Strategies for Prevention of Urinary Tract Infections in Neurogenic Bladder Dysfunction

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KEYWORDS

- Spinal cord injuries • Neurogenic bladder • Urinary tract infection
- Catheter-associated urinary tract infection (CAUTI)

KEY POINTS

- Urinary tract infection (UTI) is a clinical diagnosis, and treatment depends on the presence and severity of symptoms.
- Providers should not treat asymptomatic bacteriuria, and pyuria alone may not be an indication for treatment.
- Because of an increased incidence of resistant bacterial species in persons with spinal cord injury and disorders (SCI & D), urine culture should be obtained before the initiation of antibiotic therapy.
- Urodynamic evaluation is the standard of care to ensure safe bladder function, and intermittent catheterization is the preferred bladder management.
- Mechanical strategies for the prevention of UTIs in persons with SCI & D include use of hydrophilic, closed-system, and antibiotic-coated catheters as well as bladder irrigation and fluid restriction.
- Medical strategies for the prevention of UTIs in persons with SCI & D include antibiotic prophylaxis, cranberry compounds, D-mannose, methenamine, urinary acidifiers, and bacterial interference.

INTRODUCTION

Neurogenic bladder is a common and distressing complication of spinal cord injury and disorders (SCI & D). Individuals with neurogenic bladder dysfunction are often unable to completely empty their urinary bladders. As a result, many of these individuals must perform clean intermittent catheterization (CIC) or use indwelling urinary catheters. Use of urinary catheters is associated with high rates of urinary tract infections

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(UTIs), termed catheter-associated UTIs (CAUTI). UTIs remain the most frequent type of infection in persons with SCI & D, with an average of 2.5 episodes per year.[1,2]

Before World War II, urinary tract complications were considered to be the number 1 cause of death in the acute period after SCI. However, advances in urologic diagnosis and management through the use of urodynamic assessments and CIC have reduced acute deaths and complications, improving the urinary tract–related quality of life for persons with SCI & D. Despite these advances, morbidity from UTIs remains common. In this regard, optimal urinary tract management is critical not only for the prevention of complications and illnesses but for the optimal social integration of the person with SCI & D.

This article is not intended to provide an exhaustive review of neurogenic bladder dysfunction after SCI & D, because detailed reviews of neurogenic bladder dysfunction have previously been published[3,4] Rather, the objectives of the article are to: (1) define the problem of UTIs after SCI & D, (2) discuss the relationship of bladder management to UTIs, (3) describe mechanical strategies for UTI prevention in SCI & D, and (4) describe medical strategies for UTI prevention in SCI & D. The reader is also referred to the detailed guideline by Hooton and colleagues,[5] which details evidence and recommendations regarding practices for prevention of CAUTI.

THE PROBLEM OF UTIS AFTER SCI & D

Bacteriuria

The definitions of what represents significant bacteriuria vary. Investigators and clinicians frequently define infection based on bacteriuria levels ranging from 10^3 to 10^5 colony-forming units (CFU) per milliliter of urine. However, insufficient data exist to recommend a standardized level for the diagnosis of CAUTI.[5] Historically, the medical literature pertaining to urinary catheters has not made clear distinctions between asymptomatic bacteriuria and UTI. Often the term UTI has been used when bacteriuria (with or without symptoms) is present.[5] The key problem, then, is that persons with SCI & D who use urinary catheters commonly have bacteriuria. The standard of care among SCI & D providers is not to treat asymptomatic bacteriuria, which has been defined as 10^5 CFU of 1 or more organisms in an appropriately collected specimen in an asymptomatic person,[5] with antibiotics.

Pyuria

Pyuria, defined as white blood cells (WBC) in the urine, is also commonly seen in individuals with neurogenic bladder dysfunction and especially in catheterized patients. However, in the catheterized patient, pyuria alone is not diagnostic of either asymptomatic bacteriuria or CAUTI.[1,5] Different researchers have defined significant pyuria variably, with levels as low as 5 WBC per high-powered field being considered clinically significant. However, there is disagreement regarding a threshold for significant pyuria, because many persons with SCI & D have chronic pyuria but no overt signs of illness (eg, fevers, chills, nausea, vomiting).

