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INFLAMMATORY/INFECTIOUS BLADDER DISORDERS (MS MOURAD, SECTION EDITOR)

Neurogenic Bladder: Recurrent Urinary Tract Infections—Beyond Antibiotics

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Abstract

Purpose of Review Our goal was to identify evidenced-based strategies to prevent and treat patients with neurogenic bladder who suffer from recurrent urinary tract infections. We focused on therapy beyond standard antibiotics to address a multitude of factors implicated in these complex infections.

Recent Findings Anatomic and functional components specific to neurogenic bladder contribute to the risk of infection and require close clinical monitoring. The host-pathogen interaction is one that allows for colonization of bacteria in the bladder. We recognize that bacteriuria in the neurogenic bladder population does not equate with infection. Local antibiotic treatment and oral supplements are often not adequate to eliminate infection nor prevent recurrent infection due to biofilms. However, novel medical therapies, such as photodynamic therapy, bacterial interference, and infrared laser therapy to augment local immune cells, are promising options to prevent and treat symptomatic infection.

Summary A combination approach including management of anatomic and functional factors with medical intervention can significantly improve frequency of urinary infection. Further study of non-antibiotic therapeutic strategies is much needed as we recognize the complexity of the urinary biomes and the limitations of antibiotic therapies.

Keywords Neurogenic bladder · Neurogenic UTI · Recurrent urinary tract infection · Catheter-associated UTI

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Introduction

Recurrent urinary tract infections in persons with neurogenic bladder present special clinical challenges. These will be explored in the manuscript below and management pearls will be provided. Diagnosis of UTI is nuanced in this population for a number of reasons. Patients with neurologic disease and impaired bladder sensation do not report classic symptoms. These patients often rely on intermittent catheterization or indwelling catheters for bladder emptying, techniques associated with increased rates of bacteriuria. It is a challenge to distinguish colonization versus symptomatic infection. Expert clinicians and researchers in the field have created stricter criteria for the diagnosis of UTIs as well as a paradigm shift related to the role of bacteria in urologic disease [1]. Previous thought was that urine from healthy subjects is sterile and a negative urine culture denotes the absence of infection. Today bacteriuria does not equate with infection. Metagenomic sequencing for fastidious and anaerobic bacteria shows a broad range of organisms detected in the "sterile" bladder in healthy individuals. Biofilms, found on foreign bodies and the surface of the bladder, represent additional therapeutic obstacles because they enable bacteria to evade the killing mechanisms of many antibiotic classes [2]. As clinicians who care for these patients, it is imperative to be knowledgeable about the current strategies to prevent symptomatic UTIs and options of therapy beyond antibiotics.

Anatomic and Functional Factors

The approach to UTI requires medical, functional, and anatomic knowledge, that is best achieved within a multidisciplinary approach. Simplistically, all functional disorders of the lower urinary tract can be viewed in light of two roles: filling (storing) and emptying the bladder. Elevated bladder storage pressures from poor bladder compliance or detrusor overactivity can lead to vesicoureteral reflux, impaired peristalsis of the ureters, hydronephrosis, and a theoretical risk of bacteria traversing epithelial barriers into the bladder. Incomplete bladder emptying can result from a hypotonic detrusor muscle or obstruction (such as detrusor sphincter dyssynergia). Neurologically, Wein's functional model of voiding dysfunction gives a general expectation of the level of injury and clinical manifestations [3]. An injury above the pontine micturition center (PMC) is likely to cause neurogenic detrusor overactivity with synergistic voiding; an injury below the PMC and above the sacral motor outflow can lead to detrusor sphincter dyssynergia, and injury below the sacral motor outflow often results in detrusor acontractility. In clinical practice, urodynamic findings are variable due to incomplete or multilevel injuries, therefore broad assumptions cannot be made. Urodynamic testing should be performed in most patients with recurrent UTI in the setting of spinal cord injury, stroke, Parkinson's disease, and multiple sclerosis to evaluate the type of bladder dysfunction. Cystoscopy seeking stones, foreign body, obstructing prostate or fistula, stricture fistula, tumor, or urethral diverticulum should be performed. Upper tract imaging completes the initial workup. Renal ultrasound suffices for recurrent urinary tract infection, but renal mass protocol CT scan or MRI should be performed instead in the case of hematuria (≥ 3 red blood cells per 40× high-power microscopic view on urine sediment in the absence of infection or clearly documented genitourinary trauma).

