Special Article

Catheter-associated urinary tract infections in persons with neurogenic bladders

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Abstract: This review is based on the author's Donald Munro Lecture given at the annual conference of the Academy of Spinal Cord Injury Professionals in New Orleans, LA. Indwelling catheters play an important role in bladder management following SCI for many individuals with neurogenic bladders. There is an increased risk of UTI compared to other types of bladder management with indwelling urethral catheters but not SP catheters. To minimize the risk of symptomatic UTI, the following steps are essential: prevent bladder wall distention and resulting ischemia, maintain colonization with “good” bacteria, and prevent bladder stones. For individuals with recurrent symptomatic UTIs, try to change the environment, prevent bladder over distention, and make sure the bladder is “quiet” by using strategies such as adequate dosages of anticholinergics, onabotulinum toxin A, and preventing catheter blockage. Bacterial colonization of the bladder is common. However, bacterial colonization may have a positive effect by inhibition of colonization of pathogenic bacteria. Judicious use of antibiotics is important since antibiotics hasten the evolution of more resistant organisms. Potential prevention and treatment strategies include killing the offending organisms, changing the environment (such as urinary acidification), and modifying virulence factors and the bacterial microbiome.

Keywords: Catheter associated UTI (CAUTI), SCI, Urinary catheters, Microbiome, Neurogenic bladder

Introduction

The origins for today's standards of care stem from the efforts of pioneers in the care of veterans with spinal cord injury. This article is based on the annual lecture that memorializes Donald Munro, MD, who served as a surgeon in the Army Medical Corps in France during World War I. After the war, he joined the surgical staff of Boston City Hospital where he specialized in neurosurgery. His small unit became the model for spinal cord injury (SCI) care in the United States. Munro's work influenced the Veterans Administration to establish a national network of SCI Centers to care for wounded soldiers. His practices formed the basis for multidisciplinary, holistic care for people with SCI and inspired other dedicated pioneers, including Drs. Ernest Bors, Estin Comarr, John Young and Erich Krueger. It has been said that Dr. Munro is “best

remembered as a pioneer in optimism” for people with a condition long considered hopeless.¹

During World War I, 80% of individuals with SCI died of acute kidney infections, specifically acute pyelonephritis. With the increased availability of antibiotics, this number dropped considerably. However, in 1977, renal disease was still the major cause of death (43%) in the population with SCI.² This complication declined as clinicians learned that high bladder pressures cause poor kidney drainage, which led to closer urological monitoring and the use of anticholinergic medications to help quiet the bladder.

By 1995, pneumonia and influenza were the primary cause of death (17.7%), followed by non-ischemic heart disease (16.5%), and septicemia (12%).³ However, urinary tract infections (UTIs) are still the most common infections in persons with SCI; the frequency of UTI is approximately 2.5 infections per patient per year.⁴

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Individuals with significant disabilities are now able to be much more active due to improvements in medical care, inpatient and outpatient rehabilitation programs, accessibility, and adaptive devices. This increased independence has created an increased demand for indwelling catheters as a method of bladder management. Although this method enables people to be more active, UTIs continue to be a significant concern. This review examines the factors involved in catheter associated urinary tract infections (CAUTI), specifically in the SCI population.

Etiology of UTI

The most common cause of UTI is bladder wall ischemia and mucosal disruption from bladder wall over distention. This was well described by Dr. Lapides in 1972: "Blood flow to the bladder can be reduced by increased intravesical pressures and/or by over distention of the organ. The resulting ischemic bladder tissue is then prey to invading gram-negative organisms from the patient's own gut. Avoiding high intraluminal pressures and over distention is the key to prevention of urinary tract infections."⁵

Studies have shown that bladder distention and bladder contractions can cause decreased blood flow and resulting ischemia to the bladder wall. In addition to decreased blood flow, acute over distention of the bladder wall can cause mucosal tears, which facilitates the ability of the bacteria that have colonized the bladder to invade the submucosal bladder wall and start a UTI. Another problem caused by chronic ischemia of the bladder wall is replacement of normal muscle fibers with scar tissue (collagen), causing further bladder wall trabeculation. Trabeculation decreases the ability of the bladder wall to stretch (poor bladder wall compliance), which in turn, can exacerbate bladder wall ischemia with bladder distention.

