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## Lower urinary tract dysfunction in pediatrics progress to kidney disease in adolescents: Toward precision medicine in treatment

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### Abstract

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at birth. Most of them will develop deterioration of renal function and chronic kidney disease if they do not receive proper management. Children with NBD can develop renal damage at adolescence or earlier, which is due to high detrusor pressures resulted from poor compliance of the bladder, detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there was great progress in the treatment of children with the NBD. We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021, using the search term "neurogenic bladder children." Our search excluded diagnosis, pathophysiology, surgical treatment of spinal cord injury and spina bifida. The research identified the effectiveness of treatment regimens targeting prevention of chronic kidney disease and the indications of kidney transplantation. The results of the research showed that NBD in children should be diagnosed early in life, and the child should receive the proper management. The literature search concluded that the management of NBD in children would be personalized for every case and could be changed according to response to treatment, side effects, child compliance, availability of treatment modality and costs of treatment. The objectives of the study are to present the different options of management of NBD in children and the selection of the proper method in a personalized manner.

**Key Words:** Neurogenic bladder dysfunction; Antimuscarinics; Onabotulinum toxin A; Neural stimulations; Renal transplantations

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**Core Tip:** Neurogenic bladder dysfunction in children can lead to renal dysfunction and chronic kidney failure. This review reports treatment options including the latest modalities. The new anti-muscarinic drugs have minimal adverse effect, high tolerability, availability of solution form and dose adjustment. Children who develop adverse events from anti-muscarinics or non-compliant to clean intermittent catheterization would be candidate for detrusor muscle injection with onabotulinum toxin A, which proved to be safe with no adverse effects. Kidney transplantation would be the last resort for treatment after progressive deterioration of kidney function.

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## INTRODUCTION

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract. Most of them will develop deterioration of renal function if they do not receive proper management[1,2]. Renal damage is due to high detrusor pressures resulting from poor compliance of the bladder, detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia[3,4]. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years great progress in the treatment of children with the NBD has occurred.

NBD is classified to subcategories according to urodynamic findings: (1) sphincter overactivity combined with detrusor inactivity that results in incomplete bladder emptying; (2) sphincter overactivity during detrusor contraction that leads to affection and deterioration of upper tract; (3) incompetent sphincter associated with detrusor inactivity leading to large bladder capacity, urine leakage and incomplete emptying; and (4) detrusor hyper-reflexia and loss of bladder compliance[5-7].

Neglecting the case of NBD or improper management can end with deleterious effects on the upper tract that end with renal dysfunction and chronic kidney failure. Since the introduction of clean intermittent catheterization (CIC) for the treatment of NBD, a variety of medications and interventions were introduced. Children differ from adults in accepting certain treatment modalities, loss of compliance, and sensitivity to adverse effects. The variety of options made it possible to shift from one method to another seeking child acceptance, while aiming to avoid upper tract deterioration resulting from high pressure in the bladder. The objectives are to present different treatment options that have Food and Drug Administration and European Union approval for treatment of NBD in children. Each treatment modality has its advantage and limitations, and consequently the management can be personalized for every child.

## SEARCH METHOD

We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021 using the search term “neurogenic bladder children.” It revealed 3143 articles, and 65 articles were fulfilling the criteria of the search. Articles that were excluded from the study were those dealing with diagnosis, urodynamic, pathophysiology, surgical treatment of spina bifida and spinal cord injury. The data collected ranged from standard methods of treatment of NBC to the newly introduced pharmacological product, minimally invasive interventions and the place of kidney transplantation in cases of renal failure. The different modalities were classified to (1) standard initial management; (2) pharmacological treatment; (3) botulism toxins; (4) neural stimulation; (5) vesicostomy; and (6) kidney transplantation. Every item presented for its mode of action, adverse effects, efficacy, availability and factors influencing the choice of management. The data are presented in the narrative review.



## MANAGEMENT OF NBD IN CHILDREN

Different modalities are available for the personalized treatment of NBD in children to prevent renal deterioration. Every modality has a mode of action, adverse events, advantages and limitations. Different modalities are presented in [Table 1](#).

### **Standard initial management: CIC**

CIC in combination with anticholinergics (oxybutynin) had been considered the standard therapy for children with NBD with detrusor hyperactivity[8,9]. This treatment is feasible and effective in developing countries, where untreated neuropathic bladder is an important cause of preventable chronic renal failure[10,11].

