Medical Management of Neurogenic Bladder for Children and Adults: A Review

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Neurogenic bladder is a chronic condition affecting patients of all ages with significant medical and quality of life implications. Goals of treatment consist of protection of the upper urinary tract and promotion of reliable urinary continence. Successful management involves medications and most often bladder drainage via clean intermittent catheterization. This article reviews current literature on medical management to achieve goals of treatment. **Key words:** *catheterization, myelomeningocele, neurogenic bladder, spinal cord injury*

Neurogenic bladder describes a variety of bladder dysfunction disorders that result from a lesion at any level in the central or peripheral nervous system. Among children, congenital neural tube defects (NTD), such as myelomeningocele, spinal dysraphism, or tethered cord lesions, are the most common causes. Older patients usually acquire the condition secondary to spinal cord injury (SCI), but it can also result from malignancies in the spinal column or neurological diseases like multiple sclerosis or Parkinson's disease. Importantly, neurogenic bladder is the source of significant morbidity, no matter what the etiology. Children with NTD have increased life expectancy owing to advancements in orthopedic and neurosurgical therapies. For virtually all these patients, neurogenic bladder sequelae account for many of their health care interactions and result in disruption of quality of life. Similarly, prior to neurogenic bladder intervention and management strategies, most SCI patients died of complications such as renal failure or urosepsis.[1] While no longer the main cause of mortality, more than 80% of SCI patients report at least one symptom of bladder dysfunction.[2] All cohorts of patients benefit from early evaluation and institution of appropriate treatment.[3] Furthermore, cohorts share common goals of treatment: to minimize or prevent damage to the upper urinary tract and bladder and to maximize safe, social continence.

Pathophysiology of Neurogenic Bladder

To achieve urinary continence, the bladder must perform two functions: (1) store urine produced by the kidney, and (2) expel urine when appropriate. For success of both functions, neurological input is required from the cerebral cortex, spinal cord, and peripheral nervous system; disruption anywhere along those neural pathways can lead to various degrees of bladder dysfunction. For storage of urine, the muscles of the bladder are relaxed and the external sphincter contracted, and this is reversed when voiding is desired.[4] The detrusor muscle, bladder neck, and striated external sphincter operate as a synergistic unit for these two tasks.[4] Loss of coordination characterized by external sphincter contraction when detrusor muscles are also activated causes bladder outlet obstruction, a condition called *detrusor sphincter dyssynergia* (DSD). DSD incidence ranges from 20% to 50% among neurogenic bladder patients.[5]

The disordered interactions leading to neurogenic bladder are complex, diverse, and involve the multiple facets of the nervous system. A thorough discussion of all potential neurological disturbances would necessitate another review article. For readers who desire a more in-depth examination, Blok's chapter "Neuroanatomy Relevant to the Urologist" is an excellent resource.[6]

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Evaluation of Neurogenic Bladder

High-quality evidence guiding evaluation and follow-up for neurogenic bladder patients is lacking and based largely on expert opinion.[7] Bauer et al advocated for urinary tract evaluation to begin shortly after neonates with myelomeningocele had repair of their defect and to occur at routine intervals or with any changes in symptomatology.[8] These recommendations have been extrapolated to all infants with NTD or other neurological issues. The SCI literature offers less direction, and resolution of spinal shock is highly variable ranging from days to months post injury.[9] Consequently, experts only strongly recommend undertaking a complete neurourological evaluation including urodynamic investigations within 3 months of the initial injury in both adults and children.[10,11] However, Bywater et al demonstrated that a significant portion of early SCI patients had abnormal urodynamic parameters before 40 days post injury, and they advocated earlier targeted therapies to preserve upper and lower urinary tract function.[12] Children may experience a shorter duration of spinal shock as compared to adults, causing some experts to allow for evaluation earlier than 3 months.[11] Balancing against that recommendation, an early assessment may demonstrate poor parameters before bladder function has fully recovered, thus necessitating repeat invasive testing. Surgical interventions, irreversible by nature, should be delayed until after 1 year post-SCI to allow for the potential recovery of bladder function.[10] In children, urodynamic studies should include measurement of bladder compliance and capacity, intravesical pressure, assessment of overactivity, and detrusor leak point pressure assessment.[13] Prognostication among pediatric patients with neurogenic bladder can be divided into high- and low-risk cohorts based on intravesical pressure, with high-risk cohorts being defined by measurements greater than 40 cm H_2O.[14] Patients with such measurements have poorer glomerular filtration rates, vesicoureteral reflux, upper urinary tract deterioration, more urinary tract infections, and hydronephrosis.[15-17] Similarly, Kim et al reported that adults with SCI who had a bladder leak point pressure of 40 cm H_2O or greater had elevated rates of upper urinary tract damage and DSD.[18]

