studies (UDS) are one of the most important diagnostic tools in patients with neurogenic bladders. In newborns with spina bifida aperta, the first UD should be performed after the phase of spinal shock after closure, usually between the second and third months of life [72, 73]. Especially in newborns, performing and interpreting UDS may be difficult, because bladder function may have some immature signs, such as detrusor-sphincter dyscoordination, high voiding pressure and very low bladder capacity. In the UMPIRE study these signs were recognised, and a definition of high-risk bladders in this age group was suggested by relying on end-filling detrusor pressure and not DSD and/or DLPP [74].

After initial UDS, they should be repeated annually, depending on the clinical situation. During and after puberty, the bladder capacity, maximum detrusor pressure and detrusor leak point pressure increase significantly [75]. Therefore, during this time, a careful follow-up is mandatory.

*5.8.1 **Preparation and performing urodynamic studies***

Before any UDS a urine analysis should be undertaken to exclude an acute symptomatic UTI. In case of suspicion of a symptomatic UTI, the UDS has to be postponed and a urine culture should be taken. If positive, treatment according to the culture results is recommended. The first assessment should be done under antibiotic prophylaxis. A Cochrane analysis of nine randomised controlled trials showed that the administration of prophylactic antibiotics compared to placebo reduced the risk of significant bacteriuria from 12% to 4% after UDS. However, this was without significant difference for symptomatic UTI (20% vs. 28%), fever or discomfort [76]. If there is significant bacteriuria, antibacterial treatment should be discussed; especially in older patients a single dose may be sufficient [77]. Administering bowel management has a positive effect on bladder function and UDS findings [78, 79].

Generally, UDS-parameters should include:

- cystometric bladder capacity;
- detrusor end-filling pressure (DEFP);
- detrusor compliance;
- detrusor pressure at the moment of voiding or leakage without a contraction (DLPP);
- presence or absence of detrusor overactivity (DO);
- competence of the internal and external sphincter;
- degree of synergy of the detrusor and sphincter during voiding (DSD);
- PVR volume.
- During videourodynamics (which is highly recommended) the shape of the bladder and bladder neck during filling and voiding, appearance of the urethra during voiding, the volume and pressure when VUR occurs, and the influence of voiding on VUR can be objectively noted.

In small infants, information on detrusor end filling pressure and the pressure and bladder volume at which the child voids or leaks can be obtained.

The standards of the International Children's Continence Society (ICCS) should be applied to UDS in patients with neurogenic bladders and accordingly reported [80]. Before inserting a catheter, a uroflow is obtained if applicable. After voiding is completed, a transurethral catheter (ch 6 or 7 double lumen) is inserted and residual urine measured and urinalysis is performed. A small (8-Fr) rectal balloon catheter is inserted to record abdominal pressure changes. To study pelvic floor muscles reactivity, surface electrodes are widely used.

Avoiding general anaesthesia is important as this affects the natural state and eliminates the chance for voiding. The bladder is filled with 0.9% saline or contrast medium warmed to body temperature (37.5 C) at a rate of 5–10% of EBC per minute or < 10 mL/min).

The standards advise two rounds of filling/voiding cystometry, but a third round should be considered with a low threshold in case of conflicting data [81].

Despite these standards, variability in interpretation even in experienced hands remains high, especially for DO and DSD [82].

*5.8.2 **Uroflowmetry***

Because most children with spinal dysraphism do not void spontaneously, uroflowmetry can rarely be used. However, in children with active voiding it may be a practical tool. It provides an objective way of assessing the efficiency of voiding, while recording pelvic floor activity with electromyography (EMG) can be used to evaluate synergy between the detrusor and the sphincter. PVR urine volume is measured by US. The main limitation of uroflowmetry is the compliance of the child to follow instructions. The ICCS standards should be strictly adhered to [73].

*5.8.3 **Natural fill/ambulatory urodynamic studies***

Natural fill UDS in children with neurogenic bladder detects more overactivity compared with diagnoses delivered by conventional UDS and is not recommended as a routine assessment [83]. It may be an option in patients where the findings in the conventional UDS are inconsistent with clinical symptoms and other clinical findings [83, 84] [85, 86]. Less invasive alternative techniques are being investigated, but are still inferior to UDS [87].

*5.8.4 **Urodynamic findings predictive of (re)-tethering***

Lee *et al.* retrospectively analysed 51 patients who needed re-detethering, and found that 88% of the patients presented with urological changes especially UTI and new onset of urinary incontinence. DSD and DO occurred in 100% and 60% of the patients, respectively [88]. In the prediction of re-tethering in children with spinal dysraphism, somato-sensory evoked potential (SEP) has been used, in addition to UDS, although no prospective trials have been performed so far [89]. In this latter study, a correlation between unfavourable SEP and DSD was found. Shin *et al.* used a similar nerve conductive method, and also found the same predictors [90].

*5.8.5 **Urodynamic findings predictive of upper tract deterioration***

Detrusor leak point pressure or EFP over 40cm H_2O, and (high grade) vesico-ureteral reflux (VUR) seem to be independent predictors of upper tract deterioration or failure of conservative management [91, 92]. Also, several studies mention DSD to be related to upper tract deterioration.

The UMPIRE study analysed the first urodynamics of 157 newborns with spinal dysraphism and defined low risk bladder as end filling pressure or DLPP to be < 25 cm H_2O and DO should not be present on EMG. They defined a high-risk bladder to have poor compliance with an end filling pressure or DLPP ≥ 40 cm H_2O. Detrusor-sphincter dyssynergia was excluded from the high-risk definition because of low reliability and interobserver variability [74].

The shape of the bladder (conical or elongated) and the presence of trabeculation seem to be associated with increased DLPP or EFP, or with upper tract deterioration [93].

*5.8.6 **Voiding cystourethrogram***

If video-urodynamic equipment is not available, a VCUG with UDS is an alternative to confirm or exclude VUR and visualise the LUT including the urethra.

6. PRENATAL MANAGEMENT OPTIONS

The neurologic deficit in spinal dysraphism results from two "hits":

(1) initial failure of neural tube closure with invagination of surrounding meso- and ectoderm,

(2) ongoing injury of exposed neural tissue (to amniotic fluid) in the intrauterine environment resulting from mechanical and chemical trauma [94].

6.1 Prenatal open and endoscopic intervention

With the Management of Myelomeningocele Study (MOMS) trial and a full 30-month follow-up of the cohort, open foetal myelomeningocele (MMC) repair has demonstrated reduced ventriculoperitoneal shunting, fewer instances of hindbrain herniation at delivery, and improved motor outcomes [95].

Since then, open foetal MMC repair has become a standard option to be weighed against maternal risks, such as pulmonary oedema, surgical site infections, and combined maternal-foetal risks, such as chorioamniotic membrane separation, placental abruption, preterm premature rupture of membranes (PPROM), intrauterine infections, and preterm delivery (PTD).

Contemporary fetoscopic spina bifida repair approaches can be classified into one of three techniques: laparotomy-assisted foetoscopic repair, percutaneous foetoscopic repair, and percutaneous-minilaparotomy foetoscopic repair [96].

A three-layer foetal closure (dura substitute, myofascial layer, skin) should be performed whenever possible [97].

Endoscopic foetal MMC repair displays comparable in-hospital maternal and foetal safety profiles [98], as well as cost-saving compared with the open maternal–foetal surgery option [99].

Recently, several collaborating centres published long-term neurologic outcomes at 30 months of life, demonstrating a 46–54% independent ambulation rate in patients undergoing prenatal foetoscopic repair compared with the 42% independent ambulation rate at 30 months of life observed in the original MOMS trial [100, 101].

In summary, the current evidence suggests that foetoscopic repair of open spina bifida provides the same degree of benefit to the child as open maternal–foetal surgery while minimising the risks to the mother in the index pregnancy and future pregnancies [102].

The effect of in utero MMC repair on the urinary tract has been less clear, with early published studies unable to show a positive effect of in utero MMC repair on the lower and upper urinary tract early in life [103-105].

More recently published papers on larger series and with longer follow-up show a more realistic picture with diverse outcomes. A cohort of patients in the MOMS trial who were evaluated at school age showed less utilisations of CIC (62% vs 87%) and anticholinergic therapy (44% vs 67%) [106]. The voiding status was significantly different favouring the in utero treated patients with 24% voiding volitionally versus 4% in the post-natal group.

The Zurich group has demonstrated lower rates of CIC utilisation in newborns who underwent in utero MMC repair compared to post-natal repair, but this difference was not seen with longer follow up; nor were the majority of patients voiding spontaneously [107, 108].

Macedo *et al.* found no protective effect of prenatal closure on lower urinary tract function in their patients [109, 110].

Zaccaria *et al.* found no difference in the use of anticholinergics or CIC between the two groups (CIC > 80%, AC > 75% in both prenatal and post-natal closed patients) [111].

Early outcome UDS analyses demonstrated a lower incidence of high-risk bladders in the foetoscopic patients with a trend toward clinically significant improvement compared to the open repair group in regard to all evaluated metrics [112].

The most important limitation to more concrete outcomes data is the difficulty in critically comparing UDS across institutions: to date, UDS data have not been helpful in distinguishing a short or long-term impact of prenatal closure.

Urodynamic studies are performed using very different methods within centres and across centres making any reasonable comparison of results exceedingly difficult. It is obvious that we must strive to achieve a degree of uniformity in how we evaluate patients and how we perform UDS [113].

7. MANAGEMENT

The medical care of children with neurogenic bladder requires an on-going multi-disciplinary approach. There is some controversy about optimal timing of the management; proactive vs. expectant management [114, 115]. Even with a close expectant management, e.g. in one series 11 out of 60 needed augmentation within a follow-up of 16 years, and seven out of 58 had a decrease in total renal function, which was severe in two [116]. During the treatment it should also be taken into account that, in spinal dysraphism patients, QoL is related to urinary incontinence independent of the type and level of spinal dysraphism and the presence or absence of a liquor shunt [117]. A recent systematic review and meta-analysis including eight observational studies on 652 paediatric patients revealed that proactive management following initial assessment was associated with significantly lower risks of secondary VUR, non-febrile UTI and renal deterioration [118].

Foetal open and endoscopic surgery for MMC are performed to close the defect as early as possible in order to reduce neurological, orthopaedic and urological problems [119]. (See chapter on pre-natal management).

7.1 Proactive approach and early management with intermittent catheterisation

In all infants, starting intermittent catheterisation (IC) soon after birth and closure of the defect by a neurosurgeon has been shown to decrease renal complications and the need for later augmentation [120]. In infants without any clear sign of outlet obstruction, this may be delayed but only in very selected cases. These infants should be monitored very closely for UTIs and changes of the urinary tract with US and UDS. The early initiation of CIC in the new-born period makes it easier for caregivers to master the procedure and for children to accept it as they grow older [121]. Up to 90% of patients will perform CIC.

A Cochrane review as well as a recent study showed that there is a lack of evidence to state that the incidence of UTI is affected by use of a sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy [122, 123]. Looking at the microbiological milieu of the catheter, there was a trend for reduced recovery of potentially pathogenic bacteria with the use of hydrophilic catheters. Also, a trend was seen for a higher patient satisfaction with the use of hydrophilic catheters. Based on the current data, it is not possible to state that one catheter type, technique or strategy is better than any other [124].

7.2 Proactive approach and early start of medical therapy

Antimuscarinic/anticholinergic medication reduces and/or prevents detrusor overactivity and lowers intravesical pressure, and is generally initiated together with the start of CIC, soon after birth [125, 126]. The effects and side effects depend on the distribution of the M1-M5 receptors [127]. In the bladder, the subtype M2 and M3 are present. Oxybutynin is most frequently used in children with neurogenic bladder with a success rate of up to 93%. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision, heat intolerance, constipation, etc.) limit its use. Intravesical administration gives a significant higher bioavailability due to the circumvention of the intestinal first pass metabolism, as well as a possible local influence on C-fiber-related activity and can be responsible for a better and stronger clinical effect [128].

Intravesical administration should be considered in patients with severe side-effects, as long-term results demonstrated that it was well-tolerated, effective and safe [129]. Transdermal administration also leads to a substantially lower ratio of N-desethyloxybutynin to oxybutynin plasma levels, but treatment-related skin reactions have been shown in 12 out of 41 patients. There are some concerns about central anticholinergic adverse effects associated with oxybutynin. A double blinded cross-over trial, as well as a case control study, showed no deleterious effect on children's attention and memory [130]. Tolterodine, solifenacin, fesoterodine, trospium chloride and propiverine and their combinations can also be used in children [131].

The dosage for oral oxybutynin is between 0.1 to 0.2 mg/kg bodyweight (BW) [126] given three times daily. The intravesical dosage of oxybutynin can be up to 0.7 mg/kg BW/daily, divided over two instillations per day, and transdermally up to 0.45 mg/kg BW daily. The dosage of the other drugs is: tolterodine 0.12 mg/kg BW/day, or higher if necessary [132], solifenacin 0.07 to 0.33 mg/kg BW/day with a maximum of 10 mg per day (single dose) [133], fesoterodine 4-8 mg per day (single dose) for children > 25 kg BW, propiverine 0.8 mg/kg BW/day divided in two dosages [134] and trospium chloride up to three times 15 mg starting with three times 5 mg [135]. None of the anticholinergics is officially registered for the use in children except oxybutynin and propiverine for children over the age of 5 years. They remain as off-label use in many countries, which should be explained to the caregivers.

Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation [136]. Beta-3 agonists, such as mirabegron, as an adjuvant treatment have been shown to be effective and safe in some recent studies of children (> five years) and adolescents [137].

Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder. Doxazosin with an initial dose of 0.5 to 1.0 mg or tamsulosin hydrochloride in a medium (0.0002-0.0004 mg/kg/day) or double dose has been given to children with neurogenic bladders [138]. It was well tolerated but not effective at least in one study [139].

Botulinum toxin A injections. In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option. In children, continence could be achieved in 32-100% of patients, a decrease in maximum detrusor pressure of 32% to 54%, an increase of maximum cystometric capacity from 27% to 162%, and an improvement in bladder compliance of 28%-176%. Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [140, 141]. Also, injections into the trigone seem to be safe with regard to reflux and upper tract damage; whether it has some benefit has not been further investigated. Of the patients with failed augmentation cystoplasty, 43% responded well to intra-detrusor onabotulinum toxin A injections in a recent series of 30 patients [142].

The most used dose of onabotulinum toxin A is 8 U/kg with a maximum dose of 200 U [143]. A recent randomised trial demonstrated that 200 U have greater efficacy in reducing bladder pressure and increasing bladder capacity compared to 50 or 100 U [144]. Onabotolinum toxin A can be effective between three to twelve (0-25) months and repeated injections are effective for up to ten years [145, 146].

Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improving voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [147].

7.3 Urethral Dilatation

The aim is to lower the pop-off pressure by lowering the detrusor leak-point pressure (DLPP) by dilatation of the external sphincter under general anaesthesia up to 36 Charr. Some studies showed that, especially in females, the procedure is safe, and in selected patients, effective [148, 149].

7.4 Neuromodulation

Intravesical electrical stimulation of the bladder was introduced 40 years ago, and its practice is limited to a few centres with different results and poor evidence [150]. A randomised controlled trial failed to show efficacy [151]. Furthermore, this type of treatment is time-consuming, for patients and health care professionals.

Nerve stimulation via the percutaneous, transcutaneous and sacral route has been studied in patients with neurogenic bladder, including spinal dysraphism [152]. Transcutaneous nerve stimulation has been found to be effective in treating overactive bladder disorders in children with non-neurogenic lower urinary tract disorders, but its effectiveness has not been established for children with neurogenic detrusor sphincter dysfunction (NDSD) [153]. The same data have been reported for sacral nerve modulation (SNM), where there is no clear evidence for its effectiveness in neurogenic overactivity in the paediatric population. In a prospective study using SNM in children with NDSD, urodynamic variables revealed no statistically significant difference except that functional bladder capacity was better in the oxybutynin group and leak point pressure better in the SNM group [154]. Better results have been reported in children with acquired neurologic dysfunction, as in myelitis and partial spinal cord injury. Myelomeningocele patients never reported improvement, while different results are reported on occult spinal dysraphism in different series [155, 156]. For this reason, SNM use in spinal dysraphisma remains investigational and must be limited to well-selected cases and centres [157]. Better results have been reported on neurogenic bowel dysfunction management either with transcutaneous nerve stimulation alone or in combination with SNM [158-160].

Electrical stimulation is often associated with re-innervation procedures. At the moment there is no evidence about the efficacy of the Xiao procedure (intradural somatic-to-autonomic nerve anastomosis) and for this reason this procedure cannot be recommended outside of specific clinical trials [161, 162].

In conclusion, intravesical electrical stimulation, tibial and transcutaneous sacral nerve stimulation as well as neuromodulation, showed a weak grade of evidence, with limited and unpredictable efficacy in spinal dysraphism patients, and must be considered experimental with its use is limited to selected patients.

7.5 Vesicostomy

In some patients not responding to initial treatment, a vesicostomy, preferably a Blocksom stoma [163], may be the only solution to protect their upper tracts. The same is true if transurethral catheterisation is impossible.

In the majority this is a temporary measure: after closure, careful follow-up and evaluation remain necessary in order to determine if further measures such as augmentation etc. are necessary, but in some no other surgery is mandatory [164].

In older patients who are already managing their bowels with diapers, are wheelchair bound or who are not motivated to be continent or capable of carrying out a strict catheterisation regimen because of developmental delay, a long-term vesicostomy may offer a simple and satisfactory bladder management strategy [165].

Another possibility is a continent catheterisable vesicocutaneous fistula (VCF) as proposed by Ting *et al.* Continence is achieved in 88% with a low rate of complications [166].

A cystostomy button may be an alternative, with a complication rate (mostly UTI) of up to 34% within a mean follow-up of 37 months [167].

7.6 Management of bowel emptying problems

Children with neurogenic bladder usually also have a neurogenic bowel dysfunction. Chronic obstipation and faecal incontinence sometimes with "overflow" incontinence co-exist. Faecal incontinence may have an even greater impact on QoL, as the odour can be a reason for social isolation. The aim of each treatment is to obtain a smooth, regular bowel emptying and to achieve continence and independence. The regime should be tailored to the patient's need, which may change over time. The Pediatric Neurogenic Bowel Dysfunction Score (PNBDS) can be used to monitor the bowel management regimen, because it is validated for patients aged 6-18 years [168]. In a recently published study about "patient-reported outcomes" (PROM), only 32 out of 62 (52%) reported satisfying results with their current bowel management [169], demonstrating that there is some room for improvement.

Besides a diet with small portioned fibre food (around age + 5g/per day as a minimum) [170] and adequate fluid intake (e.g. 1-3 years around 820 ml, 4-6 years 940 ml, 7-9 years 970 ml, 10-13 years 1,170 ml, 13-15 years 1,330 ml, 15-18 years 1,530 ml [171]) to keep a good fluid balance [126], patients and caregivers should be encouraged to take care of a balanced diet including vegetables and fruits avoiding too much constipating food such as cheese and white rice.

Besides dietary changes, in the beginning, faecal incontinence is managed most commonly with mild laxatives, such as mineral oil, lactulose, polyethylene glycol, macrogol 3350, milk of magnesia, bisacodyl or sennosides [172], which can be combined with enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time, digital stimulation by parents/caregivers or in older patients by themselves as well as rectal suppositories (glycerine/glycerol, bisacodyl or sodium bicarbonate (Lecicarbon)) can be considered in specific situations [173].

There are no good data to support non-invasive electrostimulation, such as transcutaneous electrical nerve stimulation (TENS), posterior tibial nerve stimulation (PTNS) or intravesical or transrectal electrostimulation for patients with a neurogenic bowel dysfunction caused by spinal dysraphism.

Today, transanal irrigation is one of the most important treatments for patients with neurogenic bowel incontinence. Regular irrigations significantly reduce the risk for faecal incontinence also in the long run in up to 90% of the patients [174-176]. The risk of irrigation induced perforation of the bowel is estimated as one per 55,000 [177]. During childhood, most children depend on the help of their caregivers. Quality of Life (QoL) is improved by transanal irrigation, but patient training and careful follow-ups are recommended [178]. Up to 60% of patients could achieve stool continence using conservative bowel management [179].

In the long term, patients who have tried all conservative therapy options but are unable to achieve acceptable stool continence, or for whom transanal irrigation becomes difficult or impossible due to anatomical or social factors, should be offered a surgical option. One option is an antegrade irrigation using a MACE-stoma (Malone Antegrade Continence Enema), which is placed in the lower right abdomen or umbilicus. It can also be placed in the left abdomen [180, 181]. Usually, the appendix is used as a continent channel to the skin, but if the appendix is not available a short segment of ileum or a tubularised flap of the cecum/colon can be used. The operations can be done laparoscopically, robot-assisted or open with no significant instead of huge differences in the outcome [182]. In a long-term study of 105 patients with a MACE stoma, 69% had successful bowel management. They were started on normal saline, but some switched to GoLYTELY (PEG-3350 and electrolyte solution). Additives (biscodyl, glycerin etc.) were needed in 34% of patients. Stomal complications occurred in 63% (infection, leakage, and stenosis) of patients, 33% required surgical revision and 6% eventually required diverting ostomies [183]. As some patients have difficulties with flushing the ACE, protocols are available to manage these problems [184]. In addition, patients need to be informed that the antegrade irrigation is time consuming, taking at least 20-60 minutes. In a recently published long-term study, two out of 43 patients did not use their ACE-stoma any longer, 15 out of 43 used their channel almost daily, 71% complained that performing the irrigation was time-consuming, 18% reported pain during the enema and 59% were satisfied with their defecation status [185].

The use of a cecostomy tube or another button device is an alternative for the creation of a catheterisable channel from the bowel. It is placed under fluoroscopic guidance or via laparoscopy [186]. In one study 22 out of 34 (65%) patients/caregivers responded to a questionnaire 4.1 years after insertion of the tube and reported a significant improvement in QoL after initiation of the antegrade continence enema therapy [187].

A colostomy may be seen as the last option if all other techniques and options fail. If the stoma is placed correctly, patients are completely continent for stool. Patients with a colostomy are satisfied with improvements and some patients report a desire to have been informed about this option much earlier [188, 189].

7.7 Secondary Reflux

Up to 30% of children with neurogenic bladder have secondary VUR caused by detrusor external sphincter dyssynergia and/or poor bladder compliance [190]. VUR in children with neurogenic bladder increases the risk of recurrent pyelonephritis which may lead to renal scaring and chronic renal failure [47]. The treatment is primarily dependent on bladder function including CIC and anticholinergics. If all conservative management options fail, augmentation with or without reimplantation should be considered [191]. Those with high grade persistent reflux at low pressure during videourodynamic studies have a higher risk of pyelonephritis [192]. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years [193]. The open techniques have a higher success rate but an increased risk of inducing obstruction [194].

7.8 Bladder augmentation

In patients where conservative treatment including onabotulinum toxin A fails to keep a low-pressure reservoir with a good capacity and compliance, bladder augmentation should be offered. For augmentation, ileal and colonic segments can be used [32]. Gastric segments are rarely used due to associated complications such as the haematuria-dysuria syndrome as well as secondary malignancies, which arise earlier than with other intestinal segments [195-198]. Enterocystoplasty increases bladder capacity, reduces storage pressure and can improve the drainage of the upper urinary tract [199, 200]. A good continence rate can be achieved with or without additional bladder outlet procedures, depending on the function of the sphincter [201]. In those who are not able to perform CIC through the urethra, a continent cutaneous channel should be offered.

Patients with myelomeningocele do have a high rate of surgical interventions; a large study from Japan showed that patients under the age of 18 years have an average of 0.6 operations per year. In adulthood, this is reduced to one operation every five years [202]. Following augmentation, surgical complications and revision rates are high. The 30-day all over event rate in the American College of Surgeons' National Surgical Quality Database is approximately 30% (23-33%) with a re-operation rate in this short time period of 13% [203, 204]. In these patients with long-life expectancy, the complication rate clearly increases with the follow-up period, demonstrating the need for life-long follow-up [205]. The ten-year cumulative complication incidence from the Pediatric Health Information System showed a rate of bladder rupture in up to 6.4%, small bowel obstruction in up to 10.3%, bladder stones in 36%, pyelonephritis in more than a third and a re-augmentation rate of up to 13% [206]. Bladder perforation, as one of the worst complications, occurs in 3-13%. The rate of VP-shunt infections after gastrointestinal and urological procedures ranges between 0-22%. One American study showed that bowel preparation seems not to have a significant influence on the infection rate (10.5% vs. 8.3%) [207]. In addition to surgical complications, the metabolic consequences and complications associated with incorporating bowel segments must also be considered. These may include imbalances in acid-base levels, a decrease in vitamin B12 levels, and a loss of bone density. Stool frequency and diarrhoea can increase after exclusion of bowel segments [199] and in addition, these patients have a lifelong increased risk of developing secondary malignancies [208, 209]. Therefore, lifelong follow-up of these patients is required, including physical examination, US, blood gas analysis, renal function and vitamin B12 if ileum is used. Endoscopic evaluation starting ten years after augmentation is not cost-effective [210, 211], but may prevent some advanced cancer, and small stone fragments can be removed during this procedure. Patients must be informed about the increased risk of secondary malignancies. Alarming symptoms include gross haematuria and de novo upper urinary tract dilatation. UDS after bladder augmentation are only indicated if upper tract dilatation and/or incontinence re-occur or persist [212].

Adverse effects of intestinal cystoplasties can be avoided using ureterocystoplasty. However, the combination of a small, contracted bladder, associated with a severe dilation of the ureter of a non-functioning kidney is quite rare. In these very selected cases, ureterocystoplasty is an option [213, 214].

Partial detrusorectomy or detrusormyotomy (autoaugmentation) with the creation of a diverticulum avoids metabolic complications with the use of intestinal segments. The reports are conflicting; therefore, it may be used in selected cases. For a successful outcome, a pre-operative bladder capacity of 75-80% of the expected volume seems necessary [215-217]. Seromuscular cystoplasty has also not proven to be as successful as standard augmentation with intestine [218, 219].

Tissue engineering, even if successful in vitro and some animal models, does not reach the results of using intestinal segments [220, 221]. Therefore, these alternatives should be considered as experimental and used only in controlled trials [222].

7.9 Bladder outlet procedures

So far, no available pharmacological treatment including adrenergic receptor stimulation of the bladder neck has been validated to increase bladder outlet resistance [223]. An increase of outlet resistance after puberty has been demonstrated in boys because of prostate gland enlargement and, in girls, because of oestrogenisation [75].

The purpose of the bladder outlet procedure is to increase the bladder outlet resistance to achieve continence. The use of the term continence is variable and often mystifying. Most outlet procedures (except for artificial urinary sphincters) will create a fixed resistance and can attain dryness but spontaneous emptying may not be possible. As catheterising through a reconstructed bladder neck or a urethra compressed by a sling may not be easy, the bladder outlet procedure will often be combined with the creation of a continent catheterisable urinary channel to enable complete emptying [114]. Pre-operatively a good bladder capacity and adequate compliance are essential to achieve urinary continence and protect the upper urinary tract, otherwise it is safe to combine bladder augmentation with outlet procedures. The choice of a bladder outlet procedure with or without concomitant surgery such as bladder augmentation and a continent catheterisable urinary channel is influenced by the patient's needs, gender, and bladder function and the surgeon's preference.

A sling is placed around the urethra for additional coaptation to increase resistance. A continence rate between 40-100% can be achieved using fascial slings with an autologous fascial strip or artificial material. In most cases this is achieved in combination with bladder augmentation [223-228]. A bladder outlet procedure without augmentation has its own inherent risks of creating high pressure bladder resulting in an estimated 10-year cumulative incidence of augmentation cystoplasty in 30%, additional continence procedures in 70% (onabotulinum toxin A injections in > 30%), upper tract changes in greater than 50% and CKD in 20% [229, 230]. Cautious patient selection and close follow-up are crucial if considering a bladder outlet procedure without augmentation cystoplasty. Even in patients with a good bladder capacity and bladder compliance without an indication for bladder augmentation, up to 40% will need augmentation later on. In artificial slings (in contrast to autologous slings), CIC through the urethra has a high complication rate that is much higher in girls [231, 232].

A bladder neck reconstruction procedure involves narrowing the bladder neck and proximal urethra and lengthening its full thickness into the trigone. There are various techniques reported in the literature. Bladder neck reconstruction is used mostly in exstrophy patients with acceptable results. However, in children with a neurogenic bladder the results are less satisfactory [233]. In most patients, the creation of a continent catheterisable stoma is necessary due to difficulties in performing CIC via the urethra. In one series, 10% to a third still performed CIC via the urethra with a re-operation rate between 67% and 79% after a median follow-up between seven and ten years [234].

Early results of bladder outlet procedures (bladder neck reconstruction or slings) are usually far from perfect and in the long-term follow-up nearly 40% of patients will need re-intervention to achieve dryness [235]. The combination of a sling procedure together with a urethral lengthening procedure has been reported to improve continence rates [236].

