

Pharmacotherapy for Pediatric Neurogenic Bladder

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Abstract Neurogenic bladder (NB) is a nonspecific term that may describe conditions ranging from areflectic non-contractile bladder to detrusor overactivity. The most common cause of NB in children is the presence of dysraphic malformations. Urodynamic evaluations make it possible to describe bladder dysfunctions and to plan a therapeutic strategy for each patient. In a child with NB there are two major dangerous functional problems seen in urodynamic investigations: high intravesical pressure in the storage phase and high pressure during urination. The basic goals of urologic treatment for a child with NB are the protection of the urinary tract from complications and improvement of continence. Treatment for a child with NB is usually conservative, and focuses on achieving safe bladder pressures during storage with reliable emptying, via voiding or catheterization. The two most important forms of conservative treatment are clean intermittent catheterization and pharmacological treatment of functional disorders. Some drugs are used in the treatment of functional disorders in children with NB, but none of the drugs are officially approved for small children and babies.

Key Points

Pharmacotherapy is one of the most important elements in the treatment of a pediatric patient with neurogenic bladder. Some groups of drugs have been described to improve the function of the lower urinary tract.

Oxybutynin was the first drug formally approved, but only for children >5 years of age. It was followed by tolterodine and recently by solifenacin. There is not enough evidence-based medicine to prescribe all of the anticholinergics or α -blockers in children.

1 Introduction

The normal function of the urinary bladder is to store and expel urine in a coordinated, controlled fashion. This coordinated activity is regulated by the central and peripheral nervous systems. Neurogenic bladder (NB) is a term applied to a malfunctioning urinary bladder due to neurologic dysfunction or insult emanating from internal or external trauma, disease, or injury [1].

The organs of the urinary system are traditionally classified as belonging to the upper or the lower urinary tract. The lower urinary tract (LUT) anatomically comprises the bladder and sphincters, which together form one operating unit. Due to the specificity of the performed action, part of the bladder dome is known as the detrusor, and the sphincters are classified as internal and external. However, for practical reasons, we normally simplify the issue and

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talk about functional disorders of the LUT (i.e. detrusor/sphincter dysfunctions), also referred to in short as bladder dysfunctions.

Micturition, or urination, occurs involuntarily in infants and young children until the age of 3–5 years, and at this time of life is controlled only by the autonomic part of the nervous system, after which it is regulated voluntarily [2]. In older children, the correct functioning of the bladder/sphincter unit is manifested by periodic, conscious controlled urination in portions adequate to the patient's age with continence maintained between particular acts of micturition.

The evaluation of the bladder function in older children should begin with keeping, for at least three consecutive days, a voiding diary (VD), also known as a frequency/volume chart. It contains data on the hours and volumes of voided or catheterized urine. On the basis of the diary we are able to establish the three most important parameters: the number of micturitions per 24 h, the maximum voided volume testifying to the anatomical capacity of the bladder, and the functional bladder capacity—an average voided or catheterized volume. The VD also provides a reliable non-invasive estimate of bladder capacity in children with NB. However, the potential for poor agreement with urodynamic measurements means the two techniques should be seen as supplementary, rather than interchangeable, in this group [3].

The literature offers various formulas for the calculation of age-related bladder capacity for children. The most frequently used is Hjälmsås' formula, expected bladder capacity (EBC): $\text{volume (mL)} = 30 \times [\text{age (in years)} + 1]$. Bladder capacity increased with age and body weight from 30 mL in neonates to 350 mL in 12-year-old children [4–6].

2 The Practical Division of Urination Problems

Analyzing the data obtained from VD, we can identify three groups of patients:

1. Those with normal/correct bladder function. The correct condition is regular urination, fully controlled by the patient, in portions adequate to age, without complaints.
2. Those voiding, but abnormally. The child passes urine periodically but the volumes are not correct:
 - (A) Increased voiding frequency. Frequent passing of urine in decreased volumes: $<65\%$ EBC, and >8 voids per day, ("Overactive Bladder Syndrome" [OAB] with frequency and urgency symptoms).
 - (B) Decreased voiding frequency. Sporadic passing of large portions of urine: $>150\%$ EBC, <3 voids

per day, ('Lazy Bladder Syndrome', voiding postponements).

- (C) Irregular voiding characterized by considerable differences in the voided volume of urine, which is commonly accompanied by a significant amount of residual urine after urination ($>10\text{--}20\%$ of EBC).

Each of the above-described conditions may be accompanied by additional LUT symptoms, such as urgency, hesitancy, straining, or intermittency. In each group, urine incontinence or infections of the urinary tract may occur.

3. Those who have lost control over their bladder and do not urinate at all.
 - (A) Total lack of control over urination. In children with dysraphic malformations, the fibers of the efferent and afferent, motor and sensory pathways, and spinal centers responsible for controlling bladder and sphincter functions are seriously damaged. In children who have no sensation of bladder fullness and lack the urethra sensation, or in whom that sensation is considerably decreased, we observe the inability to urinate voluntarily, in a controlled manner. The result in the majority of them is uncontrolled urine leaking characteristic of severe cases of NB [7].

3 Causes of Neurogenic Lower Urinary Tract Dysfunctions

NB is a nonspecific term that may describe conditions ranging from areflectic noncontractile bladder to detrusor overactivity (DO) [1, 8].

The neural circuitry that controls the process of urine storage and voiding is complex and highly distributed, it involves pathways at many levels of the central nervous system including the brain and the spinal cord, and also the peripheral nervous system, and it is mediated by multiple neurotransmitters. Congenital malformations, acquired diseases, or injuries of the nervous system can cause the re-emergence of involuntary or reflex micturition, leading to problems with urination, loss of ability to urinate, and urinary incontinence [2, 9].

