REVIEW ARTICLE

Catheter-Associated Infections

Pathogenesis Affects Prevention

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Intravascular catheters and urinary catheters are the 2 most commonly inserted medical devices in the United States, and they are likewise the two most common causes of nosocomially acquired bloodstream infection. Biofilm formation on the surfaces of indwelling catheters is central to the pathogenesis of infection of both types of catheters. The cornerstone to any preventive strategy of intravascular catheter infections is strict attention to infection control practices. Antimicrobial-impregnated intravascular catheters are a useful adjunction to infection control measures. Prevention of urinary catheter–associated infection is hindered by the numbers and types of organisms present in the periurethral area as well as by the typically longer duration of catheter placement. Antimicrobial agents in general have not been effective in preventing catheter-associated urinary tract infection in persons with long-term, indwelling urethral catheters. Preventive strategies that avoid the use of antimicrobial agents may be necessary in this population.

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Current medical knowledge and technology enable physicians to heal critically ill patients with diseases previously thought to be incurable. Indwelling intravascular and urinary catheters are essential components of modern medical care. Unfortunately, indwelling devices significantly increase the risk of iatrogenic infection, particularly in an already fragile patient population. Most nosocomial infections in severely ill patients are associated with the very medical devices that provide life-sustaining care. For example, a recent survey of medical intensive care units in the United States revealed that 87% of primary bloodstream infections were associated with central lines, and 95% of urinary tract infections (UTIs) were catheter associated.[1] Strategies to prevent catheter-associated infections can significantly reduce morbidity, mortality, and health care costs.

This article discusses the pathogenesis and prevention of infections associated with intravascular and urinary catheters. These catheters are the 2 most commonly inserted medical devices in the United States, and they are likewise the 2 most common causes of nosocomially acquired bloodstream infection. Approximately 5 million central venous catheters are inserted per year, and of these 3% to 8% lead to bloodstream infection.[2] The attributable mortality of these bloodstream infections is 12% to 25%.[3] In contrast, the mortality rate of catheter-associated UTI is less than 5%. However, since the number of bladder catheters inserted each year is more than 30 million, at least 6 times higher than the number of central venous catheters, catheter-associated UTI is the second most common cause of nosocomial bloodstream infection.[4,5] The organisms causing catheter-associated UTI are also a major source of resistant nosocomial pathogens.[4] The differences in the pathogenesis of intravascular catheter infections and bladder catheter infections necessitate different preventive strategies.

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BIOFILM FORMATION

A thorough understanding of how biofilm forms on the surfaces of indwelling

catheters, whether intravascular or urinary, is central to understanding the pathogenesis of infection of these devices. A biofilm is not a static, filmy slime layer but rather is a living organism composed of multiple species of bacteria and their secreted polysaccharide matrix and components deposited from bodily fluids.[6-8] Although we tend to think of microbes primarily in the free-floating state, in most natural environments the microorganisms associate with a surface, thus avoiding being swept away by shear forces.[8]

The first step in formation of catheter-associated biofilm is deposition of a conditioning film on the surface of the device. The nature of this conditioning film depends on the type of fluid that bathes the device. For example, vascular catheters rapidly acquire a sleeve of fibrin and fibronectin, while urinary catheters become encrusted with proteins, electrolytes, and other organic molecules from the host's urine.[7,9] Once the catheter has acquired a conditioning film, the features of the underlying catheter surface may be partially or completely obscured. Thus, even if the bare catheter surface is inhospitable to colonization, the conditioning film may encourage microbial attachment.[6] Other factors that influence attachment include hydrophobic and electrostatic forces, cell-surface structures such as pili or flagellae, and shear stress from the fluid environment.[7,10-12]

Attached, or *sessile*, organisms divide to form microcolonies and then begin to secrete the extracellular polysaccharide matrix that forms the architectural structure of the biofilm. Ultimately, the organisms and their 3-dimensional matrix form thick pillars separated by fluid-filled spaces.[13] The pillars can be thought of as apartment buildings, and the fluid-filled spaces are the streets between the buildings through which the organisms receive nutrients, diffuse away wastes, and send chemical signals to each other.[11] Other species of bacteria may move into the biofilm, and interactions between the species can produce different microenvironments within a given biofilm.[8] Under unfavorable environmental conditions, such as exhaustion of nutrients or overcrowding, sessile organisms can detach and become free-floating, or *planktonic*.[8] The presence of planktonic organisms in the bloodstream or urine can lead in turn to symptomatic host infection.