Artificial urinary sphincters (AUS) were introduced by Scott in 1973 [237]. The continence rates in the literature in selected patients can be up to 83% [238, 239]. Post-pubertal patients, who can void voluntarily are good candidates, if they are manually dexterous. Better results were described when the AUS was implanted on a non-operated bladder neck [240]. In very selected patients, CIC through the sphincter in an augmented bladder is possible. The erosion rate can be up to 29% and the revision rate up to 100% depending on the follow-up time [227]. Placement of an AUS does not rule out CIC.

Bulking agents have a low success rate (10-40%), which is in most cases only temporary. However, it does not adversely affect the outcome of further definitive surgical procedures [241, 242].

In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterisable stoma is an option. Bladder neck closure is often seen as the last resort to gain urinary continence in those patients with persistent urinary incontinence through the urethra. In girls, the transection is performed between the bladder neck and urethra and in boys above the prostate with preservation of the neurovascular bundle. It is an effective method to achieve continence together with a catheterisable cutaneous channel +/- augmentation as a primary or secondary procedure [243, 244]. A complication rate of up to a third and a vesicourethral/vesicovaginal fistula in up to 15% should be considered [245], together with a higher risk for bladder stones, bladder perforation and deterioration of upper tract function, if the patient is not compliant with CIC and bladder irrigations [246].

7.10 Catheterisable cutaneous channel

In most patients with a neurogenic bladder CIC is required. If this is not possible transurethrally, not preferred by the patient, or very time and/or resource consuming, a continent cutaneous catheterisable channel should be offered as well as to those with bladder outlet procedures. It is especially beneficial to wheelchair-bound patients who often have difficulties with urethral catheterisation or who are dependent on others. In long-term studies, the revision rate due to stenosis or incontinence can be as high as 50-60% depending on the type of channel (Mitrofanoff- or Monti-channel and their variations) [247, 248]. In a recent publication on the long-term usage pattern of continent catheterisable channels, only 46% were satisfied or very satisfied according to an online survey [185].

The stoma can be placed at the umbilicus or in the lower right abdominal wall using a VQZ plasty [249]. It should be carefully evaluated pre-operatively: it is extremely important that the patient can reach the stoma easily. Sometimes it has to be placed in the upper abdominal wall due to severe scoliosis mostly associated with obesity. No differences have been found between open, laparoscopic and robotic appendicovesicostomy regarding post-operative complications, surgical reintervention and stomal stenosis. A shorter hospital stay was reported for the robotic approach [250, 251].

7.11 Continent and incontinent cutaneous urinary diversion

Incontinent urinary diversion should be considered in patients who are not willing or able to perform CIC and who need urinary diversion because of upper tract deterioration. Following failed augmentation procedures, an incontinent diversion may be considered [252]. In children and adolescents, the colonic conduit has been shown to have fewer complications compared to the ileal conduit [253-256]. A total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions. Any type of major bladder and/or bladder outlet reconstruction should be performed in centres with sufficient experience in the surgical techniques, and with experienced healthcare personnel to carry out post-operative follow-up [201, 257].

8. SEXUALITY AND FERTILITY

Sexuality and fertility, while not an issue in childhood, become progressively more important as the patient gets older. This section gives a short overview regarding this topic, which will be discussed and evaluated in detail in a separate paper.

This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters [258]. The prevalence of precocious puberty is higher in girls with myelomeningocele [259]. Studies indicate that at least 15-20% of males are capable of fathering children [260] and 70% of females can conceive and carry a pregnancy to term [261]. It is therefore important to counsel patients about sexual development in early adolescence.

Women seem to be more sexually active than men based on studies from the Netherlands and the USA [262]. The level of the lesion was the main predictor of sexual activity [263]. Erectile function can be improved by sildenafil in up to 80% of male patients [264]. Only 17% to one third of patients talk to their doctors about sexuality, and 25–68% were informed by their doctors about reproductive function. Continence seems to play an important role too. In a recent study, nine out eleven females without sexual dysfunction reported continence, whereas 50 out of 59 with sexual dysfunction had some urinary incontinence [265]. Therefore, early discussion about sexuality with adolescents is recommended and should be promoted by the paediatric urologist taking care of these patients.

9. MENTAL HEALTH PROBLEMS ASSOCIATED WITH SPINAL DYSRAPHISM

The aim of this chapter is to review psychological and cognitive symptoms and disorders in persons with spinal dysraphism and to formulate consensus-based recommendations for clinical practice. In summary, patients with spinal dysraphism have higher rates of cognitive and neuropsychological deficits. Among mental health disorders, attention deficit hyperactivity disorder (ADHD), anxiety and depressive disorders predominate.

An assessment of the patient's global and specific cognitive level is essential to determine special schooling and other needs. The optimal time point is at school entry. In addition, testing with standardised, multidimensional intelligence tests (such as the Wechsler tests) is possible whenever indicated [266]. These tests are easy to perform and provide essential information for patients with spinal dysraphism [267].

A full neuropsychological assessment is not needed for every patient. It is time consuming and requires additional resources [268]. If specific neuropsychological deficits are suspected or if general intelligence tests reveal a heterogeneous cognitive profile, these tests are useful to plan specific training programmes for patients with spinal dysraphism.

Not all patients with spinal dysraphism require a full mental health assessment, as many cope well without being affected by psychological disorders. The International Children's Continence Society recommends screening for psychological symptoms and disorders [269, 270]. The first step is for professionals to familiarise themselves with those prevalent disorders in spinal dysraphism (ADHD, anxiety and depressive disorders), to clinically observe and explore the symptoms of their patients. In addition, screening with validated, broadband behavioral questionnaires is recommended for all patients. This is an extremely economical method and

provides a wealth of information in a short time. The ICCS has provided an overview of screening questionnaires for clinical practice [271]. Even a short questionnaire such as the Strengths and Difficulties Questionnaire (SDQ) is a reliable and valid instrument [272]. Even more detailed information can be derived from the Child Behavior Checklist (CBCL) [273]. The Achenbach questionnaires cover different age groups from preschool children, to school children and adolescents, young adults, adults and even the elderly. Any other validated questionnaire available can be used.

If clinical screening and questionnaires reveal marked signs of mental health problems and disorders, then a full professional assessment is clearly indicated. The aim of this assessment is to confirm or to exclude a mental health disorder [274].

If the mental health assessment leads to the diagnosis of psychological disorder, then parents and patients should be counselled in every case. In many cases, provision of information, counselling and practical advice will be sufficient for patients with spinal dysraphism [275].

If a psychological disorder with incapacitation does not sufficiently respond to counselling, then treatment according to evidence-based recommendations is recommended. This will reduce emotional distress, incapacitation and will prevent the chronification of mental health disorders.

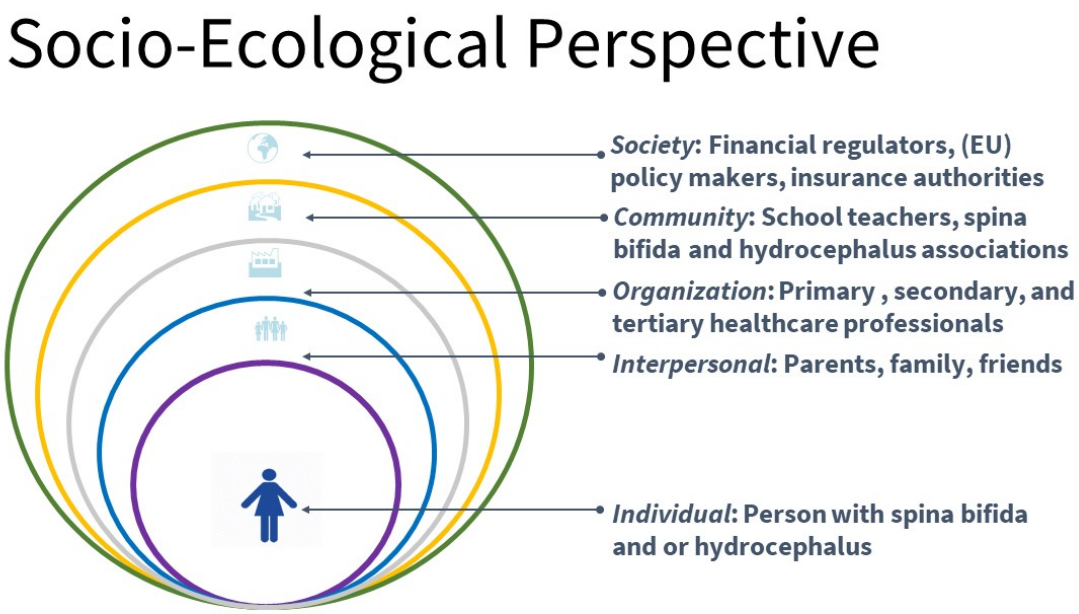
In conclusion, mental health is an important health problem which affects individuals with spinal dysraphism and their families worldwide. In particular, mental health disorders, cognitive and neuropsychological deficits need further attention.

10. PERSPECTIVES OF A SOCIO-ECOLOGICAL MODEL TOWARDS CARE

Patients with spinal dysraphism and caregivers are faced with different situations and challenges in daily life. Several environmental conditions influence patients` perspectives on one's self being and can be used to empower patients to achieve better satisfaction and participation. In this light, it is important to understand the socio-ecological model in order to enhance self-organisation of patients and caregivers and to improve clinical care [276]. Environmental levels of influence for spinal dysraphism patients could be divided as follows:

- Individual: person with spinal dysraphism
- Interpersonal: e.g. parents, family and friends
- Organisational: e.g. primary care, hospital, home care
- Community: e.g. patient/parent organisations, health care professionals, school, sport clubs
- Societal: e.g. EU policy, guidelines, health insurance

Figure 1: Environmental conditions and examples of stakeholders



Identifying stakeholders at the various levels of environmental conditions for individual patients can help initiate changes whenever needed or desired. When patients, parents, and clinicians are dealing with clinical problems, a more goal-oriented approach can be adopted [277]. Patients can identify the symptoms they find most significant, allowing the selection of the most appropriate treatment, for example, urinary incontinence. However, the experience of urinary incontinence varies among patients, and the extent to which it can be treated also depends on organisational factors at home or school. Identifying the relevant stakeholders makes it easier to achieve patient-centred goals

11. HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SPINAL DYSRAPHISM

A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [278]. A core PRO is health-related quality of life (HRQoL), a multidimensional concept that represents the patient's perception of the effect of illness and treatment on physical, psychological, and social aspects of life (1-3). Parents' reports of their child's HRQoL may additionally provide valuable information. Condition-specific HRQoL questionnaires capture issues of relevance to a specific disease and are more sensitive in providing clinical information [279-281].

Most studies show that children with spinal dysraphism have impaired HRQoL compared to the general population [282], especially a negative impact is noted particularly for physical functioning [283, 284].

Two condition-specific instruments for children with spinal dysraphism have been reported [285, 286] both of which were derived (partly) based on input from patients.

The measurement model [287, 288] of QUALAS provides an age-adapted measurement approach to HRQoL in children, teenagers and adults, and confirms that physical, social and emotional HRQoL issues related to "bladder and bowel" are consistently important throughout these age groups.

In the above-mentioned systematic review from 2016, Bakaniene *et al.* proposed that studies report the relationship between HRQoL and urinary incontinence differently, however, several of the more recent studies have shown that urinary incontinence is a main contributor to poor HRQoL issues in these children [289].

Szymanski *et al.* demonstrated that urinary incontinence may affect children with spinal dysraphism more severely with increasing age, starting at 10 years of age and continuing during the teenage years, so that the amount of urinary incontinence by then shows a strong relationship to the level of HRQoL [290]. Radojicic *et al.* showed that longer dry intervals are related to better HRQoL [289].

Faecal incontinence is related to poor HRQoL outcomes, regardless of age and amount [291]. One study has shown that after one year, treatment by bowel management in children with spinal dysraphism, overactive bladder and detrusor sphincter dyssynergia, demonstrated significant improvement for faecal constipation/incontinence, urinary incontinence and HRQoL compared to the group without bowel management (and anti-cholinergic and CIC only). The difference in HRQoL scores between these groups were significant for all domains (physical well-being, emotional well-being, self-confidence, family, friends, school, disease).

Factors related to poorer HRQoL levels in children with spinal dysraphism are also mobility difficulties, hydrocephalus or VP-shunt and cognitive dysfunction. Patient gender is generally not related to HRQoL, higher patient age is more commonly found to be associated with poor HRQoL in spinal dysraphism, including in physical and psychosocial domains [292], but these findings are not observed in more recent studies.

A consistent finding in HRQoL studies of children with spinal dysraphism is the significance of environmental factors/support. These factors include the characteristics and functioning of the child's caregivers/parents, friends, society, patient support groups and health care. HRQoL is better in families with two married or co-habitant parents, who have lower stress levels, active support from a patient advocacy group or friend support, in families with better family functioning with time to provide child support as well as in families with a higher household income or parent educational level [293].

Bakaniene *et al.* also demonstrated in the above mentioned systematic review that access to personal transportation, supplies and accessible physical layout (sidewalks, availability of ramps or elevators) at school are extremely important factors [283].

12. FOLLOW-UP, TRANSITION AND LONG-TERM CARE

Neurogenic bladder patients require lifelong follow-up including not only urological aspects but also neurological, orthopaedic, and psychological aspects as well as other disciplines, although these are out of the scope of this guideline. Regular investigation of the upper and lower urinary tract is mandatory. In patients with changes of the function of the upper and/or lower urinary tract, a complete neurological re-investigation is recommended including a total spine MRI to exclude a secondary tethered cord or worsening of the hydrocephalus. In addition, if some neurological changes are observed, a complete investigation of the urinary tract should be undertaken.

A recent study by this Guidelines Panel revealed that the priorities of patients for future expectations were as follows, in decreasing order: QoL, surgical techniques, development of new medications and sexuality/fertility issues. Male spinal dysraphism patients preferred new medications and sex/fertility issues, whereas females favoured QoL issue improvement. These factors should be considered during long-term management [294].

In those patients with urinary tract reconstruction using bowel segments, regular investigations concerning renal function, acid base balance and vitamin B12 status are mandatory to avoid metabolic complications. There is an increased risk for secondary malignancies in patients with a neurogenic bladder either with or without enteric bladder augmentations [208]. Therefore, patients need to be informed of this risk and possible signs like haematuria. Although there are insufficient data on follow-up schemes to discover secondary malignancies, after a reasonable follow-up time, an annual cystoscopy can be considered. Since the topic on transition and long-term care is of utmost importance, it will be discussed in detail in a separate document.