The distinction still holds between neurogenic LUT dysfunction or simply NB dysfunctions and non-neurogenic, idiopathic bladder dysfunctions. Various diseases and events affecting the nervous systems controlling the bladder and sphincters may cause neurogenic LUT dysfunction. The resulting NB depends grossly on the location and the extent of the neurologic lesion [1, 10]. In patients

with NB, dysfunctions of the detrusor and the sphincter complex are caused by either a known congenital defect of the nervous system or by acquired, post-traumatic, and post-inflammatory or neoplastic damage to the nervous system. The most common cause of NB in children is the presence of dysraphic malformations, or spinal dysraphism (SD). Other causes of neurogenic dysfunction involving the spine include sacral agenesis, tethered spinal cord, or malformations associated with an imperforate anus, cloacal malformations, spinal cord injuries, central nervous system abnormalities including cerebral palsy, and learning disabilities such as attention deficit hyperactivity disorder (ADHD) or attention deficit disorder [9, 11, 12].

In patients with idiopathic bladder dysfunctions (IB), neurological examinations fail to reveal any pathology in the nervous system. Diagnosis of IB is not so obvious, as some studies demonstrated various pathologies in the nervous system, such as parasympathetic hyperactivity in children diagnosed with idiopathic OAB syndrome, suggesting a neurogenic dysfunction in their autonomic nervous system [13–15].

Dysraphic malformations (SD) are characterized by a considerable variety of clinical manifestations, from occult spinal dysraphism, non-symphysis of single lumbal vertebral arches, to extensive open myelomeningocele (MMC) reaching the thoracic region with co-existing hydrocephalus [11]. The prevalence of SD was reported to be 2–6.1 per 10,000 live births [9, 12, 16, 17]. The type of urinary tract dysfunction detected is not clearly linked to the defect morphology (open, closed), the level of dysraphism, or the extensiveness of the cleft. Children with so-called *occult spinal dysraphism* form a specific group of patients in which the progressive damage of the nervous system may initially manifest itself solely in bladder dysfunction with gradually increasing incontinence. In children with occult spinal dysraphism, socially acceptable continence is achieved only in 78% of the children [18]. About 95% of children with open MMC do not urinate at all; in a study by Reiner et al. of 108 consecutive patients with MMC aged 5–12 years, only seven (6.5%) achieved spontaneous urinary continence; of these, five (5.4%) with normal micturition and two with urgency [19]. According to Jørgensen et al., even with the help of pharmacotherapy and surgical procedures, fecal and urinary continence could be achieved in only 81% and 62% patients with open SD, respectively [20]. Even in utero operations did not improve the function of LUT in children with MMC; while in utero closure of MMC has been shown to decrease rates of ventriculoperitoneal shunting and improve motor function, it is not associated with any significant improvement in LUT function compared with repair after birth. Therefore, it is recommended that patients who undergo spinal cord defect closure during

gestation be evaluated and treated in the same manner as those with MMC but without fetal intervention [12, 21–24].

4 Initial Management of a Child with Neurogenic Bladder

An infant with suspected NB after spinal cord surgery should first undergo physical examination, with particular attention paid to the condition of the genitourinary system. Physical appearance, sensation, and neurological reflexes in the perineal region should be evaluated. Special attention should be paid to the manner of urinating; spontaneous urine discharge from the urethra in droplets is often detected in children with SD, and urine leakage after pressing above the pubic symphysis is observed.

When introducing a catheter into the bladder, the examining clinician should observe the child's reactions in order to evaluate the urethra sensation. The tonus of anal sphincters should be checked, which is predominantly found to be lacking.

Further tests are performed in a certain sequence, beginning with urinalysis and urine culture followed by biochemical tests, the analysis of the morphology of the urinary tract (ultrasonography, cystography, renal scans, intravenous pielography, and computer tomography) and then the evaluation of the bladder and sphincter functions in urodynamic testing. Urodynamic evaluations make it possible to describe bladder dysfunctions and dysfunctions of the urethral sphincters, while the other tests are used to evaluate the type and severity of complications caused by the neurogenic urinary system dysfunctions.

With data from the VD, urodynamic tests can be performed in a reliable manner. In toilet-trained children, neuro-urologic evaluation should begin with the simplest urodynamic test—uroflowmetry. In order to obtain the complete picture of urination effectiveness, ultrasonographic evaluation of the amount of residual urine in the bladder after urination is always necessary. More complicated urodynamic tests such as cystometry, voiding cystometry, and video-urodynamics are recommended for patients with multi-symptomatic forms of NB [1, 7, 10, 11].

The first urodynamic tests in children after MMC surgery with suspected NB should be performed in early infancy; the subsequent tests ought to be the controls, because newborns with MMC and initially normal urodynamic studies are at risk for neurologic deterioration secondary to spinal cord tethering, especially during the first 6 years of life. Close follow-up of these children is important for early diagnosis and prevention of progressive urinary tract deterioration [25].

Conventionally, the etiology of NB is divided into the following categories: central, peripheral, or mixed. But this classification has a very small role to play in therapeutic decision making. Management is dictated by the basic state of the bladder function evaluated in urodynamic investigation [26].

Analyzing data from urodynamic investigations, Madersbacher described four groups of patients with NB:

- Detrusor overactivity with sphincter overactivity
- Detrusor inactivity with sphincter overactivity
- Detrusor overactivity with sphincter inactivity
- Detrusor inactivity with sphincter inactivity.