Biofilms have major medical significance for 2 main reasons: (1) biofilms decrease susceptibility to antimicrobial agents, and (2) microbiology laboratory results based on planktonic organisms may not apply to sessile organisms embedded within a biofilm. The decreased susceptibility to microbial agents within a biofilm arises from multiple factors, including physical impairment of diffusion of antimicrobial agents, reduced bacterial growth rates, and local alterations of the microenvironment that may impair activity of the antimicrobial agent.[11,14] Furthermore, the proximity of cells within a biofilm can facilitate plasmid exchange and hence enhance the spread of antimicrobial resistance.[8] A common problem in clinical settings is that microbiology laboratory results are misleading because they are based on pure cultures derived from free-floating organisms. First, more species may be present in the biofilm than are reflected by the pure culture results. Second, in many cases the susceptibilities of the biofilm-associated organisms may be hundreds of times higher than those of the planktonic organisms. Since abiotic surfaces, such as those of catheters, lack the intrinsic defenses present in host tissues, antibiotics frequently are not able to clear resistant bacterial biofilms from catheter surfaces.[15] Thus, even well-chosen treatment based upon laboratory results often merely suppresses a catheter-related infection until biofilm-associated organisms resurge and cause another clinical infection.

INTRAVASCULAR DEVICES

Pathogenesis of Infection

The organisms that colonize an intravascular device and subsequently disseminate into the bloodstream, causing bloodstream infection, can gain access to the device through 4 different routes: (1) invasion of the skin insertion site, (2) contamination of the catheter hub, (3) hematogenous spread from a distant site of infection, or (4) infusion of contaminated fluid through the device.[16,17] The first 2 sources of infection are by far the most important. The skin site and the catheter hub can become contaminated by the patient's endogenous skin flora and by exogenous flora carried on health care workers' hands.[17] While organisms that gain access through the skin insertion site tend to migrate along the external surface of the catheter, organisms inoculated into the hub migrate along the internal lumen of the catheter. The characteristic flora migrating to the catheter surface from the skin site include coagulase-negative staphylococci and *Staphylococcus aureus*, while nosocomial pathogens, such as *Stenotrophomonas*, *Pseudomonas*, enterococci, and *Candida*, as well as staphylococci, can reach the hub site via the hands of health care personnel.[18]

In contrast to the skin site flora and hub contaminants, hematogenously spread flora from a distant site, such as the urinary tract, are more of a theoretical than a probable source of catheter infection. Since hematogenous seeding of catheters occurs rarely, a catheter need not be removed in the presence of a bloodstream infection from a well-documented secondary source.[16,19] Although epidemics of infusate-related sepsis do occur, these cases are very rare in comparison with the numbers of cases of bacteremia arising from primary catheter infection.[16] The pathogenesis of infusate-related bacteremia, eg, contamination of parenteral nutrition and lipid solutions during preparation, also differs significantly from primary catheter-associated infection and will not be discussed further in this article.

Direct examination of vascular catheters using electron microscopy reveals that biofilm-embedded bacteria are found on catheters within the first 24 hours after insertion.[20] However, the distribution of the biofilm is related to the duration of catheter placement. External surface colonization, probably originating from the skin, predominates in short-term catheters that have been in place less than 10 days, such as peripheral intravenous (IV) lines, noncuffed and nontunneled central venous catheters, and arterial catheters. Intraluminal colonization due to hub contamination increases progressively with time, and

Table 1. Categories of Preventive Strategies

	What Works	What Probably Works	What Might Work
Vascular catheters	Use maximal sterile barriers for insertion Use 2% chlorhexidine for skin antisepsis Designated intravenous therapy team Avoid lower extremity insertion sites Antimicrobial-impregnated catheters* Good hand hygiene Catheter removal when no longer needed	Antibiotic flushes* Prevention of thrombus formation	Antimicrobial catheter hubs Catheter securement devices Active iontophoresis
Urinary catheters	Closed drainage Intermittent catheterization Ensure dependent drainage Catheter removal when no longer needed	Antimicrobial-impregnated catheters*	Bacterial interference

*In specific situations.

intraluminal colonization becomes predominant after 30 days of placement of long-term devices, such as tunneled central venous catheters, peripherally inserted central catheters (PICC lines), and subcutaneous ports.[21] These differences in pathogenesis for short-term vs long-term intravascular device–related infections affect the selection of preventive strategies. Whether or not catheter colonization progresses to symptomatic bloodstream infection is probably a quantitative phenomenon, as the number of organisms recovered from a catheter surface by the roll-plate method clearly correlates with the probability of catheter-related septicemia.[22]

To summarize, the pathogenesis of infections of intravascular devices is a multifaceted interaction. Bacterial factors, such as the predilection of *S aureus* to bind to host tissue ligands, and device factors, such as the surface properties of the device material, all play a role. The factor that probably carries the most weight in terms of whether an intravascular device infection arises is the virulence properties of the colonizing organisms. However, the factors that we as health care providers may influence the most are the properties of the device itself.[2]

