Surgical and nonsurgical treatment options for pediatric neurogenic bladder

The treatment of children with neurogenic bladder has evolved from the simple wearing of diapers and applying abdominal stoma, to better understanding of the bladder pathophysiology, and the introduction into clinical practice of the principles of clean intermittent catheterization, artificial sphincter implantation, continent urinary conduits and a wide spectrum of medications that modulate the function of the lower urinary tracts. In this review we discuss the recent developments in the medical therapy of children with neurogenic bladders, examine the surgical options, and briefly refer to the future perspectives for the management of this group of patients.

KEYWORDS: medical treatment ■ neurogenic bladder ■ surgical treatment

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The most common cause of neurogenic bladder dysfunction in children is neurospinal disruption, such as primary open back lesion or myelomeningocele (MMC) [1–5]. Other causes of neurogenic dysfunction involving the spine include sacral agenesis, tethered spinal cord associated with imperforate anus, cloacal malformation and spinal cord injuries. CNS abnormalities include spastic diplegia (cerebral palsy) and learning disabilities (i.e., attention-deficit hyperactivity disorder [ADHD]). The main goals of the urologic management of a child with neurogenic bladder dysfunction concentrate on maintenance of normal renal function and gaining urinary continence. Over 90% of the children with spina bifida will have a normal upper urinary tract (kidney and ureters) at birth. With no follow-up, half of the children will suffer considerable upper urinary tract damage due to lower urinary tract (bladder and urethra) hostility. With appropriate urological management, children at risk for renal damage can be identified at an early stage and intervention can be undertaken to prevent the long-term compromise of the kidney function. During early childhood, the urological focus on a child's health is based on the maintenance of normal kidney function [6,7]. As the child begins to approach school age, interest will be directed toward gaining urinary continence. From the beginning of the follow-up, no one will be able to state which of the children with spinal lesions or other nervous system anomalies will be able to preserve the bladder or kidney function, and who will be more likely to present with deterioration of the bladder function with subsequent upper urinary tract damage. For these reasons, children with neurogenic bladder dysfunction require close urologic follow-up and evaluation, and prompt treatment when indicated.

Medical therapy

It is well-known that in untreated spina bifida patients, progressive deterioration by the age of 3 years may be observed in up to 58% of the patients [1–3]. Several reports have shown this deterioration to be directly related to increased intravesical pressures. In 1981, the bladder pressure at which urethral leakage occurred was found to be a useful predictor of unsafe bladder function. The detrusor leak-point pressure, as it is now commonly referred to, has become accepted as one of the urodynamic parameters that allow clinicians to differentiate between patients who are at relatively low and high risk of subsequent upper urinary tract deterioration. In 1984, detrusor external sphincter dyssynergia (DSD) was identified as an important factor leading to functional obstruction, and intravesical pressure was recognized as the pathophysiological mechanism of subsequent upper urinary tract deterioration. The cornerstone of optimal management of neurogenic bladder sphincter detrusor dyssenrgia (NBSD) is early identification and characterization, and the institution of proactive therapy. Crucial for the long-term prognosis of patients with NBSD is the fact that the management must start before consequences of bladder dysfunction become apparent. From the outset, the goals of management are to prevent or minimize secondary damage to the upper urinary tracts and the bladder and to achieve safe

social continence. Thus, long before continence becomes an issue, starting from the first year of life, management is directed at creating a low-pressure reservoir and ensuring complete and safe bladder emptying. Overall, the treatment of children with neurogenic bladder falls into several major categories including behavioral therapy, pharmacological therapy (often accompanied by clean intermittent catheterization [CIC] or self-catheterization [CISC]) and utilization of electronic stimulation.

Behavioral therapy describes a group of treatments centered on education, whereby the incontinent patient can be educated about the condition and can develop strategies to minimize or eliminate the incontinence. There are different components of behavioral therapy, such as timed voiding, fluid dietary management, voiding diary, urge inhibition, reinforcement and pelvic muscle training [8].