For individuals on intermittent catheterization, the most common reason for bladder wall overdistention and resulting ischemia is a large fluid intake combined with infrequent bladder catheterizations. The risk is higher for people with overactive bladders and/or poor bladder wall compliance, since these contribute to high bladder pressures. This in turn, increases the bladder wall ischemia. With indwelling catheters, anything that obstructs catheter drainage can cause bladder overdistention. Common causes include kinked catheter tubing, overfilled leg bag, or slow drainage or obstruction from catheter encrustation or stones. Therefore, prevention strategies for UTIs need to focus on preventing over distension and forceful

bladder contractions that can cause bladder wall ischemia.

This concept is reflected in the recommendations of the Consortium for SCI Medicine Bladder Management Guideline, which states that one should "consider the use of anticholinergic medications in individuals with suprasacral lesions using chronic indwelling catheterization." The guideline also notes that for those on intermittent catheterization, "Bladder capacity can be increased and uninhibited contractions can be decreased with the use of anticholinergic medications or with botulinum toxin injections."⁶

Studies also suggest that treating an overactive bladder with injections of onabotulinum toxin A (Botox) will decrease UTIs. In one study of persons with neurogenic bladders, the UTI rate was evaluated for 6 months before and for 6 months post-Botox injections. The UTI rate declined from 1.75 per person to 0.2 per person at 6 months ($P=0.003$), a significant decrease.⁷ Two other studies showed that bladder wall histology improved after treatment with botulinum toxin A, presumably due to the decreased force and frequency of involuntary bladder contractions and improved blood flow through the bladder wall. In one study, patients undergoing Botox injections had significantly less fibrosis of the bladder ($P < 0.00073$) compared to those who did not have Botox injections.⁸ In another study, individuals given Botox injections over a 6-year period had improved bladder wall compliance on urodynamics and decreased bladder wall fibrosis.⁹

Bladder management

Intermittent and indwelling catheters

The majority of individuals with SCI who have neurogenic bladders are managed with either intermittent catheterization or indwelling catheters. Intermittent catheterization (IC) is considered to be the gold standard in bladder management for SCI. However, there are reasons why IC may not be the recommended method of bladder management. Some of the SCI Medicine Consortium recommendations for "considering avoiding intermittent catheterization" include:

- Inability to independently catheterize due to poor hand function
- Lack of a willing caregiver to perform catheterization
- Abnormal urethral anatomy (false passage)
- Bladder capacity less than 200 ml
- High fluid intake regimen (e.g., receiving intravenous fluids)⁶

The inability to self-catheterize is associated with problems that often affect quality of life. A family member (husband, wife, parents or significant other)

suddenly becomes the caregiver. There is a loss of independence for both the person with SCI and caregiver, as well as guilt or blame if the person develops a UTI. Individuals with SCI at T6 and above are at risk for developing autonomic dysreflexia from a distended bladder, which has the potential of causing life threatening hypertension if no one is available to immediately drain the bladder.

Indwelling catheters

Several studies have looked at how well indwelling catheters are tolerated compared to intermittent catheterization. One study found that at 30 years post injury, only 20% of those who were on intermittent catheterization initially were still using intermittent catheterization; 80 percent had switched to another method of bladder management. This same study found that at 30 years post-injury, 70% of those who started with an indwelling catheter were still using an indwelling catheter. Another study found that 80% of patients with tetraplegia preferred an indwelling catheter to other types of bladder management for social and practical reasons.^{10,11}

Indwelling catheter complications

The true incidence of complications from indwelling catheters is not known. Retrospective chart reviews make it difficult to determine whether the catheter caused the described complication, or whether the catheter was inserted as “a last resort” because the person had a complication.¹² Complications due to bladder stones, decreased bladder capacity, and UTI (for indwelling urethral catheter) are more common with indwelling catheters compared to other types of bladder management.^{13,14}

There are few studies comparing the incidence of UTI with various types of bladder management. One prospective study did compare the incidence of UTI among people with normal voiding and those using suprapubic tubes, clean intermittent catheterization, or reflex voiding (with an external condom catheter in place and male indwelling catheter). The incidence of UTI was expressed as number episodes per 100 patients daily or person-days. The incidence for normal voiding was 0.06; for female suprapubic catheterization, 0.34; for clean intermittent catheterization, 0.41; for external condom catheter, 0.36; and for male indwelling urethral catheter, 2.72. The incidence of UTI with indwelling urethral catheters was twice as high as for other types of management, emphasizing the importance of careful catheter management and judicious use of antibiotics in these individuals.¹⁵

Defining UTIs: Symptomatic versus asymptomatic

When considering evaluation and treatment of UTIs in those with neurogenic bladders, it is important to be familiar with the two types of UTIs discussed in the literature: asymptomatic and symptomatic.

