AJIC state of the science report

Role of biofilm in catheter-associated urinary tract infection

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The predominant form of life for the majority of microorganisms in any hydrated biologic system is a cooperative community termed a "biofilm." A biofilm on an indwelling urinary catheter consists of adherent microorganisms, their extracellular products, and host components deposited on the catheter. The biofilm mode of life conveys a survival advantage to the microorganisms associated with it and, thus, biofilm on urinary catheters results in persistent infections that are resistant to antimicrobial therapy. Because chronic catheterization leads almost inevitably to bacteriuria, routine treatment of asymptomatic bacteriuria in persons who are catheterized is not recommended. When symptoms of a urinary tract infection develop in a person who is catheterized, changing the catheter before collecting urine improves the accuracy of urine culture results. Changing the catheter may also improve the response to antibiotic therapy by removing the biofilm that probably contains the infecting organisms and that can serve as a nidus for reinfection. Currently, no proven effective strategies exist for prevention of catheter-associated urinary tract infection in persons who are chronically catheterized. (Am J Infect Control 2004;32:177-83.)

Health care providers have traditionally envisioned bacteria in their free-floating or planktonic state, and planktonic organisms have been the focus of traditional microbiologic methods of sampling and culture.[1] However, the predominant form of life for the majority of microorganisms in any hydrated biologic system, such as the human body, is a cooperative community termed a "biofilm."[2]

A formal definition of biofilm includes 3 components: (1) adherence of the microorganisms, either to a surface or to each other; (2) a change in gene expression resulting in a different phenotype from the planktonic state; and (3) an extracellular matrix composed of host components and secreted bacterial products.[3,4] A functional definition of biofilm also includes the fact that biofilm results in chronic, persistent infections that are difficult to eradicate with antimicrobial therapy.[5] The relevance of biofilm to catheter-associated urinary tract infection (UTI) (CAUTI) is that a foreign body, such as an indwelling urethral catheter, connecting a normally sterile, hydrated body site to the outside world will inevitably become colonized with microorganisms.[4] Thus, the central character in the story of CAUTI is really the biofilm on the urinary catheter.

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Supported by NIH-NICHHD grant 1 K23 HD42014-01.

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0196-6553/$30.00

doi:10.1016/j.ajic.2003.08.005

PATHOGENESIS OF URINARY CATHETER–ASSOCIATED BIOFILM

The pathogenesis of CAUTI is related to the susceptibility of inert catheter material to microbial colonization. On the surface of normal bladder mucosa, binding of bacteria triggers an inflammatory response that results in an influx of neutrophils and sloughing of epithelial cells with bound bacteria.[6-9] Both processes contribute to clearance of the bacteria from the mucosal surface. In contrast, catheter surfaces have no inherent defense mechanisms. The first step in biofilm formation on a urinary catheter is deposition of a conditioning film of host urinary components, including proteins, electrolytes, and other organic molecules.[4] This conditioning film can transform the surface of the urinary catheter and neutralize any antiadhesive properties.[3] Free-swimming bacteria attach to the surface through hydrophobic and electrostatic interactions and through the use of flagella.[4,10] Attachment is followed by cell division, recruitment of additional planktonic bacteria, and secretion of extracellular matrix. Cell-to-cell signaling directs the formation of loosely packed 3-dimensional structures with fluid channels between them to permit exchange of nutrients and wastes.[11,12] Detachment of individual organisms from the biofilm completes the cycle and can also seed the urine with pathogens.

The reason that biofilm is so prevalent on urinary catheters is that it conveys a survival advantage to the

Table 1. Bacterial lifestyles: A comparison of free-floating with biofilm-associated organisms