CIC enables complete bladder emptying, and thus avoids bladder residues and the consequent risks for infections [1,2,6,8]. In the high-risk bladder with DSD, CIC also allows bladder empting before the occurrence of high voiding pressures, which is known to be detrimental for kidney function and drainage. Which of the wide variety of available materials and techniques is used for CIC does not seem to affect the efficacy and safety, as long as some basic principles are applied: proper education and training, clean and atraumatic application and achievement of good patient compliance on a long-term basis. For education, training and further guidance during follow-up, a dedicated continence nurse is invaluable. It is beneficial to begin the catheterization early in life, in order to identify the small group of children who are at risk for carrying significant residual urine. In addition, all families become familiar with the technique of catheterization, which can be very helpful if this treatment is recommended at a later stage. Subsequently, CISC can be successfully taught to boys and girls who are motivated and who have developed the required dexterity, mostly around the age of 6 years. The required frequency of catheterization depends on several factors including fluid intake, bladder capacity and bladder filling/voiding pressures. In practice, it is recommended to catheterize six times a day in infants (linked with feeding time) and five times a day in school-aged children. Although the reported incidences of CIC-related infection risks are variable, it is generally agreed that the risk is low as long as complete bladder emptying is achieved. Furthermore, re-used supplies are not related to

a higher rate of urinary infections. If symptomatic infections occur, these are mainly caused by incomplete bladder emptying, and the CIC technique by the child or the caregiver needs to be optimized. Nonreusable low-friction catheters are considered valuable in high-risk male patients with urethral false passage, or very tense sphincters, but are unnecessary in routine cases. In order to maintain therapeutic compliance with CISC in adolescents, psycho-social support is often required. Neurogenic bowel dysfunction with constipation and fecal soiling can interfere with the institution of a successful CIC treatment. Retained stools may mechanically impair bladder filling, increase detrusor irritability or contribute to urine retention. Stool incontinence increases the risk of bladder contamination and urinary tract infection. An effective bowel management program is therefore needed.

However, CIS alone is not sufficient to maintain a low-pressure reservoir and avoid upper renal tract damage. Thus, a combination of CIS and pharmacological therapy, aiming to decrease bladder pressure, is considered as the standard therapy in these children [2,9]. Currently, antimuscarinic agents are the first-line choice for the pharmacologic treatment of overactive bladder (OAB) (TABLE 1). Antimuscarinic therapy, such as oxybutynin, tolterodine, trospium chloride, darifenacin and solifenacin, increases bladder capacity and delays the initial urge to void, thereby reducing the symptoms of OAB. Pharmacotherapy, most often with an antimuscarinic agent, is an established approach to managing neurogenic-mediated OAB. Antimuscarinic agents, particularly oxybutynin, are associated with typical anticholinergic side effects that may limit treatment. These side effects may include dry mouth, gastrointestinal effects such as constipation and CNS effects. Only oxybutynin is approved for use in children. However, since its introduction into the market, tolterodine has been extensively used in children as an off-label drug with virtual absence of side effects [9].

Since the new generation of the antimuscarinic agents may be used in children only as off-label drugs, and ditropan has a well-known profile of side effects, alternative routes of ditropan administration have been explored in order to increase the clinical effectiveness and to decrease side effects. One of the ways to avoid the aforementioned side effects and to increase the clinical efficacy of oxybutynin is to deliver the agent via intravesical instillation [10]. The antimuscarinic effect of oxybutynin is comparable with oral administration, but the severity and the

