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Prevention of catheter-associated urinary tract infection

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Abstract

Purpose of review—The underlying cause of catheter-associated urinary tract infection is biofilm formation by uropathogens on the urinary catheter. Biofilm is a relatively new concept in medicine, and current measures to prevent biofilm formation are inadequate. Considerable work is being done in this area, but little clinical progress has been made. The purpose of this review is to analyze recent publications concerning prevention of catheter-associated urinary tract infection.

Recent findings—Several recent studies have elucidated aspects of biofilm formation in catheter-associated urinary tract infection. Other researchers are working on methods to disrupt biofilm formation on catheter surfaces. At the same time, the magnitude of the problem of catheter-associated urinary tract infection has increased awareness of the effectiveness of basic infection control measures. A modern approach to infection control may include computerized ordering systems that minimize unnecessary days of catheterization. Finally, consumption of cranberry juice products and bacterial interference are two novel approaches to urinary tract infection prevention.

Summary—Biofilm-disrupting strategies offer promise for the future but have little immediate applicability. Implementation of infection control measures to improve catheter function and remove unnecessary catheters can be done at the present time. In general, prevention of catheter-associated urinary tract infection remains an elusive goal. More basic research at the level of pathogenesis is needed so that novel strategies can be designed.

Keywords

biofilm; urinary catheter; urinary tract infection

Introduction

Catheter-associated urinary tract infection (CAUTI) is a common problem with considerable economic impact [1,2•]. The underlying cause of CAUTI is formation of a pathogenic biofilm on the surface of the indwelling urinary catheter, and currently we have few, if any, effective strategies to impede this process.

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Understanding the pathogenesis of CAUTI is essential to designing and evaluating preventative strategies. A foreign body in a moist environment, such as a urinary catheter in the bladder, inevitably becomes colonized with sessile microorganisms living in a biofilm community [3]. Thus, individuals with an indwelling urinary catheter develop bacteriuria at the rate of 3–10% per day [4], and the incidence of bacteriuria approaches 100% in individuals who are chronically catheterized [5]. The biofilm lifestyle conveys a survival advantage to micro-organisms in terms of their ability to withstand drying, shear forces, ultraviolet radiation, and antimicrobial agents. The practical consequence is that an indwelling urinary catheter. As long as the colonized catheter remains in place, biofilm-associated organisms can seed the urine with bacteria.

A clear understanding of the distinction between urinary tract infection (UTI) and asymptomatic bacteriuria is essential to the critical assessment of the literature concerning prevention of CAUTI. The presence of bacteria in the bladder, a normally sterile site, triggers an inflammatory response [6-8]. However, more than 90% of cases of nosocomial catheter-associated bacteriuria are asymptomatic, or subclinical infections [1,9•]. The presence of bacteria in the urine of an asymptomatic person is termed asymptomatic bacteriuria and is distinguished from a symptomatic UTI by the absence of symptoms attributable to infection of the urinary tract. Since the majority of cases of asymptomatic bacteriuria do not progress to UTI, clinical trials that use bacteriuria as an endpoint are methodologically flawed. Another common misunderstanding is that measures to prevent bacteriuria during short-term catheterization (\leq 14 days) are erroneously assumed to be effective at preventing UTI in persons with chronic, indwelling urinary catheters (>30 days).

The purpose of this article is to analyze the reports published in the past year on prevention of CAUTI. Several studies have elucidated aspects of biofilm formation; these studies advance the field by contributing to a better understanding of pathogenesis. Other basic science studies have explored techniques to disrupt biofilm formation on medical devices in general. Although these ideas show promise, the only biofilm-impeding strategy that has been tested in clinical trials is impregnating urinary catheters with antimicrobial silver. Recent publications also reiterate that attention to infection control measures helps prevent CAUTI. Finally, two novel approaches to UTI prevention in general have recently reached the stage of clinical trial: consumption of cranberry products and bacterial interference.

Understanding the pathogenesis of catheter-associated urinary tract infection

Several publications from the past year elucidate the pathogenesis of CAUTI. Sabbuba and colleagues [10•] used molecular epidemiology to prospectively study *Proteus mirabilis* in the urinary flora of catheterized patients. A striking finding was that the same strain of *Proteus* colonized one patient for 121 days despite eight catheter changes, an 8-day course of antibiotics (which temporarily eliminated *P. mirabilis* from the urine), and a 20-day period during which the bladder was not catheterized. This finding suggests that uropathogens may persist in a reservoir within the urinary tract itself, rather than re-entering from the stool; the latter mechanism would be expected to result in bladder invasion by different strains.

A recent publication in *Science* [11••] suggests that this reservoir may be within the living tissue of the bladder itself. Anderson *et al.* found that clinical isolates of uropathogenic *Escherichia coli* formed tightly-packed, biofilm-like pods in mouse bladder epithelial cells. This article is the first description of biofilm formation within eukaryotic cells, and the accompanying images are striking. If supported by further studies, these intracellular

biofilms could certainly account for the persistence of pathogens in the damaged mucosa of a catheterized urinary tract [12]. A refined understanding of the pathogenesis of CAUTI may lead to novel mechanisms to prevent this disease.