Growth phase	Free-floating	Biofilm
Location	Ubiquitous	Ubiquitous
Phenotype	Planktonic	Sessile
Prevalence	$<0.1\%$ of aquatic microbes[2]	Predominant
Growth	Rapid	Slow
Sensitivity to bactericidal agents	High	Low
Survival function	Disseminate	Cooperate

microorganisms; for this same reason urinary catheter biofilm is difficult to eradicate (Table 1). Organisms in a biofilm function as a community and communicate closely with one another.[12] Survival advantages conferred by the biofilm community include resistance to being swept away by simple shear forces, resistance to phagocytosis, and resistance to antimicrobial agents.[1,2] For example, in a rabbit model of CAUTI, 400 mg/kg of amdinocillin was required to eliminate *Escherichia coli* from the surface of the urinary catheter, although the minimum inhibitory concentration of amdinocillin against this organism in the planktonic state was 0.5 μg/mL.[13] Because several studies show that antibiotics can penetrate mature biofilms thoroughly,[14-16] the slow growth rates of organisms in biofilms is probably the major factor in conferring resistance. In addition, the juxtaposition of microorganisms of 1 or more species within a biofilm facilitates the transfer of antimicrobial resistance genes.[17] A practical consequence of catheter-associated urinary biofilms is that the results of microbiology studies can be misleading, both in terms of the species identified and their susceptibilities, for these results reflect only those organisms that were free-floating at the time the urine was collected.[18]

Not only does the urinary catheter invite biofilm formation, but the presence of the catheter itself impairs many of the normal defense mechanisms of the bladder. The urinary catheter connects the heavily colonized perineum with the normally sterile bladder, and it provides a route for bacterial entry along both its external and internal surfaces.[19] Urine often pools in the bladder or in the catheter itself, and urinary stasis encourages bacterial multiplication.[20] Obstruction of the catheter can lead to overdistension and ischemic damage of the bladder mucosa, thus, increasing its susceptibility to bacterial invasion.[21] The catheter also damages the bladder mucosa by triggering an inflammatory response and by mechanical erosion.[18,22]

Once organisms gain access to the catheterized urinary tract, low-level bacteriuria usually progresses to $>10^5$ colony-forming units/mL within 24 to 48 hours in the absence of antimicrobial therapy.[23] For patients with an indwelling urethral catheter, the daily rate of acquisition of bacteriuria is 3% to 10%.[24] A study of 20 patients who were chronically catheterized found that 98% of 605 consecutive weekly urine specimens contained $>10^5$ bacteria/mL of urine, and 77% of the urine specimens contained multiple species.[25] Monthly urine cultures for patients with long-term indwelling catheters show that the bacterial flora is constantly shifting and changing, regardless of antibiotic use.[26]

DIAGNOSIS AND TREATMENT OF CAUTI

Although chronic urinary catheterization is essentially synonymous with bacteriuria, bacteriuria is not synonymous with symptomatic UTI. The presence of bacteria in the urine does trigger an inflammatory response in terms of pyuria and urinary interleukins,[27-29] but more than 90% of cases of nosocomial catheter-associated bacteriuria are asymptomatic.[30] Most cases of asymptomatic bacteriuria (ABU) should not be treated with antibiotics as the risk of complications from ABU is low, treatment does not prevent recurrence of ABU, and treatment can promote the development of antimicrobial resistance in the patient's flora.[19,30-34] Therefore, the distinction between ABU and symptomatic CAUTI is important and must be made on the basis of clinical findings.

In the 2 most commonly catheterized populations, persons with spinal cord injury (SCI) and residents of long-term care facilities (LTCF), the signs and symptoms of UTI may be subtle. Persons with SCI who have insensate bladders may experience spasticity, dysreflexia, abdominal discomfort, diaphoresis, fever, or a combination of these as their only symptoms of a CAUTI.[32] Elderly residents of a LTCF with a UTI may present with delirium, anorexia, or weakness.[35] Frequently the diagnosis of CAUTI is established in retrospect when the patient's symptoms resolve in response to targeted urinary tract therapy.

Because patients with chronic indwelling catheters are almost universally bacteriuric, the presence of bacteria in the urine of a patient who is febrile and catheterized does not necessarily predict UTI. Indeed, a study in institutionalized elderly persons found that the positive predictive value of bacteriuria for febrile UTI was only 11%.[36] Pyuria also lacks diagnostic specificity in patients who are chronically bacteriuric; a careful study in patients with SCI found that neither the level nor the trend of pyuria proved to be helpful in predicting when ABU would become symptomatic UTI.[37] Even the urine culture results can be misleading, as numerous studies have shown that urine cultures collected through an "old" indwelling catheter have more species and higher numbers of organisms than urine cultures collected through a newly inserted catheter or through suprapubic bladder aspiration.[38-41]