CIC enables complete bladder emptying and thus avoids bladder residual urine with its consequences of repeated urinary tract infection. Complete bladder emptying with CIC prevent the occurrence of high-pressure voiding that led to detriment for kidney function. CIC requires proper education and training and good patient compliance on a long-term basis. Patients and caregivers must learn how to catheterize properly. CIC by parents for newborns and infants would become a part of their everyday routine. CIC can be successfully taught to boys and girls around the age of 6 years. The required frequency of catheterization depends on several factors differs from one child to another. Most children are not able to perform CIC, where this task is taken by the mother who may not completely be dedicated to do this job, particularly working women.

### **Pharmacological treatments**

**Anti-muscarinics:** (1) Oral oxybutynin suppresses detrusor hyper-reflexia and eliminates uninhibited detrusor contractions leading to urinary leakage. It prevents high-pressure bladder storage and high-pressure emptying. The frequent side effects (SEs) of oxybutynin is dry mouth, which leads most patients and particularly children to discontinue the treatment. There is cumulative evidence that prolonged use of bladder anti-muscarinic drugs would increase the risk to develop of dementia[12]; (2) Intravesical oxybutynin. Anti-muscarinic is considered the gold standard treatment for patients having overactive bladder (OAB). It is effective in most cases. Patients who developed SEs or reported no improvement discontinue the treatment[13,14]. Patients who experience intolerable SEs would benefit from intravesical oxybutynin chloride, which is an effective therapy for NBD[13,15,16]. The effect of intravesical oxybutynin is often transient. Supplementation of oxybutynin with hydroxypropyl cellulose (HPC), which adheres to the mucosal layer, reduces the absorption of oxybutynin from bladder mucosa and diminishes the systemic SEs. It is termed modified intravesical oxybutynin therapy, which proved to be safe and showed excellent efficacy[17,18]. It had been shown that children with NBD who had been treated with intravesical oxybutynin hydrochloride combined with HPC had superior efficacy over oxybutynin alone or oral anticholinergic drugs or children who showed intolerance to oral medications for NBD. Following catheterizing of the bladder and emptying it, the modified oxybutynin chloride solution was instilled into the bladder at a dosage of 5 mL each time and remained until the next catheterization. This procedure would be repeated twice daily. Intravesical oxybutynin chloride is an effective method with fewer SEs than oral medication. The modified oxybutynin chloride solution is injected into the bladder at a dose of 5 mL twice daily; follow-up at 6 mo showed favorable effects with no side effect[19,20]. Intravesical oxybutynin hydrochloride in a daily dose of 2.5 mg combined with HPC was safe with effective outcome in long-term treatment for children with NBD. The modified intravesical oxybutynin treatment for children with NBD offers a new option for improving continence and bladder compliance[21]; and (3) New anti-muscarinic drugs. These newly introduced anti-muscarinic drugs antagonize the muscarinic receptors in detrusor muscle and consequently decrease intravesical pressure and the uninhibited bladder overactivity. The pediatric population with OAB NBD had limited treatment options. Formerly the only widely available anti-muscarinic was oxybutynin, which had many SEs that are not tolerated by the children. The main SEs are dry mouth, headache, blurred vision, flushing and cognitive impairment. The newly developed anti-muscarinic drugs overcame most adverse effects of oxybutynin[22-24].

**Solifenacin:** Controlled studies suggest that solifenacin may be useful for pediatric NBD. It is available in the form of oral suspension that is given to children as once daily with possibility of dose adjustment[25-28]. Once-daily oral suspension of solifenacin is available that allows greater dosing flexibility in all patients[25-28]. Once daily oral suspension demonstrated superiority over placebo for the change from