An asymptomatic UTI is not a true infection, but rather colonization of the bladder with organisms. Asymptomatic UTI may be defined by the following criteria: No symptoms and initial counts of 10^2 cfu /mL or higher (except for indwelling catheters). With indwelling catheters, any detectable bacteria is considered colonization of the bladder. Bladder colonization may actually provide a protective role to the bladder flora as will be discussed later (Table 1).^{16,17}

The definition of a “symptomatic” UTI for those with SCI has received consensus from two groups.^{18,19} The criteria for a “true” symptomatic UTI are: 1. Increased bacterial urine colony counts, 2. Increased WBCs in the urine (pyuria), and 3. New onset of symptoms. These may include typical symptoms such as cloudy, malodorous urine, discomfort or pain over the bladder or kidney areas, dysuria, malaise, fever, lethargy or general feeling of “unwellness”, increased incontinence, or symptoms specific to the population with SCI such as increased spasticity or autonomic dysreflexia (Table 1). Regarding symptoms, a study by Massa *et al.* reported that overall, “cloudy urine” had the highest accuracy (83.1%), and “leukocytes in the urine” had the highest sensitivity (82.8%) for UTI in those with SCI. The highest specificity was for “fever” (99.0%); however, the sensitivity was very low (6.9%).²⁰

Fever is rare in patients with bladder infections.²⁰ Therefore, when a person with SCI presents with a fever, other sources for infection should be carefully investigated before assuming the cause is a bladder infection. The following case is illustrative. An

Table 1 Symptomatic versus asymptomatic UTI.

Definition – Asymptomatic Bacterial Colonization in Those with Neurogenic Bladders^{16,17}

- No symptoms, and ...
- Initial colony counts of 10^2 cfu /mL or higher (in all but indwelling catheters)
- For individuals with indwelling catheters, any detectable bacteria

Definition - “Symptomatic” UTI – with Neurogenic Bladders^{18,19}

- Increased colony counts
- Increased WBCs
- Symptoms (new onset) – such as cloudy urine with odor, discomfort or pain over the bladder or kidney areas, dysuria, increased incontinence, increased spasticity, malaise, fever, lethargy or general feeling of “unwellness”, autonomic dysreflexia

individual with complete paraplegia for many years called in from home complaining of a high fever, which he felt was caused by a UTI. He reported he felt too sick to come in and could we just call in some “Cipro” to his pharmacy? He was told that it was important he come in for an evaluation. Later, he called from the parking lot saying he felt too sick to come into the clinic. Could we come out to the car to get the urine sample? We went to his car. He had a fever of 102°F, tachycardia, and profuse sweating. We sent him immediately to the emergency room, where he underwent an evaluation and emergency surgery for acute appendicitis. The ‘take-home’ point is that is important to evaluate patients who complain of a UTI, particularly if they have fever.

Predicting presence of UTI

Over a 9-month period, we prospectively evaluated 147 individuals with SCI who came to the urology clinic because they felt they had a UTI. Individuals were divided into two groups: at or above T6 and below T6. Based on urine samples and evaluations, the accuracy of self-predicting a UTI was 61%; 39% were not accurate at predicting they had a UTI, regardless of the level of their injury.²¹ Similar findings were found in another study. The question was asked, “How certain are you that you do or do not have a UTI?” The overall accuracy for individuals who felt they had a UTI was 66.2%. However, among those who did not feel they had a UTI, 82.8% were correct. In other words, participants were much better at predicting when they did not have a UTI than when they did have a UTI.²⁰

In addition to having difficulty predicting when a person has a UTI, there is often confusion about the difference between colonization (asymptomatic infection) and a symptomatic infection in individuals with neurogenic bladder. The following case is illustrative. A 56 year-old woman with a C-5 SCI and an indwelling catheter presented for her annual evaluation. “I have this PICC (peripherally inserted central catheter) line in because my doctor told me I have had a bladder infection for 6 months that keeps recurring despite several courses with oral antibiotics. Now the bacteria are resistant to oral antibiotics, so my doctor is going to try to eradicate my bladder infection with 2 weeks of (intravenous) IV antibiotics.” When asked, “What kind of symptoms have you had?” she replied “I haven’t had any symptoms. I feel fine.” The “take-home” point is the need to continue to educate both consumers, and more importantly, health care providers, that bacteriuria is expected in individuals with SCI and does not require

treatment unless there are symptoms (or risk for stone formation).