Of all four types, only the combination of sphincter inactivity and detrusor inactivity is inherently 'safe' in that, untreated, it will not lead to urinary tract damage, although it does result in incontinence and increased rates of urinary tract infection. The European Association of Urology recommends Madersbacher's modified functional classification for motor function of LUT based on urodynamic and clinical findings. Based on this simple, but clinically useful, classification of detrusor-sphincter dysfunction, the therapeutic strategy is provided for each patient [10, 27].

5 Risk Factors

Many parameters are evaluated in the urodynamic test; however, the following are the most important for predicting risk of complications:

1. The detrusor leak point pressure (DLPP)—the lowest value of detrusor pressure at which leakage is observed in the absence of abdominal strain or detrusor contraction. An increased risk of development of complications occurs in patients with DLPP >40 cm H₂O.
2. Bladder compliance or detrusor compliance. Relationship between change in bladder volume (ΔV) and change in detrusor pressure (ΔP_{det}): $C = \Delta V / \Delta P_{det}$ (mL/cm H₂O). Patients with a bladder compliance of <20 mL/cm H₂O are 4.3 times more likely to have bladder diverticuli or vesicoureteral reflux (VUR) compared with patients with compliance >20 mL/cm H₂O.
3. Detrusor sphincter dyssynergia (DSD) is a detrusor contraction concurrent with an involuntary contraction of the urethra and/or periurethral striated musculature. Up to 72% of children with DSD will develop complications without proper treatment.
4. Elevated storage pressure with decreased bladder capacity. Both are caused by detrusor overactivity (DO). DO is expressed by involuntary detrusor

contractions during filling, spontaneous or provoked. The diagnosis of DO is made based on the urodynamic investigations. If those contractions are caused by a neurogenic condition we call them neurogenic detrusor overactivity (NDO). According to current knowledge, elevated storage pressure in the bladder, either alone or combined with VUR, is the most important risk factor for renal damage [6, 10, 28–33].

According to Madersbacher's classification, the most dangerous findings for a child with NB is a combination of DO with sphincter overactivity. In this type of NB there are two major dangerous functional problems:

- high intravesical pressure in the storage phase, and/or
- high pressure during leakage of urine or during urination.

From a practical point of view for the patient, DO leads to a decrease in functional bladder capacity and to urinary incontinence. On the other hand, sphincter overactivity leads to ineffective voiding or makes voiding impossible. High pressure in the storage phase is caused mainly by DO and/or by decreased bladder wall compliance.

OAB is a syndrome consisting of urinary urgency/frequency, with or without urinary incontinence, in the absence of a causative infection or pathological conditions [6].

Patients, with symptoms of OAB, where the cause is neurogenic, are often referred to as having neurogenic OAB (nOAB). The symptoms of OAB usually stem from DO. Where the cause of DO is neurogenic, the condition is known as neurogenic DO (nDO). nDO is most commonly seen in patients with SD and spinal cord injury, but also multiple sclerosis or Parkinson's disease. In the majority of cases in the literature, urinary incontinence among patients with underlying neurological conditions was found to be associated with nOAB and attributable to DO [8, 34, 35]. The prevalence of urologic symptoms ranged from 12% in an Italian study of children with occult spinal dysraphism to 94.9% children with SD in Taiwan [18, 36].

Decreased compliance is often associated with irreversible changes in detrusor muscle ultrastructure, and is often caused by increased activity of the cholinergic part of the autonomic nervous system. Some authors observed an improvement in bladder compliance after anticholinergic therapy, others observed no improvement. There are also papers describing histopathologic changes, such as an increase in connective tissue with subsequent decrease in muscle tissue in fibrotic bladder wall specimens in children with decreased bladder compliance. Also, observations of lack of improvement after Botox injections in children with decreased bladder compliance suggest that in some cases decreased compliance could be resistant to any pharmacotherapy [33, 37–41].

A decrease in intravesical pressure could be achieved mainly by abolishing DO. Some drugs are used in pharmacotherapy for DO.

6 Proactive versus Expectant Management

The philosophy of expectant management comes from the assumption that <10% of children with congenital NB will develop satisfactory bladder control without the need for clean intermittent catheterization (CIC); all parents are initially counseled and reminded at periodic follow-up to expect this intervention by the age of toilet training if urodynamic evaluation does not indicate earlier management [42].

Proactive management, which is more popular among urologists, is based on data from urodynamic evaluations performed in a newborn and early institution of CIC and anticholinergics.

The most frequently used proactive approach is defined by early and regular urodynamic testing. Ideally, CIC with or without pharmacotherapy is started early based on urodynamic findings, before the development of upper tract changes. Proactive bladder treatment with the prophylactic institution of intermittent catheterization and pharmacologic, anticholinergic therapy in the newborn significantly reduced the incidence of complication development, upper urinary tract deterioration, and need for surgical intervention [7, 9, 30, 43–45].

7 Goals of Treatment

The treatment of patients with NB is a multi-directional and complicated process. There are three basic goals of urologic treatment of a child with NB:

- optimization of bladder emptying,
- protection of the urinary tract from complications,
- improvement of continence.

Treatment for a child with NB begins with the conservative methods. The two most important forms of conservative treatment for a child with NB are CIC and pharmacologic treatment of functional disorders found in urodynamic studies.