Bacterial Colonization

Colonization of the bladder with bacteriuria is the norm in persons with SCI & D who use urinary catheters, either indwelling or intermittent.[1,6] As noted earlier, treatment with antibiotics is not justified based on the presence of bacteriuria alone. Because of the risk of recurrent infections and development of resistant organisms in individuals with SCI & D, urine cultures should be obtained before initiation of antibiotic therapy in symptomatic persons. Empirical therapy may then be initiated with the opportunity of adjusting antimicrobial therapy based on culture results.

UTI Symptoms

The differentiation between asymptomatic bacterial colonization and clinical UTI can be difficult and is compounded by a lack of consensus regarding what constitutes UTI symptoms, the combination of symptoms and laboratory findings necessary for the diagnosis, and the symptoms that require antibiotic treatment (vs being managed with conservative measures, such as increasing fluid intake or catheterizations). UTI symptoms in individuals with SCI & D are diverse in both type and severity. These symptoms may include fever, rigors, chills, nausea and vomiting, abdominal discomfort, sweating, muscular spasms, fatigue, and autonomic dysreflexia (AD). Individuals may also present with cloudy or malodorous urine, increased urinary sediment, and catheter blockage. However, typical presenting symptoms experienced by individuals without SCI & D, such as dysuria, urinary frequency, and urinary urgency, may be absent.

As discussed further later, there is a need for consistency of reporting of various signs and symptoms of UTI. This factor has led to the development of clinical data sets to facilitate this process.[7] Signs and symptoms vary in their usefulness for UTI diagnosis. Massa and colleagues[8] reported that cloudy urine had the highest accuracy (83.1%) and leukocytes in the urine had the highest sensitivity (82.8%) for the presence of UTI. Fever had very high specificity (99%) but very low sensitivity (6.9%). In addition, AD was found to be both insensitive and nonspecific, because AD may be triggered by multiple causes. Other symptoms, including kidney/bladder discomfort, increased spasticity, feeling sick, sense of unease, increased need to perform catheterization, feeling tired, incontinence, and foul-smelling urine, all had high sensitivity (77%–95%) but very low specificity (<50%). Persons with SCI & D are not always able to accurately predict the presence of a UTI based on their symptoms.[9]

UTI Diagnosis

A UTI is characterized by the new onset of symptoms and not merely the presence of bacteria or WBC in the urine. To make the diagnosis, relevant laboratory findings, including bacteriuria (seen on urinalysis, dipstick, or culture), pyuria (leukocyturia), or a positive urine culture, must be accompanied by symptoms (see earlier section).[10] In individuals with neurogenic bladder dysfunction, asymptomatic bacteriuria of varying degrees is the norm.[1] Persons with SCI & D often do not present with similar symptoms to those in the general population, because of impaired or absent pain sensation.

Data Sets and Consensus Statements

Interpretation of UTI signs and symptoms is not standardized across systems of care or in different regions of the world. Led by Biering-Sorenson and colleagues,[11] international data sets for SCI & D have been developed. Recently, a basic data set for UTI was developed to standardize collection and reporting of the minimal amount of information required to define a possible UTI in daily practice.[7] This data set also makes it possible to evaluate and compare the results from various published studies. The importance of the urinary tract in SCI & D is evident in that data sets have been developed not only for UTI but also lower urinary tract function, imaging, and urodynamics.[12–14] Data sets are incorporated into the National Institute of Neurological Disorders and Stroke common data elements to facilitate sharing of data from different studies.[15]

THE RELATIONSHIP OF BLADDER MANAGEMENT TO UTIS

Neurourology

There is tremendous complexity in the functioning of both the bladder and external urethral sphincter as distinct anatomic and functional units. However, the key to their

proper functioning is the process through which these organs work together in a tightly orchestrated and reciprocal fashion. Thus, for effective urine storage to occur, the bladder must be in a state of relaxation while the external urethral sphincter is simultaneously in a state of tight contraction. Alternatively, when the voiding phase is initiated, a specific sequence of events needs to occur: first, the urethral sphincter relaxes, and then, the bladder contracts. This coordinated reciprocal control of the bladder and the external urethral sphincter is mediated by a control center in the brainstem called the pontine micturition center (PMC).[16]