Table 1. Anticholinergic therapy in neurogenic bladder.		
Medication	**Brand name**	**Dosage**
Oxybutynin*	Ditropan®	0.4 mg/kg per day
Oxybutynin	Ditropan XL®	5–10 mg once daily, extended release
Oxybutynin	Oxytrol®	3.9 mg per day system applied extended-release twice weekly (every 3–4 days), transdermal patch
Tolterodine‡	Detrol®	1–2 mg twice daily
Tolterodine	Detrol LA®	2–4 mg once daily, extended release
Darifenacin	Enablex®	7.5–15 mg once daily
Solifenacin	VESIcare®	5–10 mg once daily
Trospium chloride	Sanctura®	20 mg twice daily
Trospium chloride	Sanctura XR®	60 mg once daily, extended release
*Oxybutynin – the only approved agent for use in children ‡Tolterodine – off-label use with good safety profile.		

frequency of side effects is lower. In most reports, intravesical oxybutynin is used in dosages of 0.3–0.6 mg/kg per day in two or three doses. Given its better tolerability compared with oral treatment, if required, intravesical dosages can be increased up to 0.9 mg/kg per day. However, one should be aware that in spite of intravesical instillation, oxybutynin may still produce CNS-related side effects [9]. Consequently, it is held that oxybutynin should be administered intravesically in those patients who have either failed with other antimuscarinic treatment modalities (such as oral) or who had unbearable side effects from them.

In children who showed no symptoms of bladder-wall relaxation and decrease of intravesical pressure following the administration of the antimuscarinic therapy, different methods of bladder 'denervation' are indicated [11–14]. Botulinum-A toxin injections into the detrusor muscle have been shown to be a potentially valuable approach in the neurogenic overactive bladder. Repeated botulinum-A toxin injections (as an alternative or as an additive to anticholinergics) could be considered to postpone or prevent surgical procedures in the small minority of children who do not respond to a standard therapy with CIC or anticholinergics. Although the use of botulinum toxin for the treatment of OAB and detrusor overactivity (DO) is currently not approved by the US FDA or by the European regulatory agencies, its use in investigational protocols and 'off-label' continues to grow. Botulinum-A toxin has been successfully used in the pediatric population, although, in most cases, more than one session was required [12]. The published data support the efficacy of botulinum-A toxin for refractory DO in the pediatric population, whether it is of neurogenic or non-neurogenic origin, although caution must be taken in interpreting these results, as all the studies were off-label and retrospective. Consideration must be given to the fact that general anesthesia is required for the administration of this medication, especially in children. Moreover, further investigation is required concerning the cost and the long-term efficacy and safety of prolonged botulinum-A toxin administration.

Electronic stimulation

Sacral neuromodulation is an established and FDA-approved treatment for patients with refractory urgency and urge incontinence and idiopathic urinary dysfunctional voiding. It allows direct afferent nerve stimulation by direct implantation of a sacral device [15]. The principle of sacral neuromodulation is that the reflex control of the lower urinary tract can be 'modulated' through continuous low-level nerve stimulation. It has been shown to significantly affect all the parameters related to the elimination syndrome, such as incontinence and urgency. It should be stressed that this technique is not indicated by the FDA in the spina bifida population; therefore, further studies in this population are awaited.

Surgical management

There is a group of children with significant bladder overactivity who do not respond well to medication, catheterization or nerve stimulation. When this occurs, operative intervention may be required. The most effective surgical procedure to eliminate urine incontinence and to decrease the pressure in an infant is creation of vesicostomy, which allows the neurogenic bladder to grow while keeping the pressure low. Reconstruction with closure of the vesicostomy and augmentation is typically performed when

the child begins school, when the patient and the family are ready to accept the responsibility of intermittent catheterization.

As the child ages and the upper urinary tract remains normal, the interest can be shifted to focus on gaining urinary continence. It is usually practical to consider urinary continence when a child enters school. Prior to an operative intervention two main questions should be answered: is the bladder volume acceptable and the urinary sphincter competent, or does the child require augmentation and/or a procedure to improve the outlet resistance, in order to achieve continence? [5,16,17]. Prior to the surgical correction of incontinence, urodynamic evaluation with fluoroscopic imaging is thus performed. Since emptying in patients with a neurogenic bladder will require intermittent catheterization, preoperative assessment determines whether the catheterization should be performed through the urethra, or whether an abdominal stoma will be necessary.