Nonsurgical Management of Neurogenic Bladder

Reflex voiding and bladder expression

Triggered reflex voiding is now a rarely used practice following the introduction of clean intermittent catheterization (CIC). However, it may still serve a role, especially in resource-poor areas. Triggered reflex voiding requires various maneuvers performed by the patient or caregiver to elicit an unphysiological sacral reflex to stimulate detrusor fibers in the bladder allowing voiding. Maneuvers are unique to each patient but examples include suprapubic tapping or jabbing, pulling on pubic hair, thigh scratching, touching the penile skin or clitoris, or ano-rectal manipulation.[19] Bladder expression is another voiding technique that relies on applying a force to overcome outlet resistance of the external sphincter usually via the Valsalva (an individual increases intraabdominal pressure via breath-holding techniques) or Credé (increasing abdominal pressure through external manual pressure) maneuvers. These techniques are difficult to master, must only be tried in patients with confirmed safe urodynamic parameters, and have been associated with poor bladder emptying, subsequent hydronephrosis, and upper tract disease.[20] For these reasons and better documented outcomes with CIC, these techniques are no longer routinely recommended.

Condom catheter drainage

Condom catheters are an option for male neurogenic bladder patients who have incontinence or use reflex voiding/bladder expression. As a non-indwelling catheter, condom catheters may appear safe and to have lower rates of urinary tract infection (UTI), the most common catheter-associated infection. However, the external device can exert a tourniquet-like force on the penis, leading to devastating penile injury, edema, necrosis, urinary retention, hydronephrosis, and even death.[21-24] Regarding UTI rates in patients using condom catheters, the literature presents mixed results. Roth et al and Saint et al both reported lower rates of UTI compared to indwelling catheters users, Gao et al found higher rates, and

the Neurogenic Bladder Turkish Research Group found no significant effect on UTI rate.[25-28] Thus condom catheter use warrants close monitoring in patients with cognitive or dementia issues, difficulty maintaining hygiene, abnormal sensory conditions, poor skin integrity, or retracted penis.

Intermittent bladder catheterization

Experts accept intermittent catheterization as the preferred method of bladder drainage for neurogenic bladder patient, even without high-quality randomized controlled trials directly comparing bladder drainage methods.[29] There are reports of this type of bladder emptying technique dating back to Roman and Egyptian eras, when reeds or silver tubes served as catheters.[30] Originally conceptualized as a "sterile" procedure, high costs and challenges with using this method in outpatients gave way to recommendations for "clean" catheterization in the landmark paper by Lapides in 1972.[31] When used routinely, CIC effectively preserves kidney function by preventing overdistention of the bladder and reducing pressures, thereby promoting consistent blood flow to bladder walls.[32] CIC improves continence among neurogenic bladder patients, facilitating greater community participation and decreasing home confinement. Patients have successfully learned to perform CIC as young as 4 years of age, allowing for their increased inclusion in mainstream education and improved quality of life.[33]

Despite all its benefits, CIC does not come without compromises and chief among these is the acquisition of asymptomatic bacteriuria (ASB). ASB is defined as a positive urine culture from a patient who does not exhibit or complain of any urinary symptoms. In sensate patients this definition is apt; but among the SCI and NTD populations, sensation may be altered and symptoms cannot be reliably reported. Many excellent efforts by antimicrobial stewardship groups to curb inappropriate antibiotic use for ASB have been largely successful.[34-36] However, patients with neurogenic bladder are often excluded from those guidelines, with the exception of the recommendation against routine screening for ASB in SCI.[36] The lack of inclusion of these patients in guidelines may be related to a failure to develop a consistent definition of UTI versus ASB among neurogenic bladder patients leading to difficulties comparing literature.[37] This in turn leads to significant heterogeneity of evaluation and management of these patients even among urologists.[38] Antibiotic prophylaxis has been shown to reduce ASB in neurogenic bladder patients, but it does not reduce symptomatic UTIs.[39] The exception to that statement is pregnant females who perform CIC, in which case, prophylactic antibiotics are associated with fewer symptomatic UTIs.[40]

UTIs present another clinical challenge associated with CIC use. Uropathogens interact with catheter surfaces, and the act of catheterization provides these pathogens direct access to the urinary tract.[41] Frequency of CIC is dictated by fluid intake and urodynamic parameters, but most patients require the procedure 4 to 6 times per day. Catheterization performed less often is a risk factor for UTI development, stemming from bladder overdistention.[42] To prevent UTIs, it is important to educate patients on routine use of CIC, avoidance of bladder overfilling, and careful hygiene.[29] Catheters of alternative materials, including hydrophilic catheters, those impregnated with antimicrobial materials, and chlorohexidine-coated catheters, have been proposed as another preventative measure demonstrating some promising results.[43-47]