Colonization – friend or foe?

An article on the topic of bacterial skin colonization stated: “A new hypothesis is that skin microbes directly benefit the host and rarely exhibit pathogenicity.” For example, *Staphylococcus epidermidis*, which comprises approximately 90% of the resident flora, was found to down-regulate virulence factors and affect signaling of competing bacteria (such as *Staphylococcus aureus*), ultimately leading to colonization inhibition. The by-products of *Pseudomonas aeruginosa* have such potent antibacterial activity that several have been turned into commercial products. Pseudomonic acid A (mupirocin) is an effective topical antibiotic used to treat *S. aureus* and streptococcal pathogens. *Pseudomonas aeruginosa* has also been found to suppress fungal growth.^{22,23} Like on skin, future studies may show that bacteria colonized in the bladder also provide a protective role in preventing more pathogenic bacteria or other organisms such as yeast to also colonize the bladder.

Impact of antibiotics on bowel flora

Antibiotics are known to affect the gastrointestinal (GI) flora. One study carefully evaluated the distal gut microbiota of three individuals over a 10-month period that spanned 2 courses of ciprofloxacin. The study involved analyzing more than 1.7 million bacterial 16S rRNA sequences from 52 to 56 samples per subject. Day-to-day variability occurred but the average community composition was stable over several months in the absence of antibiotics. The effect of ciprofloxacin on the gut microbiota was profound and rapid, with a loss of diversity and a shift in community composition occurring within 3 to 4 days of drug initiation. By one week after the end of each course, communities began to return to their initial state, but the return was often incomplete. In all subjects, the composition of the gut microbiota stabilized by the end of the experiment, but was altered from its initial state. The conclusion was that antibiotic use may cause a shift to an alternative stable state, the full consequences of which remain unknown.²⁴

Human microbiome project

A study that has provided considerable insight regarding colonization is the Human Microbiome Project (HMP), an 8-year \$194 million trans-National Institutes of Health (NIH) initiative to characterize the normal microbiota of 250 healthy adults in a Western population. Samples were obtained from five body sites in women, and four sites in men (the GI tract, the

mouth, the skin, the nasal cavity, and the vagina) In addition to cultures, 16S rRNA gene sequencing was performed on samples from the body sites. A human microbiome was defined as the collective microbial community (bacteria, viruses, molds, fungi) that reside in/on a person.²⁵

The HMP yielded a number of new findings. For example, individuals have 10 times as many bacterial cells as their own human cells. However, because of their small size, microorganisms make up only about 1 to 3 percent of our body mass (that's 2 to 6 pounds of bacteria in an adult). As we learn more about the human microbiota, we are finding out that it plays a number of extremely important roles.²⁶ For example, bowel microbiota break down food for more efficient extraction of nutrients, prime the body's immune system, produce local antibiotics, help with fat breakdown in the GI tract (biligenic bacteria), produce neurotransmitters, and can even affect anxiety levels (animal studies). Therefore, it is important to avoid disrupting a person's microbiome as much as possible.²⁷

The traditional thought is that we all are colonized with similar organisms and therefore should have similar responses to treatment strategies. However, the HMP also revealed that each of us has a unique microbiome. Among individuals, there are vastly different types and abundance of organisms.²⁸

When using a certain strategy in an attempt to reduce the incidence of UTI (e.g., cranberry extract, Lactobacillus, methenamine), it is not uncommon for some individuals to report that an intervention works beautifully and others to say it is ineffective. For example, consumer reviews on Amazon.com of a commonly used Lactobacillus supplement contained a variety of comments, including: "The best probiotic on the market"; "Not sure it works"; "Excellent product!"; "It didn't work for me"; "After 2 days, it made me bloated and gave me stomach cramps."²⁹

The HMP helps explain the differences in opinions and results from various products. It also helps to explain why some individuals may be more susceptible to infections than others, why some treatments are more effective in some individuals than in others, and why a "universal" treatment to treat a microbiome or bacterial biofilm may not be practical.