13. RECOMMENDATIONS

Recommendations	Strength rating
Urodynamic studies should be performed in every patient with spinal dysraphism as well as in every child with a 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.	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity, starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and the lower tract (UDS).	Strong
Start early anticholinergic medication in newborns with a suspicion of an overactive detrusor.	Strong
The use of suburothelial or intradetrusoral injection of onabotulinum toxin A is an alternative and less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	Strong
Treatment of bowel emptying problems is important to gain continence and independence. Treatment should be started with regular fluid intake and dietary measures as well as mild laxatives, rectal suppositories, and digital stimulation. If insufficient, transanal irrigation is recommended, and if this is not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	Strong
Ileal or colonic bladder augmentation is recommended in patients with therapy resistant detrusor overactivity, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risks of surgical and non-surgical complications and consequences outweigh the risk of permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing IC through the urethra.	Weak
A life-long follow-up of renal function should be available and offered to every patient.	Strong
Addressing sexuality and fertility starting before/during puberty should be offered.	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	Weak
Performing and reporting of urodynamic studies should be done according to ICCS standards.	Strong
The QUALAS, which measures HRQoL related to bladder and bowel in patients with spinal dysraphism, should be used across childhood and adolescence in research, but also form part of routine follow-up care over time, enabling the provision of targeted interventions.	Weak

Special attention should be paid to monitoring HRQoL in the clinical care of children with neurogenic bladder and bowel because they are a known risk group for poor HRQoL.	Weak
In order to maintain or improve the health-related quality of life in children with spinal dysraphism, parent and family support should be provided as part of routine follow-up care in the families of the affected individuals.	Weak
At the moment the evidence is too weak to recommend prenatal intervention to improve urological outcome and should be reserved for specialised centres in properly designed studies.	Weak
Screen for psychological symptoms and disorders with validated, broadband behavioural questionnaires at school entry or whenever indicated clinically.	Strong
If the screening is positive and reveals signs and symptoms of psychological disorders, a full professional mental health assessment should follow.	Strong
If a psychological disorder of clinical relevance and with incapacitation is present, counselling should be offered in every case.	Strong
If a mental health disorder is present and counselling alone is insufficient, treatment according to evidence-based guidelines is recommended.	Strong

14. REFERENCES

1. Phillips, B., *et al.* Oxford Centre for Evidence-Based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. 2014. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009
2. Guyatt, G.H., *et al.* Going from evidence to recommendations. BMJ, 2008. 336: 1049. https://pubmed.ncbi.nlm.nih.gov/18467413/
3. Yavuz, A., *et al.* The Relationship Between Nocturnal Enuresis and Spina Bifida Occulta: A Prospective Controlled Trial. Urology, 2018. 120: 216. https://pubmed.ncbi.nlm.nih.gov/30099128/
4. EUROCAT. European network of population-based registries for the epidemiological surveillance of congenital anomalies. https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-network/eurocat-network-overview_en
5. Best, B.J., *et al.* Trends in the early care of infants with myelomeningocele in the United States 2012-2018. Childs Nerv Syst, 2023. 39: 2413. https://pubmed.ncbi.nlm.nih.gov/36308541/
6. Liu, S., *et al.* Association of maternal risk factors with the recent rise of neural tube defects in Canada. Paediatr Perinat Epidemiol, 2019. 33: 145. https://pubmed.ncbi.nlm.nih.gov/30920008/
7. Bakker, M.K., *et al.* Analysis of Mortality among Neonates and Children with Spina Bifida: An International Registry-Based Study, 2001-2012. Paediatr Perinat Epidemiol, 2019. 33: 436. https://pubmed.ncbi.nlm.nih.gov/31637749/
8. Orioli, I.M., *et al.* The Latin American network for congenital malformation surveillance: ReLAMC. Am J Med Genet C Semin Med Genet, 2020. 184: 1078. https://pubmed.ncbi.nlm.nih.gov/33319501/
9. Salazar-Reviakina, A., *et al.* Characterization of Risk Factors for Neural Tube Defects: A Case-Control Study in Bogota and Cali, Colombia, 2001-2018. J Child Neurol, 2021. 36: 509. https://pubmed.ncbi.nlm.nih.gov/33393845/
10. Bhide, P., *et al.* A national estimate of the birth prevalence of congenital anomalies in India: systematic review and meta-analysis. BMC Pediatr, 2018. 18: 175. https://pubmed.ncbi.nlm.nih.gov/29801440/
11. Kondo, A., *et al.* Real prevalence of neural tube defects in Japan: How many of such pregnancies have been terminated? Congenit Anom (Kyoto), 2019. 59: 118. https://pubmed.ncbi.nlm.nih.gov/30883906/
12. Liu, J., *et al.* Sex differences in the prevalence of neural tube defects and preventive effects of folic acid (FA) supplementation among five counties in northern China: results from a population-based birth defect surveillance programme. BMJ Open, 2018. 8: e022565. https://pubmed.ncbi.nlm.nih.gov/30413501/
13. Atlaw, D., *et al.* Magnitude and determinants of neural tube defect in Africa: a systematic review and meta-analysis. BMC Pregnancy Childbirth, 2021. 21: 426. https://pubmed.ncbi.nlm.nih.gov/34126936/

14. Oumer, M., *et al.* Prevalence of Spina Bifida among Newborns in Africa: A Systematic Review and Meta-Analysis. Scientifica (Cairo), 2020. 2020: 4273510.
https://pubmed.ncbi.nlm.nih.gov/33083093/
15. Ssentongo, P., *et al.* Birth prevalence of neural tube defects in eastern Africa: a systematic review and meta-analysis. BMC Neurol, 2022. 22: 202.
https://pubmed.ncbi.nlm.nih.gov/35650541/
16. Blencowe, H., *et al.* Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. Ann N Y Acad Sci, 2018. 1414: 31.
https://pubmed.ncbi.nlm.nih.gov/29363759/
17. Kancherla, V., *et al.* Factors Associated with Early Neonatal and First-Year Mortality in Infants with Myelomeningocele in California from 2006 to 2011. Am J Perinatol, 2021. 38: 1263.
https://pubmed.ncbi.nlm.nih.gov/32473597/
18. Berihu, B.A., *et al.* Maternal risk factors associated with neural tube defects in Tigray regional state of Ethiopia. Brain Dev, 2019. 41: 11.
https://pubmed.ncbi.nlm.nih.gov/30075882/
19. Bitew, Z.W., *et al.* Magnitude and Associated Factors of Neural Tube Defects in Ethiopia: A Systematic Review and Meta-Analysis. Glob Pediatr Health, 2020. 7: 2333794x20939423.
https://pubmed.ncbi.nlm.nih.gov/32743026/
20. Mai, C.T., *et al.* Changes in Spina Bifida Lesion Level after Folic Acid Fortification in the US. J Pediatr, 2022. 249: 59.
https://pubmed.ncbi.nlm.nih.gov/35772508/
21. Dixon, M., *et al.* High potential for reducing folic acid-preventable spina bifida and anencephaly, and related stillbirth and child mortality, in Ethiopia. Birth Defects Res, 2019. 111: 1513.
https://pubmed.ncbi.nlm.nih.gov/31424635/
22. Shlobin, N.A., *et al.* Folate fortification and supplementation in prevention of folate-sensitive neural tube defects: a systematic review of policy. J Neurosurg Pediatr, 2020. 27: 294.
https://pubmed.ncbi.nlm.nih.gov/33338998/
23. Saing, S., *et al.* Real-World Cost Effectiveness of Mandatory Folic Acid Fortification of Bread-Making Flour in Australia. Appl Health Econ Health Policy, 2019. 17: 243.
https://pubmed.ncbi.nlm.nih.gov/30617458/
24. WHO, Periconceptional folic acid supplementation to prevent neural tube defects, in: e-Library of Evidence for Nutrition Actions (eLENA). 2023.
25. Kancherla, V., *et al.* Reductions in child mortality by preventing spina bifida and anencephaly: Implications in achieving Target 3.2 of the Sustainable Development Goals in developing countries. Birth Defects Res, 2019. 111: 958.
https://pubmed.ncbi.nlm.nih.gov/30070775/
26. Obrycki, J.F., *et al.* A case-control analysis of maternal diet and risk of neural tube defects in Bangladesh. Birth Defects Res, 2019. 111: 967.
https://pubmed.ncbi.nlm.nih.gov/30989821/
27. Torre, M., *et al.* Long-term urologic outcome in patients with caudal regression syndrome, compared with meningomyelocele and spinal cord lipoma. J Pediatr Surg, 2008. 43: 530.
https://pubmed.ncbi.nlm.nih.gov/18358295/
28. Maerzheuser, S., *et al.* German network for congenital uro-rectal malformations: first evaluation and interpretation of postoperative urological complications in anorectal malformations. Pediatr Surg Int, 2011. 27: 1085.
https://pubmed.ncbi.nlm.nih.gov/21792651/
29. Hinman, F., *et al.* Vesical and Ureteral Damage from Voiding Dysfunction in Boys Without Neurologic or Obstructive Disease. J Urol, 2017. 197: S127.
https://pubmed.ncbi.nlm.nih.gov/28012756/
30. Ochoa, B. Can a congenital dysfunctional bladder be diagnosed from a smile? The Ochoa syndrome updated. Pediatr Nephrol, 2004. 19: 6.
https://pubmed.ncbi.nlm.nih.gov/14648341/
31. Stein, R., *et al.* EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment. Neurourol Urodyn, 2020. 39: 45.
https://pubmed.ncbi.nlm.nih.gov/31724222/
32. Stein, R., *et al.* EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part II operative management. Neurourol Urodyn, 2020. 39: 498.
https://pubmed.ncbi.nlm.nih.gov/31794087/
33. Meneses, V., *et al.* Latex allergy guidelines for people with spina bifida. J Pediatr Rehabil Med, 2020. 13: 601.
https://pubmed.ncbi.nlm.nih.gov/33285646/
34. Bauer, S.B. Neurogenic bladder: etiology and assessment. Pediatr Nephrol, 2008. 23: 541.
https://pubmed.ncbi.nlm.nih.gov/18270749/

35. Tarcan, T., *et al.* Long-term followup of newborns with myelodysplasia and normal urodynamic findings: Is followup necessary? J Urol, 2001. 165: 564.
https://pubmed.ncbi.nlm.nih.gov/11176436/
36. Hopps, C.V., *et al.* Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup. J Urol, 2003. 169: 305.
https://pubmed.ncbi.nlm.nih.gov/12478177/
37. Thorup, J., *et al.* Urological outcome after myelomeningocele: 20 years of follow-up. BJU Int, 2011. 107: 994.
https://pubmed.ncbi.nlm.nih.gov/20860652/
38. Veenboer, P.W., *et al.* Upper and lower urinary tract outcomes in adult myelomeningocele patients: a systematic review. PLoS One, 2012. 7: e48399.
https://pubmed.ncbi.nlm.nih.gov/23119003/
39. Lloyd, J.C., *et al.* Reviewing definitions of urinary continence in the contemporary spina bifida literature: a call for clarity. J Pediatr Urol, 2013. 9: 567.
https://pubmed.ncbi.nlm.nih.gov/23507290/
40. Wiener, J.S., *et al.* Bladder Management and Continence Outcomes in Adults with Spina Bifida: Results from the National Spina Bifida Patient Registry, 2009 to 2015. J Urol, 2018. 200: 187.
https://pubmed.ncbi.nlm.nih.gov/29588216/
41. Orphanet, Knowledge on rare diseases and orphan drugs.
https://www.orpha.net/en/other-information/about-orphan-drugs
42. Panicker, J.N., *et al.* Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol, 2015. 14: 720.
https://pubmed.ncbi.nlm.nih.gov/26067125/
43. Panicker, J.N. Neurogenic Bladder: Epidemiology, Diagnosis, and Management. Semin Neurol, 2020. 40: 569.
https://pubmed.ncbi.nlm.nih.gov/33065745/
44. Polfuss, M., *et al.* Weight Status of Children Participating in the National Spina Bifida Patient Registry. Pediatrics, 2022. 150.
https://pubmed.ncbi.nlm.nih.gov/36416007/
45. Stepanczuk, B.C., *et al.* Young adults with spina bifida may have higher occurrence of prehypertension and hypertension. Am J Phys Med Rehabil, 2014. 93: 200.
https://pubmed.ncbi.nlm.nih.gov/24088776/
46. Adams, C.M., *et al.* Age-based risk of end-stage kidney disease in patients with myelomeningocele. J Pediatr Urol, 2023. 19: 195.e1.
https://pubmed.ncbi.nlm.nih.gov/36628830/
47. Ekberlİ, G., *et al.* Risk determination for upper urinary tract damage in children with neuropathic bladder. J Paediatr Child Health, 2023. 59: 863.
https://pubmed.ncbi.nlm.nih.gov/36999336/
48. Chu, D.I., *et al.* Estimated kidney function in children and young adults with spina bifida: A retrospective cohort study. Neurourol Urodyn, 2019. 38: 1907.
https://pubmed.ncbi.nlm.nih.gov/31286557/
49. Dangle, P.P., *et al.* Cystatin C-calculated Glomerular Filtration Rate-A Marker of Early Renal Dysfunction in Patients With Neuropathic Bladder. Urology, 2017. 100: 213.
https://pubmed.ncbi.nlm.nih.gov/27542858/
50. Millner, R.O., *et al.* Albuminuria in Pediatric Neurogenic Bladder: Identifying an Earlier Marker of Renal Disease. Urology, 2019. 133: 199.
https://pubmed.ncbi.nlm.nih.gov/31454657/
51. Mayo, S., *et al.* Clinical laboratory automated urinalysis: comparison among automated microscopy, flow cytometry, two test strips analyzers, and manual microscopic examination of the urine sediments. J Clin Lab Anal, 2008. 22: 262.
https://pubmed.ncbi.nlm.nih.gov/18623125/
52. Ben-David, R., *et al.* Asymptomatic bacteriuria and antibiotic resistance profile in children with neurogenic bladder who require clean intermittent catheterization. Spinal Cord, 2022. 60: 256.
https://pubmed.ncbi.nlm.nih.gov/34446838/
53. Zegers, B.S., *et al.* Urinary tract infections in children with spina bifida: an inventory of 41 European centers. Pediatr Nephrol, 2009. 24: 783.
https://pubmed.ncbi.nlm.nih.gov/19066975/
54. Madden-Fuentes, R.J., *et al.* Variation in definitions of urinary tract infections in spina bifida patients: a systematic review. Pediatrics, 2013. 132: 132.
https://pubmed.ncbi.nlm.nih.gov/23796735/
55. Forster, C.S., *et al.* Defining Urinary Tract Infections in Children With Spina Bifida: A Systematic Review. Hosp Pediatr, 2021. 11: 1280.
https://pubmed.ncbi.nlm.nih.gov/34697071/