■ Bladder augmentation

Historically, various different segments of bowel have been used for bladder augmentation [18]. The most commonly used segment for augmentation is ileum. Classic clam augmentation cystoplasty has been utilized successfully both in adults and in children. It is important to isolate the segment at least 10 cm from the ileocecal valve, so as not to interfere with bowel control, especially in patients with myelodysplasia who already have bowel continence issues. Detubularization on the antimesenteric border provides a low-pressure reservoir and increases capacity when fashioned into either a U or W shape. The bladder plate needs to be widely opened to prevent an hourglass deformity when anatomizing the patch to the bladder. Sigmoid augmentation has also been successful, although there are reports of increased rhythmic contraction when this segment is used. In select cases, gastric augmentation has been quite successful, having the advantage of less mucous production and less changes in metabolic parameters. Proper patient selection, which includes neurogenic patients who are insensate, is critical to avoid the clinical syndrome of hematuria/dysuria, related to irritation of native urethelium by the acidic urine [19].

Patients with ileal augmentation are subject to metabolic acidosis, mucous production and urolithiasis, as well as a risk of cancer at the anastomotic site. It has been shown that metabolic changes do not have an adverse affect on linear growth or bone density in children undergoing augmentation. Finally, patients with any type of intestinal augmentation are at risk for perforation, especially if compliance with catheterization is suboptimal. Since the long-term complications following bladder augmentation can not be brushed aside and an ideal material for bladder enlargement is still to be found, some have questioned the rational for routine bladder augmentation in all patients with urinary incontinence. Snodgrass et al. published their experience with bladder neck sling without augmentation in 30 neurogenic bladder patients [20]. All patients underwent a 360° fascial sling without augmentation for high leak-point pressure and stress urinary incontinence. Satisfactory continence was achieved in 83% of all patients. Only one patient needed bladder augmentation due to being refractory to the anticholinergics therapy. The authors concluded that elevated bladder pressure with decreased bladder compliance does not require bladder augmentation in neurogenic bladder patients. This experience needs to be supported by longer follow-up studies in order to become a routine practice in this group of patients.

■ Bladder neck reconstruction

In children with poor urethral outlet resistance, bladder neck reconstruction may be necessary to obtain continence [5,21]. The literature is filled with a myriad of papers describing different methods to increase urethral resistance, while at the same time allowing ease of catheterization.

In females, the majority prefer to utilize a fascial sling that is placed just distal to the bladder neck, with the concomitant creation of an abdominal stoma. The sling can be placed abdominally, if a concomitant augmentation is performed. To safely identify the space between the urethra and the vagina (urethra and rectum in males), the posterior midline approach behind the bladder is used. Since the human cadaveric fascia and xenotropic sling material are available, there is no need for an abdominal incision and autologous sling harvest in every case. In the majority of cases, the urethral sling allows catheterization through the urethra, eliminating the need to construct an abdominal stoma for catheterization [22].

In males, it is hard to find one operation that can be applied to every patient. We do prefer to utilize Young–Dees–Leadbetter bladder neck reconstruction, which consists of reimplantation of the ureters to a higher position in the bladder, and tubularization of the mucosa over a 5F feeding tube. Some prefer to use a modified Kropp

bladder neck tube or Pippe–Salle bladder neck reconstruction [5,21]. Both procedures involve utilization of the anterior bladder wall strip that is subsequently tubularized over the catheter and brought through the submucosal tunnel.