Emptying

Voiding is a protective mechanism against UTI, with one animal study showing that 99.9% of bacteria injected into the bladder are eliminated by voiding [4]. Consequently, incomplete voiding and resultant urinary stasis are well-described risk factors for urinary infection, with as little as 20 ml of persistent urine found to be associated with recurrent UTI [3, 5, 6]. A randomized controlled trial found that self-monitoring urine flow to enhance emptying in patients with an indwelling catheter did not reduce catheter-associated UTIs (CAUTIs) [7]. The higher the post-void residual volume (PVR), the higher the risk of UTI found. In a study of 188 patients undergoing stroke rehabilitation, Kim et al. found that patients with a PVR of greater than 100 ml were 4.87 times more likely to develop UTI [8]. Dromerick found that in 101 patients undergoing stroke rehabilitation, the odds of a UTI were significant at a PVR of 150 ml and 200 ml (odds ratio 3.25 and 3.71, respectively) [9]. Post void residual volumes should be interpreted with respect to the overall bladder capacity. There are rules of thumb within urology that a void of 2/3 of the total bladder volume and a PVR below 150 ml are acceptable, but in refractory cases the data above support more aggressive management of emptying.

Catheters

Patients with neurogenic bladder often require introduction of a foreign body either in the form of indwelling catheters or clean intermittent catheterization. In a retrospective study evaluating characteristics of patients with neurogenic bladder, the emptying method was found to be the most important predictor of symptomatic UTIs [10]. Indwelling catheterization posed the highest risk [10]. If patients cannot perform self-catheterization due to limited hand function, the alternative options other than indwelling catheterization include sphincterotomy, ileovesicostomy, and ileal loop urinary diversion [11]. Whereas ileal loop is counseled by some as the gold standard management, the data do not support superior outcomes compared to the other options [11].

Stones

Urinary stasis as well as infection can cause urinary calculi, which in turn may act as nidi for infection [12]. Obstructing or large stones should be removed. Non-obstructing small upper urinary tract stones are usually thought to be benign. However, in a retrospective review of 120 patients with non-obstructing asymptomatic renal calculi and recurrent UTIs who underwent surgical extraction, nearly 50% of the patients remained infection-free after the stone removal [13]. This raises the question of whether small non-obstructing stones contribute to the risk of urinary tract infection, but without a prospective randomized study, this conclusion cannot be determined. Additionally, the improved patient outcomes may be confounded by the more frequent urology visits these patients were sure to have had.

Obstruction

Obstruction along any region of the urogenital system can have dire clinical effects. Renal obstruction can occur at the level of the ureteropelvic junction (UPJ), any segment of the ureter, or ureterovesicular junction (UVJ) secondary to urolithiasis, scarring, or congenital abnormalities (e.g., valves or crossing vessels). The bladder is often a source of obstruction due to elevated pressures, detrusor sphincter dyssynergia, pre-existing prostatic obstruction, or anterior vaginal wall prolapse. Of note, when the bladder is the cause of obstruction, the upper urinary tract abnormalities are usually bilateral. If ureteric obstruction is suspected and initial imaging is not definitive, a MAG-3 renal scan with furosemide with a catheter in place draining the bladder can help rule in or rule out impaired drainage. Ileal loop urinary diversion is performed to remove obstruction, but over time should be monitored by RUS. It can be obstructed at the level of the stoma or the ureteroileal anastomosis. Gentle digitalization, catheterization for draining residual, and loopogram looking for reflux are the best means for evaluation of an ileal loop. Obstruction anywhere in the urinary tract needs to be addressed to prevent loss of renal function, decompensation of the obstructed unit (e.g., bladder), and prevention of infection.

Constipation

Constipation and fecal incontinence are both thought to increase the propensity toward urinary tract infection. Mechanisms include perineal contamination, combined bladder and defecatory dysfunction via neural crosstalk, and trans-colonic migration of bacteria. Intervention to address constipation or incontinence should be encouraged as part of the treatment plan for the UTI.