Although practice guidelines are neutral on this topic, we recommend changing the urinary catheter as part of the therapy for CAUTI.[42] The catheter can be changed before the urine is collected for culture, in which case the microbiology laboratory will be spared workup of spurious species and the patient may be spared unnecessary antibiotics.[43] A small clinical trial found that changing the catheter before obtaining urine for culture and before starting antibiotic therapy was associated with a shorter time to afebrile status, improved clinical status, and a lower rate of symptomatic relapse.[44] The results of this trial make sense in terms of the pathogenesis of CAUTI, because the catheter-associated biofilm can seed the bladder again with the same organisms.[37,44] Urinary catheter change is usually a benign procedure, both in elderly persons[45,46] and in persons with SCI, in whom the method of choice for bladder management is intermittent catheterization.[47]

Most experts recommend treating CAUTI in the patient who is chronically catheterized with 5 to 10 days of targeted antibiotic therapy.[45,47,48] A blinded autopsy study of 75 elderly residents of LTCF showed that 38% of patients who had an indwelling urinary catheter at the time of death also had acute renal inflammation.[49] Thus, although a shorter course of antibiotics may be desirable to limit the emergence of resistance,[45] a longer course of antibiotics may be required to treat occult pyelonephritis. Many clinicians empirically start with parenteral antibiotics to cover occult bacteremia,[20] but the benefit of parenteral antibiotics is not well-established.

Although nontreatment of most cases of ABU in patients who are chronically catheterized is well-supported by clinical trials,[34,45,50-52] treatment of ABU is recommended in certain patient groups. These groups include patients undergoing renal transplant,[33] pregnant women,[53] patients about to undergo genitourinary procedures,[54] and possibly women who are bacteriuric after removal of a short-term, indwelling catheter.[55] These exceptions to the general rule of nontreatment of ABU apply mainly to persons with short-term indwelling catheters and are intended to prevent complications such as bacteremia, not to eradicate the ABU per se.

PREVENTION OF CAUTI

Strategies for prevention of CAUTI are really measures to delay the onset of bacteriuria, and no strategy can effectively prevent bacteriuria and CAUTI indefinitely in a person who is chronically catheterized. In terms of delaying the onset of bacteriuria, preventative strategies can be categorized as effective, possibly effective, effective only for short-term catheterization, ineffective, and novel approaches.

Effective strategies

These include closed drainage and catheter removal. Closed drainage, in which the collection tube is fused to the drainage bag, reduces the incidence of bacteriuria from 95% after 96 hours of open drainage to 50% after 14 days of closed drainage for men and 50% after 11 days of closed drainage for women.[56] Simply removing the indwelling catheter is possible more often than it is done in practice. One study in elderly residents of a LTCF found that 117 of 124 patients converted successfully to catheter-free care after introduction of a continence training program.[57] An incidental finding in this study was that antibiotic use dropped by 90% on the catheter-free wards in comparison with control wards. Another study in a geriatric LTCF found that more than 50% of new admissions to the facility from hospitals could have their indwelling catheter removed permanently.[58] The presence of an indwelling urinary catheter is a risk factor for bacteremia (conferring an odds ratio of 39 in 1 study)[59] and is strongly correlated with mortality.[60,61] Certainly the presence of an indwelling catheter can impair the already limited mobility of a frail elderly person, and some argue convincingly that urinary catheters are "1-point restraints."[24] Although confounding variables, such as debilitating illnesses that make the indwelling catheters necessary, prevent the establishment of a cause-and-effect relationship between the catheter and mortality, clearly a nonessential indwelling urinary catheter can be harmful.[61]

Possibly effective strategies

A system that reminds physicians who among their patients have urinary catheters might shorten the duration of catheterization and, thus, decrease the incidence of CAUTI.[62] Studies of the appropriateness of use of urinary catheters indicate that 21% to 38% of initial urinary catheterizations are unjustified, and one-third to one-half of days of continued catheterization are unjustified.[63-65] When inpatient physicians and students at 4 academic medical centers were asked whether or not each of their patients had a urinary catheter, they incorrectly reported that their patient did not have a catheter 28% of the time.[64] The rate of unawareness of inappropriate urinary catheterization was even higher (41%).[64] In a recent controlled study, instituting a computerized urinary catheter order and a computer-generated stop order 72 hours after insertion reduced the duration of catheterization by about one-third (3 days).[62] Thus, a computerized reminder system might reduce CAUTI by prompting removal of "forgotten" catheters.[32]