Injectable therapy

Injectable (bulking) agents may be effective in decreasing or eliminating urinary incontinence by increasing bladder-outlet resistance and/or increasing urethral length. Bulking agents are injected into the submucosal tissues of the urethra or bladder neck and/or into the tissues adjacent to the urethra [23]. The injections increase tissue bulk and thereby increase outlet resistance. Treatment-related adverse events are uncommon and relatively minor, the most common being dysuria, urinary urgency, transient urinary retention and acute urinary retention. These procedures may be performed using local anesthesia in an outpatient or office setting. The best candidates for treatment with injectable materials are those patients with a normal bladder capacity and compliance, poor urethral function or intrinsic sphincter deficiency (ISD) and good anatomic support. Contraindications to the use of injectable materials include untreated detrusor overactivity, active urinary tract infection and known hypersensitivity to the proposed injectable agent. A number of materials have been proposed for the injection into the bladder neck. Crosslinked bovine collagen implant, autologous fat, carbon particles, macroplastique and polytetrafluoroethylene (PTFE) have been reported to achieve improvement or dryness in children with incontinence. However, the low safety profile and poor long-term efficacy did not support this therapy. US FDA approval of dextranomer/hyaluronic acid (Dx/HA; Deflux®) as a tissue-augmenting substance for the treatment of VUR has driven the introduction of this substance also for the treatment of urinary incontinence due to bladder neck incompetence.

Artificial urinary sphincter

An artificial urinary sphincter (AUS) is the only device that most closely simulates the function of a biological urinary sphincter. The AMS-800, introduced in 1982, is the current model of the artificial genitourinary sphincter. The artificial urinary sphincter is a useful adjunct in gaining urethral continence. The disadvantages of the artificial sphincter include infections, which require removal, as well as the need for replacing pump, reservoir or tubing should malfunction occur [24–26]. In prepubertal children, the cuff must be placed at the bladder neck, while in post-puberty it can be placed around the bulbar urethra.

Bladder neck closure

Bladder neck closure is a last resort in those patients who have undergone alternative procedures with refractory incontinence [27]. The procedure can be performed retropubically, transvesically or transvaginally in girls. This procedure is carried out in combination with the creation of an abdominal stoma, and can be difficult in patients with previous bladder neck surgery. The amount of scarring often requires opening the bladder to gain access to the bladder neck. The key to a successful operation is wide mobilization and division of the bladder neck. Omentum is frequently interposed between the bladder neck and the urethra.

Catheterizable stomas

All continent catheterizable stomas employ a flap valve (Mitrofanoff) principal to maintain continence. Continence is achieved as the bladder fills and the intravesical pressure is transmitted to the conduit. The proximal end is brought out to the abdominal wall, either through the lower quadrant or through the umbilicus, and is spatulated and anastamosed to a V-shaped skin flap created to prevent stenosis. If the appendix is not available, ileum and colon can also be fashioned into a conduit utilizing the Monti procedure: a 2 cm segment of ileum or colon is isolated and opened on the antimesenteric border and retubularized; if the length is inadequate, two segments can be fashioned and anastamosed to each other. Alternatively, a single segment can be split in the middle, opened from opposite ends and rolled over a feeding tube to create a spiral Monti. This provides adequate length in most cases, avoiding the need to harvest two separate intestinal segments. Complications of the catheterizable channel are a frequent and challenging problem, and include cutaneous stenosis (6%), channel stricture (6%), stomal prolapse (5%) and channel leak (21%) [28]. These complications appear to occur throughout the life of the channel, mostly developing within the first 2 years.

Conclusion

In patients with neurogenic bladder the primary goal is to preserve the upper tract function with concomitant attainment of urinary and fecal continence. In order to accomplish these goals, each child requires evaluation,

with the institution of intermittent catheterization and/or medical therapy upon diagnosis. Meticulous care prevents the need for reconstructive surgery, and protects the upper tract in the majority of children with neurogenic bladder. If the child develops recurrent infection or increasing hydronephrosis early on, a vesicostomy is needed until the child is old enough for reconstruction. Otherwise, patients should be followed until school age when continence issues can be addressed. Only when the patient and his/her family are ready and understand the consequences of surgery should augmentation, bladder neck reconstruction or the creation of a continent catheterizable stoma be performed.