Accordingly, any neurologic injury above the PMC leads to suppression of inhibitory inputs from higher cortical centers and results in neurogenic detrusor overactivity with intact coordination of the external urethral sphincter and bladder. Injuries to the spinal cord below the PMC but above the sacral motor outflow result in neurogenic detrusor overactivity with a lack of external urethral sphincter and bladder coordination, a condition known as detrusor sphincter dyssynergia. This is the situation seen in most individuals who have complete (American Spinal Injury Association Impairment Scale A) suprasacral spinal cord injury. The problem in this situation is that the lack of coordination can lead to sustained high pressures in the bladder, with corresponding increases in complications, including UTIs, vesicoureteral reflux, calculi, hydronephrosis, and kidney damage.[16] Thus, knowing some basic neurourology and the main location of a neurologic injury, the likely form of neurogenic bladder dysfunction can be predicted. Forms of neurogenic bladder dysfunction and descriptions based on location of neurologic injury are presented in **Table 1** according to the functional model of voiding dysfunction originally described by Wein.[17,18]

Bladder Management in Neurogenic Bladder Dysfunction

As described earlier, an understanding of the lower urinary tract pathophysiology in an individual with neurogenic bladder dysfunction is key to developing an optimized plan for long-term bladder management. The goal is to ensure complete bladder emptying before the occurrence of high-pressure, uncoordinated involuntary detrusor contractions. Thus, when patients or clinicians ask about the correct time

Table 1
A simple classification of neurogenic bladder dysfunction[a]

	Condition
Sphincter function	
Too loose	Neurogenic incompetent urethral closure mechanism
Too tight	Detrusor sphincter dyssynergia
Bladder function	
Underactive	Neurogenic detrusor acontractility
Overactive	Neurogenic detrusor overactivity
Injury location	
Above the PMC	Neurogenic detrusor overactivity
Below the PMC and above SMO (S2–4)	Neurogenic detrusor overactivity with detrusor sphincter dyssynergia
At or below SMO (S2–4)	Detrusor acontractility with or without incompetent urethral closure mechanism

Abbreviations: PMC, pontine micturition center; SMO, sacral motor outflow.
[a] Based on the functional model of voiding dysfunction by Wein.[17,18]

interval for the performance of CIC, these individuals should be redirected to think about bladder management in terms of appropriate volume intervals. Volume intervals are best determined through the use of a well-performed urodynamics evaluation.

The urodynamic study should be performed in all individuals with neurogenic bladder dysfunction as soon as stable bladder functioning has been achieved, and again, when there is a change in clinical urologic status.[16] For example, an individual who has been performing CIC for 5 years without complications does not specifically need a new urodynamics test, because the risks of testing (stricture formation, infections) do not justify the small anticipated benefit. On the other hand, individuals with neurogenic bladder dysfunction who report increased rates of UTIs, difficulty catheterizing, leakage between catheterizations, development of new urinary calculi, hydronephrosis, or deterioration in renal function would clearly benefit from a repeat urodynamics test, because the cause of many of these conditions may be improper bladder management.

The urodynamics test involves placement of a urinary catheter and a rectal catheter to simultaneously measure bladder and intra-abdominal pressures.[16] The bladder is then infused with sterile saline at a defined rate to rapidly reproduce the filling-voiding cycle. During the filling phase, the compliance (elasticity) of the bladder can be calculated. Several studies have shown that poor compliance (equivalent to high stiffness) is associated with greater rates of upper tract deterioration and other urologic complications.[19,20] The presence, pressures, and volume at which any involuntary bladder contractions occur are recorded. The voiding phase is analyzed by simultaneously recording the urinary flow rate and the detrusor pressure. These data are then plotted on to various nomograms such as the International Continence Society nomogram. This strategy allows the urodynamicist to determine if the voiding cycle is obstructed (defined as high bladder pressures in the presence of a low urinary flow rate) or unobstructed. The patient's clinical history, pattern of pressure data, and the simultaneous collection of sphincter electromyographic activity and fluoroscopic images helps the urodynamicist determine the likely cause of neurogenic bladder dysfunction. For example, bladder outlet obstruction in a 25-year-old man with complete suprasacral spinal cord injury is likely caused by detrusor sphincter dyssynergia. Similar obstruction in an elderly man without known neurologic disease is most likely caused by benign prostatic hyperplasia.