Traditional thought – urine is sterile

The HMP did not evaluate urine samples. One reason may be that the traditional thought is that urine is sterile. This is based on standard urine culture protocols in which urine is plated aerobically at 35–37°C for 18–24 hours and then inspected for bacterial growth and

reported as "growth, or no growth". These urine cultures are designed to detect organisms that are fast growing (24-hour urine growth).³⁰ However, in a recent study, 65 urine specimens (41 from those with overactive bladders and 24 controls) were evaluated using standard urine cultures and more detailed expanded quantitative urine cultures. Urine specimens were plated and incubated in anaerobic conditions for 48 hours and aerobically at 35°C for 5 days. If growth was visually detected, samples were then plated and incubated aerobically and anaerobically for an additional 48 hours, and genomic DNA was extracted using previously validated protocols. Using the standard urine culture protocol, 92% were reported as *no growth* at 10³ cfu/ml. Using expanded quantitative urine cultures, 80% grew bacterial species. In the 65 urine samples, 35 different genera and 85 different species were identified. This study showed that urine is not sterile. Regarding the question, bacterial colonization - friend or foe? - it was found that organisms/microbiota differed between the overactive bladder group and the control group. Therefore, just as on the skin and in the bowel, bladder colonization may actually play a number of roles, both positive and negative, in many more ways than we are aware.³¹

Treatment strategies

In discussing treatment strategies, a useful analogy would be an apple tree that has become infected with a fungal pathogen called cedar apple rust (*Gymnosporangium juniperi-virginianae*). This fungus has a somewhat complicated life cycle in that it also requires juniper plants. In the spring, apple blossoms and small leaves first appear. Also during spring's rainy weather, spore horns develop on infected junipers. Spores spread via wind and rain to the leaves of apple trees. As the summer progresses, trees infected with the cedar apple rust fungus begin to develop small yellow orange spots on the leaves, which on closer inspection are small growths filled with spores. These growths are called "cedar apple rust". Over time, the infestation increases and weakens the tree.³²

Several strategies could be used to help control this problem. The first would be to kill the offending organism on the apple tree leaves with a fungicide. Another would be to change the environment by removing the juniper plants, and the third would be to strengthen the host with optimal pruning and fertilizers.

In the same way, one or more strategies may be used to manage UTIs in SCI. The most common way would be to kill the offending organism with antibiotics. Another way would be to change the environment of

the bladder microbiome. Some of the possible interventions to change the environment may involve prophylactic administration of probiotics, acidification of the urine (using methenamine hippurate) or bacterial interference (replacing the colonized bacteria with different bacteria). A third strategy would be to strengthen the host. Some possible interventions to strengthen the host would be to minimize urinary retention and optimize voiding by correcting anatomical problems such as urethral strictures, removing sources of infection such as bladder stones, prescribing pre biotics and probiotics, reducing bacterial adhesion to the bladder wall with agents such as cranberry extract and D-mannose (which may inhibit the formation of bacterial biofilm), and methods to strengthen the individual's overall immune system. Many of these other strategies are still investigational. Potential research areas are outlined in Table 4.

Considerations for antibiotic strategies

When a person presents with a possible UTI and a urine sample is obtained, the first question is whether to begin empiric treatment with antibiotics or wait for the culture results. There are a number of considerations such as duration of symptoms (acute or chronic), the level of injury (risk for autonomic dysreflexia), history of allergy to antibiotics, and past history of febrile episodes with UTI (suggesting vesicoureteral reflux). In a prospective study, 265 individuals with UTIs initially received empiric antibiotic therapy. As soon as culture results were available, they were randomly placed on culture-specific therapy or kept on the empiric antibiotic therapy. At one week, 82% of those on culture-specific antibiotics had no recurrent symptoms and 79% of those on empiric antibiotics had no recurrent UTIs (no statistical significance). However, at one-month follow up, 73% of those on culture-specific antibiotics had no recurrence vs. 58% of those on empiric antibiotic therapy (a trend towards less recurrent UTI with culture – specific antibiotics, but still not statistically significant).³³ This study suggests closer follow up may be warranted for those who are placed on empiric antibiotics.