8 Intermittent Catheterization

Jack Lapidus introduced CIC in the 1970s. This method is a simple and effective way of achieving all the goals of treatment mentioned above [46]. CIC done at regular intervals from the newborn period has several advantages:

it empties the bladder adequately without leaving any residual urine and hence there is no risk of infection, it keeps the upper tracts safe from reflux prior to high pressure voiding, and later is a valuable tool to keep the child dry [31–33, 44]. What is important is the early institution of CIC, as it seems to improve the compliance of caregivers and their ability to assist the child in coping with his/her condition [47].

9 Pharmacotherapy

The second tool in the conservative treatment for a child with NB is pharmacotherapy. Pharmacologic therapy is defined as any therapy based on drugs [6].

9.1 Antimuscarinic Drugs

Antimuscarinic or anticholinergic drugs represent the mainstay of pharmacologic treatment for both idiopathic and neurogenic DO. Involuntary contractions of the detrusor muscle during the filling phase are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors. Since oxybutynin was introduced in the early 1970s, antimuscarinic medications have been extensively studied in patients with nDO, with encouraging results. Relative to placebo, anticholinergic drugs are associated with a 40% increased likelihood of cure or improvement, and a significantly decreased number of leakage and voiding episodes [48, 49].

Most antimuscarinics are tertiary amines and are metabolized by the P450 enzyme system to active or inactive metabolites. Only trospium chloride is a quaternary amine. The most commonly involved P450 enzymes are CYP2D and CYP3A4 [50]. These drugs act against the muscarinic receptors on the wall of the detrusor muscle, relax it, and thereby decrease intravesical pressures and overactive contractions and indirectly increase functional bladder capacity. Acetylcholine is generated and released from the cholinergic nerves, but also from the urothelium, binding to M2 and M3 receptors. Those receptors have been shown to evoke smooth muscle contraction. Antimuscarinics have anti-spasmodic but also local anesthetic and calcium channel blocking properties that augment their effect on the DO [49, 51–54].

M1 receptors are found in the brain, salivary glands, and sympathetic ganglia, which account for most of the side effects noted with antimuscarinic drugs. Dry mouth and constipation are the most common symptoms. Gastroesophageal reflux, blurry vision, urinary retention, and cognitive side effects can also occur; these symptoms are generally less frequent and bothersome in children than in adult patients [55–57].

Compliance and persistence with antimuscarinic therapy remain poor as this is generally considered to be due to lack of efficacy or because of the troublesome side effects [58]. A study based on prescription data from the UK estimated that discontinuation rates at 12 months for patients on antimuscarinics ranged between 65 and 86% [59]. That was an adult study, but in 2009 a disproportionately high number of central nervous system adverse event cases were reported in pediatric patients compared with adult patients, so some studies were undertaken on this issue [60].

Giramonti, in a double-blinded crossover trial, found that oxybutynin and tolterodine do not have a deleterious effect on children's attention and memory [61]. More recently, no significant differences in behavior were found between children with NB with and without long-term use of antimuscarinics [62].

Seven different antimuscarinics are currently marketed for the treatment of DO: oxybutynin, tolterodine, propiverine, trospium, solifenacin, darifenacin, and fesoterodine. Not all of those drugs are equally available on the market in different countries. It is the same with the formulation, oxybutynin syrup, patches, gels or extended-release (ER) tablets of oxybutynin and tolterodine are available, but not in every country. The most popular antimuscarinic drug is oxybutynin in a 5-mg immediate-release (IR) tablet formulation [63].

According to Madhuvrata et al., in many studies of children and grown-up patients, none of the antimuscarinic drugs have been shown to be superior to one another [64]. The review by Buser et al., including randomized controlled trials of different formulations and dosages of antimuscarinics, concluded that there was no clinically relevant difference in efficacy between antimuscarinics, but in terms of safety, high dosages of oxybutynin and propiverine were associated with a greater risk of adverse events [65]. Novara et al. reported that ER formulations offered advantages in terms of efficacy and safety compared with IR formulations [66]. In adult trials, quantitative electroencephalographic data suggest that oxybutynin has more CNS effects than trospium or tolterodine [67]. None of the antimuscarinic drugs are authorized for use in infants and small children. Oxybutynin became the first one approved by the US Food and Drug Administration (FDA), followed by tolterodine, but only for children above 5 years of age [68]. In a study by Blais et al., the most prescribed antimuscarinic drug as a first-line therapy of DO in children in Canada was oxybutynin followed by tolterodine, trospium, solifenacin, and darifenacin [55]. In the US, the most common prescriptions for NB in children were for oxybutynin (78%) and tolterodine (17%) [63].

9.1.1 Oxybutynin

Oxybutynin hydrochloride is a tertiary amine that is well absorbed and undergoes hepatic metabolism by the cytochrome P450 system into metabolites, with N-desethyl-oxybutynin as the primary one. It has a high affinity for muscarinic receptors, higher for M3 and M1 than for M2 subtypes [69, 70]. Oxybutynin was the first formally approved antimuscarinic drug for use in children [33, 71, 72].

Oxybutynin is safe and efficacious in treating pediatric NB. Oxybutynin is available in several formulations: syrup, IR and ER tablets, and also transdermal patches and a solution for intravesical instillation. The drug is tolerable and the safety profile suggests that adjustment of dosage for age may not be strictly observed. It is administered orally in a dosage of 0.2/0.4/0.6 mg/kg/day in two to four divided doses. The dose has to be limited sometimes in view of the side effects [73, 74].

In 2014, Momper et al. analyzed data from trials submitted to the US FDA showing that only oxybutynin demonstrated efficacy in children with NB. The lack of demonstrable efficacy for the remainder of the antimuscarinics illustrates that future trials should give careful attention to testing a range of doses, using objectively measured, clinically meaningful endpoints, and selecting clinical trial designs that are both interpretable and feasible [75]. The current experience with drugs other than oxybutynin is still limited in children with NB.