If the urinary catheter cannot be removed, a possible solution is to move it from the urethra to another

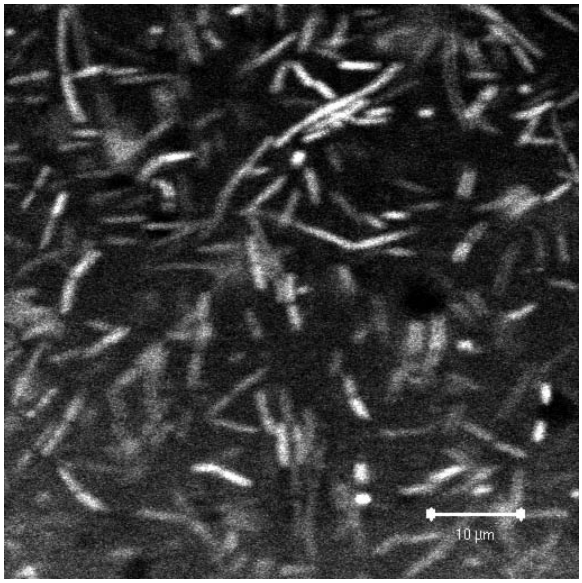

Fig 1. Abundant biofilm of *Escherichia coli* is clearly visible on siliconized latex surface. A 1-cm^2 piece of siliconized latex was incubated in LB Broth, Lennox (Fisher Scientific, Fairlawn, NJ) with *E coli* J96 (uropathogenic strain) for 2 days at 37°C with broth changes twice daily. Squares were removed and rinsed 4 times with phosphate-buffered saline. A 20-μM solution of DRAQ5 (Biostatus Ltd, Leicestershire, United Kingdom) was applied directly to each square. DRAQ5 (Biostatus Ltd) was chosen to bind cellular DNA, which in *E coli* fills nearly entire cell. Examination of stained squares was performed using confocal laser-scanning microscope (LSM 510, Zeiss, Jena, Germany). System consisted of laser-scanning module mounted on inverted microscope (Axiovert 100 M BP, Zeiss), and argon laser (488 nm) and helium-neon laser (633 nm). Oil objective was 63x. Images were recorded at excitation wavelength of 633 nm and emission wavelength of 647 to 722 nm. Images were stored and viewed with software (LSM 5, Zeiss).

location. The limited data available suggest that suprapubic catheters, external catheters (in men), and intermittent catheterization may be associated with lower rates of bacteriuria, UTI, or both than intraurethral catheters.[52,66-69] Of course, in both geriatric patients and individuals with SCI, the patient's functional status often influences the type of bladder management, so randomized comparisons of these various drainage methods are not possible.[50,70,71]

Strategies effective only for short-term catheterization

Although changing catheter materials to render the catheter surface inhospitable to biofilm formation is a clever idea, this approach is effective for prevention of UTI only in the setting of short-term catheterization. Given adequate time, perineal flora will find a way to colonize a moist catheter surface. For example, several studies reported that gram-negative bacteria adhered less to siliconized rubber than to other catheter materials.[4,72] Fig 1 shows a confocal microscopy image of a siliconized latex surface that had been incubated with *E coli* in broth for only 48 hours; a thick biofilm is clearly visible. Impregnating urinary catheters with antimicrobial agents, such as silver ions or nitrofurazone,[73] has also been attempted. Although meta-analysis found that silver-containing catheters were potentially effective in preventing bacteriuria for patients undergoing short-term catheterization, these catheters merely delayed the onset of bacteriuria in patients with chronically catheterized SCI.[74,75] Because no material has been created that prevents bacterial colonization and biofilm formation, the choice of catheter materials should be on the basis of what causes the least friction and is, thus, most comfortable for the patient.[4]