Based on the results of the urodynamics test in conjunction with recommended annual studies, including upper tract imaging with a renal/bladder ultrasonography and laboratory tests to evaluate bladder function, a plan for bladder management is developed and implemented. Effective implementation of a bladder management plan likely includes a combination of behavioral modification (fluid restriction), pharmacotherapy, and CIC. Pharmacotherapy can be used to help suppress involuntary bladder contractions, increase bladder capacity, and lower bladder pressures. Second-line therapies, including injection of botulinum toxin, can be tried for refractory cases. Surgical diversions are available for the most severely affected individuals. Use of indwelling urinary catheters should be strongly discouraged because of high rates of infections and other severe complications. However, for some individuals, this option is the only available means to achieve bladder emptying.

Catheterization should be timed such that the bladder is emptied before the volume at which high-pressure involuntary contractions develop. A team approach is required, with necessary involvement from nurse educators, clinicians, occupational therapists, social workers, and family members/caregivers.[16] The bladder management plan is continually adjusted based on evolving patient needs and circumstances.

Recurrent UTIs in Individuals with Neurogenic Bladder Dysfunction

We would like to emphasize that many conditions such as recurrent UTIs are best controlled through the implementation of a well-designed bladder management plan. Therefore, patients with neurogenic bladder dysfunction who present with recurrent UTIs should first be treated by attempting to optimize their bladder management. In addition, a search for treatable sources of infection with imaging studies and cystourethroscopy should be implemented to identify treatable causes, including infected calculi, diverticuli, and strictures. However, after all available attempts have been exhausted, patients can be directed to use various preventive strategies, which is comprehensively reviewed in the following sections.

MECHANICAL STRATEGIES FOR UTI PREVENTION AFTER SCI & D

Several mechanical strategies have been developed to prevent UTIs in individuals who use urinary catheters. These strategies include use of sterile technique, closed-system kits, antibiotic-coated catheters, and changing of indwelling catheters on a more frequent basis. The following sections review the evidence for UTI prevention when using these strategies.

Intermittent Catheterization

Intermittent catheterization (IC), or intermittent self-catheterization, has become the standard of care for persons with SCI who have adequate hand function or caregiver support. IC may be performed using sterile technique, but clean technique, referred to as CIC, is more commonly used. IC should be performed every 4 to 6 hours. Persons with SCI & D using IC need to catheterize frequently enough to keep volumes lower than predetermined levels defined by urodynamic studies. Generally, the urodynamic goal is a storage pressure lower than 40 cm H_2O.[21] Future studies are needed to determine what factors influence the rate of UTIs in those who perform CIC.[22]

Catheter reuse

Reuse of catheters for IC is controversial and has never been approved by the US Food and Drug Administration for any catheter type. Many patients and providers argue that there is a theoretic increased infection risk. However, current evidence suggests that reuse after cleansing may be appropriate in certain circumstances.[23] In patients on IC, ascension of bacteria colonizing the urethra into the bladder is more likely to be the source of bacteriuria than introduction of new bacteria.[5] Rinsing with water, air-drying, microwaving, or soaking catheters in various agents are all effective in reducing bacteria on catheters. However, there are no published trials evaluating the effectiveness of any of these cleaning methods in preventing bacteriuria or CAUTI.[5]

Closed-system versus open-system catheters

There is no high-level evidence showing the superiority of sterile versus clean technique for reducing CAUTI. Likewise, evidence has not shown the superiority of closed or self-contained (also called no-touch) IC kits versus sterile technique. Use of the no-touch technique (in which the catheter and preattached collecting system are not touched by the patient) reduces microbial contamination of the catheter.[24] There is some evidence that use of sterile prepackaged catheter collection kits can reduce the frequency of UTIs in SCI.[23,25] However, these kits are expensive and must be justified to payers. They are generally tried only when an individual presents with recurrent UTIs. There is no catheterization technique that can be carried out without any risk of introducing organisms into the urinary tract.[1] It has been shown that most urethral

bacteria exist in the distal 15 mm of the urethra. This finding led to the development of intermittent catheter kits using an introducer tip to bypass the distal urethra, which was shown to decrease UTIs in hospitalized men with SCI & D.[26]