56. t Hoen, L.A., *et al.* Update of the EAU/ESPU guidelines on urinary tract infections in children. J Pediatr Urol, 2021. 17: 200.
https://pubmed.ncbi.nlm.nih.gov/33589366/
57. Zhou, G., *et al.* Association of Renal Function (Estimate Glomerular Filtration Rate) with the Number of Febrile Urinary Tract Infections in Children with Neurogenic Bladder. Eur J Pediatr Surg, 2023. 33: 499.
https://pubmed.ncbi.nlm.nih.gov/36720248/
58. Mariani, F., *et al.* The impact of constant antibiotic prophylaxis in children affected by spinal dysraphism performing clean intermittent catheterization: a 2-year monocentric retrospective analysis. Childs Nerv Syst, 2022. 38: 605.
https://pubmed.ncbi.nlm.nih.gov/34523011/
59. Zegers, S.H., *et al.* The influence of antibiotic prophylaxis on bacterial resistance in urinary tract infections in children with spina bifida. BMC Infect Dis, 2017. 17: 63.
https://pubmed.ncbi.nlm.nih.gov/28081719/
60. Williams, G., *et al.* Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev, 2023. 4: Cd001321.
https://pubmed.ncbi.nlm.nih.gov/37068952/
61. Liu, J., *et al.* Value of sufficient clean intermittent catheterization in urinary tract infection and upper urinary tract protection in children with neurogenic bladder. J Pediatr Urol, 2022. 18: 499.e1.
https://pubmed.ncbi.nlm.nih.gov/35527206/
62. Huen, K.H., *et al.* Neomycin-polymyxin or gentamicin bladder instillations decrease symptomatic urinary tract infections in neurogenic bladder patients on clean intermittent catheterization. J Pediatr Urol, 2019. 15: 178.e1.
https://pubmed.ncbi.nlm.nih.gov/30611650/
63. Kanaheswari, Y., *et al.* Urinary tract infection and bacteriuria in children performing clean intermittent catheterization with reused catheters. Spinal Cord, 2015. 53: 209.
https://pubmed.ncbi.nlm.nih.gov/25420498/
64. Fernbach, S.K., *et al.* Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol, 1993. 23: 478.
https://pubmed.ncbi.nlm.nih.gov/8255658/
65. Togo, M., *et al.* Can ultrasound measurement of bladder wall thickness be a useful adjunct for regular urodynamics in children with spina bifida? J Pediatr Urol, 2021. 17: 734.e1.
https://pubmed.ncbi.nlm.nih.gov/34332835/
66. Sturm, R.M., *et al.* Bladder wall thickness in the assessment of neurogenic bladder: a translational discussion of current clinical applications. Ann Transl Med, 2016. 4: 32.
https://pubmed.ncbi.nlm.nih.gov/26889485/
67. Shiroyanagi, Y., *et al.* The significance of 99mtechnetium dimercapto-succinic acid renal scan in children with spina bifida during long-term followup. J Urol, 2009. 181: 2262.
https://pubmed.ncbi.nlm.nih.gov/19296988/
68. Levine, D.N. The pathogenesis of syringomyelia associated with lesions at the foramen magnum: a critical review of existing theories and proposal of a new hypothesis. J Neurol Sci, 2004. 220: 3.
https://pubmed.ncbi.nlm.nih.gov/15140600/
69. Wu, W., *et al.* Validation of a shortened MR imaging protocol for pediatric spinal pathology. Childs Nerv Syst, 2023. 39: 3163.
https://pubmed.ncbi.nlm.nih.gov/36997725/
70. Yamada, S., *et al.* Pathophysiology of tethered cord syndrome: correlation with symptomatology. Neurosurg Focus, 2004. 16: E6.
https://pubmed.ncbi.nlm.nih.gov/15209489/
71. Borgstedt-Bakke, J.H., *et al.* The incidence and effect of tethered cord release for tethered cord syndrome in patients with myelomeningocele: a population-based study. J Neurosurg Pediatr, 2020. 26: 269.
https://pubmed.ncbi.nlm.nih.gov/32470933/
72. Bauer, S.B., *et al.* International Children's Continence Society's recommendations for initial diagnostic evaluation and follow-up in congenital neuropathic bladder and bowel dysfunction in children. Neurourol Urodyn, 2012. 31: 610.
https://pubmed.ncbi.nlm.nih.gov/22532312/
73. Bauer, S.B., *et al.* International Children's Continence Society standardization report on urodynamic studies of the lower urinary tract in children. Neurourol Urodyn, 2015. 34: 640.
https://pubmed.ncbi.nlm.nih.gov/25998310/
74. Tanaka, S.T., *et al.* Urodynamic characteristics of neurogenic bladder in newborns with myelomeningocele and refinement of the definition of bladder hostility: Findings from the UMPIRE multi-center study. J Pediatr Urol, 2021. 17: 726.
https://pubmed.ncbi.nlm.nih.gov/34011486/
75. Almodhen, F., *et al.* Postpubertal urodynamic and upper urinary tract changes in children with conservatively treated myelomeningocele. J Urol, 2007. 178: 1479.
https://pubmed.ncbi.nlm.nih.gov/17706702/

76. Foon, R., *et al.* Prophylactic antibiotics to reduce the risk of urinary tract infections after urodynamic studies. Cochrane Database Syst Rev, 2012. 10: Cd008224.
https://pubmed.ncbi.nlm.nih.gov/23076941/
77. Shekarriz, B., *et al.* Lack of morbidity from urodynamic studies in children with asymptomatic bacteriuria. Urology, 1999. 54: 359.
https://pubmed.ncbi.nlm.nih.gov/10443739/
78. Milivojevic, S., *et al.* The influence of bowel management on urodynamic findings in spina bifida children with detrusor overactivity and detrusor sphincter dyssynergia. J Pediatr Urol, 2020. 16: 556.e1.
https://pubmed.ncbi.nlm.nih.gov/32376289/
79. Milivojevic, S., *et al.* The correlation between the transverse rectal diameter and urodynamic findings in children with neurogenic bowel and bladder dysfunction. Front Pediatr, 2022. 10: 957123.
https://pubmed.ncbi.nlm.nih.gov/36245719/
80. Bauer, S.B., *et al.* Predictive value of urodynamic evaluation in newborns with myelodysplasia. Jama, 1984. 252: 650.
https://pubmed.ncbi.nlm.nih.gov/6737668/
81. Ergun, R., *et al.* Detrusor Pressures Change with Repeat Filling Cystometry in Myelodysplastic Children with Neurogenic Lower Urinary Tract Dysfunction. J Urol, 2021. 205: 577.
https://pubmed.ncbi.nlm.nih.gov/32897763/
82. Dudley, A.G., *et al.* Interrater Reliability in Interpretation of Neuropathic Pediatric Urodynamic Tracings: An Expanded Multicenter Study. J Urol, 2018. 199: 1337.
https://pubmed.ncbi.nlm.nih.gov/29291418/
83. Jorgensen, B., *et al.* Natural fill urodynamics and conventional cystometrogram in infants with neurogenic bladder. J Urol, 2009. 181: 1862.
https://pubmed.ncbi.nlm.nih.gov/19233391/
84. Zermann, D.H., *et al.* Diagnostic value of natural fill cystometry in neurogenic bladder in children. Eur Urol, 1997. 32: 223.
https://pubmed.ncbi.nlm.nih.gov/9286658/
85. Huen, K.H., *et al.* Home bladder pressure measurements correlate with urodynamic storage pressures and high-grade hydronephrosis in children with spina bifida. J Pediatr Urol, 2022. 18: 503.e1.
https://pubmed.ncbi.nlm.nih.gov/35792042/
86. Cooper, C.S., *et al.* Pilot study of a home use cystomanometer in patients with a neurogenic bladder. J Pediatr Urol, 2022. 18: 466.
https://pubmed.ncbi.nlm.nih.gov/35717327/
87. Bortolini, T., *et al.* Can dynamic ultrasonography replace urodynamics in the follow-up of patients with myelomeningocele? A prospective concurrent study. Neurourol Urodyn, 2019. 38: 278.
https://pubmed.ncbi.nlm.nih.gov/30350876/
88. Lee, S.B., *et al.* Clinical and urodynamic features of secondary tethered cord syndrome: How can they be found longitudinally? Neurourol Urodyn, 2022. 41: 365.
https://pubmed.ncbi.nlm.nih.gov/34783385/
89. Erdogan, E.T., *et al.* Determination of tibial somatosensory evoked potentials predicts detrusor sphincter dyssynergia in children with neurogenic bladder dysfunction. Neurourol Urodyn, 2023. 42: 1132.
https://pubmed.ncbi.nlm.nih.gov/37185999/
90. Shin, H.I., *et al.* Electrodiagnostic findings of retethering in children with spinal dysraphism. Acta Neurochir (Wien), 2023. 165: 915.
https://pubmed.ncbi.nlm.nih.gov/36862215/
91. Corona, L.E., *et al.* Urodynamic and imaging findings in infants with myelomeningocele may predict need for future augmentation cystoplasty. J Pediatr Urol, 2019. 15: 644.e1.
https://pubmed.ncbi.nlm.nih.gov/31653462/
92. Timberlake, M.D., *et al.* Streamlining risk stratification in infants and young children with spinal dysraphism: Vesicoureteral reflux and/or bladder trabeculations outperforms other urodynamic findings for predicting adverse outcomes. J Pediatr Urol, 2018. 14: 319.e1.
https://pubmed.ncbi.nlm.nih.gov/30253979/
93. Hannallah, A., *et al.* Imaging characteristics predicting elevated detrusor pressures in patients with spina bifida. J Pediatr Urol, 2023. 19: 65.e1.
https://pubmed.ncbi.nlm.nih.gov/36333199/
94. Meuli, M., *et al.* In utero surgery rescues neurological function at birth in sheep with spina bifida. Nat Med, 1995. 1: 342.
https://pubmed.ncbi.nlm.nih.gov/7585064/
95. Adzick, N.S., *et al.* A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med, 2011. 364: 993.
https://pubmed.ncbi.nlm.nih.gov/21306277/
96. Sanz Cortes, M., *et al.* Experience of 300 cases of prenatal fetoscopic open spina bifida repair: report of the International Fetoscopic Neural Tube Defect Repair Consortium. Am J Obstet Gynecol, 2021. 225: 678.e1.
https://pubmed.ncbi.nlm.nih.gov/34089698/

97. Sanz Cortes, M., *et al.* Proceedings of the First Annual Meeting of the International Fetoscopic Myelomeningocele Repair Consortium. Ultrasound Obstet Gynecol, 2019. 53: 855.
https://pubmed.ncbi.nlm.nih.gov/31169957/
98. Mikulski, M.F., *et al.* Open and endoscopic fetal myelomeningocele surgeries display similar in-hospital safety profiles in a large, multi-institutional database. Am J Obstet Gynecol MFM, 2023. 5: 100854.
https://pubmed.ncbi.nlm.nih.gov/36587805/
99. King, B.C., *et al.* Economic analysis of prenatal fetoscopic vs open-hysterotomy repair of open neural tube defect. Ultrasound Obstet Gynecol, 2021. 58: 230.
https://pubmed.ncbi.nlm.nih.gov/32438507/
100. Lapa, D.A., *et al.* Percutaneous fetoscopic spina bifida repair: effect on ambulation and need for postnatal cerebrospinal fluid diversion and bladder catheterization. Ultrasound Obstet Gynecol, 2021. 58: 582.
https://pubmed.ncbi.nlm.nih.gov/33880811/
101. Diehl, D., *et al.* Fully percutaneous fetoscopic repair of myelomeningocele: 30-month follow-up data. Ultrasound Obstet Gynecol, 2021. 57: 113.
https://pubmed.ncbi.nlm.nih.gov/32510722/
102. Chmait, R.H., *et al.* Advances in Fetal Surgical Repair of Open Spina Bifida. Obstet Gynecol, 2023. 141: 505.
https://pubmed.ncbi.nlm.nih.gov/36735401/
103. Brock, J.W., 3rd, *et al.* Bladder Function After Fetal Surgery for Myelomeningocele. Pediatrics, 2015. 136: e906.
https://pubmed.ncbi.nlm.nih.gov/26416930/
104. Parizi, J.L.G., *et al.* A Comparative Analysis of Bladder Pattern of Patients who Underwent In Utero Versus Postnatal Myelomeningocele Repair. J Urol, 2020. 203: 194.
https://pubmed.ncbi.nlm.nih.gov/31479395/
105. Lee, N.G., *et al.* In utero closure of myelomeningocele does not improve lower urinary tract function. J Urol, 2012. 188: 1567.
https://pubmed.ncbi.nlm.nih.gov/22917751/
106. Brock, J.W., 3rd, *et al.* Effect of Prenatal Repair of Myelomeningocele on Urological Outcomes at School Age. J Urol, 2019. 202: 812.
https://pubmed.ncbi.nlm.nih.gov/31075056/
107. Horst, M., *et al.* Prenatal myelomeningocele repair: Do bladders better? Neurourol Urodyn, 2017. 36: 1651.
https://pubmed.ncbi.nlm.nih.gov/27862250/
108. Mazzone, L., *et al.* Urological Outcome after Fetal Spina Bifida Repair: Data from the Zurich Cohort. Fetal Diagn Ther, 2020. 47: 882.
https://pubmed.ncbi.nlm.nih.gov/32894833/
109. Macedo, A., Jr., *et al.* In utero myelomeningocele repair and high-risk bladder pattern. a prospective study. Int Braz J Urol, 2022. 48: 672.
https://pubmed.ncbi.nlm.nih.gov/35373958/
110. Macedo, A., Jr., *et al.* In utero myelomeningocele repair and incidence of lower urinary tract surgery. Results of a prospective study. J Pediatr Urol, 2021. 17: 769.
https://pubmed.ncbi.nlm.nih.gov/34452829/
111. Zaccaria, L., *et al.* Comparison of risk of anticholinergic utilization for treatment of neurogenic bladder between in utero or postnatal myelomeningocele repair. J Pediatr Urol, 2021. 17: 525.e1.
https://pubmed.ncbi.nlm.nih.gov/34074608/
112. Gerber, J.A., *et al.* Prevalence of high-risk bladder categorization with prenatal and postnatal myelomeningocele repair types. Neurourol Urodyn, 2021. 40: 829.
https://pubmed.ncbi.nlm.nih.gov/33604950/
113. Clayton, D.B., *et al.* Fetal repair of myelomeningocele: current status and urologic implications. J Pediatr Urol, 2020. 16: 3.
https://pubmed.ncbi.nlm.nih.gov/31902678/
114. Snow-Lisy, D.C., *et al.* Update on Urological Management of Spina Bifida from Prenatal Diagnosis to Adulthood. J Urol, 2015. 194: 288.
https://pubmed.ncbi.nlm.nih.gov/25839383/
115. Kessler, T.M., *et al.* Early proactive management improves upper urinary tract function and reduces the need for surgery in patients with myelomeningocele. Neurourol Urodyn, 2006. 25: 758.
https://pubmed.ncbi.nlm.nih.gov/16986135/
116. Jørgensen, B., *et al.* Long-term follow-up in spinal dysraphism: outcome of renal function and urinary and faecal continence. Scand J Urol Nephrol, 2010. 44: 95.
https://pubmed.ncbi.nlm.nih.gov/20187759/
117. Olesen, J.D., *et al.* The association between urinary continence and quality of life in paediatric patients with spina bifida and tethered cord. Paediatr Child Health, 2013. 18: e32.
https://pubmed.ncbi.nlm.nih.gov/24421717/