**Table 1 Management of neurogenic bladder dysfunction to prevent upper tract deterioration**

| Management of neurogenic bladder dysfunction in children |                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                        |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ref.                                                     | Mode of action and advantages                                                                                                                                                                                                                                                                                                                                                                                                                                         | Limitations                                                                                                                                            |
| CIC[8-11]                                                | Enable complete bladder emptying and prevent high bladder pressure and urinary tract infection                                                                                                                                                                                                                                                                                                                                                                        | Required proper education and compliance, pediatrics and some children are not able to perform CIC                                                     |
| Oral oxybutynin[12]                                      | Antimuscarinic, suppress detrusor hyper-reflexia, prevent high pressure                                                                                                                                                                                                                                                                                                                                                                                               | Dry mouth, abdominal pain that leads to discontinuation of treatment. Limited availability of liquid oxybutynin for children. Risk to develop dementia |
| Intravesical oxybutynin[13-21]                           | Intravesical oxybutynin chloride combined with hydroxypropyl cellulose leads to mucosal adhesion and minimal side effects                                                                                                                                                                                                                                                                                                                                             | Administered with urethral catheter twice daily                                                                                                        |
| Solifenacin succinate [22-31]                            | Works against muscarine receptors in detrusor muscles, relaxes it and decreases intravesical pressure. It is a competitive muscarinic receptor antagonist. Available as one daily oral suspension and is used in pediatric population                                                                                                                                                                                                                                 | Minimal adverse effects                                                                                                                                |
| Tolterodine[32]                                          | Antimuscarinic and calcium channel modulating properties. Available for children as a solution or as tablet. Oral solution is available for children from 5-16 yr                                                                                                                                                                                                                                                                                                     | Low incidence of adverse effects (1.5%)                                                                                                                |
| Propiverine hydrochlorid[33,34]                          | Antimuscarinic and calcium channel modulating properties. Low incidence of adverse events. Superior tolerability over oxybutynin                                                                                                                                                                                                                                                                                                                                      | Minimal adverse effects                                                                                                                                |
| Trospium chloride [35,36]                                | Antimuscarinic and calcium channel modulating properties. Dosage 10-45 mg administered three times per day. Is tolerated by children                                                                                                                                                                                                                                                                                                                                  | Minimal adverse effects                                                                                                                                |
| Mirabegron                                               | $\beta_3$ -adrenoceptor agonist, demonstrated to be effective in adults with overactive bladder                                                                                                                                                                                                                                                                                                                                                                       | Still not approved for children                                                                                                                        |
| Onabotulinum toxin A (Botox—BTX-A) [45-48]               | Is injected in the detrusor muscle, leading to fits relaxation. The dose should not exceed 6 U/kg, ranging from 50, 100 and 200 U. 200 U are a well-tolerated and effective treatment for children aged 5-17 yr with NBD. Patients may be considered for reinjection when the clinical effect of the previous injection diminishes (median 6-12 mo in most children)                                                                                                  | Repeated injections are safe and effective in children                                                                                                 |
| Neural stimulations [49-54]                              | Sensory fibers in the pudendal nerve (afferents) innervates the urethra sensation of urine flow. This will lead to reflex generation of positive feedback to enhance bladder contraction in amplitude and duration and inhibit contraction of the external urethral sphincter. Electrical activation of pudendal nerve afferents provides a new approach to restore efficient bladder emptying. Long-term outcome in children showed good results maintained for 2 yr | Maintenance treatment was necessary in 29% of children. Cost-effective as a primary treatment                                                          |
| Vesicostomy[55-62]                                       | Patients with impaired renal function before kidney transplantation would improve or stabilize kidney function after vesicostomy. The long-term outcomes of vesicostomy in NBD patients are effective in reversing the deleterious consequences when conservative treatment fails                                                                                                                                                                                     | Vesicostomy is an incontinent abdominal stoma. The child will have a social embarrassment                                                              |
| Renal transplantations[63-65]                            | Children with renal insufficiency due to NBD can receive a renal allograft and achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation                                                                                                                                                                                    | There is no one technique for the urinary drainage of the lower urinary tract, it should be individualized for each case                               |

CIC: Clean intermittent catheterization; NBD: Neurogenic bladder dysfunction.

baseline to normality. It was well tolerated in children aged 5-12 years, adolescents aged 12-18 years and in pediatric populations[29-31].

Tolterodine is available as an oral solution. A dose of 0.2–2.0 mg twice daily was described for pediatric age group 4 mo to 4 years. For older children, 5–10 years, the dose is solution of 0.5–4.0 mg twice daily. At adolescence, the dosage is oral capsules or tablets 4–6 mg once daily[32].

Propiverine hydrochloride: It has a low incidence rate of SEs (less than 1.5%). Recommended dose is 0.7–0.8 mg/kg body weight/day. It was shown that it has superior tolerability over oxybutynin[33,34].