Another issue that commonly occurs in those with neurogenic bladders is the presence of multiple organisms. In a recent study, it was found that this was particularly true in those with indwelling catheters. In this study, ≥ 2 organisms were found in 14.3% of the IC group, 71% of the indwelling urethral catheters group, and 67% of the suprapubic catheters group.³⁴ Not knowing which bacteria are causing the symptomatic UTI, more than one antibiotic may be needed

depending on the clinical signs and symptoms and the culture and sensitivities.

Another important consideration when treating a bladder infection is the possibility of a bladder stone, especially in the presence of an indwelling catheter. The likelihood of a bladder or kidney stone is greater if the urine culture is positive for urease-producing bacteria (e.g., *Proteus*), in persons with persistent UTIs with alkaline urine, or when there is blockage or encrustation of the catheter. Most of these stones are composed of magnesium ammonium phosphate (most common) or calcium phosphate (second most common). When a stone is suspected, the workup should include cystoscopy and imaging of the upper urinary tracts. The urease-producing bacteria cannot be completely eradicated until the individual is free of stones.

In summary, antibiotics do play a key role in treating UTIs; however, the possibility of a bladder stone needs to be considered, particularly in those with an indwelling catheter. It is also important to keep in mind the person's microbiome and to use antibiotics judiciously (Table 2).

Role of prophylactic antibiotics

There is a strong consensus that prophylactic antibiotics should not be used in individuals with an indwelling catheter.^{35–38} This is due in part to the fact that bacteria can quickly develop a protective biofilm making the prophylactic antibiotic less effective, which promotes a change in the microbiome to bacteria with increased antibiotic resistance. There is less consensus on the use of prophylactic antibiotics in individuals without a catheter. Meta-analysis of 15 trials by Morton *et al.* showed that the incidence of symptomatic infections did not significantly change with prophylactic use of antibiotics, but asymptomatic bacteriuria was reduced. Additionally, a twofold increase in antibiotic resistance was noted.³⁸ Also of concern is that the urine culture may show “no growth” despite bacteria in the urine, because of the high concentration of the prophylactic antibiotic.

Table 2 Antibiotic treatment considerations.

- Antibiotic treatment – use a short course of a culture specific antibiotic
- Consider probiotics while on antibiotics
- Consider not obtaining a post treatment urine for C&S (unless still with symptoms or a stone forming organism)
- Post treatment (and routine catheter change) urine cultures will likely be positive for bacteria and may encourage health care providers to prescribe more antibiotics.

Table 3 Potential CAUTI research areas.

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- Newer types and classes of antibiotics
 - Ways to augment the effectiveness of current antibiotics
 - Manipulate the microbiome /Change the environment
 - Bacterial interference
 - Acidify the urine?
 - Ways to change the host biome (strengthen the host)
–reintroduce beneficial organisms (lactobacilli), recolonize with a more friendly (less virulent) organism
 - Ways to modify a bacteria's virulence factors (such as less adhesiveness of the pili, less effective biofilm) RATHER than "trying to eradicate the bacteria" with antibiotics (and building up resistance)
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Table 4 Steps of biofilm formation in catheters.⁴⁸

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- Reversible attachment of platonic bacteria to the catheter surface
 - Host proteins adhere to the catheter surface to make a "conditioning layer"
 - Irreversible attachment of bacteria to host proteins
 - Bacteria produce mucopolysaccharide coating to establish a biofilm
 - The biofilm then protects bacteria from host defenses and antibiotics,
 - Bacterial shedding (detachment) to create an expanding biofilm
-

Future directions

Currently, no single preventative agent has been identified as a gold standard therapy. More research is needed (Table 3). One alternative to developing new antibiotics may be to augment the effect of antibiotics that are currently in use. The proteolytic enzyme bromelain (from pineapple) and trypsin may enhance the effectiveness of antibiotics. In a double-blind trial, people with UTIs received antibiotics plus either bromelain/trypsin in combination (400 mg per day for 2 days) or a placebo. Of the participants who received the enzymes, 100% had resolution of their infections, compared with only 46% of those given the placebo.³⁹