118. Li, Y., *et al.* Systematic review and meta-analysis to study the outcomes of proactive versus delayed management in children with a congenital neurogenic bladder. J Pediatr Urol, 2023. 19: 730.
https://pubmed.ncbi.nlm.nih.gov/37726188/
119. Araujo Júnior, E., *et al.* Outcomes of infants followed-up at least 12 months after fetal open and endoscopic surgery for meningomyelocele: a systematic review and meta-analysis. J Evid Based Med, 2016. 9: 125.
https://pubmed.ncbi.nlm.nih.gov/27305320/
120. Elzeneini, W., *et al.* Early start of clean intermittent catheterization versus expectant management in children with spina bifida. J Pediatr Surg, 2019. 54: 322.
https://pubmed.ncbi.nlm.nih.gov/30558962/
121. Lindehall, B., *et al.* Long-term intermittent catheterization: the experience of teenagers and young adults with myelomeningocele. J Urol, 1994. 152: 187.
https://pubmed.ncbi.nlm.nih.gov/8201663/
122. Prieto, J.A., *et al.* Intermittent catheter techniques, strategies and designs for managing long-term bladder conditions. Cochrane Database Syst Rev, 2021. 10: Cd006008.
https://pubmed.ncbi.nlm.nih.gov/34699062/
123. Madero-Morales, P.A., *et al.* Randomized Clinical Trial Using Sterile Single Use and Reused Polyvinylchloride Catheters for Intermittent Catheterization with a Clean Technique in Spina Bifida Cases: Short-Term Urinary Tract Infection Outcomes. J Urol, 2019. 202: 153.
https://pubmed.ncbi.nlm.nih.gov/30916625/
124. Lucas, E.J., *et al.* Comparison of the microbiological milieu of patients randomized to either hydrophilic or conventional PVC catheters for clean intermittent catheterization. J Pediatr Urol, 2016. 12: 172.e1.
https://pubmed.ncbi.nlm.nih.gov/26951923/
125. Andersson, K.E., *et al.* Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. Curr Opin Urol, 2009. 19: 380.
https://pubmed.ncbi.nlm.nih.gov/19448545/
126. Rawashdeh, Y.F., *et al.* International Children's Continence Society's recommendations for therapeutic intervention in congenital neuropathic bladder and bowel dysfunction in children. Neurourol Urodyn, 2012. 31: 615.
https://pubmed.ncbi.nlm.nih.gov/22532368/
127. Abrams, P., *et al.* Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol, 2006. 148: 565.
https://pubmed.ncbi.nlm.nih.gov/16751797/
128. Krause, P., *et al.* Pharmacokinetics of intravesical versus oral oxybutynin in healthy adults: results of an open label, randomized, prospective clinical study. J Urol, 2013. 190: 1791.
https://pubmed.ncbi.nlm.nih.gov/23669567/
129. Humblet, M., *et al.* Long-term outcome of intravesical oxybutynin in children with detrusor-sphincter dyssynergia: with special reference to age-dependent parameters. Neurourol Urodyn, 2015. 34: 336.
https://pubmed.ncbi.nlm.nih.gov/24436114/
130. Giramonti, K.M., *et al.* The effects of anticholinergic drugs on attention span and short-term memory skills in children. Neurourol Urodyn, 2008. 27: 315.
https://pubmed.ncbi.nlm.nih.gov/17828786/
131. Ramsay, S., *et al.* A randomized, crossover trial comparing the efficacy and safety of fesoterodine and extended-release oxybutynin in children with overactive bladder with 12-month extension on fesoterodine: The FOXY study. Can Urol Assoc J, 2020. 14: 192.
https://pubmed.ncbi.nlm.nih.gov/31977308/
132. Ellsworth, P.I., *et al.* Use of tolterodine in children with neurogenic detrusor overactivity: relationship between dose and urodynamic response. J Urol, 2005. 174: 1647.
https://pubmed.ncbi.nlm.nih.gov/16148673/
133. Nadeau, G., *et al.* Long-term use of solifenacin in pediatric patients with overactive bladder: Extension of a prospective open-label study. Can Urol Assoc J, 2014. 8: 118.
https://pubmed.ncbi.nlm.nih.gov/24839481/
134. Marschall-Kehrel, D., *et al.* Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol, 2009. 55: 729.
https://pubmed.ncbi.nlm.nih.gov/18502028/
135. Lopez Pereira, P., *et al.* Trospium chloride for the treatment of detrusor instability in children. J Urol, 2003. 170: 1978.
https://pubmed.ncbi.nlm.nih.gov/14532838/
136. Lee, A.S., *et al.* How early is early? Effect of oxybutynin on bladder dynamics within the first year of life in patients with spina bifida. J Pediatr Urol, 2020. 16: 168.e1.
https://pubmed.ncbi.nlm.nih.gov/32115375/

137. Rittig, S., *et al.* The pharmacokinetics, safety, and tolerability of mirabegron in children and adolescents with neurogenic detrusor overactivity or idiopathic overactive bladder and development of a population pharmacokinetic model-based pediatric dose estimation. J Pediatr Urol, 2020. 16: 31.e1.
https://pubmed.ncbi.nlm.nih.gov/31787582/
138. Austin, P.F., *et al.* alpha-Adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction. J Urol, 1999. 162: 1064.
https://pubmed.ncbi.nlm.nih.gov/10458432/
139. Homsy, Y., *et al.* Phase IIb/III dose ranging study of tamsulosin as treatment for children with neuropathic bladder. J Urol, 2011. 186: 2033.
https://pubmed.ncbi.nlm.nih.gov/21944133/
140. Horst, M., *et al.* Repeated Botulinum-A toxin injection in the treatment of neuropathic bladder dysfunction and poor bladder compliance in children with myelomeningocele. Neurourol Urodyn, 2011. 30: 1546.
https://pubmed.ncbi.nlm.nih.gov/21674597/
141. Danacioglu, Y.O., *et al.* Factors predicting the success of intradetrusor onabotulinum toxin-A treatment in children with neurogenic bladders due to myelomeningocele: The outcomes of a large cohort. J Pediatr Urol, 2021. 17: 520.e1.
https://pubmed.ncbi.nlm.nih.gov/33712371/
142. Toia, B., *et al.* The efficacy of onabotulinumtoxinA in patients with previous failed augmentation cystoplasty: Cohort series and literature review. Neurourol Urodyn, 2020. 39: 1831.
https://pubmed.ncbi.nlm.nih.gov/32572987/
143. Hascoet, J., *et al.* Outcomes of intra-detrusor injections of botulinum toxin in patients with spina bifida: A systematic review. Neurourol Urodyn, 2017. 36: 557.
https://pubmed.ncbi.nlm.nih.gov/27187872/
144. Austin, P.F., *et al.* OnabotulinumtoxinA for the treatment of neurogenic detrusor overactivity in children. Neurourol Urodyn, 2021. 40: 493.
https://pubmed.ncbi.nlm.nih.gov/33305474/
145. Sager, C., *et al.* Repeated injections of intradetrusor onabotulinumtoxinA as adjunctive treatment of children with neurogenic bladder. Pediatr Surg Int, 2014. 30: 79.
https://pubmed.ncbi.nlm.nih.gov/23958929/
146. Pellegrino, C., *et al.* Onabotulinum Toxin A Intradetrusor Injections in Children with Neurogenic Lower Urinary Tract Dysfunction: Long-Term Histological Effects on the Bladder Wall. Biomedicines, 2023. 11.
https://pubmed.ncbi.nlm.nih.gov/37238971/
147. Mokhless, I., *et al.* Botulinum A toxin urethral sphincter injection in children with nonneurogenic neurogenic bladder. J Urol, 2006. 176: 1767.
https://pubmed.ncbi.nlm.nih.gov/16945643/
148. Wan, J. The role of urethral dilation in managing pediatric neurogenic bladder dysfunction. Curr Urol Rep, 2009. 10: 153.
https://pubmed.ncbi.nlm.nih.gov/19239821/
149. Park, J.M., *et al.* External urethral sphincter dilation for the management of high risk myelomeningocele: 15-year experience. J Urol, 2001. 165: 2383.
https://pubmed.ncbi.nlm.nih.gov/11371982/
150. Hagerty, J.A., *et al.* Intravesical electrotherapy for neurogenic bladder dysfunction: a 22-year experience. J Urol, 2007. 178: 1680.
https://pubmed.ncbi.nlm.nih.gov/17707024/
151. Boone, T.B., *et al.* Transurethral intravesical electrotherapy for neurogenic bladder dysfunction in children with myelodysplasia: a prospective, randomized clinical trial. J Urol, 1992. 148: 550.
https://pubmed.ncbi.nlm.nih.gov/1640520/
152. De Gennaro, M., *et al.* Current state of nerve stimulation technique for lower urinary tract dysfunction in children. J Urol, 2011. 185: 1571.
https://pubmed.ncbi.nlm.nih.gov/21419450/
153. Capitanucci M.L., *et al.* Percutaneous Tibial Nerve Stimulation (PTNS) and Transcutaneous Electrical Nerve Stimulation (TENS), in: Clinical Urodynamics in Childhood and Adolescence. 2018, Springer, Cham.
154. Guys, J.M., *et al.* Sacral neuromodulation for neurogenic bladder dysfunction in children. J Urol, 2004. 172: 1673.
https://pubmed.ncbi.nlm.nih.gov/15371787/
155. Chen, G., *et al.* The Effect of Sacral Neuromodulation in Ambulatory Spina Bifida Patients with Neurogenic Bladder and Bowel Dysfunction. Urology, 2021. 153: 345.
https://pubmed.ncbi.nlm.nih.gov/33556449/
156. Jansen I., *et al.*, Sacral Neuromodulation in Children, in: *Clinical Urodynamics in Childhood and Adolescence.* 2018, Springer, Cham.
157. Lay, A.H., *et al.* The role of neuromodulation in patients with neurogenic overactive bladder. Curr Urol Rep, 2012. 13: 343.
https://pubmed.ncbi.nlm.nih.gov/22865208/

158. Marshall, D.F., *et al.* Altered bladder and bowel function following cutaneous electrical field stimulation in children with spina bifida--interim results of a randomized double-blind placebo-controlled trial. Eur J Pediatr Surg, 1997. 7 Suppl 1: 41.
https://pubmed.ncbi.nlm.nih.gov/9497117/
159. Lansen-Koch, S.M., *et al.* Sacral nerve modulation for defaecation and micturition disorders in patients with spina bifida. Colorectal Dis, 2012. 14: 508.
https://pubmed.ncbi.nlm.nih.gov/21689346/
160. Southwell, B.R. Electro-Neuromodulation for Colonic Disorders-Review of Meta-Analyses, Systematic Reviews, and RCTs. Neuromodulation, 2020. 23: 1061.
https://pubmed.ncbi.nlm.nih.gov/32017319/
161. Xiao, C.G., *et al.* An artificial somatic-central nervous system-autonomic reflex pathway for controllable micturition after spinal cord injury: preliminary results in 15 patients. J Urol, 2003. 170: 1237.
https://pubmed.ncbi.nlm.nih.gov/14501733/
162. Tuite, G.F., *et al.* Urological Outcome of the Xiao Procedure in Children with Myelomeningocele and Lipomyelomeningocele Undergoing Spinal Cord Detethering. J Urol, 2016. 196: 1735.
https://pubmed.ncbi.nlm.nih.gov/27288694/
163. Blocksom, B.H., Jr. Bladder pouch for prolonged tubeless cystostomy. J Urol, 1957. 78: 398.
https://pubmed.ncbi.nlm.nih.gov/13476506/
164. Sharifiaghdas, F., *et al.* Can transient resting of the bladder with vesicostomy reduce the need for a major surgery in some patients? J Pediatr Urol, 2019. 15: 379.e1.
https://pubmed.ncbi.nlm.nih.gov/31060966/
165. Fischer, K.M., *et al.* Follow-up and Outcomes of Patients With Long-term Cutaneous Vesicostomies at a Single Institution. Urology, 2020. 144: 255.
https://pubmed.ncbi.nlm.nih.gov/32580017/
166. Ting, C.S., *et al.* Vesicocutaneous fistula: continent vesicostomy, an easier route for comfortable clean intermittent catheterization. J Pediatr Urol, 2020. 16: 354.e1.
https://pubmed.ncbi.nlm.nih.gov/32171665/
167. Mosiello, G., *et al.* Button Cystostomy: Is it Really a Safe and Effective Therapeutic Option in Pediatric Patients With Neurogenic Bladder? Urology, 2017. 101: 73.
https://pubmed.ncbi.nlm.nih.gov/27693876/
168. Kelly, M.S., *et al.* Development, reliability and validation of a neurogenic bowel dysfunction score in pediatric patients with spina bifida. Neurourol Urodyn, 2016. 35: 212.
https://pubmed.ncbi.nlm.nih.gov/25400229/
169. Träff, H., *et al.* Patient-Reported Outcomes of Bladder and Bowel Control in Children with Spina Bifida. Children (Basel), 2021. 8.
https://pubmed.ncbi.nlm.nih.gov/33802114/
170. A summary of conference recommendations on dietary fiber in childhood. Conference on Dietary Fiber in Childhood, New York, May 24, 1994. American Academy of Pediatrics. Pediatrics, 1995. 96: 1023.
https://pubmed.ncbi.nlm.nih.gov/7494675/
171. GNS Science, Reference Level Water. 2023.
https://www.gns.cri.nz/assets/About-us/About-us-files/Annual-Reports/AR-2023-Part-1-Highlights.pdf
172. Mosiello, G., *et al.* Neurogenic Bowel Dysfunction in Children and Adolescents. J Clin Med, 2021. 10.
https://pubmed.ncbi.nlm.nih.gov/33924675/
173. Koch, V.H., *et al.* Multidisciplinary management of people with spina bifida across the lifespan. Pediatr Nephrol, 2024. 39: 681.
https://pubmed.ncbi.nlm.nih.gov/37501019/
174. Alhazmi, H., *et al.* Long-term results using a transanal irrigation system (Peristeen(®)) for treatment of stool incontinence in children with myelomeningocele. J Pediatr Urol, 2019. 15: 34.e1.
https://pubmed.ncbi.nlm.nih.gov/30245057/
175. Mosiello, G., *et al.* Consensus Review of Best Practice of Transanal Irrigation in Children. J Pediatr Gastroenterol Nutr, 2017. 64: 343.
https://pubmed.ncbi.nlm.nih.gov/27977546/
176. Patel, S., *et al.* Impact of Transanal Irrigation Device in the Management of Children With Fecal Incontinence and Constipation. J Pediatr Gastroenterol Nutr, 2020. 71: 292.
https://pubmed.ncbi.nlm.nih.gov/32404764/
177. Christensen, P., *et al.* Long-term outcome and safety of transanal irrigation for constipation and fecal incontinence. Dis Colon Rectum, 2009. 52: 286.
https://pubmed.ncbi.nlm.nih.gov/19279425/
178. Ausili, E., *et al.* Short versus mid-long-term outcome of transanal irrigation in children with spina bifida and anorectal malformations. Childs Nerv Syst, 2018. 34: 2471.
https://pubmed.ncbi.nlm.nih.gov/29948136/