Trospium: Dosage of 10 mg and up to 25 mg for children with bladder overactivity showed good response and was well tolerated with minimal adverse effects[35]. A dose of 15–45 mg administered three times per day showed a significant increase in bladder capacity that was tested with a urodynamic study[36].

**Anticholinergic agents:** Mirabegron, a  $\beta_3$ -adrenoceptor agonist, was approved by the Food and Drug Administration for adults and children. It is safe and effective in children.

### ***Onabotulinum toxin A (Botox—BTX-A)***

Intradetrusor injection has been proven to be an effective and safe long-term therapy for the management neurogenic detrusor overactivity (NDO), which is defined as detrusor hyper-reflexia leading to involuntary detrusor contractions during the bladder filling leading to incontinence, reflux and consequently deterioration of renal function. The case is due to the interruption of the signaling pathways that control bladder function.

Neurological causes of NDO include spinal cord injury, multiple sclerosis, myelomeningocele, spina bifida occulta, split cord malformation, lipomyelomeningocele and tethered spinal cord[37,38]. Children with NBD whose urodynamic investigation shows detrusor pressure of 40 cm H<sub>2</sub>O or higher, are at risk of upper tract deterioration and renal failure. The target of treatment of NDO in children is to keep low detrusor pressure and adequate storage[39]. Early treatment with CIC for children with NDO is recommended by European Association of Urology and European Society for Pediatric Urology[40].

CIC combined with oral anticholinergic is recommended by the International Children's Continence Society[41]. Children who do not respond to these regimens of treatment are more than 15%, in addition to the reported SEs[42-44].

Onabotulinum toxin A 200 U is effective and tolerated treatment option for adults with NDO who were not well controlled with anticholinergic therapy[45]. Onabotulinum toxin A showed positive efficacy and safety in children at doses up to 360 U. It was shown that 32%–100% of children achieved continence, detrusor pressure was reduced by 32% to 54%, and the maximum pressure was below the 40 cm H<sub>2</sub>O threshold[46].

The dose should not exceed 6 U/kg, ranging from 50, 100 and 200 U treatment for children aged 5–17 years who were inadequately managed with other therapies. Onabotulinum toxin A 200 U is well-tolerated and effective. The 200 U dose demonstrated objective and clinically subjective significant greater improvement; urodynamic assessment showed increases in functional bladder capacity. Repeat treatment with onabotulinum toxin A showed continued safety and efficacy[47].

Patients may be considered to receive second injection in case the clinical effect of the previous one gets diminished, which was observed after 6-12 mo in most patients. Repeat injections of botulinum toxin A have been shown to be safe, and do not lead to increased risk of fibrosis in the bladder wall. It is safe and effective in children with NBD with a positive effect on their dryness, quality of life and protection of the upper tract[48].

### ***Neural stimulations***

NBD leads to urinary retention due to bladder hypocontractility and/or increases in the outlet resistance. Chronic urinary retention led to reflux, upper urinary tract deterioration, urinary tract infection and incontinence. Children who are not compliant to CIC or refractory to pharmacologic approaches would benefit from percutaneous tibial nerve stimulation (PTNS).

The scientific background is that pudendal afferent sensory fibers innervate the urethra sensation of passage of urine. This will lead to reflex generation of positive feedback to stimulating the bladder to contract in amplitude and duration. Another sequence is to relax the external urethral sphincter. Electrical stimulation of pudendal nerve afferents significantly improves voiding efficiency. Pudendal sensory has an important feedback role in an efficient bladder emptying. Activation of afferents of the pudendal restore efficient bladder emptying[49].

Sacral nerve stimulation is becoming the latest advancement in treatment of NBD after technical development and showed successful results in clinical studies[50-52]. Long-term outcome in children treated with PTNS for dysfunctional voiding and OAB showed good results and remained stable after 2 years[53].

Neural stimulation improved both storage and voiding and functions of the bladder in about 60% of the patients. Neural stimulation has its limitation for cost-effective compared to anti-muscarinics. Neural stimulation is the ideal option in refractory OAB or when the child does not tolerate anti-muscarinics[54].

### ***Vesicostomy***

The aim of urological treatment and follow-up in children with NBD is to avoid upper tract deterioration[55]. Early diagnosis and establishment of proper treatment would minimize the consequences of dysfunction of bladder. Lower urinary tract dysfunction in childhood will affect bladder function at puberty in both storage and emptying functions that will precipitate renal failure[56].