9.1.2 Tolterodine

Tolterodine is available for children as a solution, or as IR or ER tablets. In a study by Reddy et al. in children with NB, drug formulation and dosing were based on age (4 months–4 years, tolterodine oral solution 0.2–2 mg twice daily; 5–10 years, oral solution 0.5–4 mg twice daily; 11–16 years, ER capsules 2, 4, or 6 mg once daily). Both tolterodine formulations were effective and well tolerated [76].

Three open-label, dose-escalating studies were conducted in children with NB and DO. In studies 1 (patients aged 1 month to 4 years) and 2 (5–10 years), patients received tolterodine solution 0.03, 0.06, and 0.12 mg/kg twice daily for 4 weeks each. In study 3 (patients aged 11–15 years), patients received tolterodine extended-release capsules 2, 4, and 6 mg once daily for 4 weeks each. Tolterodine was well tolerated, and there was no apparent relationship between tolterodine dosage and adverse events in any study [77].

In another group of children with NB and DO, tolterodine received orally in a dosage of 0.1 mg/kg daily, divided into two doses, was better tolerated than, and

equally effective as, the standard drug oxybutynin chloride [78]. In a multicenter, open-label, double-blind, placebo-controlled study, long-term treatment with tolterodine ER was well tolerated in children aged 5–11 years [79].

Medhi et al. examined the efficacy, safety, and tolerability of tolterodine in children in comparison with oxybutynin treatment as demonstrated in randomized clinical trials and other studies. The dose of tolterodine used in different settings ranged from 0.5 to 8 mg/day. Both ER and IR preparations of tolterodine were shown to have comparable efficacy. Tolterodine proved to have comparable efficacy with better tolerability than oxybutynin in these studies [80–84].

9.1.3 Propiverine

Another antimuscarinic drug is propiverine. Propiverine hydrochloride, with its anti-muscarinic and calcium-channel modulating properties, has been of proven efficacy in patients with nDO, including children and adolescents, and even in some of those cases unresponsive to other anticholinergics, with a low incidence rate (<1.5%) of adverse events [85]. It was also evaluated during long-term treatment of children with NB at a dosage of 0.7–0.8 mg/kg body weight/day. Some studies demonstrated the superior tolerability of propiverine over oxybutynin, with comparable efficacy in children [74, 86–88]. In children and adolescents with IDO or nDO, propiverine was generally more effective and better tolerated than oxybutynin and provides a valuable option for the treatment of DO [89–91].

9.1.4 Trospium

Lopez Pereira et al. assessed the efficacy and dosage of trospium chloride 10, 15, 20, or 25 mg for managing bladder overactivity in 58 children compared with a placebo. Trospium was effective and well tolerated, although 10% of patients showed adverse effects [92]. In another uncontrolled study from 2001, the efficacy of trospium was assessed in children with NB. A group of 14 patients received trospium 15–45 mg administered three times per day. During therapy, urodynamic investigations showed a significant increase in bladder capacity. The therapy was also well tolerated. A definite recommendation for the use of trospium chloride in children cannot be given due to insufficient data. However, preliminary results indicate that its use may have potential advantages in children [93].

9.1.5 Solifenacin (*Vesicare*)

At least two antimuscarinic drugs, darifenacin and solifenacin, with selective M3 receptor antagonist action and fewer systemic anticholinergic side effects than currently

available agents, are yet to be studied in children [94]. Solifenacin is a tertiary amine with excellent bioavailability and a long half-life, and potentially a superior side-effect profile due to M3 subtype receptor selectivity [95]. The efficacy and safety of solifenacin 1.25–10 mg in the treatment of 244 children with non-neurogenic DO and NB refractory to oxybutynin or tolterodine was evaluated by Nadeau et al. In this non-randomized uncontrolled study, high subjective and objective success rates were maintained over a longer follow-up with an adjusted-dose regimen of solifenacin. A very interesting observation was that, even if more than half of the children required an adult dose of solifenacin, most of the adverse effects were acceptably low in frequency, of minor severity, and self-limiting [72, 96].

Solifenacin pediatric drug trials are finished and the drug is now waiting for review and approval from the US FDA.

9.1.6 Fesoterodine and Darifenacin

Data regarding fesoterodine and darifenacin therapy in children with NB are lacking.

9.2 Alternative Route of Administration of Antimuscarinic Drugs

9.2.1 Intravesical Oxybutynin Instillation

As an alternative route of administration, intravesical and transdermal oxybutynin has also been evaluated for its potential to decrease the side effects by reducing metabolism in the liver while maintaining systemic efficacy and bioavailability. Oxybutynin is available formulated for intravesical administration. As the majority of children with NB are on CIC, intravesical drug instillation seems to be a reliable method of treatment. This route of drug delivery will of course be very disputable in children with recurrent urinary tract infections and should be avoided in children with known VUR.

It was demonstrated that a reduced first-pass metabolism of oxybutynin after intravesical instillation resulted in reduced generation of the N-desethyl metabolite. This may explain the clinically relevant reduction of systemic side effects of intravesical oxybutynin compared with oral therapy [97].

Some research showed that intravesically administered oxybutynin, apart from blocking muscarinic receptors in the bladder wall, acts by blocking the bladder cooling reflex mediated by C-fibers in patients with an incomplete neurogenic lesion and DO [98].