179. Kelly, M.S., *et al.* Neurogenic bowel treatments and continence outcomes in children and adults with myelomeningocele. J Pediatr Rehabil Med, 2020. 13: 685.
https://pubmed.ncbi.nlm.nih.gov/33325404/
180. Malone, P.S., *et al.* Preliminary report: the antegrade continence enema. Lancet, 1990. 336: 1217.
https://pubmed.ncbi.nlm.nih.gov/1978072/
181. Anselmo, C.B., *et al.* Left-colon antegrade enema (LACE): Long-term experience with the Macedo-Malone approach. Neurourol Urodyn, 2017. 36: 111.
https://pubmed.ncbi.nlm.nih.gov/26417710/
182. Saoud, R., *et al.* Antegrade Colonic Enema Channels in Pediatric Patients Using Appendix or Cecal Flap: A Comparative Robotic vs Open Series. J Endourol, 2022. 36: 462.
https://pubmed.ncbi.nlm.nih.gov/34931548/
183. Siddiqui, A.A., *et al.* Long-term follow-up of patients after antegrade continence enema procedure. J Pediatr Gastroenterol Nutr, 2011. 52: 574.
https://pubmed.ncbi.nlm.nih.gov/21502828/
184. Roth, J.D., *et al.* Troubleshooting problems with antegrade continent enema flushes: The Indiana university algorithm. J Pediatr Urol, 2021. 17: 446.e1.
https://pubmed.ncbi.nlm.nih.gov/33707132/
185. Kim, J., *et al.* Long-term usage pattern and satisfaction survey of continent catheterizable channels. J Pediatr Urol, 2022. 18: 77.e1.
https://pubmed.ncbi.nlm.nih.gov/34895819/
186. Bevill, M.D., *et al.* Outcomes and satisfaction in pediatric patients with Chait cecostomy tubes. J Pediatr Urol, 2017. 13: 365.
https://pubmed.ncbi.nlm.nih.gov/28545800/
187. Brophy, S., *et al.* Comparing quality of life improvement after antegrade continence enema (ACE) therapy for patients with organic and functional constipation / encopresis. J Pediatr Surg, 2022. 57: 855.
https://pubmed.ncbi.nlm.nih.gov/35115169/
188. Beckers, G.M., *et al.* Peritonitis after endoscopic caecostomy with a Chait Trapdoor catheter: what lessons can be learned? J Pediatr Gastroenterol Nutr, 2012. 55: 217.
https://pubmed.ncbi.nlm.nih.gov/21857245/
189. Boucher, M., *et al.* Early Colostomy Formation Can Improve Independence Following Spinal Cord Injury and Increase Acceptability of Bowel Management. Top Spinal Cord Inj Rehabil, 2019. 25: 23.
https://pubmed.ncbi.nlm.nih.gov/30774287/
190. Sidi, A.A., *et al.* Vesicoureteral reflux in children with myelodysplasia: natural history and results of treatment. J Urol, 1986. 136: 329.
https://pubmed.ncbi.nlm.nih.gov/3723683/
191. Wu, C.Q., *et al.* Management of vesicoureteral reflux in neurogenic bladder. Investig Clin Urol, 2017. 58: S54.
https://pubmed.ncbi.nlm.nih.gov/28612061/
192. Soygur, T., *et al.* The need for ureteric re-implantation during augmentation cystoplasty: video-urodynamic evaluation. BJU Int, 2010. 105: 530.
https://pubmed.ncbi.nlm.nih.gov/19583716/
193. Polackwich, A.S., *et al.* Long-term followup after endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid copolymer in patients with neurogenic bladder. J Urol, 2012. 188: 1511.
https://pubmed.ncbi.nlm.nih.gov/22910250/
194. Engel, J.D., *et al.* Surgical versus endoscopic correction of vesicoureteral reflux in children with neurogenic bladder dysfunction. J Urol, 1997. 157: 2291.
https://pubmed.ncbi.nlm.nih.gov/9146655/
195. Boissier, R., *et al.* What is the outcome of paediatric gastrocystoplasty when the patients reach adulthood? BJU Int, 2016. 118: 980.
https://pubmed.ncbi.nlm.nih.gov/27322857/
196. Mingin, G.C., *et al.* Gastrocystoplasty: long-term complications in 22 patients. J Urol, 1999. 162: 1122.
https://pubmed.ncbi.nlm.nih.gov/10458445/
197. Bogaert, G.A., *et al.* The physiology of gastrocystoplasty: once a stomach, always a stomach. J Urol, 1995. 153: 1977.
https://pubmed.ncbi.nlm.nih.gov/7752376/
198. Casey, J.T., *et al.* Long-term follow-up of composite bladder augmentation incorporating stomach in a multi-institutional cohort of patients with cloacal exstrophy. J Pediatr Urol, 2017. 13: 43.e1.
https://pubmed.ncbi.nlm.nih.gov/27889222/
199. Stein, R., *et al.* Bladder augmentation and urinary diversion in patients with neurogenic bladder: surgical considerations. J Pediatr Urol, 2012. 8: 153.
https://pubmed.ncbi.nlm.nih.gov/22264521/

200. Herschorn, S., *et al.* Patient perspective of long-term outcome of augmentation cystoplasty for neurogenic bladder. Urology, 1998. 52: 672.
https://pubmed.ncbi.nlm.nih.gov/9763092/
201. Medel, R., *et al.* Urinary continence outcome after augmentation ileocystoplasty as a single surgical procedure in patients with myelodysplasia. J Urol, 2002. 168: 1849.
https://pubmed.ncbi.nlm.nih.gov/12352374/
202. Nonaka, M., *et al.* Number of surgeries performed during the lifetime of patients with myelomeningocele. J Neurosurg Pediatr, 2022. 29: 479.
https://pubmed.ncbi.nlm.nih.gov/35180700/
203. McNamara, E.R., *et al.* 30-Day morbidity after augmentation enterocystoplasty and appendicovesicostomy: A NSQIP pediatric analysis. J Pediatr Urol, 2015. 11: 209.e1.
https://pubmed.ncbi.nlm.nih.gov/26049255/
204. Du, K., *et al.* Enterocystoplasty 30-day outcomes from National Surgical Quality Improvement Program Pediatric 2012. J Pediatr Surg, 2015. 50: 1535.
https://pubmed.ncbi.nlm.nih.gov/25957024/
205. Romero-Maroto, J., *et al.* Long-term effectiveness and safety of bladder augmentation in spina bifida patients. Neurourol Urodyn, 2021. 40: 1576.
https://pubmed.ncbi.nlm.nih.gov/34082472/
206. Schlomer, B.J., *et al.* Cumulative incidence of outcomes and urologic procedures after augmentation cystoplasty. J Pediatr Urol, 2014. 10: 1043.
https://pubmed.ncbi.nlm.nih.gov/24766857/
207. Casperson, K.J., *et al.* Ventriculoperitoneal shunt infections after bladder surgery: is mechanical bowel preparation necessary? J Urol, 2011. 186: 1571.
https://pubmed.ncbi.nlm.nih.gov/21855924/
208. Garnier, S., *et al.* Malignancy after Augmentation Enterocystoplasty: A Nationwide Study of Natural History, Prognosis and Oncogene Panel Analysis. J Urol, 2020. 204: 136.
https://pubmed.ncbi.nlm.nih.gov/31957550/
209. Biardeau, X., *et al.* Risk of malignancy after augmentation cystoplasty: A systematic review. Neurourol Urodyn, 2016. 35: 675.
https://pubmed.ncbi.nlm.nih.gov/25867054/
210. Higuchi, T.T., *et al.* Annual endoscopy and urine cytology for the surveillance of bladder tumors after enterocystoplasty for congenital bladder anomalies. J Urol, 2011. 186: 1791.
https://pubmed.ncbi.nlm.nih.gov/21944100/
211. Kokorowski, P.J., *et al.* Screening for malignancy after augmentation cystoplasty in children with spina bifida: a decision analysis. J Urol, 2011. 186: 1437.
https://pubmed.ncbi.nlm.nih.gov/21855939/
212. López Pereira, P., *et al.* Are urodynamic studies really needed during bladder augmentation follow-up? J Pediatr Urol, 2009. 5: 30.
https://pubmed.ncbi.nlm.nih.gov/18774747/
213. Johal, N.S., *et al.* Ureterocystoplasty: long-term functional results. J Urol, 2008. 179: 2373.
https://pubmed.ncbi.nlm.nih.gov/18436249/
214. Husmann, D.A., *et al.* Ureterocystoplasty: indications for a successful augmentation. J Urol, 2004. 171: 376.
https://pubmed.ncbi.nlm.nih.gov/14665935/
215. Cartwright, P.C. Bladder autoaugmentation (partial detrusor myectomy)--where does it stand after 2 decades? J Urol, 2013. 190: 1643.
https://pubmed.ncbi.nlm.nih.gov/23954194/
216. Chrzan, R., *et al.* Detrusorectomy reduces the need for augmentation and use of antimuscarinics in children with neuropathic bladders. J Pediatr Urol, 2013. 9: 193.
https://pubmed.ncbi.nlm.nih.gov/22364713/
217. Hansen, E.L., *et al.* Promising long-term outcome of bladder autoaugmentation in children with neurogenic bladder dysfunction. J Urol, 2013. 190: 1869.
https://pubmed.ncbi.nlm.nih.gov/23707450/
218. Bandi, G., *et al.* Comparison of traditional enterocystoplasty and seromuscular colocystoplasty lined with urothelium. J Pediatr Urol, 2007. 3: 484.
https://pubmed.ncbi.nlm.nih.gov/18947800/
219. González, R., *et al.* Determinants of success and failure of seromuscular colocystoplasty lined with urothelium. J Urol, 2009. 182: 1781.
https://pubmed.ncbi.nlm.nih.gov/19692035/
220. Joseph, D.B., *et al.* Autologous cell seeded biodegradable scaffold for augmentation cystoplasty: phase II study in children and adolescents with spina bifida. J Urol, 2014. 191: 1389.
https://pubmed.ncbi.nlm.nih.gov/24184366/

221. Atala, A., *et al.* Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet, 2006. 367: 1241.
https://pubmed.ncbi.nlm.nih.gov/16631879/
222. Sloff, M., *et al.* Tissue engineering of the bladder--reality or myth? A systematic review. J Urol, 2014. 192: 1035.
https://pubmed.ncbi.nlm.nih.gov/24769032/
223. Austin, P.F., *et al.* Advantages of rectus fascial slings for urinary incontinence in children with neuropathic bladders. J Urol, 2001. 165: 2369.
https://pubmed.ncbi.nlm.nih.gov/11398778/
224. Guys, J.M., *et al.* Endoscopic treatment of urinary incontinence: long-term evaluation of the results. J Urol, 2001. 165: 2389.
https://pubmed.ncbi.nlm.nih.gov/11371983/
225. Holmes, N.M., *et al.* Placement of artificial urinary sphincter in children and simultaneous gastrocystoplasty. J Urol, 2001. 165: 2366.
https://pubmed.ncbi.nlm.nih.gov/11371944/
226. Kassouf, W., *et al.* Collagen injection for treatment of urinary incontinence in children. J Urol, 2001. 165: 1666.
https://pubmed.ncbi.nlm.nih.gov/11342951/
227. Kryger, J.V., *et al.* Surgical management of urinary incontinence in children with neurogenic sphincteric incompetence. J Urol, 2000. 163: 256.
https://pubmed.ncbi.nlm.nih.gov/10604371/
228. Kryger, J.V., *et al.* Long-term results of artificial urinary sphincters in children are independent of age at implantation. J Urol, 2001. 165: 2377.
https://pubmed.ncbi.nlm.nih.gov/11371981/
229. Weaver, J.K., *et al.* Clinical outcomes after increasing bladder outlet resistance without augmentation cystoplasty in neurogenic bladder. J Pediatr Urol, 2021. 17: 235.e1.
https://pubmed.ncbi.nlm.nih.gov/33342678/
230. Smith, M.C., *et al.* Need for botulinum toxin injection and bladder augmentation after isolated bladder outlet procedure in pediatric patients with myelomeningocele. J Pediatr Urol, 2020. 16: 32.e1.
https://pubmed.ncbi.nlm.nih.gov/31839471/
231. Groen, L.A., *et al.* The AdVance male sling as a minimally invasive treatment for intrinsic sphincter deficiency in patients with neurogenic bladder sphincter dysfunction: a pilot study. Neurourol Urodyn, 2012. 31: 1284.
https://pubmed.ncbi.nlm.nih.gov/22847896/
232. Pannek, J., *et al.* Clinical usefulness of the transobturator sub-urethral tape in the treatment of stress urinary incontinence in female patients with spinal cord lesion. J Spinal Cord Med, 2012. 35: 102.
https://pubmed.ncbi.nlm.nih.gov/22525323/
233. Hayes, M.C., *et al.* The Pippi Salle urethral lengthening procedure; experience and outcome from three United Kingdom centres. BJU Int, 1999. 84: 701.
https://pubmed.ncbi.nlm.nih.gov/10510119/
234. Szymanski, K.M., *et al.* Long-term outcomes of the Kropp and Salle urethral lengthening bladder neck reconstruction procedures. J Pediatr Urol, 2016. 12: 403.e1.
https://pubmed.ncbi.nlm.nih.gov/27687531/
235. Noordhoff, T.C., *et al.* Long-term follow-up of bladder outlet procedures in children with neurogenic urinary incontinence. J Pediatr Urol, 2019. 15: 35.e1.
https://pubmed.ncbi.nlm.nih.gov/30314731/
236. Churchill, B.M., *et al.* Improved continence in patients with neurogenic sphincteric incompetence with combination tubularized posterior urethroplasty and fascial wrap: the lengthening, narrowing and tightening procedure. J Urol, 2010. 184: 1763.
https://pubmed.ncbi.nlm.nih.gov/20728163/
237. Scott, F.B., *et al.* Treatment of incontinence secondary to myelodysplasia by an implantable prosthetic urinary sphincter. South Med J, 1973. 66: 987.
https://pubmed.ncbi.nlm.nih.gov/4582131/
238. Gonzalez, R., *et al.* Artificial sphincters in children with neurogenic bladders: long-term results. J Urol, 1982. 128: 1270.
https://pubmed.ncbi.nlm.nih.gov/7154183/
239. Khene, Z.E., *et al.* Artificial Urinary Sphincter in Male Patients with Spina Bifida: Comparison of Perioperative and Functional Outcomes between Bulbar Urethra and Bladder Neck Cuff Placement. J Urol, 2018. 199: 791.
https://pubmed.ncbi.nlm.nih.gov/29037862/
240. Simeoni, J., *et al.* Artificial urinary sphincter implantation for neurogenic bladder: a multi-institutional study in 107 children. Br J Urol, 1996. 78: 287.
https://pubmed.ncbi.nlm.nih.gov/8813930/
241. Alova, I., *et al.* Long-term effects of endoscopic injection of dextranomer/hyaluronic acid based implants for treatment of urinary incontinence in children with neurogenic bladder. J Urol, 2012. 188: 1905.
https://pubmed.ncbi.nlm.nih.gov/22998918/