Considerations in Diagnosis of UTI and Antibiotic Usage

The microbiome of patients with neuropathic bladder is intrinsically different from those with normal functioning bladders. *Lactobacillus* is the prevalent species in healthy women and *Corynebacterium* in men; specimens from those with healthy neurogenic bladders were notable for a lack of these organisms [14]. When infection is present, *Enterobacteriaceae* species, which includes *Escherichia coli* and *Klebsiella*, is the most prevalent in neurogenic bladder [15, 16]. The type of organism varies depending on either a community or hospital setting [17]. Patients in the hospital are more likely to have *Pseudomonas*, *Acinetobacter*, and *Enterococcus* species with extensive resistance patterns. These data warrant avoidance of treating urinary infections until the susceptibilities of the target organism are known.

All UTIs in neurogenic bladder patients are considered "complex." In accordance with IDSA Guidelines, catheter-associated UTIs, which include indwelling and intermittent catheterization, are defined as the presence of clinical symptoms along with > 10^3 colony-forming units/ml of one or more bacterial species obtained from a clean catheterized specimen [18]. For those with indwelling catheters or suprapubic tube, the specimen should be obtained from the new tube after the catheter has been exchanged. Changing the catheter will improve the accuracy of identifying a culprit organism and also may improve the response to antibiotic therapy by removing the biofilm that serves as a scaffold for reinfection [19].

Bacteriuria from simple colonization in the neurogenic bladder will not always be symptomatic. Symptoms associated with true infection in these patients include cloudy malodorous urine, incontinence, increased spasticity, fever, lethargy, a sense of unease, mental status change, and autonomic dysreflexia [20]. Both clinical symptoms and culture data are necessary for diagnosis of a UTI. Treatment of asymptomatic bacteriuria is not recommended as it results in resistant bacterial strains without improvement in patient outcomes [20]. Furthermore, urine screening for asymptomatic bacteriuria is not advised as positive results may lead a clinician to treat the patient [21]. An exception to this rule is the practice of sterilizing the urine prior to urologic intervention, as manipulation and high irrigation pressures can convert bacteriuria to a symptomatic and even dangerous infection. Urinalysis is not sufficiently sensitive or specific in this population and is therefore excluded from diagnostic criteria. Urine sediment has more diagnostic certainty. One study found the composite of > 10 urinary WBCs on sediment and either moderate or large leukocyte esterase had a negative predictive value of 90%, but a very poor positive predictive value [22]. This suggests that the above criteria may be useful in ruling out the presence of urinary infection. However, greater than 10 urinary WBCs per high-power field cannot be used to diagnose a UTI.

For duration of antibiotic therapy, guidelines recommend a 7-day course for those who have prompt resolution of symptoms [18]. For those with a delayed response, 10–14 days is an appropriate treatment course. Indwelling catheters should be exchanged in the setting of infection to obtain the specimen of the new catheter and to improve the likelihood of successful treatment [18]. In difficult cases, the authors will change the indwelling catheter a second time once on appropriate antibiotics. Institutional antimicrobial biograms can help guide empiric treatment if the patient is unstable—otherwise, the best practice is to await organism sensitivities to guide therapeutic management.

Systemic antimicrobial prophylaxis should not be used for those with neurogenic bladder and recurrent UTIs. Several studies have examined the use of nitrofurantoin, fluoroquinolones, and trimethoprim/sulfamethoxazole as prophylaxis [23–26]. A Cochrane review concluded that the benefits of antibiotic prophylaxis do not clearly outweigh the adverse effects such as antimicrobial resistance [27].

Pathogen-Host Interactions in the Bladder

As we consider therapies other than antibiotics for urinary tract infections in those with neurogenic bladder, it is critical to consider the target organ of the infection, the responses that occur there, and special nature of those responses in the context of neurogenic bladder. Approximately 80% of urinary tract infections are caused by uropathogenic *E. coli* (UPEC). It is this pathogen which has been most studied and for which there is the most pathophysiologic data.

Evidence suggests that UPEC is able to harness the complex innate immune responses of the bladder to enable bacterial survival and colonization. A recent murine model demonstrated physiologic immune dampening in the setting of recurrent UTIs via release of the cytokine interleukoin-10 by resident mast cells [28]. Mast cells in the bladder serve a unique function of tempering harmful immune responses to the many antigens in the urine when the protective epithelial coating is damaged [28]. The bladder contains specialized mucosal tissue richly endowed with mast cells that serve an important role to inhibit the local adaptive immunity against persistent bacterial antigens [29].

