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Prevention of Urinary Tract Infection for Patients with Neurogenic Bladder

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Abstract Urinary tract infection is a common problem among patients with neurogenic bladder dysfunction that can be costly and challenging to manage. Current literature on the topic of preventing urinary tract infections in this heterogeneous patient population is challenged by the difficulty in defining urinary tract infections and by the lack of long-term data from controlled randomized studies. New research suggests that intradetrusor injection of onabotulinumtoxin A may be a useful adjunct in preventing urinary tract infections, and further studies are needed to determine if probiotics, bacterial interference, and/or vaccines will prove to be of use in the population.

Keywords Neurogenic bladder · Neuropathic bladder · Spinal cord injury · Intermittent catheterization · Urinary tract infection · Complications

Introduction

One of the more troubling and morbid complications in patients with neurogenic bladder (NGB) is urinary tract infections (UTIs). These occur frequently in this population given their unique susceptibility to bacteria both entering the urinary tract and causing infection. This review will summarize the most recent data on urinary tract infection in NGB with a focus on the patients with incomplete bladder emptying requiring catheterization who are specifically at risk.

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Scope of the Problem

It is difficult to estimate the incidence of UTI in this diverse population, but according to medical claims data, 29–36 % of persons with NGB are diagnosed with a lower UTI every year and 1.4–2.2 % are diagnosed with pyelonephritis [1]. In a clinical series following patients with spinal cord injury (SCI) for a 7-year period, 86 % of those with an indwelling catheter had at least one symptomatic lower UTI and 75 % had recurrent UTIs. Of SCI patients who did not drain their bladder with an indwelling catheter, 53 % developed a UTI in the same time period [2]. In another clinical series, involving 128 patients with SCI who had urine sampling and symptoms assessed every 10 days, the overall incidence of UTI was 2.5 per year, but 9.9 per year for those with indwelling catheters [3••].

These UTIs are troubling for many reasons. From a patient perspective, they can experience worsening of their urinary symptoms of urgency, frequency, and incontinence, and UTIs are potentially impactful on patient and caregiver quality of life. Patients may also have increased spasticity or autonomic dysreflexia. Patients with neurodegenerative disorders can have exacerbations of other symptoms and general decline in function. Urine cloudiness and foul odor are also bothersome to patients, many of whom are self-conscious and possibly socially isolated due to these concerns. Patients also can have difficulty obtaining treatment for these UTI episodes since transportation to submit a urine specimen may be limited.

For providers, UTIs in this population are equally troubling. Patients may have altered sensation and baseline lower urinary tract dysfunction making symptoms difficult to assess. In a study on symptom assessment by patients with SCI, the positive predictive value of asking a patient if they had a UTI was only 32.6 %, meaning they were very poor at actually predicting that they had a UTI. However, patients were much

better at identifying when they did not have a UTI with a negative predictive value of their self-assessment at 82.8 % [4]. Even more challenging is the confusion surrounding the definition of a UTI in this population. Bacteriuria without symptoms is very common (18.4 episodes per person year) [5] and, based on current consensus statements, does not require treatment [6]. The National Institute on Disability and Rehabilitation Research has defined UTI in this population as pyuria plus bacteriuria with threshold counts based on the type of bladder management and at least one UTI sign or symptom. However, a recent systematic review of UTI screening in SCI noted only one of the 12 articles reviewed utilized this definition [7]. Another systematic review of both the pediatric and adult literature on UTIs in spina bifida found that only 36 % of all studies actually listed a definition for UTI and that these definitions were heterogeneous [8]. If the medical literature cannot utilize a single definition, it is no wonder practitioners and patients struggle, and not without consequences.

The high prevalence of bacteriuria in this population frequently leads to overtreatment with antibiotics. In a retrospective analysis of emergency department visits by veterans with SCI, 22.8 % of all visits had an antibiotic prescription and the rate of antibiotics prescribed increased over the 2002–2007 time period. Of those antibiotics, 59 % were considered broad spectrum and 60 % of these were for "urinary tract infection" [9]. This increase in prescribing is concerning since clinical guidelines for judicious use of antibiotics in this population do exist but, based on this data, are not being followed [10].

The risks of antibiotic overtreatment are not small. One must consider the cost to insurance providers and patients and the morbidity and mortality from complications that stem from bacterial resistance and changes to the microbiome, as well as other adverse effects, including pseudomembranous colitis due to *Clostridium difficile*.