242. De Vocht, T.F., *et al.* Long-term results of bulking agent injection for persistent incontinence in cases of neurogenic bladder dysfunction. J Urol, 2010. 183: 719.
https://pubmed.ncbi.nlm.nih.gov/20022056/
243. De Troyer, B., *et al.* A comparative study between continent diversion and bladder neck closure versus continent diversion and bladder neck reconstruction in children. J Pediatr Urol, 2011. 7: 209.
https://pubmed.ncbi.nlm.nih.gov/20488754/
244. Kavanagh, A., *et al.* Bladder neck closure in conjunction with enterocystoplasty and Mitrofanoff diversion for complex incontinence: closing the door for good. J Urol, 2012. 188: 1561.
https://pubmed.ncbi.nlm.nih.gov/22910244/
245. Shpall, A.I., *et al.* Bladder neck closure with lower urinary tract reconstruction: technique and long-term followup. J Urol, 2004. 172: 2296.
https://pubmed.ncbi.nlm.nih.gov/15538252/
246. Landau, E.H., *et al.* Bladder neck closure in children: a decade of followup. J Urol, 2009. 182: 1797.
https://pubmed.ncbi.nlm.nih.gov/19692069/
247. Deuker, M., *et al.* Long-term outcome after urinary diversion using the ileocecal segment in children and adolescents: Complications of the efferent segment. J Pediatr Urol, 2016. 12: 247.e1.
https://pubmed.ncbi.nlm.nih.gov/27282550/
248. Faure, A., *et al.* Bladder continent catheterizable conduit (the Mitrofanoff procedure): Long-term issues that should not be underestimated. J Pediatr Surg, 2017. 52: 469.
https://pubmed.ncbi.nlm.nih.gov/27707652/
249. Landau, E.H., *et al.* Superiority of the VQZ over the tubularized skin flap and the umbilicus for continent abdominal stoma in children. J Urol, 2008. 180: 1761.
https://pubmed.ncbi.nlm.nih.gov/18721990/
250. Juul, N., *et al.* Robot-Assisted vs. Open Appendicovesicostomy in Pediatric Urology: A Systematic Review and Single-Center Case Series. Front Pediatr, 2022. 10: 908554.
https://pubmed.ncbi.nlm.nih.gov/35685916/
251. Gander, R., *et al.* Pediatric laparoscopic mitrofanoff procedure- preliminary results of a simplified technique. J Pediatr Urol, 2022. 18: 112.e1.
https://pubmed.ncbi.nlm.nih.gov/35063366/
252. Szymanski, K.M., *et al.* Additional Surgeries after Bladder Augmentation in Patients with Spina Bifida in the 21st Century. J Urol, 2020. 203: 1207.
https://pubmed.ncbi.nlm.nih.gov/31951496/
253. Stein, R., *et al.* Urinary diversion in children and adolescents with neurogenic bladder: the Mainz experience. Part III: Colonic conduit. Pediatr Nephrol, 2005. 20: 932.
https://pubmed.ncbi.nlm.nih.gov/15864655/
254. Cass, A.S., *et al.* A 22-year followup of ileal conduits in children with a neurogenic bladder. J Urol, 1984. 132: 529.
https://pubmed.ncbi.nlm.nih.gov/6471190/
255. Dunn, M., *et al.* The long-term results of ileal conduit urinary diversion in children. Br J Urol, 1979. 51: 458.
https://pubmed.ncbi.nlm.nih.gov/534825/
256. Middleton, A.W., Jr., *et al.* Ileal conduits in children at the Massachusetts General Hospital from 1955 to 1970. J Urol, 1976. 115: 591.
https://pubmed.ncbi.nlm.nih.gov/1271557/
257. Shekarriz, B., *et al.* Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients. Urology, 2000. 55: 123.
https://pubmed.ncbi.nlm.nih.gov/10654908/
258. Verhoef, M., *et al.* Sex education, relationships, and sexuality in young adults with spina bifida. Arch Phys Med Rehabil, 2005. 86: 979.
https://pubmed.ncbi.nlm.nih.gov/15895345/
259. Elias, E.R., *et al.* Precocious puberty in girls with myelodysplasia. Pediatrics, 1994. 93: 521.
https://pubmed.ncbi.nlm.nih.gov/8115222/
260. Spinoit, A.F., *et al.* Fertility and sexuality issues in congenital lifelong urology patients: male aspects. World J Urol, 2021. 39: 1013.
https://pubmed.ncbi.nlm.nih.gov/32067073/
261. De Win, G., *et al.* Fertility and sexuality issues in congenital lifelong urology patients: female aspects. World J Urol, 2021. 39: 1021.
https://pubmed.ncbi.nlm.nih.gov/32989556/
262. Cardenas, D.D., *et al.* Sexual functioning in adolescents and young adults with spina bifida. Arch Phys Med Rehabil, 2008. 89: 31.
https://pubmed.ncbi.nlm.nih.gov/18164327/

263. Gatti, C., *et al.* Predictors of successful sexual partnering of adults with spina bifida. J Urol, 2009. 182: 1911.
https://pubmed.ncbi.nlm.nih.gov/19695634/
264. Bong, G.W., *et al.* Sexual health in adult men with spina bifida. Sci World J, 2007. 7: 1466.
https://pubmed.ncbi.nlm.nih.gov/17767363/
265. Motta, G.L., *et al.* The impact of neurogenic bladder bowel dysfunction in the sexuality of female spina bifida patients. J Pediatr Urol, 2021. 17: 288.e1.
https://pubmed.ncbi.nlm.nih.gov/33546979/
266. Brown, T.M., *et al.* Factors of biological risk and reserve associated with executive behaviors in children and adolescents with spina bifida myelomeningocele. Child Neuropsychol, 2008. 14: 118.
https://pubmed.ncbi.nlm.nih.gov/18306076/
267. Kohleis, K., *et al.* [Risk Factors for Mental Health Problems in Children with Cerebral Palsy and Spina Bifida]. Klin Padiatr, 2019. 231: 28.
https://pubmed.ncbi.nlm.nih.gov/30180264/
268. Dennis, M., *et al.* The cognitive phenotype of spina bifida meningomyelocele. Dev Disabil Res Rev, 2010. 16: 31.
https://pubmed.ncbi.nlm.nih.gov/20419769/
269. Austin, P.F., *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn, 2016. 35: 471.
https://pubmed.ncbi.nlm.nih.gov/25772695/
270. von Gontard, A., *et al.* Psychological and psychiatric issues in urinary and fecal incontinence. J Urol, 2011. 185: 1432.
https://pubmed.ncbi.nlm.nih.gov/21349549/
271. Chase, J., *et al.* Diagnostic scores, questionnaires, quality of life, and outcome measures in pediatric continence: A review of available tools from the International Children's Continence Society. J Pediatr Urol, 2018. 14: 98.
https://pubmed.ncbi.nlm.nih.gov/29429829/
272. Goodman, R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry, 1997. 38: 581.
https://pubmed.ncbi.nlm.nih.gov/9255702/
273. Achenbach, T.M. International findings with the Achenbach System of Empirically Based Assessment (ASEBA): applications to clinical services, research, and training. Child Adolesc Psych Ment Health, 2019. 13: 30.
https://pubmed.ncbi.nlm.nih.gov/31312253/
274. Kritikos, T.K., *et al.* Mental health guidelines for the care of people with spina bifida. J Pediatr Rehabil Med, 2020. 13: 525.
https://pubmed.ncbi.nlm.nih.gov/32986630/
275. von Gontard, A., *et al.* Neurodevelopmental disorders and incontinence in children and adolescents: Attention-deficit/hyperactivity disorder, autism spectrum disorder, and intellectual disability-A consensus document of the International Children's Continence Society. Neurourol Urodyn, 2022. 41: 102.
https://pubmed.ncbi.nlm.nih.gov/34586694/
276. Roozen, S., *et al.* Fetal Alcohol Spectrum Disorders (FASD): an Approach to Effective Prevention. Curr Dev Disord Rep, 2016. 3: 229.
https://pubmed.ncbi.nlm.nih.gov/27891300/
277. Reuben, D.B., *et al.* Goal-oriented patient care--an alternative health outcomes paradigm. N Engl J Med, 2012. 366: 777.
https://pubmed.ncbi.nlm.nih.gov/22375966/
278. F.D.A., Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009.
https://www.fda.gov/media/77832/download
279. Haverman, L., *et al.* Paediatric health-related quality of life: what is it and why should we measure it? Arch Dis Child, 2017. 102: 393.
https://pubmed.ncbi.nlm.nih.gov/27831905/
280. Rajmil, L., *et al.* Quality of life and rare diseases. Adv Exp Med Biol, 2010. 686: 251.
https://pubmed.ncbi.nlm.nih.gov/20824450/
281. Bullinger, M., *et al.* Quality of life as patient-reported outcomes: principles of assessment. Dialogues Clin Neurosci, 2014. 16: 137.
https://pubmed.ncbi.nlm.nih.gov/25152653/
282. Canaz, H., *et al.* Health-related quality of life in non-paraplegic (ambulatory) children with myelomeningocele. Childs Nerv Syst, 2017. 33: 1997.
https://pubmed.ncbi.nlm.nih.gov/28656385/
283. Bakaniene, I., *et al.* Health-related quality of life in children with myelomeningocele: a systematic review of the literature. Child Care Health Dev, 2016. 42: 625.
https://pubmed.ncbi.nlm.nih.gov/27381478/
284. Lawson, N., *et al.* Socioeconomic Status and Parental Perceived Social Support in Relation to Health-Related Quality of Life in Youth with Spina Bifida. Undergrad Res J Psychol UCLA, 2018. 5: 40.
https://pubmed.ncbi.nlm.nih.gov/35224569/

285. Bakanienė, I., *et al.* Clinical and Environmental Predictors of Health-Related Quality of Life in Lithuanian Children and Adolescents with Spina Bifida: A Cross-Sectional Analysis of a Nationally Represented Sample. Medicina (Kaunas), 2018. 54. https://pubmed.ncbi.nlm.nih.gov/30344290/
286. Kawahara, T., *et al.* Development and validation of the Japanese version of the Quality of Life Assessment of Spina Bifida in Teenagers (QUALAS-T-J). Pediatr Int, 2019. 61: 1232. https://pubmed.ncbi.nlm.nih.gov/31487089/
287. Szymański, K.M., *et al.* Validation of QUALAS-T, a health-related quality of life instrument for teenagers with spina bifida. Cent Eur J Urol, 2017. 70: 306. https://pubmed.ncbi.nlm.nih.gov/29104796/
288. Vande Velde, S., *et al.* Development and validation of a spina bifida-specific pediatric quality of life questionnaire: the Spina Bifida Pediatric Questionnaire, SBPQ. Childs Nerv Syst, 2016. 32: 105. https://pubmed.ncbi.nlm.nih.gov/26362680/
289. Radojicic, Z., *et al.* The impact of bowel management on the quality of life in children with spina bifida with overactive bladder and detrusor sphincter dyssynergia. J Pediatr Urol, 2019. 15: 457. https://pubmed.ncbi.nlm.nih.gov/31202611/
290. Szymanski, K.M., *et al.* Incontinence affects health-related quality of life in children and adolescents with spina bifida. J Pediatr Urol, 2018. 14: 279.e1. https://pubmed.ncbi.nlm.nih.gov/29606358/
291. Rozensztrauch, A., *et al.* The Quality of Life of Children with Myelomeningocele: A Cross-Sectional Preliminary Study. Int J Environ Res Public Health, 2021. 18. https://pubmed.ncbi.nlm.nih.gov/34682497/
292. Karmur, B.S., *et al.* Medical and socioeconomic predictors of quality of life in myelomeningocele patients with shunted hydrocephalus. Childs Nerv Syst, 2018. 34: 741. https://pubmed.ncbi.nlm.nih.gov/29249073/
293. Spoor, J.K.H., *et al.* Newborns with myelomeningocele: their health-related quality of life and daily functioning 10 years later. J Neurosurg Pediatr, 2023. 31: 3. https://pubmed.ncbi.nlm.nih.gov/36334287/
294. Dogan, H.S., *et al.* Are EAU/ESPU pediatric urology guideline recommendations on neurogenic bladder well received by the patients? Results of a survey on awareness in spina bifida patients and caregivers. Neurourol Urodyn, 2019. 38: 1625. https://pubmed.ncbi.nlm.nih.gov/31102557/

15. CONFLICT OF INTEREST

All members of the EAU – ESPU - ERN eUROGEN - ERN ITHACA – ERN ERKNet – IFSBH Guidelines on spinal dysraphism in children and adolescents have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest as per the COI policies for their respective organisations.

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