Disrupting biofilm formation with novel catheter coatings

Since biofilm on the urinary catheter is the central factor in pathogenesis of CAUTI, many scientists seek to alter the catheter surface in order to inhibit biofilm formation. No surface can resist biofilm formation indefinitely in the urinary tract, but impeding biofilm formation may suffice if the catheter is intended for short term use. Readers seeking background information about biomaterials currently licensed for use in the urinary tract should refer to a review article by Beiko *et al.* in the *Journal of Urology* [13•].

The type of urinary catheter modification that has undergone the most extensive clinical testing is impregnating the catheter with antimicrobial agents, most commonly with silver. In 2004 the *Cochrane Database of Systemic Reviews* published a comprehensive assessment of impregnated catheters intended for short-term use in hospitalized adults [14••]. Eight differently-designed trials compared silver alloy catheters with standard catheters. Pooled results indicated that the risk of asymptomatic bacteriuria was significantly reduced in the silver alloy group at less than 1 week of catheterization (RR 0.36; 95% CI 0.25–0.52) and, to a lesser degree, at greater than 1 week (RR 0.67; 95% CI 0.50–0.90). The risk of symptomatic UTI was also lower in the groups with silver alloy catheters (RR 0.60; 95% CI 0.50–0.73), although the symptoms used to define UTI were not specified. None of the trials tested for emergence of resistance to silver. The Cochrane reviewers noted that methods of randomization and blinding were unclear, various types of silver alloy coatings were used, and only one trial did a cost–benefit analysis [15].

What are we to conclude about the use of antimicrobial-impregnated urinary catheters? Silver alloy catheters temporarily delay the onset of bacteriuria, as evinced by the increase in bacteriuria between 1 week of catheterization and greater than 1 week of catheterization. Systemic antimicrobial prophylaxis can have the same effect. However, systemic antimicrobial agents are not used to prevent nosocomial CAUTI because the benefits of preventing largely asymptomatic bacteriuria are dubious and the risk of selecting resistant flora is high [16]. Silver-resistant bacteria are common in environments where silver antiseptics are widely used, such as in burn units [17•]. To summarize, the use of the more expensive, silver-coated catheters to prevent CAUTI is not supported by quality data, and resistance to silver is likely to become a problem with widespread use. These concerns are applicable to other agents used to impregnate urinary catheters, including chlorhexidine [18•] and nitrofuroxone [19•]. Currently the guiding principle in selecting a urinary catheter should be patient comfort; both hydrophilic coatings and all-silicone surfaces reduce frictional irritation of the urethra [13•,20•].

Many substances are being tested for their potential as biofilm-disrupting catheter coatings. Some of these substances have been recently discovered, such as quorum-sensing inhibitors, while others are currently used for different medical purposes. The most recent studies of the use of the quorum-sensing inhibitors to prevent biofilm formation have been done with staphylococcal graft infections [21•,22•]. Coating dacron vascular catheters with RNAIII-inhibiting peptide, a peptide that disrupts staphylococcal cell–cell communication, reduced graft infection in a rat model [23•]. Although this work was done with vascular catheters, the concept is relevant to urinary catheter infections; quorum-sensing regulation of biofilm formation is well-described in *Pseudomonas* [24] and *Escherichia coli* [25], both common agents of CAUTI. None of the quorum-sensing inhibitors have been tested in humans.

Several agents with a long history of medical use in humans are currently being investigated for the purpose of controlling urinary catheter-associated biofilms. These agents include heparin, N-acetylcysteine, and aspirin. An in-vitro study of urinary catheters exposed to *Proteus mirabilis* showed that the time to encrustation was significantly longer for heparin-coated catheters than for control hydrogel-coated latex catheters (28.1 h versus 58.2 h, respectively) [26•]. These same authors performed a pilot study in 20 patients and found that heparin-coated stents developed less encrustation over 2–6 weeks than control stents [26•]. Two other studies added a potential anti-biofilm agent to the microbial growth medium rather than to the catheter surface. In one study [27•] N-acetylcysteine, a mucolytic agent, reduced biofilm formation by *E. coli* on polystyrene wells, and in the other study [28•] aspirin inhibited biofilm formation by *Candida albicans* on polyvinyl chloride. A weakness of the latter two trials is that the effect of the agent on biofilm formation was not clearly distinguished from the effect of the agent on viability of the pathogens. Although these established agents may eventually prove to be anti-biofilm drugs, at this time no clinical data exists to support their use for prevention of CAUTI.

Infection control measures

Currently one well-tested strategy is available that can prevent catheter-associated infections. This often neglected strategy is to implement infection control measures to ensure that urinary catheters are maintained properly and removed promptly when no longer needed.