It has been reported to be effective in suppressing DO with low incidence of side effects in children and adult patients with NB. In most studies, children with NB

received oxybutynin 10 mg daily (range 10–20 mg/day or 0.1–0.2 kg/day) instilled into the bladder with a urethral catheter. Intravesical oxybutynin was shown to be a safe and effective therapeutic option for children with NB who experienced intolerable side effects or were unresponsive to oral antimuscarinics. However, adverse effects such as cognitive impairment can also occur in children treated in this way and patients must be closely monitored because these effects may differ from those had with oral administration [7, 45, 54, 57, 97, 99, 100].

Intravesical instillation of oxybutynin is an accepted and effective treatment in children with neuropathic bladder-sphincter dysfunction, when oral oxybutynin results in inadequate suppression of DO or intolerable side effects. In a study by Humblet et al., intravesical oxybutynin provided more than adequate suppression of detrusor activity, without side effects, over a period of 15 years [38].

The most commonly reported side effects after intravesical instillation of oxybutynin include dry mouth, facial flushing, constipation, blurred vision, and orthostatic hypotension or dizziness. Discontinuation of treatment due to side effects was reported in 28 patients (9%), and an additional 38 patients (13%) were reported to have withdrawn due to other causes [7].

9.2.2 Intravesical Atropine Instillation

Atropine is a cheap and easily obtainable antimuscarinic drug [101]. In 1993, Ekström et al. described improvement in six of eighteen patients with NB treated with intravesical atropine instillations. Others also observed improvement with no side effects after the intravesical instillation of atropine [102–104]. Similar data were also obtained in children with NB and DO treated with 10^{-6} solution of atropine; six of twelve improved in bladder capacity, with no side effects [105]. In a study of 57 patients with multiple sclerosis, intravesical atropine was as effective as oral oxybutynin for increasing bladder capacity, with fewer antimuscarinic side effects. It was concluded that intravesical atropine should be made available to patients with neurogenic detrusor overactivity requiring intermittent catheterization as an alternative to oral therapy [106].

9.2.3 Transdermal Patch

Transdermal delivery mechanisms may offer increased tolerability and patient acceptability whilst maintaining efficacy. It is available as a patch that is changed every 3–4 days, a gel available in individual sachets, or via a metered-dose pump that is applied daily. Transdermal oxybutynin has been compared with placebo and with tolterodine. Transdermal oxybutynin significantly reduced incontinence episodes and increased volume voided.

Therapy was effective in reducing the number of adverse effects related with antimuscarinic therapy, but it was associated with significant skin site reactions. In a study of 35 children with OAB, with a mean age of 8 years, 97% reported good symptom response. The main side effect was skin irritation in 35% of participants, leading to discontinuation in 20% [107–110].

9.3 β 3-Adrenoceptor Agonist—Mirabegron (Betmiga)

Mirabegron has been developed for the treatment of DO. Mirabegron is a β 3-adrenoceptor agonist. The β 3-adrenoceptor plays a role in the relaxation of the detrusor smooth muscle. Mirabegron relaxes the detrusor smooth muscle during the storage phase by activation of β 3 receptors, which increases bladder capacity [111, 112]. Cytochrome P4503A4 is the primary isoenzyme responsible for the hepatic oxidative metabolism of mirabegron in vitro, with the CYP2D6 isoenzyme playing a minor role. Mirabegron is cleared by multiple metabolic enzymes, with no single enzyme being dominant [113].

In randomized trials, Mirabegron 25- and 50-mg tablets were superior to placebo for improved voiding outcomes—urgency and incontinence episodes. It was also better tolerated than placebo [114–119]. Mirabegron also appeared as a safe and effective alternative for children with OAB refractory to antimuscarinics. In a study by Blais et al., a total of 58 patients with a median age of 10.1 years were on mirabegron 25–50 mg for a median of 11.5 months. Median bladder capacity increased from 150 mL to 200 mL with continence improvement in 52 of 58 children. Eight of the patients reported mild or moderate side effects [120, 121]. In a group of 39 children with NB, non-NB dysfunctions, and DO, patients received mirabegron 50-mg tablets with dosage depending on body weight: patients <20 kg received 12.5–25 mg once a day; patients 20–40 kg received 25–50 mg once a day; patients >40 kg received 50 mg once a day. Mirabegron was effective in 82% of children, increasing bladder capacity and decreasing urine incontinence, with no serious side effects. (Kroll P., unpublished data).

Also, in recent study on two off-label antimuscarinic drugs administered in children with DO, mirabegron with solifenacin were effective and well tolerated [121].

9.4 Double Anticholinergic Therapy

It was also shown that in children with refractory DO, double anticholinergic therapy is an efficient and serious alternative. Combinations of oxybutynin and/or solifenacin and/or trospium and/or tolterodine were tested in several studies [121–125].

In a group of 33 children with NB using two anticholinergic medications simultaneously (oxybutynin 10–30 mg, tolterodine 4 mg, and/or solifenacin 5–10 mg), Bolduc et al. optimized the medical therapy for children in whom single-agent anticholinergic therapy failed. Continence improved in all patients. No, mild or moderate side effects were reported by 12, 16, and 5 patients, respectively [122]. Also, adding mirabegron to solifenacin appears to be a safe alternative for children with refractory overactive bladder. Dual therapy is well tolerated and the adjusted dose regimen appears safe [121].