The cost of this immune dampening enables UPEC to colonize and establish intracellular bacterial communities (IBCs). Persistent infection is associated with increased mast cell infiltration, suggesting a positive feedback loop that favors formation of IBCs [28]. Chan et al. concluded that the limited immune response observed in bladder infections, but not pyelonephritis, was due to the effects of mast cells and interleukin-10 found in the bladder wall [28].

Bacteria can persist for several weeks protected from both antibiotics and the host immune system. Biofilms are complex structures with both dormant, deeply protected bacteria and superficial planktonic organisms. Antibiotic minimal inhibitory concentrations (MIC) are 100–1000-fold higher for the dormant–phase bacteria than for the classical planktonic forms found in the voided urine [30, 31]. Given these facts, it is not surprising that over one half of all recurrent episodes of cystitis are by the same strain as the initial infection [32].

Unique host factors associated with neurogenic bladder provide additional risk for infection. Investigators at Duke have demonstrated that spinal cord-injured animals require fewer bacteria to establish infection and have exaggerated inflammatory responses with decreased clearing of infection compared to uninjured controls [33]. This suggests that spinal cord injury itself has a profound effect on the immune system. There is increasing evidence for interactions between the autonomic nervous system and the immune system, as reviewed by Tracey [34].

Local Preventative Therapies

As mentioned above, the method of bladder emptying contributes to the risk of urinary infection. A prospective study for 38 months evaluated 128 patients with spinal cord injury for the risk of UTI based on differing voiding techniques. Indwelling urethral catheters were found to have a tenfold increased incidence of UTI compared to other methods [10, 35] As a result, clean intermittent catheterization has become the standard of care for patients who cannot effectively empty the bladder [20]. There are limitations to this technique. In order to perform clean intermittent catheterization appropriately, one must be motivated, educated on proper technique, and have adequate use of the upper extremities or a willing 24-h caregiver, and be willing to catheterize with consistent frequency (once-daily protocols can introduce bacteria without allowing for consistent emptying and therefore increase the chance of UTI). Patients who initially use intermittent catheterization often switch to indwelling catheters if they develop recurrent UTIs, incontinence, kidney stones, dependence on caregivers, or urethral strictures [36]. It is important to educate patients that other factors rather than the intermittent catheterization are often the cause of the infections.

Indwelling catheters are widely used in the neurogenic population despite what is known about risk for UTI. In order to reduce CAUTI, the US Centers for Disease Control recommends minimizing the use and duration of indwelling urinary catheters [37]. Insertion of an indwelling urinary catheter should only be used for the following circumstances: acute urinary retention, bladder outlet obstruction, comfort for end-of-life care, need for accurate measurements of intake and output in critically ill patients, during surgery, healing open sacral or perineal wounds, and prolonged immobilization from spinal or traumatic injuries (CDC). Patients should be informed that the risk of CAUTI increases with the length of time that the indwelling urinary catheter remains in the bladder [38]. Nurse-driven protocols for screening patient eligibility for receiving an indwelling urinary catheter and timely catheter removal have been effective in CAUTIs [39••]. There are a variety of successful single and bundled nursing interventions focused on screening, monitoring, and stop orders to consider in developing a protocol [40]. Other strategies target maintenance of sterile technique for catheter insertion using direct observation [41] or two-person teams [42]. Steps in the entire process of preventing CAUTIs have been summarized into a pocket algorithm that can be used for staff training [43]. These protocols can be adapted to persons with neurogenic bladder, and where possible, we aim to replace indwelling catheters with intermittent catheterization. In the end, a significant number of patients with neurogenic bladder will be managed with indwelling catheter, and it is important to recognize this is a compromise among conflicting treatment goals, addressed further below.