Risk Factors for Urinary Tract Infection

An effective prevention strategy for symptomatic UTIs would be ideal. To plan an approach for prevention, one first needs to consider what makes patients with NGB uniquely susceptible to UTIs. Recent experiments in a rat SCI model have revealed that those animals with SCI have an exaggerated immune response after *Escherichia coli* (*E. coli*) UTI and have delayed clearance of the bacteria. These possibly neurally mediated pathway alterations could be partly responsible for the increased susceptibility to UTI [11].

Risk factors for UTI in all individuals include female gender, sexual activity, diabetes and immune suppression. New data also suggests that, at least in women, there is a strong genetic component for increased susceptibility to UTIs [12]. People with SCI are uniquely at risk for UTIs due to a high rate of risk factors including bladder overdistention, high-pressure voiding, vesicoureteric reflux, incomplete bladder emptying and urinary stasis. Urinary calculi in the bladder or upper tract which are all too common in NGB patients can also harbor bacteria, increasing the risk of UTI.

Bladder management with an indwelling catheter (suprapubic or urethral) or urinary diversions has higher rates of bacteriuria [6] as well as infection [2, 3••, 13], than bladder management without these risk factors. This risk is not inconsequential; among SCI patients, 80 % eventually transition to an indwelling catheter over time [14]. Catheter use among patients with multiple sclerosis is much less common than in patients with NGB secondary to SCI, with an estimated 11 % of multiple sclerosis (MS) patients utilizing catheters currently, and notably over 80 % of these are performing intermittent self-catheterization (ISC) [15].

Also, requiring catheterization by a caregiver due to increased disability puts one at greater risk for UTI [6]. Some of these risk factors are modifiable or treatable which would be a first step in prevention of UTI.

Prevention of Urinary Tract Infection

Conservative Strategies

Education. Providers should counsel all patients with NGB dysfunction on simple conservative strategies for maintaining hygiene, prompt and proper toileting, and scheduled bowel and bladder emptying as the first line of therapy for preventing UTIs. It stands to reason that patients who empty frequently enough, completely enough, and with good atraumatic technique would be less prone to infections; however, there is little literature to support this strategy. One study of an educational program that aimed to educate patients with SCI regarding prevention of UTIs did show a significant decrease in urinary bacterial counts in patients who were randomized to the program but not a decrease in symptomatic UTIs [16]. Another study of a clinic nursing educational program by spinal cord injury nurses did show that counseling sessions decreased UTI rates but that multiple sessions were often necessary [17].

Fluid Intake. Moderating the volume of urine output by adjusting fluid intake, especially in patients with a history of urolithiasis, sediment from indwelling tubes, catheters, or mucous production from reconstruction involving bowel, is another practical approach to prevent stasis, stone formation, and bacterial overgrowth. Fluid modulation has not been rigorously studied in the NGB population as a strategy to prevent complications; however, increasing urine volume to a certain threshold (typically 2 L per day [18]) does decrease risk of stone formation in recurrent stone formers.

Hygiene. During acute infection, indwelling catheters should be changed, and patients who void reflexively may need to be catheterized intermittently to fully empty. There is no evidence that disinfecting the skin or catheters can prevent UTIs; however, for patients with external catheters (condom catheters), changing the catheters less than once per day has been shown to increase infection rates [19•, 20, 21•]. Catheters with an introducer tip that attempt to bypass the fossa navicularis to prevent introduction of bacteria further into the urinary tract have not proven to be effective [22].

Catheterization Frequency. For those who catheterize intermittently, many factors go into determining the number of catheterizations per day: convenience, patient and caregiver schedules, and urine production. If urodynamics have been performed recently, and a safe volume established, then catheterization can be done often enough to maintain volumes below this threshold. One older study has found that catheterizing only three times per day correlated with higher rates of infection than six times per day [23].