Hydrophilic catheters

Hydrophilic catheters have been developed with the goal of reducing friction and thereby reducing trauma during the catheterization process. De Ridder and colleagues,[27] in a randomized 1-year prospective trial in 2005, found a statistically significant reduction in UTIs with hydrophilic versus noncoated catheters. However, 64% of persons using hydrophilic catheters (vs 82% for noncoated catheters) still had 1 or more UTIs during the study period. Furthermore, there was no significant difference in bleeding, bacteriuria, or pyuria between the 2 groups. Stensballe and colleagues[28] found a reduction in hematuria and pain and higher patient preference for hydrophilic catheters. One study found no difference in the number of symptomatic UTIs versus noncoated catheters.[29] However, a more recent study by the same group[30] found that the use of a hydrophilic catheter reduced the risk of UTI in the acute period and significantly delayed the time to first UTI versus a plastic uncoated catheter. Hydrophilic catheters may also be useful for persons with urethral strictures or discomfort during catheterization.

External Catheters

Bladder management using an external catheter (also referred to as a condom or Texas catheter) is an option for some men with SCI & D. There is no effective equivalent option in common use for women. Some men with SCI & D use an external catheter to collect urine that leaks in between ICs; others use external catheters exclusively. Urodynamic evaluation is indicated to determine important variables such as the detrusor leak point pressure. Procedures to decrease bladder outlet resistance, including transurethral sphincterotomy and urethral stent placement, have been used in men with increased leak point pressures. Men with chronic suprasacral SCI & D using external catheters have more severe bladder trabeculation compared with other methods of bladder management.[31] In addition, it is important to recognize that penile retraction or abdominal obesity can make it difficult or impossible to maintain a proper fit with an external catheter. Furthermore, the use of external catheters does not prevent chronic bacterial colonization and pyuria. Residual urine with pyuria, worsening urinary retention, and hydronephrosis caused by increased pressure and poor emptying are all potential problems with external catheter usage.[32]

Indwelling Catheters

Persons with SCI & D who require indwelling catheters for long-term bladder management may nonetheless benefit from the addition of antimuscarinic medication. Use of the antimuscarinic oxybutynin in persons with SCI & D and chronic indwelling catheters has been associated with better bladder compliance and less hydronephrosis.[33] Suprapubic indwelling catheters may be used to decrease the risk of urethral trauma associated with indwelling catheters. As reviewed by Feifer and colleagues,[34] early studies evaluating the use of suprapubic catheters "…reported accelerated renal deterioration and lower urinary tract complications, including stones, recurrent infections and blocked catheters. Procedural complications were generally rare. In contrast, recent investigations, in which patients were managed with anticholinergic medications, frequent catheter changes and bladder washing, and volume maintenance procedures demonstrated similar morbidity profiles to CIC.[34]"

Silver-coated and antibiotic-coated catheters

Recently, new catheters coated with silver or antibiotics have been developed to potentially reduce the CAUTIs. A large multicenter trial[35] evaluating short-term use of antimicrobial catheters in hospitalized adults did not find evidence to support their routine use. Neither silver-coated nor nitrofural-coated catheters produced clinically significant reductions in CAUTI in a randomized trial of hospitalized adults. Numerous others have assessed silver-coated or nitrofurazone-coated catheters, some finding short-term reductions in bacteriuria or CAUTI.[36] However, long-term evidence is lacking.

Bladder irrigation

Irrigation is commonly performed by persons with SCI & D who use chronic indwelling catheters for long-term bladder management. In addition, bladder irrigation with antimicrobial agents is sometimes used for persons on IC. However, current guidelines do not recommend routine use of this practice, because evidence is lacking for reduction in CAUTI,[5] and the practice of irrigation may itself increase the risk of CAUTI. No difference in effectiveness has been found between saline and other irrigants, including antibiotic solutions, at reducing bacteriuria.[37] Irrigation solutions in general are not believed to be effective in eliminating bacteriuria.[38]

Fluid Restriction

Fluid management for persons with neurogenic bladder dysfunction can be a challenge. Fluid restrictions of 2 L per day are often used for persons using IC. In addition, persons may need to restrict fluid intake before bedtime. Many persons need to catheterize 1 or more times during the night, especially if a significant postural diuresis occurs. Complicating fluid management further is the dry mouth that may occur with antimuscarinic medications used routinely to improve urine storage capacity. There are no studies specifically evaluating optimal fluid intake in persons with SCI & D.