9.5 Botulinum Toxin-A

For several years, Botulinum toxin-A (BTX) has been successfully used in neuromuscular diseases associated with an increased muscular tension. It is administered to extremity muscles in children with spastic forms of cerebral palsy and is also used in the treatment of torticollis, blepharospasm, and in aesthetic surgery. Efficacy of BTX has been well documented in patients with either NB or non-neurogenic voiding dysfunctions. Less frequent have been reports on efficacy of BTX in the treatment of NB in children. In urology, BTX has been used mainly to inject the detrusor muscle in order to abolish DO, but it has also been applied to overactive sphincters. Efficacy of injections to the detrusor in children with DO has been noted in 60–80% of children with NB. BTX is available in various preparations, but only one, onabotulinum (Botox), has formal registration for cystoscopic treatment of patients with NB and DO. There are also reports on abobotulinum (Dysport) injections in children with NB, but only onabotulinum has been investigated in properly powered, multicenter, randomized controlled trials for the treatment of nDO and urinary incontinence [126–128].

The optimal dosage of BTX both in children and adolescents is still under discussion. Some authors have shown no clear dose-related effect for either onabotulinum or abobotulinum. In adults, intradetrusor application of BTX has been reported at a dosage of 100–300 units of onabotulinum or 500–1500 units of abobotulinum per patient. In children with NB, 2.5–12 units/kg bodyweight of onabotulinum or 10–30 units/kg bodyweight of abobotulinum have been used [126–131].

In children with NB and DO, the toxin is administered in divided doses into 20–30 sites of the bladder dome. BTX activity in the urinary bladder persists for 6–9 months, and can then be repeated. Repeated intradetrusor BTX injections have been found to be just as effective as the first application [129, 132, 133].

Endoscopic administration of BTX should be considered as an alternative method in cases of overactive NB where there is lack of efficacy with or side effects from oral

antimuscarinic treatment, or lack of parental consent to surgical treatment (cystostomy, intestinal bladder augmentation).

If it is considered to be an alternative to surgery, then the obvious limitation of BTX therapy is the transient effect of the endoscopic procedure. Although many questions remain regarding the optimal use of this minimally invasive option for urologic applications, the opportunity for expanding indications will provide urologists with more options for addressing difficult challenges in voiding dysfunction.

10 α -Blockers

Ineffective voiding is one of the principal problems in a child with NB. The sympathetic part of the autonomic nervous system is primarily responsible for urine continence in the bladder. In the sphincter and bladder neck muscles, a prevalence of α_1 -adrenergic receptors is found. Their activation increases the sphincter mechanism tension, and inactivation enables voiding [134, 135].

The consequence of increased sphincter activity is the storage of urine in the bladder at high pressures and its leakage from the bladder only if the pressure exceeds values considered harmful to the kidneys. Urodynamic examinations are essential for the assessment of LUT functioning. Of greatest significance in children with NB is determining the value of leak point pressure (LPP). LPP >40 cm H₂O is considered dangerous [28–30].

Even if a child with NB is urinating, lack of CNS control over the urinary tract elements results in detrusor–sphincter dyscoordination: during bladder contraction, no sphincter relaxation is observed, creating the subvesical obstruction. Micturition is ineffective and urine stream is weak, irregular, or interrupted with significant residual urine.

α_1 -Adrenergic receptors are dominant in the sphincter muscles and urinary bladder neck muscles. Activation of these receptors increases activity of the α -adrenergic part of the autonomic nervous system and sphincter tension, assisting in the maintenance of urinary continence. Since the 1970s, α -blockers have been used to reduce increased sphincter tension and to eliminate subvesical functional obstruction. α -Blockers act through periodic, reversible blocking of α_1 -adrenergic receptors in the muscles of the bladder neck and urethra sphincters [136–138].

Several preparations are available in the group of α -blockers: non-selective preparations like phenoxybenzamine (Dibenzylin) or α_1 -selective drugs such as prazosin (Minipress), terazosin (Hytrin), silodosin (Rapaflo), alfuzosin (Dalfaz), doxazosin (Doxar), and tamsulosin (Omnic). None of those drugs were approved for usage in children, so treatment with any α -blocker is off-label.

The efficacy of selective α -blockers in patients with subvesical obstruction caused by benign prostatic hypertrophy is well documented [139, 140]. There are few reports on the use of α -blockers in patients with NB, fewer dealing with children with NB or non-NB dysfunctions. Data from those studies are conflicting, showing a variable degree of efficacy when using selective α_1 -blockers in children with NB and non-NB dysfunctions.

First, phenoxybenzamine was described as effective in patients with NB and subvesical obstruction [136, 137]. In 1976, de Voogt and van der Sluis confirmed the usefulness of α -blockers in children with NB with outflow resistance, especially if detrusor activity was absent [141]. In an uncontrolled study of 17 children with NB from 2002, Schulte-Baukloh et al. showed that alfuzosin decreases the DLPP significantly, and should be considered an alternative or addition to intermittent catheterization in selected patients [142]. One year later, Abrams et al. [143] showed the efficacy and safety of tamsulosin treatment in patients with NB due to suprasacral spinal cord injury; in another study, Kakizaki et al. proved tamsulosin reduced functional urethral resistance during voiding and improved flow rate in 24 patients with NB [144]. In the same year, Cain et al. reported on 55 children with a mean age of 7.9 years diagnosed with increased post-void residual (PVR), treated with doxazosin. Therapy was effective with 88% reduction in residual urine. The conclusion was that α -blocker therapy might be used as either a replacement for or in addition to biofeedback in patients with urinary retention [145]. Two years later, in a comparative study of 28 children with a mean age of 6.25 years, Yucel et al. showed that doxazosin therapy seems to be an alternative to biofeedback in dysfunctional voiding in children with urinary retention [146]. In a placebo-controlled study, doxazosin decreased the number of incontinent episodes weekly and improved the dysfunctional voiding scores over placebo, but the differences were not statistically significant [147].