Ensuring unobstructed flow of urine is one of the most effective measures to prevent CAUTI. A recent study [29•] in persons with spinal cord injury using intermittent catheterization for bladder drainage confirmed that the risk of UTI increases with the amount of residual urine in the bladder. Similarly, an investigation performed by a large home-nursing care agency found that catheter blockage and low urine flow were significantly associated with CAUTI [30•]. The concept that catheter obstruction leads to stagnant urine, an overdistended bladder, and UTI is hardly novel, yet how many hospitals have a mechanism to ensure gravity-dependent, unobstructed drainage at all times? A study in two intensive care units in a hospital in Buenos Aires, Argentina [31•] tested the effect of implementing two infection control practices: (1) handwashing before insertion of a urinary catheter and (2) positioning the catheter so that it was not compressed by the patient's leg. During the 21-month intervention period, compliance with both infection control measures increased significantly, and the rate of CAUTI decreased significantly from 21.3 to 12.4 per 1000 catheter-days (RR, 0.58; 95% CI 0.39–0.86; P = 0.006). Likewise, in an intensive care unit in Paris, implementation of an infection control program that ensured unobstructed catheter flow led to a decrease in CAUTI from 21.1 to 12.9 per 1000 catheter days over the 5 years of the study (P = 0.0006) [32•]. While neither of these studies proves that the decreased incidence of UTI over the trial period was due solely to changes in the infection control practices, the results of both trials argue strongly for attention to these simple, affordable measures.

Another effective means to prevent CAUTI is to avoid unnecessary days of catheterization. Approximately 30% of initial urinary catheterizations are unjustified, and one-third to one-half of days of continued catheterization are unjustified [33-35]. Many of these catheters are inserted in the emergency room without a documented order, and providers are not aware that the catheter is in place in 21–38% of cases [35]. A logical solution to this problem would be to require entry of a computer order for each urinary catheter. The computer system could request the indication for catheterization and prompt an automatic catheter removal date. A recent controlled study of such an ordering system was found to decrease

the duration of catheterization by 3 days (from 8 to 5 days' P = 0.03) [36••]. This promising strategy awaits testing in a full-scale trial designed to measure the impact on CAUTI.

Novel methods to prevent urinary tract infection in general

Two novel methods to prevent urinary tract infection, not specifically CAUTI, have been tested in clinical trials in humans: consumption of cranberry products and bacterial interference (using nonpathogenic bacteria to prevent infection by pathogens).

The *Cochrane Database of Systemic Reviews* recently published an analysis of cranberry products for prevention of UTI [37••]. Overall, the amount and type of cranberry products given to participants varied widely. Of seven trials that met inclusion criteria, only two randomized, controlled studies were suitable for meta-analysis [38,39]. The summary risk ratio for cranberry products (juice or capsules) versus placebo for recurrent UTI in the 300 adult, non-catheterized women in these two trials was 0.61 (95% CI 0.40–0.91). The high dropout rates suggested that cranberry juice consumption was not a well-accepted therapy [40•]. Thus, the clinical evidence supporting cranberry juice for prevention of UTI is weak.

Bacterial interference is unique among preventative approaches in that the goal of bacterial interference is to select benign organisms to form a catheter-associated biofilm rather than to prevent biofilm formation. The appeal of this concept is that humans do not have to outsmart the bacteria, who throughout history have repeatedly demonstrated their ability to evade human defenses. A pilot trial of direct instillation of a benign strain of *E. coli* into the neurogenic bladders of persons with spinal cord injury showed that direct bladder instillation was safe, did not produce symptoms of UTI, and reduced the frequency of UTI as compared with the patients' historical baselines [41]. A multicenter, prospective, placebo-controlled trial of direct bladder instillation of benign *E. coli* to prevent UTI in persons with spinal cord injury began recently. *In vitro*, incubating urinary catheters with this same strain of non-pathogenic *E. coli* prior to exposing the catheters to a variety of uropathogens effectively impeded catheter colonization by uropathogens [42,43•]. A pilot trial of inserting *E. coli*-coated urinary catheters into the bladders of persons with spinal cord injury is underway. Since biofilms on urinary catheters are notoriously difficult to eradicate, perhaps we can exploit biofilm formation in order to induce durable bladder colonization with benign flora.

Conclusion

CAUTI is a significant problem for the millions of persons who receive urinary catheters each year. Unfortunately, the most effective preventative strategy developed to date is the use of a closed drainage system, introduced almost a century ago [44]. The next most effective strategy is to remove the catheter as soon as it is no longer needed, a maneuver which may be prompted by automated computer stop orders [36••]. In addition to these two measures, strict attention to infection control practices, especially ensuring gravity-dependent drainage of urine, can also decrease CAUTI. All of the forgoing measures require little expenditure and can be implemented immediately.

Techniques for preventing formation of a pathogenic biofilm on the urinary catheter surface are being developed; none has proven clinical efficacy. Bacterial interference is an antimicrobial-sparing approach that may prevent CAUTI by colonizing the urinary catheter and the bladder with benign flora. Basic science research continues to elucidate the complexity of biofilm formation in the catheterized urinary tract, thereby encouraging the development of novel means to prevent CAUTI.

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Abbreviations

CAUTI catheter-associated urinary tract infection

UTI urinary tract infection

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