Vesicostomy could be the best treatment for the hostile bladder in myelodysplastic [57]. Vesicostomy is a temporary procedure to maintain low detrusor pressure and to stabilize renal function in children not responding to anticholinergics and CIC. It can be reversed at any age. Vesicostomy provided overall resolution, improvement or stabilization of the preoperative parameters. Hydronephrosis would achieve complete resolution or stabilization of the renal function. Patients with impaired renal function before surgery would improve or stabilize kidney function after vesicostomy.

Vesicostomy would be closed at any age. Children who will be candidates for kidney transplantation would have an additional procedure during closure that could be anti-reflux procedure for the refluxing ureters or augmentation cystoplasty. At the time of closure, a bladder capacity of > 300 mL would not need augmentation cystoplasty.

Vesicostomy could be considered an emergency option when the child presents with renal failure, and the aim is to stabilize renal function and reverse the deleterious consequences of NBD, aiming at preparing the patient for definitive treatment[58-62].

### **Renal transplantations**

Children who developed renal failure secondary to lower urinary tract dysfunction are treated with regular ambulatory hemodialysis that will be followed with renal transplantation. Optimization of bladder function before transplantation will ensure the safety and survival of the allograft. The technique and therapeutic option are personalized and differ from one case to another[63-65]. The decision for kidney transplantation would be considered early in life when measures to control NBD are not satisfactory and the kidney shows progressive deterioration.

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## **RESULTS**

Innovations in the treatment of NBD in children solved the dilemma of the ideal treatment. There are many options that would be used in treatment of NBD and guard against upper tract deterioration. Newly introduced drug delivery systems using intravesical oxybutynin chloride solution supplemented with HPC, which is a mucosal adhesive substance, reduced systemic SEs and proved to be safe and showed excellent efficacy[17,18].

Drug delivery systems using fluid suspension of the newly introduced anti-muscarinics made it possible to treat pediatric population without the need for clean intermittent catheterization. These drugs included: solifenacin[30,31], tolterodine[32], propiverine[33,34] and trospium[35]. Studies demonstrated the superior tolerability of these drugs over oxybutynin, with higher efficacy and minimal SEs.

Onabotulinum toxin A (Botox – BTX-A) intradetrusor injection has been proven to be an effective and safe long-term therapy for the management of NDO and NBD. It prevents incontinence and reflux and consequently deterioration of renal function. It can be repeated without causing fibrosis of the detrusor muscle.

Neural stimulation with PTNS or sacral nerve stimulation for children who are not compliant to CIC or refractory to pharmacologic approaches would benefit from the progressive improvements in these modalities. PTNS can modulate the voiding and storage function of the bladder leading to an overall subjective improvement of symptoms in about 60% of the patients and 47%-56% improvement of filling and voiding function parameters[53,54]. Children with renal insufficiency due to NBD can receive a renal allograft and achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation[63-65]. Urinary diversion or vesicostomy are resorted to before transplantation to stabilize and improve kidney function. Availability of different effective and safe treatment modalities made it unacceptable for a child with NBD to develop renal impairment. The variety of options facilitates safe and effective control of the deleterious effect of NBD on the upper tract.

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## **CONCLUSION**

NBD in children can end with deleterious effects on the upper tract that end with renal dysfunction and chronic kidney failure. This would indicate dialysis or kidney transplantation. Choice of proper management will differ from one child to another, where the management would be personalized. CIC combined with oral oxybutynin is

the basic and standard treatment. Children who receive oxybutynin and develop adverse effects that lead to discontinuation of treatment would shift intravesical oxybutynin. The new anti-muscarinic drugs have minimal adverse effects, high tolerability, availability of solution form and dose adjustment. Mirabegron is a  $\beta_3$ -adrenoceptor agonist that is a promising drug for children with NBD. Children who develop adverse events from anti-muscarinics,  $\beta_3$ -adrenergic agonist drugs or are non-compliant to CIC would be candidates for detrusor muscle injection with onabotulinum toxin A, which proved to be safe with no adverse effects.

PTNS is an emerging modality for treatment of NBD in children. It has no adverse effects, which is accepted by the child and parents. Kidney transplantation would be the last resort for treatment of NBD in children when they have progressive deterioration of kidney function and the child did not respond to other treatments. The type of management for NBD in children would be personalized for every case and could be changed accordingly.

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