In a comparative, non-placebo controlled study of 60 children with ineffective voiding and significant PVR, both methods (oral doxazosin therapy vs behavioral treatment and rehabilitation [standard urotherapy]) showed similar effectiveness [148]. Also, Gołębiowski reported significant improvement in effectiveness of bladder emptying (PVR decreased to a mean of 12 mL, compared with 74 mL before treatment) in a group of 208 children with non-neurogenic voiding dysfunctions treated with doxazosin [149].

In the study by Abraham et al. on children with significant PVR urine after posterior urethral valve ablation, another α_1 -blocker, terazosin, has proved to be safe and results in significant reduction in residual urine [150]. In the study from 2009 on children with mean age 8.9 years (range 5–16), the most selective α_1 -blocker, tamsulosin,

proved to be a safe and effective treatment option for LUT symptoms in children with voiding dysfunctions [151]. In another group of children treated with tamsulosin, Van Batavia et al. showed that α_1 -blocker therapy continued to benefit children with primary bladder neck dysfunction even after a longer period of time [152]. Data from a randomized trial on tamsulosin in 135 children with NB were very interesting: although 51 (37.8%) patients were LPP ‘responders’, no statistically significant difference was found in LPP response rates between tamsulosin and placebo groups [153].

A similar observation of the significant decrease in LPP in some patients, along with the lack of significant efficacy of α -blockers in the whole study group of children with NB treated with selective α -blockers, was reported recently [154].

10.1 Dosage of α -Blockers

Several published papers have proposed a variety of dosage regimens for α -blockers, mainly starting with a quarter of the appropriate adult dosage.

In a study from 2004 in a group of 30 children treated with doxazosin, an old rule of calculating off-label drugs was adopted and the following regimen was proposed with dosage depending on body weight: for patients >40 kg, adult dosage of 2.0 mg once a day; in children 20–40 kg, 1.0 mg; and for children <20 kg, 0.5–1.0 mg once a day was recommended [155]. In other studies, the initial dose of doxazosin in children was 0.5–2.0 mg once daily [145–149, 156, 157], or 0.03 mg/kg bodyweight/day [154, 158]. For terazosin, a starting dose of 0.5 mg increasing to 2 mg was proposed [143, 159]. In the study by VanderBrink et al., in children with a mean age of 8.9 years, an initial dose of tamsulosin 0.2 mg was given once a day, increasing to 0.4 mg. The authors concluded that a dose of 0.4 mg was safe and necessary in the majority of patients [151]. In another study, 51 children with a mean age of 11.6 years (range 3.5–17.8) were also taking tamsulosin at a mean dose of 0.4 mg (range 0.2–0.8 mg) [152]. Alfuzosin was used to decrease the elevated DLPP in 17 children with NB (mean age 6.3 years) in an oral formulation (2.5–7.5 mg/day) [142].

10.2 α -Blocker Side Effects

Importantly, when prescribed off-label, there were no reports of serious adverse events associated with α -blocker treatment in children. To date, no serious adverse events have been reported in relation to α -blocker therapy in children with NB.

In the biggest study of 208 children with bladder dysfunctions treated with α -blockers, minor side effects were

observed in only five children [149]. In another study of 55 patients also treated with doxazosin, minor side effects were observed in two children, and in another group of 16 boys there were no significant adverse effects. Decreases of systolic and diastolic blood pressure were negligible [145, 156]. In a group of 17 children 3–15 years old treated with 0.5–1.0 mg doxazosin, only one patient had mild postural hypotension, which resolved with dose reduction [157]. In another study of 14 children, one boy who experienced drowsiness and a decrease in blood pressure failed to complete the study [154]. In another study of 28 patients receiving doxazosin, no drug-related side effects were reported [146]. In a comparative study of 60 children, 30 children with a mean age of 9.2 years were treated with doxazosin 0.5–2 mg. Side effects were noted in six children, and included headache and vertigo related to hypotension, with epistaxis in two children. None of those children stopped α -blocker therapy [148].

In the group of 51 children treated with tamsulosin, no patient had any major side effects; blood pressure and heart rate remained normal in all children, and only two patients reported light-headedness and somnolence—in neither patient were the side effects bothersome enough to stop the medication. In another group of 23 children followed for 20 months, tamsulosin demonstrated no clinically significant effect on blood pressure [151, 152].

Alfuzosin therapy was also well tolerated; side effects were rare and not severe [142]. In a study of 42 children after posterior urethral valve ablation, only one patient reacted to terazosin, with hypotension necessitating its withdrawal [150].

10.3 Other Drugs

There is no evidence that any pharmacotherapy is effective in children with NB and areflectic detrusor. There is no data that any drug is able to improve sphincter function in children with NB and sphincter inactivity.

11 Conclusions

In conclusion, it should be stated that there is enough evidence on the benefit of pharmacological decrease of elevated detrusor pressure in children with NB, but unfortunately only one drug is currently approved for children. There is no doubt that urological pharmacology has some valuable drugs to offer for children with nDO, but they have yet to be evaluated in the proper manner in prospective studies. Theoretically, pharmacotherapy with selective α -blockers should be of benefit for children with NB and elevated LPP. However, at present there is no evidential proof of their action on sphincters in children

with NB. A lack data from prospective, multicenter, randomized, placebo-controlled studies is evident, but some studies (i.e., tamsulosin, alfuzosin and mirabegron) in children with NB have been started [160].

Compliance with Ethical Standards

Conflict of interest The author (PK) declares that there are no conflicts of interest.

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