Bladder Irrigation. Bladder irrigation with various solutions has been studied in indwelling and intermittent catheter users. van den Heijkant et al. published a small uncontrolled primary prevention study of saline or saline with acetylcysteine solution for bladder irrigation and found a low rate of UTIs and stones in pediatric patients performing irrigations on ISC after augmentation ileocystoplasty [24]. Chlorhexidine solution was found to decrease bacteriuria but was mostly active against gram-positive bacteria. This study utilized a very strict and probably clinically irrelevant definition of bacteriuria, with no evidence of decrease in symptomatic UTIs [22]. Aminoglycoside bladder instillations have been described in several small human series over the last several decades. Van Nieuwkoop et al. published a case report of two patients with recurrent UTIs successfully managed with intravesical gentamycin, as well as a systematic review of the evidence for aminoglycoside bladder instillations which found, although there is no robust evidence, this appears to be a safe and effective secondary prevention strategy for UTIs in patients who intermittently catheterize [25•]. In our clinical experience, we have had significant success in patients with recalcitrant recurrent UTIs with prevention using daily prophylactic gentamicin bladder instillations at the last catheterization before bedtime in patients managed with ISC with very little report of intolerance or side effects.

Screening with Urine Cultures. Routine cultures in a population of patients with SCI (n=46) and polytrauma (N=28) all without indwelling catheters showed significant species turnover and concluded that there is little value of routine urine cultures for surveillance or for documenting successful treatment [26].

Outside of concerns for symptomatic UTIs, Weld and Dmochoski showed in a large cohort that intermittent catheterization had the lowest overall rate of urologic complications [27]. A retrospective review of bladder management of 164 newly spinal cord-injured patients showed that only 57.7 % of patients remained compliant with CIC, and 8.6 % reverted to indwelling catheters [28]. One potential strategy for prevention of genitourinary complications in NGB patients would be to encourage compliance with a standardized method of ISC and tailor UTI prevention efforts to this method of bladder drainage.

Catheter Type

Indwelling. Patients with short-term indwelling catheters have been studied to determine if catheter type influences the development of urinary tract infection. A multicenter, randomized clinical trial of neurologically intact adults catheterized on a short-term basis found that silver alloy-coated catheters were not effective at reducing symptomatic UTI and that although there was a reduction in UTI with nitrofural-impregnated catheters, this reduction was not clinically important, and their use is not recommended [29]. Although these results cannot be extrapolated to long-term catheterization in NGB patients, it would be even less likely that these types of catheters would be an effective prevention strategy in this population.

Suprapubic Versus Urethral Location. Hunter et al. published a scoping review looking at the literature and research activity around suprapubic catheterization because of the lack of sufficient evidence to perform a systematic review or meta-analysis. They found that most studies again lacked a standard definition of UTI, most were retrospective and not randomized, but that this clinical evidence showed that there is likely no difference between urethral and suprapubic catheters in terms of UTI development [30].

Catheters for Intermittent Use. Clean technique and reusing catheters have not been shown to be inferior to sterile technique or single use catheters, respectively [31].

The search for the ideal catheter materials/coatings is ongoing. Two recent meta-analyses of hydrophilic catheters by Li et al. and Bermingham et al. provide the most robust evidence of the topic to date. In 2013, Li et al. published the results of a meta-analysis and found that both UTIs and hematuria are less frequently associated with the use of hydrophilic-coated catheters for ISC in patients with SCI, supporting their use in this population [32]. A systematic review and meta-analysis of eight studies on the most effective and cost-effective catheter type for ISC—hydrophilic polymer coated, packaged with water-based lubricant (gel reservoir), or non-coated catheters that are used once (sterile) or washed and

reused (clean)—did show a small benefit for gel reservoir and hydrophilic catheters, but these differences were small, and because of gaps in the evidence, they concluded that catheter type made little difference in the risk of symptomatic UTI [31]. Payors do play a role in determining what types of catheters are affordable for patients, and the superiority of more expensive options will need to be well established before these catheter types will be covered for many patients. Compact catheters have been shown to improve quality of life [33], and patient preferences should be taken into account in future studies.

Non-antibiotic Prophylaxis

There have been many attempts at finding non-antibiotic chemoprophylactic agents over the years, resulting in trials of ascorbic acid (vitamin C), D-mannose, methenamine, chlorhexidine, cranberry products, probiotics, and topical vaginal estrogen replacement in females.

Manipulating the urinary pH to make the urinary tract a less hospitable environment for uropathogens has been a repeated target of UTI prevention strategies in multiple at-risk populations. Changing the urine pH has been attempted with many agents, including sodium bicarbonate, acetazolamide, and ascorbic acid. There are limited contemporary data for these agents in patients with NGB, but in older studies, ascorbic acid alone was not found to have clinical benefit in spinal cord injury patients [34].