Several intermittent catheter techniques have been evaluated for risk of UTI including sterile versus clean technique, single or multi-use catheters, exchange of multi-use catheters daily or weekly, and use of coated or uncoated catheters. Sterile technique involves sterile gloves and drapes whereas clean technique does not. Coated catheters are hydrophilic or prelubricated with a water-soluble gel. Hydrophilic catheters have a layer of polymer coating on the surface that reduces friction and urethral inflammation with insertion. Many small, methodologically weak studies have compared these techniques [44–48], but the largest Cochrane review and meta-analysis found no superior method to prevent UTIs [49, 50]. The cost of catheters, limited third-party insurance reimbursement, and increased environmental waste are issues associated with single use, sterile catheters. The Cochrane conclusions are to allow patient preference to guide management. Manufacturers and supply companies have persistently recommended single use catheters due to single-use labeling. Traditionally, catheters with a siliconized or polyvinyl chloride, non-prelubricated, non-hydrophilic surface have been rewashed without evidence of inferiority. There are serious environmental arguments in favor of rewashing catheters, as the patient is only reexposed to his or her own bacterial environment. It should be noted in rewashing that the catheter surface does eventually erode. For patients who rewash catheters, the authors recommend changing to a new catheter every week, washing with water and clear-rinsing dish soap, then drying the catheter in open air. Alternatively, for convenience, some patients use reusable catheters at home and single-use catheters while out.

Suprapubic catheter often becomes the management of choice for neurogenic bladder. This method is favored due to low-impact placement, reduced UTI risk, and urethral complications versus urethral catheter, reversibility, and convenience for patients who cannot catheterize themselves. The interval time period of indwelling catheter exchange and UTI incidence in persons with neurogenic bladder has been studied. A Cochrane review of three randomized control trials including a total of 107 patients did not find any difference between changing the catheter regularly and waiting until it was clinically indicated (symptomatic UTIs or obstruction) [51]. Furthermore, the use of antibiotics during the exchange did not alter the incidence of infection [51]; thus, the use of antibiotics at the time of catheter change is not recommended. The authors change the catheters monthly, or earlier if indicated (clogging, symptomatic infection), as this allows for elective changes and avoidance of morbidity. Lastly, catheters used for suprapubic drainage should be larger bore (18–22 French), flexible for comfort, and short-tipped to prevent erosion of the bladder surface.

Local preventative therapies such as antibiotic irrigation are still used clinically. There has been conflicting data to support this technique. A meta-analysis examining intravesical aminoglycoside treatment found two studies with a significant decrease in bacteriuria with antibiotic bladder irrigation [52]. However, within the same review, two other studies found no significant difference between the incidences of UTIs [52]. Given this insufficient and conflicting information, guidelines recommend against the use catheter irrigation with antimicrobial agents [18, 53]. A review of seven European studies found that hyaluronic acid and chondroitin sulfate bladder instillations decrease the frequency of UTIs, result in prolonged time to UTI, and improved quality of life [54]. The studies used were all retrospective but suggest that restoring the glycosaminoglycan bladder layer with non-antibiotic irrigation therapy may be an option to prevent recurrent UTIs. Further prospective investigation is needed in this area. In the meantime, individual clinicians do employ irrigation strategies with select patients.

There are two routes of biofilm development on indwelling catheters: intraluminal and extraluminal. Intraluminal biofilm formation occurs when organisms gain access to the internal lumen of the catheter through failure of the closed drainage system or contamination of the collection bag. This occurs when organisms are introduced from exogenous sources like the hands of healthcare professionals [55, 56]. Intraluminal contamination of the leg bag was found to account for 35% of catheter-related UTIs [57]. A closed-catheter drainage system should be used to reduce urinary infections. There is inadequate evidence to recommend single-use or daily change of urinary leg drainage bags to reduce UTIs [58]; therefore, the authors recommend a leg bag-changing interval between 5 days up to 1 month [58, 59]. Randomized controlled trials to establish the optimum time interval between changing drainage bags are needed.