Strategies to change the environment

One way to attempt to prevent recurrent UTIs in a person who is colonized with bacteria is to change the environment of the urinary tract. Acidifying the urine with methenamine has been described; however, reviews have been mixed. In one study, 39 patients with SCI who were on ICP were randomized into 2 groups - with and without methenamine prophylaxis. In the methenamine group, UTI occurred in 9/17 (53%) vs. 19/22 (86%) in the placebo group, a difference that was statistically significant ($P = 0.02$).⁴⁰

Another placebo-controlled study looked at 305 people with SCI with neurogenic bladder and stable bladder management, who were randomized to receive either methenamine hippurate 1 gram twice daily or cranberry extract 800 mg twice daily. The main outcome measure was the time to occurrence of a symptomatic UTI. Multivariate analysis revealed that patients randomized to methenamine did not have a significantly longer UTI-free period compared to placebo (HR 0.96, 95% CI: 0.68–1.35, $P = 0.75$). Patients randomized to cranberry extract likewise did not have significantly longer UTI-free periods compared to placebo (HR 0.93, 95% CI: 0.67–1.31, $P = 0.70$).⁴¹ In the author's experience, methenamine works well for those with recurrent UTI, but not as a "universal" treatment for everyone. This supports the idea that methenamine hippurate changes the environment in those with recurrent UTI. However, if a person already has a microbiome that does not predispose to recurrent UTIs, there is no need to use methenamine hippurate to change the environment/microbiome. It also explains why there are conflicting papers on the effectiveness of methenamine on preventing UTI if "all comers" were included in the study rather than just those with recurrent UTI.

Another preventive strategy that is being investigated is known as bacterial interference, using one type of bacteria to block colonization by another type of bacteria. In one study, bladders of 17 patients with SCI were inoculated with "friendly" *E. coli* HU2117. There were 10 in the placebo control group. At one-year follow up, it was found that 30% of the inoculated group had > 1 symptomatic UTI. However, 70% of controls had > 1 UTI over one year. Therefore, it was concluded that colonization reduced symptomatic UTI. However, this study had several limitations. The first was that a 3-day intensive inoculation cycle (clamped for one hour, repeated once×3 days) was required to colonize the bladder. Even with this inoculation program, the colonization rate was only 37%. The group is now investigating the use of bacteria-impregnated catheters as a method to colonize the bladder.⁴²

While these were promising results, this study emphasizes that further research is needed. Specifically, there is a need for better techniques to colonize the bladder and for bacteria that are more suitable for bladder wall colonization. The authors report that they are working on ways to colonize (create a biofilm) on the catheter rather than inoculating by bladder instillation.⁴²

Strategies to strengthen the host

Rather than trying to eradicate an organism, an alternative strategy is to strengthen the host. A

careful urological evaluation may reveal potentially reversible causes predisposing to urinary tract infections such as urinary retention, high voiding pressures due to detrusor sphincter dyssynergia or urethral strictures, or bladder or kidney stones. More research is needed with regards to the effects of probiotics, blocking bacterial adhesion to the bladder urothelium, inhibiting the formation of the bacterial biofilm and strengthening the immune system.

Prebiotics/probiotics

Research on the use of prebiotics (specialized plant fiber that beneficially nourishes the good bacteria already in the large bowel or colon) and probiotics to specifically inhibit urinary tract infections is limited. However, one study did show the potential effectiveness of probiotics. It was found that in menopausal women, the microbiota changes and lactobacilli are replaced by other communities, such as uropathogenic *Escherichia coli* (UPEC), which cause more than 85% of UTIs. Another study found that *Lactobacillus* supplementation was effective at decreasing UTIs in post-menopausal women.⁴³

Blocking adhesions to the host/bladder urothelium

Most strains of uropathogenic *Escherichia coli* (UPEC) encode filamentous adhesive organelles called type 1 pili. Type 1 pili adhesin, FimH, mediates not only bacterial adherence, but also invasion of human bladder epithelial cells. Therefore, blocking these pili from adhering to the bladder epithelial cells may be a very effective way to prevent UTIs.