Methenamine salts (methenamine hippurate and methenamine mandalate) have been found to break down to formaldehyde within the bladder especially at urine pH <5.5. Because the formaldehyde is thought to act as a bacteriostatic agent, there is no development of resistance. This, along with a favorable adverse effects profile, has led to these being used extensively for prophylaxis against urinary tract infections. A 2012 Cochrane review of controlled studies of methenamine hippurate found that the published evidence would suggest that this intervention, especially in the short term, may be effective in preventing UTI in patients without genitourinary tract or renal abnormalities. However, in the studies regarding patients with neurogenic bladder, there were many problems with the evidence, such as variable definitions of UTI and lack of urinary acidification, and the authors concluded that methenamine hippurate is not effective for long-term UTI prophylaxis in this population [35].

The use of cranberries and cranberry-derived products for prevention of urinary tract infections is widespread. A commonly cited study by Gupta et al. showed that cranberry products can inhibit *E. coli* adherence to cells in models of cultured bladder and vaginal epithelial cells and that this relationship is dose dependent [36]. A Cochrane review of cranberry products, notably the third update on the topic, evaluated evidence from trials of cranberry products (juice, concentrate, capsules or tablets—noting there to be no standardization for active ingredient—proanthocyanidins) compared to placebo, no treatment, water, methenamine hippurate, antibiotics, or lactobacillus. Overall, the analysis showed that although previous meta-analyses had shown promise for decreased rates of UTIs in patients with recurrent cystitis, the addition of recent data shows no statistically significant difference in rates of recurrent UTIs. A subgroup analysis of patients with neuropathic bladder also showed no difference for the various cranberry products over placebo [37].

Further studies continue to be published on the use of cranberries in patients with NGB. A small randomized placebo-controlled crossover trial of children with NGB secondary to myelomeningocele on intermittent catheterization was recently published. Twenty children received 6 months of placebo and 6 months of cranberry tablets separated by a washout period. Symptomatic UTI rate and pyuria rate were significantly lower during once daily cranberry tablet use than during placebo use [38]. Another recent study of 171 MS outpatients receiving 36 mg of proanthocyanidins per day of cranberry extract versus placebo twice daily for 1 year showed no difference in time to the first symptomatic UTI [39]. More research is needed to determine if standardized doses of cranberry products can be effective at preventing UTIs.

D-mannose is a sugar that is involved in many aspects of metabolism and is purported to act with a similar mechanism to cranberry in preventing adhesion of bacteria to cells in the urinary tract. A recent study in neurologically normal women with recurrent UTIs showed effectiveness in preventing infections that was similar to nitrofurantoin and significantly better than no prophylaxis over a 6-month period [40]. This population is again very different from the NGB population, and there is no evidence currently that D-mannose is a viable prevention strategy.

Some strategies for UTI prevention, such as the use of probiotics and vaginal estrogen, have been most well studied in post-menopausal women with recurrent UTIs. Topical vaginal estrogen replacement has been shown in animal and translational models [41] to have a potentially useful role for preventing urinary tract infections in post-menopausal women. This intervention could be an adjunct in some patients with NGB but is thus far untested. Probiotics, and specifically certain strains of lactobacillus, have been studied in post-menopausal women and in children [42, 43], but there is limited data that these strains produce any meaningful clinical effect in patients with NGB, although a case study did show that the inflammatory marker (urinary TNF-α) was decreased with the oral probiotic in a male spinal cord injured patient [44].

Non-antibiotic Interventions

The neuropathic bladder often stores urine poorly, with problems such as high-pressure uninhibited detrusor contractions

that can impact the risk for developing UTIs. Intradetrusor injection of onabotulinumtoxin A is one intervention that has shown promise for better control over detrusor overactivity and incontinence, as well as for preventing UTIs in patients with NGB [45, 46•]. Patients who showed less improvement in urodynamic parameters showed less reduction in symptomatic UTIs. Although the injection procedure itself carries a risk of UTI and proper prophylaxis should be used [47], onabotulinumtoxin A injection shows great promise in decreasing the rate of UTIs in this population and larger, longer-term studies are warranted.