MEDICAL STRATEGIES FOR UTI PREVENTION AFTER SCI & D

Medical strategies for the prevention of UTIs in individuals with SCI & D have been largely unsuccessful. Therefore, identification of novel agents that can successfully reduce rates of UTIs in individuals with SCI & D is a critical clinical and research objective. The following section reviews the evidence for UTI prevention when using these strategies.

Antibiotic Prophylaxis

Antibiotics are not indicated unless signs or symptoms of illness are present. Signs of systemic illness or sepsis are obvious indications for treatment. Other signs such as changes in the degree of spasticity may or may not indicate a need for antimicrobial therapy. Furthermore, improvement of symptoms after antibiotic treatment does not necessarily correlate with permanent eradication of the infecting organism. Reid[39] reported persistence of antibody labeled bacteria in the bladders of persons with SCI & D on antibiotic therapy.

Use of antibiotic prophylaxis, which is often successful in individuals without neurogenic bladder dysfunction, is less effective in the population with SCI & D. This situation may be because of rapid recolonization and development of bacterial resistance. In addition, non–antibiotic-based medical therapies, including methenamine salts (mandelate or hippurate), have also been unsuccessful. Individuals with SCI & D who use urinary catheters have high rates of bacterial colonization that occur within

30 days of initial catheterization and return to baseline levels after discontinuation of antibiotic therapy.[1] Therefore, follow-up urine cultures are usually unhelpful.

Nonantibiotic Prophylaxis

A multitude of over-the-counter and prescription products exist for prevention or treatment of UTIs (**Table 2**). Many of these products are poorly studied, studied in limited populations, or have been studied with mostly negative or conflicting results. The wide variety of agents attests to the scope of UTIs as a public health problem.

Cranberry

Cranberry products have been shown to reduce the ability of bacteria to adhere to the urinary tract walls. Results with standard cranberry preparations have been mixed. In the largest study to date, Lee and colleagues[40] found no benefit of oral cranberry capsules, methenamine hippurate, or the combination in preventing UTIs. Because of a lack of evidence to support the addition of urinary acidification, it was not used in the study. Hess and colleagues[41] reported benefits in reduction of UTI in 47 patients with SCI & D for any given month while on cranberry over a 6-month period. However, almost 75% of this group used external/condom catheters as their primary method of bladder drainage, making results difficult to interpret. Linsenmeyer and colleagues,[42] in a 4-week study, found no difference in bacteria or leukocyte counts for patients with SCI & D randomized to cranberry supplementation compared with placebo.

Table 2
Nonantibiotic agents used for prevention of bladder infection

Agent	Level I Evidence?
Ascorbic acid	No
Cranberry compounds (*Vaccinium macrocarpon*)	Yes (1b)
Concentrated proanthocyanidins (ellura [Trophikos, LLC Atlanta, GA])	Yes (1b)
Cran-Actin (ascorbic acid, D-mannose, cranberry) (Solaray, Neutraceutical International Corp, Park City, UT)	No
D-Mannose	Yes (1b)
Hyophen (Star Pharmaceuticals, Stellar Biopharma, East Brunswick, NJ)[a,b]	No
Methenamine hippurate/mandelate	No
Methylene blue	No
Herbals	No
Green tea extract (*Camellia sinensis*)	No
Probiotics	No
Lactobacillus spp	No
Bacterial interference	Yes (1b)
Nonpathogenic *Escherichia coli*	Yes (1b)
OM-89 (immunostimulant)	Yes (1b)
Intravesical irrigation/installation	No
Heparin, gentamycin, neomycin, acetic acid, saline	No

[a] Contains: methenamine hippurate, benzoic acid, phenyl salicylate, methylene blue, hyoscyamine sulfate.
[b] Also known as: Atrosept, Cystemms-V, Darcalma, Darpaz, Dolsed, Hyophen, MHP-A, MSP-Blu, Phosenamine, Phosphasal, Prosed DS, Prosed EC, Trac Tabs 2x, UR N-C, Urapine, Urelle, Uretron, Uretron DS, Uribel, Urimar-T, Urimax, Urin D/S, Urised, UriSym, Uritact DS, Uritact-EC, Uritin, Uro Blue, Usept, Ustell, Uta, UTICAP, Utira, Utira-C, Utrona, Utrona-C.