Cranberry extract contains A-type proanthocyanidins (PACs), which have the ability to block pili adhesion in *E. coli*. Use of cranberry extract to prevent UTIs received much attention following a randomized crossover study that showed that daily ingestion of 300 ml of cranberry juice reduced the odds of bacteriuria with pyuria to 42% of that of controls.⁴⁴ Unfortunately, cranberry supplements were not found to be effective at changing urinary pH or reducing bacterial counts, urinary WBC counts, or UTIs in individuals with neurogenic bladders. A likely explanation is that cranberry specifically blocks adhesion of *E. coli* pili; however, those with SCI frequently have multiple organisms and often have organisms other than *E. coli*.^{45,46} D-mannose has also been studied as an agent to block adhesion of *E. coli*. In one study of 308 able-bodied women with history of recurrent UTIs, prophylaxis with d-mannose powder significantly reduced the risk of recurrent UTI (14.6%) versus the no prophylaxis group (60.8%) ($P < 0.001$).⁴⁷ Further work is needed to develop agents

that will prevent bacterial adhesions in individuals with bladders that are colonized with multiple organisms and those with organisms other than *E. coli*.

Block/inhibit the biofilm

Another method that has received attention is to inhibit the biofilm formation from bacteria on urinary catheters. There are specific steps in biofilm formation, which include bacterial attachment to the catheter, bacterial mucopolysaccharide coating to protect against host defenses and antibiotics, and bacterial shedding and repeating the above steps to further increase the biofilm. See Table 4 for further details. Some new therapeutic approaches being evaluated include catheters coated with hydrogels or antibiotics, nanoparticles, iontophoresis, biofilm enzyme inhibitors, liposomes, bacterial interference, bacteriophages, quorum sensing inhibitors, low-energy surface acoustic waves, and anti adhesion agents.⁴⁸

Biofilm inhibition

One area of study is the use of microscopic particles called nanoparticles. These particles inhibit biofilm formation by both *E. coli* and *S. aureus*. Urease, the enzyme that allows *Proteus mirabilis* to hydrolyze urea to ammonium ions, has been an important target in the study of new anti-biofilm compounds. Developing ways to block the formation of biofilm would have significant impact on preventing UTIs.⁴⁹

Strengthen the immune system

Another method to help prevent UTIs is the use of immuno-biotherapy. A good example of this type of agent is Uro-Vaxom®, an extract of *E. coli*. Uro-Vaxom® is made up of immunoactive *E. coli* fractions, which are given orally, pass through the stomach and are absorbed in the ileum and jejunum. Once absorbed, these antigenic components are recognized as “danger signals”, thereby activating the innate immune system. In a one-year study involving able-bodied individuals, antibiotic use was considerably reduced following Uro-Vaxom® prophylaxis.⁵⁰ It was also useful as an adjuvant with antibiotics. A total of 112 patients with recurrent lower UTIs completed the 6-month trial. Patients were treated for 3 months under double-blind conditions, with one capsule daily of either Uro-Vaxom® or placebo, together with an antibiotic or chemotherapeutic agent when necessary, and observed for a further 3 months. During the 6 months of the trial, a significant decrease in the number of recurrences ($P < 0.0005$) was noted in the treatment group as compared to the placebo group. A total of 67.2% of the patients had no recurrences ($P < 0.0005$). Uro-Vaxom

is a useful adjuvant for the management of UTIs and for the prevention of recurrences.⁵¹

Summary

Indwelling catheters play an important role in bladder management following SCI for many individuals with neurogenic bladders. Indwelling urethral catheters -but not SP catheters- pose an increased risk of UTI compared to other types of bladder management. However, there is often confusion that the presence of asymptomatic bacteria in the urine, which don't need treatment, represents a bladder infection which does need treatment. Bacterial colonization of the bladder is common in those with both neurogenic and non-neurogenic bladders. This colonization likely has a positive effect by inhibiting colonization of pathogenic bacteria. Therefore, judicious use of antibiotics for symptomatic UTIs is important in order to prevent disruption of a person's microbiome and evolution of more resistant organisms. For those with an indwelling catheter, there are a number of steps to minimize the risk of a symptomatic catheter associated UTI. These include preventing bladder wall over distention and resulting ischemia by keeping the leg bag from over distending and avoiding kinking of the catheter, maintaining a "quiet" bladder (using such treatments as anticholinergic medications or onabotulinum toxin A) and preventing bladder stones. For individuals with recurrent symptomatic UTIs, in addition to above, rule out anatomical problems and urinary calculi, and try to change the environment (urinary acidification). Newer strategies under development to help prevent CAUTIs include "strengthening the host" with prebiotics/probiotics, blocking adhesions to the host/bladder urothelium, bacterial biofilm inhibition and immunobiotherapy.

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