Antimicrobial agents used to coat urinary catheters have been a focus of intervention for several decades and are an obvious target for industry. There are two terms used to describe the properties of these coatings. Antifouling materials do not kill microbes directly but prevent the attachment of bacteria to surfaces preventing biofilm formation. Hydrophilic and polyzwitterion are materials within this class and work through mechanisms such as steric repulsion, electrostatic repulsion, and low surface energy. Biocidal materials kill microbes and include coatings such as antibiotics and silver ions. The research for silver has remained controversial with some studies supporting its use [60, 61], and those that find no clinical significance [62–64]. Data at the present time support the use of antibiotic coated catheters such as minocycline, rifampin, and nitrofurazone-impregnated materials [65, 66] for a short duration only [18]. Long-term catheterization (> 30 days) was assessed in a Cochrane review of randomized trials, but the authors were unable to report a definitive conclusion due to inadequate evidence [67]. Priyadarshini et al. highlighted many coating agents that are still in research such as antimicrobial peptides, bacteriophages, chlorhexidine, and nitric oxide [68•]. However, the authors emphasize that simple impregnation of an antimicrobial agent will not prevent UTIs. They propose antimicrobial coatings that attack pathogens through a multi-mechanistic approach to improve efficacy and prevent resistance. A greater understanding of synergy between the antimicrobial agents on catheters and biofilm interactions is needed [68•, 69].

Bacterial interference is the introduction of non-virulent bacterial strains into the bladder to prevent colonization by pathogenic organisms. A randomized crossover study with 20 patients evaluated non-pathogenic *E. coli* 83972 inoculations compared to normal saline [70]. Those treated with *E. coli* 83972 had longer time to UTI incidence and a decreased number of symptomatic UTIs over 1 year. Subsequent studies also support this conclusion of fewer UTIs in spinal cord injured patients [71, 72]. Notably of the 21 patients in the study, only 13 achieved successful long-term bladder colonization which took a mean duration of 12 months [70]. Colonized subjects reported improvement in quality of life with respect to urinary tract infection [70]. There is criticism of these studies regarding the lack of intention-to-treat analysis which would undermine the randomization process and bias the results [73]. Bacterial interference with non-pathogenic *E. coli* is a potential strategy to prevent symptomatic urinary infections, however further studies with appropriately powered randomized controlled trials are needed.

The therapeutic challenges with biofilms have prompted novel approaches using light, or photodynamic therapy (PDT), to eradicate biofilm infections [30]. In a model of catheterized mice, infection was eradicated using a combination of laser illumination and instilled methylene blue with potassium iodide [74••]. If the light is administered shortly after the photosensitizing methylene blue is instilled, the short distance traveled by the reactive oxygen species kills the bacteria that take up the dye quickly, while leaving urinary epithelium undamaged. This could be further calibrated to attack biofilms. Additional studies suggest that certain antibiotics, such as tetracyclines, may also be illuminated by a fiberoptic catheter to render resistant organisms be sensitive again [75•]. Wang et al. have shown profound antimicrobial effects with illumination by blue light directly, which interacts with bacterial porphyrins [76••]. For patients with neurogenic bladder constantly subjected to catheterization, a fiberoptic catheter may hold promise in future development.

The immunology of the bladder plays a critical role. The chemokine CCL12/receptor CXCR4 axis can be manipulated systemically or locally [77, 78]. Mast cells, significant in altering immune function in the bladder, are amenable to both pharmacologic and light manipulation. We have developed a near-infrared laser adjuvant that enhances immunity by activating local immune cells upon infrared illumination, and increases the transport of antigen from the skin to draining lymph nodes [79••, 80, 81]. The near-infrared laser adjuvant activates and partially degranulates mast cells [82]. We believe that this function can be potentially manipulated in the urinary bladder. We have demonstrated in mice the feasibility of treating infection with light alone or in conjunction with antibiotics [74••, 75•].

It is clear that current antimicrobial therapy is not enough to restore quality of life in those with recurrent UTIs, and hopefully novel approaches such as the above may offer new benefit.

Oral Preventive Therapies

The efficacies of numerous oral preventive therapies have been evaluated, including cranberry products, probiotics, ascorbic acid, methenamine salts, and D-mannose.

Cranberry

There is conflicting literature regarding cranberry supplements, in part due to the significant heterogeneity and lack of standardization of the supplements as well as the clinical outcomes evaluated (i.e., complicated or recurrent UTIs) [83, 84]. In vitro laboratory studies have demonstrated that the proanthocyanidins in cranberry juice inhibit the adherence of P-fimbriae of *E. coli* to uroepithelial cells [85], while the fructose in cranberries blocks type 1 fimbriae [86]. While a 2008 Cochrane Review found some evidence of benefit from cranberries, an update in 2012 concluded that there was no statistically significant difference on recurrent UTIs with the addition of larger studies [87]. However, as Beereport and Geerlings note, two of the additional studies included in the updated Cochrane Review did not focus on recurrent UTIs but rather acute UTI and symptom amelioration [88]. There is currently a double-blind randomized controlled trial underway investigating standardized high-dose and low-dose proanthocyanidin extract for prevention of recurrent UTIs [89].