Jepson and Craig, in a Cochrane review published in 2008, reported that "there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. Its effectiveness for other groups was less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable as a long-term treatment option. However, properly designed studies with relevant outcomes are needed.[43]" The investigators concluded that cranberry products cannot be recommended for prevention of recurrent UTIs. More recently, a cranberry supplement with a higher concentration of the presumed active ingredient, proanthocyanidins, has shown efficacy in women.[44] Studies in SCI & D have not been completed, but we are currently conducting a clinical trial evaluating the effects of a standard-dose proanthocyanidin compound, available as an oral supplement called ellura (Trophikos, LLC Atlanta, GA), on both bacteriuria and pyuria in the SCI & D population.

The in vitro effects of cranberry proanthocyanidins in the prevention of adhesion by P-fimbriated uropathogenic *Escherichia coli* are well described. Specifically, a dose-response relationship between proanthocyanidins and a decrease in bacterial virulence has been established.[45,46] However, only a few in vivo trials have examined the use of cranberry ingredients to reduce the recurrence of UTIs in patients in the general population over an extended period.[44,47,48] Comparisons are difficult to make because of the lack of characterization of the supplements used and nonstandardized amount of proanthocyanidins present in the treatments.

D-Mannose

Products containing D-mannose alone or in combination with cranberry based compounds (eg, Cran-Actin [Solaray, Neutraceutical International Corp, Park City, UT]) are in frequent use. Kranjcec and colleagues found a lower risk of recurrent UTIs in women taking D-mannose powder (15%) or nitrofurantoin (20%) versus no prophylaxis (60%) during a 6-month period.[49,50] In addition, the D-mannose group had significantly fewer side effects. Women with interstitial cystitis, diabetes, urinary tract anomalies, or those taking hormone therapy were excluded. We found no studies of D-mannose specifically in persons with SCI & D.

Methenamine

Kevorkian and colleagues[51] found a lower occurrence of UTI in a small group of persons with SCI & D taking methenamine plus urinary acidification with ammonium chloride versus no treatment. As mentioned earlier, Lee and colleagues[40] found no effect of methenamine alone. There are also a variety of prescription products containing methenamine mandelate or hippurate combined with methylene blue, salicylates, and urinary acidifiers (benzoic acid) or pH buffers (sodium phosphate). Whether these cocktail formulations have superior efficacy is not known, because these agents are not well studied. Recent CAUTI guidelines state that methenamine salts should not be used routinely for prevention, but when used, urinary pH should be maintained lower than 6.0.[5]

Bacterial interference

Darouiche and colleagues,[52,53] in 2 separate prospective studies, have found that persons whose bladders were colonized with *E coli* 83972 are significantly less likely to develop a UTI during follow-up. Beereport and colleagues[54] performed a recent review and meta-analysis of randomized controlled trials of nonantibiotic prophylaxis for adults with recurrent UTIs. These investigators evaluated the efficacy, safety, and tolerability of available agents. Seventeen studies met criteria for analysis. The oral immunostimulant OM-89 decreased the rate of UTI recurrence, with a good safety

profile. However, there are no specific studies of this agent, which is derived from heat-killed *E coli* serotypes, in persons with neurogenic bladder dysfunction. These investigators' meta-analysis also reported efficacy for cranberry in reducing UTI recurrence in 2 studies.

SUMMARY

There is no broadly applied equipment, medication, or management strategy that has been successful in reducing UTIs to zero or near-zero levels in a population of persons with SCI & D. The incidence of UTIs and recurrent UTIs in persons with SCI & D remains at high levels. Further research and development of nonantimicrobial agents, as well as treatments to normalize function, are important to reduce the impact of this important problem.

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