Less common complications associated with CIC are mechanical issues related to repeatedly performing the procedure. Lesions can occur from damage to the urethral mucosa causing stricture, bleeding, leaking, or the development of false tracts. In pediatric patients, catheterizable channel complications require revision at a rate of 25% to 30%. Interestingly, patients older than 21 when their channel is surgically created have higher revision rates, ranging between 31% to 54%.[48]

Indwelling catheters

Indwelling urethral catheters

Placement of an indwelling urethral catheter (IUC) is a common practice for patients in the acute stage following an SCI, allowing for close monitoring of a patient's fluid balance. IUCs must

be inserted under sterile conditions, and they are worn continuously. While there are advantages with a single insertion and continuous bladder drainage, IUCs are associated with higher rates of cystitis and pyelonephritis as compared to CIC.[49-52] Acquisition of bacteriuria occurs at a rate of 3% to 8% for each day an IUC remains in place, and length of IUC placement is the main risk factor for conversion to an UTI.[53] Furthermore, IUCs cause a greater risk of urethral erosion, development of urethral stricture, upper urinary tract deterioration, kidney stones, or infectious complications such as epididymitis and urethral abscess.[29] IUC should be reserved for circumstances in which patients are unable to perform CIC or during defined periods of time when careful fluid balance is necessary.

Suprapubic catheters

Suprapubic catheters (SPC) can be placed in a surgically created channel for common indications such as persistent incontinence despite CIC, inability to perform CIC, channel stricture or other damage, or progression of neurological disease.[54] Some distinctive benefits of indwelling catheter placement via an SPC include improved independence by reduced need to perform catheterization multiple times per day, improved body image, and sexual function.[55,56] SPC users experience higher rates of UTI and nephrolithiasis as compared to their CIC counterparts who do not have an indwelling foreign body, but rates of urosepsis, epididymitis, and pyelonephritis are comparable.[57]

Pharmacological management of neurogenic bladder

Alpha-blocker medications

In the sphincter and bladder neck muscles, activation of α1-adregenic receptors results in sphincter mechanism tension and inactivation of those receptors allows for voiding. In patients with increased sphincter activity, overfilling of the bladder leads to elevated intravesicular pressures. In these patients, α-blockers are used to reduce the sphincter tension to facilitate voiding, thereby reducing incontinence episodes and decreasing catheterization frequency.[58] In adults with SCI or multiple sclerosis, use of α-blockers improves postvoid residuals, increases urine flow rates, improves autonomic dysreflexia, and decreases detrusor overactivity.[59,60] α-Blockers prescribed in children have shown some decrease in bladder outlet resistance, but only in a small numbers of patients because this use is off-label.[61] Formulations of α-blockers available include alfuzosin, tamsulosin, and doxazosin. Side-effect profiles for these medications include drowsiness and decreased blood pressure, which may be more significant among pediatric patients.[61]

Anticholinergic medications

Anticholinergic medications are typically considered first-line therapy for neurogenic bladder patients. They act on muscarinic receptors in the bladder to reduce the contraction of the detrusor muscles, especially during the storage phase. Their use in patients with detrusor overactivity demonstrates reduced intravesicular pressure and increased bladder capacity during the storage phase and decreased episodes of leaking, incontinence, and frequency voiding.[62,63] Oxybutynin has been prescribed since the 1970s, so it has the most data supporting its use; it is available in oral, transdermal, and intravesical instillation solution formulations. Other anticholingeric drugs include tolerodine, propiverine, trospium, solifenacin, darifenacin, and fesoterodine, which having varying levels of selectivity among muscarinic receptors. Oxybutynin and tolerodine have US Food and Drug Administration (FDA) approval for use in children older than 5 years of age.[64] Muscarinic receptors are widely distributed in the body, so potential side effects range from blurry vision, cognitive impairment, dry mouth, gastroesophageal reflux, constipation, and urinary retention. Children generally tolerate these side effects better than adults, but they can be cause for discontinuation.[65,66] There is insufficient evidence to recommend one anticholinergic medication over another, but some pediatric trials are pending among the more selective medications such as solifenacin.[62,64]

Botulinum neurotoxin

Botulinum toxin is produced by the facultative anaerobic bacteria *Clostridium botulinum.* When

injected in the detrusor muscle, it inhibits the release of acetylcholine achieving an effect analogous to that of anticholinergic medications.[67] For patients intolerant or refractory to the previously presented oral medications, botulinum toxin may be a good alternative. In children, injection effectively increased bladder capacity and decreased intravesical pressure with overall improvement in continence.[68-70] Children tolerate multiple injections and effects last for 6-9 months, much longer than when botulinum toxin is injected into skeletal muscle.[69,71-74] Application drawbacks specific to pediatric patients relate to the requirement of general anesthesia for the procedure, but otherwise, few side effects are reported.[75] A few small case series evaluated intravesical instillation of botulinum toxin without general anesthesia and reported good clinical results, but participants also experienced adverse events of urinary retention, injection site pain, UTIs, and hematuria.[76-78] Drug delivery alternatives have been developed, and a small case series of myelomeningocele patients with resistant detrusor dysfunction used an electromotive drug administration of botulinum toxin intravesically. Six years after follow-up, these patients still experienced improved continence and decreased detrusor pressure. This drug delivery method does not require anesthesia, can be performed in the outpatient clinic, and is painless for pediatric patients.[79]