Ineffective strategies

Strategies that have proven ineffective for prevention of CAUTI include use of antimicrobial agents, either systemically or instilled directly into the bladder, and catheter irrigation. Chronic antibiotic suppression of ABU in individuals who are catheterized for the purpose of preventing symptomatic UTI leads to the emergence of resistant flora and to adverse drug effects in the patients.[26,52,76] Indeed, the main beneficial effect of antimicrobial prophylaxis may be that it makes the physicians feel better, for in 1 study patients taking chronic urinary antimicrobial suppression received significantly fewer nonprotocol antibiotics from their physicians than did patients in the untreated control group.[34] Likewise, antimicrobial drainage bag solutions and antimicrobial bladder washes achieve only short-term suppression of bacteriuria.[77-81] Daily irrigation of long-term urinary catheters with normal saline also failed to reduce febrile episodes and bacteriuria[82]; this finding is not surprising because catheter-associated biofilm by definition will not be dislodged by a saline rinse.

Novel approaches

Disrupt quorum sensing. Because biofilm formation is central to the pathogenesis of CAUTI, novel methods to hinder or alter biofilm formation on the surface of urinary catheters might assist in prevention of CAUTI. Biofilm-associated bacteria on the surface of urinary catheters produce quorum-sensing signal molecules that regulate expression of genes essential to biofilm

formation.[83] Mutant strains of *Pseudomonas aeruginosa* that cannot produce these signals are able to attach to surfaces but do not differentiate into mature 3-dimensional biofilms.[11] Disruption of quorum sensing in *Staphyloccocus epidermidis* prevented biofilm formation on plastic and reduced biofilm formation in a Dacron graft (Albograft, Sorin Biomedica Cardio) rat model.[84] Also, addition of furanone, a quorum-sensing disrupter, to cultures of *E coli* markedly decreased biofilm thickness.[85] These studies suggest that manipulating evolutionarily conserved cell-to-cell signaling methods may be a means to prevent or limit biofilm formation by uropathogens. Unfortunately, the clinical use of furanones is limited by potential toxicity and by variable efficacy in different studies.

Iron-scavenging catheters. Another promising approach is to create a catheter surface that scavenges nutrients, particularly iron, that are necessary for biofilm growth. Preliminary data suggest that catecholamine inotropes encourage biofilm formation by *S epidermidis* by transferring iron to the bacteria from the host iron-binding protein transferrin.[5] Conversely, adding lactoferrin, another host-derived iron-chelating agent, to cultures of *P aeruginosa* prevented the formation of cell clusters and biofilm.[86] Perhaps urinary catheters made from an iron-scavenging biomaterial would resist biofilm formation on their surfaces, but such catheters have not yet been developed for clinical trials.[87]

Bacterial interference. Another approach to prevention of biofilm-associated UTI might be to manipulate the composition of the biofilm rather than to prevent its formation. Bacterial interference, or the use of benign bacteria to prevent symptomatic infection, has great potential for prevention of CAUTI. Pilot trials of direct bladder instillation of a nonpathogenic strain of *E coli* in persons with neurogenic bladders secondary to SCI have shown that direct bladder instillation is safe, does not produce symptoms of UTI, and appears to reduce the frequency of UTI as compared with the patient's historic baselines.[88] In vitro studies with this same strain of nonpathogenic *E coli* have shown that incubating urinary catheters with this organism before exposing the catheters to a wide variety of uropathogens effectively impeded catheter colonization.[89,90] The appeal of using bacterial interference to prevent CAUTI is that we humans do not have to outsmart the bacteria, but rather we encourage nonpathogenic bacteria to drive out pathogenic bacteria. Decades of research have taught us that bacteria can overcome defenses that human beings create, but overcoming the defenses of their own kind may be more difficult. A prospective, randomized clinical trial of using bacterial interference to prevent UTI in persons with neurogenic bladders secondary to SCI is ongoing.

Conclusions

Biofilm is the predominant mode of growth in aquatic ecosystems and, as such, plays a central role in the pathogenesis of CAUTI. Most aspects of the diagnosis, treatment, and prevention of CAUTI are influenced by the tenacity of biofilm-associated uropathogens. The biofilm mode of living is a highly advantageous response of the microorganisms to the environmental stresses of the urinary tract environment. Whether or not we human beings can overcome or subvert this ancient survival mechanism is an open question.

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