Future perspective

Currently, gastrointestinal segments are used in patients with neurogenic bladder whenever pharmacological therapy with or without CIC has failed. Unfortunately, those patients are not free of the complications such as urinary tract infections, metabolic disturbances, stones and development of malignant processes in the augmented bladders. The use of tissue-engineering techniques may be a good alternative to the previously described surgical methods, omitting their associated complications.

The goal of tissue-engineering techniques in bladder reconstruction is to create a biological substance that may restore and maintain a normal organ function and avoid rejection [29,30].

Several synthetic materials such as polyvinyl sponge, Teflon® and silicone have been used for bladder reconstruction but have failed due to mechanical malfunctioning or urinary stone formation. It seems that only selective cell transplantation may provide a reasonable basis for the regeneration of the urothelial and muscular layers and provide the right conditions for bladder replacement. At present, the search for the proper scaffold on which the matrices and cells for bladder augmentation may be implanted is still ongoing. The first clinical experience with tissue engineering of human bladders was recently published by Atala *et al.* [31]. Seven patients with myelomeningocele, aged 4–19 years, with high-pressure or poorly compliant bladders, were identified as candidates for cystoplasty. A bladder biopsy was obtained from each patient and the urothelial and muscle cells were grown in culture and seeded on a biodegradable bladder-shaped scaffold made of collagen, or a composite of collagen and polyglycolic acid. Approximately 7 weeks after the biopsy, the autologous engineered bladder constructs were implanted either with or without an omental wrap. Postoperatively, the mean bladder leak-point pressure decreased at capacity, the volume and compliance increased, bowel function and renal function were normal and no metabolic consequences nor urinary calculi were noted during a follow-up period of 46 months. Despite the advances in this field,

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Executive summary

Medical therapy
- In untreated spina bifida patients, progressive deterioration may be observed in up to 58% by the age of 3 years.
- The leak-point pressure, as it is now commonly referred to, has become accepted as one of the urodynamic parameters that allows clinicians to differentiate patients with relatively low and high risk for subsequent upper urinary tract deterioration.
- The treatment of children with neurogenic bladder falls into the following major categories: behavioral therapy, pharmacological therapy (often accompanied by clean intermittent catheterization [CIC] or self-catheterization) and utilization of electronic stimulation.
- CIC enables complete bladder empting and thus avoids bladder residues and consequent risks for infections.
- Antimuscarinic agents are the first-line choice for the pharmacologic treatment of overactive bladder.
- The published data support the efficacy of botulinum-A toxin administration.

Surgical therapy
- The most effective surgical procedure to eliminate urine incontinence and to decrease the pressure in an infant is the creation of vesicostomy.
- The most commonly used segment for bladder augmentation is ileum.
- Gastrocystoplasty shows its benefits only in patients with chronic renal insufficiency, metabolic acidosis or short-gut syndrome.
- In children with poor urethral outlet resistance, bladder neck reconstruction may be necessary to obtain continence.
- Bladder neck closure is the last resort in those patients who have undergone alternative procedures with refractory incontinence.
- All continent catheterizable stomas employ a flap valve principal to maintain continence.

Conclusion
- The primary goal of treatment in patients with neurogenic bladder is to preserve the upper tract function with concomitant attainment of urinary and fecal continence.
- Each child requires evaluation, with the institution of intermittent catheterization and/or medical therapy upon diagnosis.
- Only when the patient and his/her family are ready and understand the consequences of surgery should augmentation, bladder neck reconstruction or creation of a continent catheterizable stoma be performed.

significant efforts should still be made in order to find biological materials that may improve tissue regeneration.

Another field that should be intensively investigated is bladder neuromodulation. This therapy directly addresses the root of the problem in patients with neurogenic bladder, namely the abnormal relationship between the nerves and the bladder wall. Various approaches have been introduced, including transurethral bladder electrostimulation, sacral neuromodulation and neurosurgical techniques such as selective sacral rhizotomy and artificial somatic–autonomic reflex pathway construction [32,33], but none of them has been widely incorporated into routine clinical work yet.

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