In adult patients with SCI or multiple sclerosis, botulinum toxin is reserved for detrusor muscle inhibition refractory to oral anticholinergic medications or when such medications are not tolerated due to their side effects.[80-88] Well-designed trials with randomization and placebo control document improved urodynamic parameters and quality of life measures among adults with neurogenic bladder dysfunction and detrusor overactivity.[89-94] UTI is the most common adverse event, and urinary retention or incomplete bladder emptying is reported with botulinum toxin dose escalation. Kennelly et al presented a long-term study with 4-year follow-up of patients receiving multiple injections of botulinum toxin, describing that effects last a median time of 9 months. Adverse events included UTIs and incomplete bladder emptying. The authors also sought to address potential concerns about the development of antibodies in response to botulinum toxin use, a phenomenon reported in patients receiving injections into the large skeletal muscles of the neck, but detection levels were low and half of those patients continued to report clinical benefit despite seroconversion.[95]

Alternative medications for neurogenic bladder management

Mirabegron is a β3-adrenoceptor agonist that acts to relax the detrusor smooth muscle during the storage phase. As a non-anticholinergic bladder relaxant, mirabegron has a more desirable side-effect profile than anticholinergics, but there is more limited evidence to support its use.[24] Trials in children with a small number of participants showed increased bladder capacity and decreased incontinence.[64] Probiotics are another therapy with the potential to support neurogenic bladder patients. A Cochrane review looked for studies using probiotics as a UTI prevention strategy for patients with neurogenic bladder and turned up very little evidence. There were no studies identified that evaluated oral probiotics effects, but there were three studies looking at intravesical instillation of nonpathogenic strains of *E. coli*. These studies included only 110 patients overall. Authors concluded that while there is likely to be minimal harm from these methods, there is insufficient evidence to support their use at this time.[96]

Future Directions

Normal bladder storage and voiding occur through a complex interplay of multiple neurological systems. Preclinical trials and even a few human trials have looked at electrical stimulation at various targets in SCI patients utilizing physiological neural control mechanisms. One small case series demonstrated preservation of bladder compliance, decreased detrusor overactivity, and improved bowel and erectile function in SCI patients who were introduced to early sacral neuromodulation.[97] Another case series followed SCI patients after a program of repeated electrical stimulation treatments. Those patients had increased bladder capacity, improved bladder

emptying, and lower intravesical pressure at 2-year follow-up.[98] Techniques that show promising results include pudendal nerve stimulation and high-frequency nerve stimulation for bladder control.[99] Randomized trials for implanted devices that stimulate the neurogenic bladder are ongoing and may present another alternative to permanent surgery interventions.[100]

Transitions of Care: An Important Crossroads for Patients and Caregivers

Improved life expectancy has created a new challenge for patients with neurodevelopmental disorders and their caregivers — navigation of the transition from child-centered to adult-centered medical care. Fragmented care is estimated to cause one-third of hospitalizations among adults with myelomeningocele for admissions considered preventable, and even academic centers with a well-established multidisciplinary clinic fail to do this well.[101-103] A likely multifactorial problem, patients cite hesitancy to leave pediatric providers, insurance coverage issues, unreliable transportation, health care fatigue, and communication difficulties as barriers.[104,105] For their part, pediatric practitioners can fail to release their patients to adult providers in a timely manner, and adult providers may be disinterested or feel inadequately trained to care for special needs populations.[106] Tools have been validated for assessing readiness for transition, and these may assist providers by identifying barriers prior to attempting transition.[107-109] Anecdotally, I believe there is no substitute for deliberate and repeated communication between pediatric providers, patients, and their caregivers and with preselected adult providers to promote successful transition.

Conclusion

Medical management for adults and children with neurogenic bladder generally follows similar principles, and the goals of treatment remain the same — minimize damage and deterioration of the upper urinary tract and maximize quality of life. Clinicians have a variety of medications and mechanical maneuvers to optimize and personalize treatment of patients with neurogenic bladder. No one therapy is definitive, and often combinations of treatments are used to manage this lifelong condition. The future holds potential for more targeted drug therapies and new technologies directed at ameliorating disordered neurological patterns that lead to neurogenic bladder.

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