Antibiotic Prophylaxis

Continuous suppressive or prophylactic antibiotic use in any patient population is controversial. The evidence for the use of antibiotic prophylaxis was evaluated in a recent Cochrane review [48]. This meta-analysis separated data for patients on ISC and with indwelling catheters and evaluated antibiotic prophylaxis against giving antibiotics when clinically indicated, as well as antibiotic prophylaxis against and giving antibiotics when microbiologically indicated. For patients managed with ISC, there was weak evidence that favored prophylaxis for preventing symptomatic and asymptomatic bacteriuria, but longer-term studies with further evaluation of adverse events are needed before this strategy can be recommended. For patients with indwelling catheters, the results were inconclusive. There was not enough evidence to separate out the effects of individual antibiotics, and both the effectiveness and risk may not be the same for each agent. The routine use of antibiotic prophylaxis for patients with NGB is currently not recommended regardless of type of bladder management.

Bacterial Interference

The idea behind bacterial interference grew from the observation that asymptomatic bacteriuria with commensal nonpathogenic bacteria was protective against symptomatic UTIs. In 2000, Hull et al. published results of a study of 13 patients who were colonized with the commensal *E. coli* 83972 for a mean of 12.3 months (range 2 to 40). All subjects were documented to have had recurrent UTIs prior to inoculation, and none had symptomatic UTIs while colonized. They reported zero infections per 18.4 patient-years in colonized patients and reported an improvement in quality of life while colonized [49].

Another study of *E. coli* 83972 was undertaken in 20 patients with incomplete bladder emptying (residual urine 100 mL or greater, many on ISC) with a history of three or more UTIs per year. Using a self-reported definition of UTI, they reported an increase in the time to the first UTI (median 11.3 months with colonization vs. 5.7 months without), and in analysis after crossover with a total of 202 months with and 168 months without *E. coli* 83972, fewer UTIs were reported with versus without (13 vs. 35 episodes) (p=0.009; CI 0.31–1.89). There were no adverse events related to colonization; however, several patients required reinoculation [50].

Darouiche et al. studied a related strain of *E. coli* (HU2117) and found that bladder colonization with *E. coli* HU2117 was safe and effective at reducing the risk of symptomatic UTI in patients with NGB [51]. The practicality of achieving and maintaining colonization with particular strains of *E. coli* could be challenging in the NGB population because of the need to reinoculate and the need to test for specific strains on urine specimens, as well as the task of educating providers regarding the use of antibiotics in these patients, but this strategy could be promising if an inexpensive, convenient method of keeping patients colonized is developed.

Vaccines

Because of the cost of both complicated and uncomplicated UTI, and the recent focus on antibiotic stewardship, studies are ongoing to create a vaccine against the most prominent cause, uropathogenic *E. coli* (UPEC). A review of the progress toward vaccine development noted the challenges (typically having a UTI does not protect against having a subsequent UTI, there are commensal *E. coli* that should not be targeted, etc.) of developing a UPEC vaccine and described notable advances in this field [52].

There are vaccines in every stage of development, including some that have been available and marketed in Europe and elsewhere for several years. Much of the testing that has moved beyond animal models has been focused on neurologically normal women with recurrent UTIs that are caused by these strains of *E. coli*. None of these vaccines are available or have been tested in a population of patients with NGB dysfunction.

Not all UTIs are preventable, and preventing escalation of antibiotic resistance by following guidelines to ensure that symptomatic UTIs are treated completely with tailored antibiotics is also an important consideration in patients with NGB.

Conclusion

The criteria that make up the definition of a urinary tract infection have not been standardized in the literature, and this makes the already daunting task of establishing a prevention strategy for an ill-defined end-point even more difficult. Stakeholders in the care of these patients should focus efforts on agreeing on a definition for UTI so that these interventions can be rigorously studied. An important concept is that patients with NGBs commonly have asymptomatic bacteriuria

and that the presence of bacteria is not grounds for treatment in this population. Eliminating bacteriuria is not feasible and should not be attempted with very specific exceptions, for example, for patients who are planned for surgical procedures and for recurrent stone formers who are colonized with urea-splitting organisms. It is imperative that patients and their care teams are educated that treatment should be reserved for symptomatic UTIs. When focusing on the most recent data, using patient and caregiver education to encourage compliance with standardized protocols of intermittent catheterization, possibly with hydrophilic catheters, and employing onabotulinumtoxin A injections and gentamicin bladder instillation when breakthrough infections continue are the best prevention strategies for symptomatic urinary tract infection in NGB.

Compliance with Ethics Guidelines

Conflict of Interest Lindsey Cox and Anne P. Cameron declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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