Probiotics

A 2015 Cochrane Review examined nine quasi-randomized controlled trials and randomized controlled trials evaluating the use of probiotics, predominantly *Lactobacillus* species. They concluded that there was no significant benefit demonstrated for probiotics, but because there was insufficient data, a benefit could not be ruled out [90].

Ascorbic Acid

It is thought that the mechanism by which ascorbic acid prevents UTI is by preventing the alkalization of urine [91]. There is one positive, though methodologically limited trial that investigated ascorbic acid for UTI prophylaxis in pregnant women; the authors found that a daily dose of 100 mg of ascorbic acid reduced the incidence of UTI [92]. Two small studies in patients with spinal cord injury found that a daily dose of 2 to 4 g of ascorbic acid daily did not result in statistically different changes in urine pH [93, 94].

Methenamine Salts

Methenamine salts work by converting to formaldehyde in acidic urine, which then exhibits nonspecific antiseptic activity that is dependent on dwell time [95]. A 2012 Cochrane Review found that methenamine hippurate may be effective as a short-term prophylaxis in preventing UTI in patients without renal tract abnormalities; however, it did not appear to be effective long-term prophylaxis in patients with neurogenic bladders [96]. In neurogenic bladder managed by indwelling catheter, there is decreased dwell time—therefore methenamine salts may have limited use.

D-Mannose

Similar to the fructose in cranberries, D-mannose is thought to work by inhibiting bacterial adherence to urothelial cells by blocking type 1 fimbriae [97]. There is one randomized controlled trial consisting of 308 women that investigated the effects of D-mannose for 6 months against no prophylaxis as well as nitrofurantoin prophylaxis. They found that D-mannose and nitrofurantoin both significantly decreased the risk of recurrent UTI and there was no statistically significant difference between these two interventions for prophylaxis [98].

Vaccines/Oral Immunostimulants

OM-89, an oral immunostimulant consists of an extract of 18 different serotypes of heat-killed uropathogenic *E. coli*, is thought to decrease recurrent UTIs by stimulating innate immunity. While an initial systematic review and meta-analysis of a total of 891 patients was promising with significant lower risk of UTI in the OM-89 group (RR 0.61, 95% CI 0.48–0.78), a recent randomized control trial of OM-89S, an OM-89 manufactured using a modified lytic process, found no difference between OM-89S and placebo [99].

Another strategy currently under development is the use of vaccines. One vaginal vaccine available in Europe, Urovac, is a vaccine incorporating 10 heat-killed uropathogenic *E. coli*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Morganella morganii*, and *Enterococcus faecalis*, with a phase 2 clinical trial showing women who had the initial vaccination and boosters (total of six vaginal suppositories) had an increased time to recurrent UTI compared to placebo-treated women, though there was no statistically significant difference between the initial vaccination only group and placebo [100]. Other vaccines under development include an intranasal vaccine based on adhesin proteins in uropathogenic *E. coli* and *P. mirbalis* [101].

When to Change Management Strategies

Management decisions in neurogenic bladder are informed by patient goals, abilities, overall health, and social support. Therapeutic strategies often change within the first year after injury due to status of rehabilitation, coping, and care settings. Delay in the evaluation of neurogenic bladder can have lasting effects on the health of the patient's urinary system. Incontinence, greater than two symptomatic UTIs in 6 months or three in 1 year, hydronephrosis, stone development, high filling, or voiding pressure on urodynamics, all call for consideration of a change in management strategy.

Conclusion

The improvement in care for persons with neurogenic bladder over the last several decades has improved renal morbidity, mortality, and overall quality of life. A combination approach including management of anatomic and functional factors with careful medical intervention can significantly improve frequency of urinary infection. Further study of non-antibiotic therapeutic strategies is much needed as we recognize the complexity of the urinary biomes and the limitations of antibiotic therapies.

Compliance with Ethical Standards

Conflict of Interest The authors 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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- •• Of major importance

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