Prevention of Infections

In recent years considerable progress has been made in the area of prevention of intravascular device infection. Economic issues have driven some of this progress, as each episode of catheter-associated bloodstream infection may incur more than $25 000 in additional hospital expenditures.[23] However, the fact that the pathogenesis of intravascular device infections is amenable to intervention at many steps has also spurred the development of novel preventive approaches. These novel approaches can be divided into 3 categories based on the level of supporting evidence: (1) what works, (2) what probably works, and (3) what might work (**Table 1**). At the top of the list of "what works" is probably the least "novel" of the novel technologies—risk factor modification. In other words, application of basic principles of infection control is currently the most effective preventive measure for intravascular device infections.[24] However, the antimicrobial-impregnated catheters, which are a relatively recent innovation, also have proven efficacy in preventing intravascular device infections in appropriate patient populations. The "what probably works" category includes antimicrobial catheter flushes and prevention of thrombus formation; these promising strategies are supported by clinical data but need further study. Finally, the "what might work" category includes novel ideas that bear investigation in a clinical setting—antimicrobial hubs, active iontophoresis, and novel catheter securement devices.[25]

Risk factor modification is probably the least glamorous yet most effective strategy to prevent intravascular device infections. Risk factors fall into 3 general categories: (1) patient-related risk factors, (2) device-related risk factors, and (3) risk factors pertaining to catheter insertion and care. While patient-related risk factors such as immunosuppression or extremes of age[26] are not generally subject to modification, the other categories permit considerable risk reduction.

Device-related risk factors include the number of lumens, the location of the catheter, and the duration of placement. Nonrandomized clinical trials have suggested that multilumen catheters are associated with a higher risk of infection than single-lumen catheters, probably because more ports increase the frequency of catheter manipulation.[27,28] Another discretionary factor in catheter placement that affects the risk of infection is the insertion site. A recent, randomized trial comparing femoral and subclavian sites for venous catheterization found a higher rate of infectious and thrombotic complications at the femoral site. The rates of overall and major mechanical complications were similar in the 2 groups.[29] Although the internal jugular site was not evaluated in this study, nonrandomized studies have found a higher rate of infectious complications at the internal jugular site than at the subclavian site.[30] For peripheral IV lines, lower extremity sites are associated with a higher risk of infection than are upper extremity sites and should be avoided if possible.[3,31] Finally, the best way to prevent a catheter from becoming infected is to take it out; physicians should be aggressive about removing intravascular catheters as soon as the device is no longer essential to patient care.[3]

Considerable progress has been made in elucidating the factors in

catheter insertion and maintenance that most effectively reduce the risk of infection. Well-designed, prospective trials provide strong evidence for the use of maximal sterile barriers during catheter insertion.[32] In a prospective, randomized trial comparing standard insertion techniques (sterile gloves and small drape) vs maximal sterile barriers (mask, cap, sterile gloves, gown, large drape) for placement of nontunneled central venous catheters, the rate of catheter-related septicemia was 6.3 times higher in the standard barriers group. Additionally, 67% of the infections in the standard barriers group occurred during the first 2 months after catheter insertion, while only 25%, or 1 of 4, of the infections in the maximal barriers groups occurred in the first 2 months.[32] These findings suggest that the early infections probably originated in touch contamination of the guidewire or catheter at the time of insertion, while the later infections probably arose through hub contamination with extended use of the catheter.[33] However, as anyone who has used maximal sterile barriers can attest, the process of assembling and donning the required items is a bit cumbersome, particularly for harried house staff. Educating physicians about the infection control advantages of maximal sterile barriers can provide them with the necessary impetus for using this technique, and can decrease the rate of catheter-related infection.[34]

Other technical issues pertaining to catheter insertion and care that can reduce the rate of infection basically fall under the heading of "know and respect your catheters." For example, 2% chlorhexidine is the preferred skin disinfectant for both catheter insertion and maintenance.[35] Numerous studies have documented a decrease in catheter-associated infections when catheter insertion and care is provided by a designated IV therapy team rather than by house staff.[3,36] Along similar lines, catheters placed outside of the hospital or under emergent conditions may easily have been contaminated during insertion and should be replaced as soon as possible.[3] Once placed, catheters should be manipulated as little as possible; for example, hemodialysis catheters should be used only for hemodialysis.[3] Finally, as always, hand washing is the cornerstone of infection control and should be practiced before and after inserting, replacing, accessing, or dressing an intravascular catheter.[3] Although many of these recommendations are inconvenient, even annoying, for clinicians to follow on a daily basis, in the long run these simple preventive measures can markedly reduce the rate of intravascular catheter–associated infections.

Antimicrobial-impregnated central venous catheters are an effective adjunct to proper catheter insertion and care in the battle against catheter-associated infections. The premise of antimicrobial-impregnated catheters is that modifying the catheter surface to prevent attachment and biofilm formation by microorganisms will likewise prevent catheter-associated infection. The 2 types of antimicrobial-impregnated central venous catheters that have been studied the most thoroughly are the chlorhexidine/silver sulfadiazine–impregnated catheters and the minocycline/rifampin–impregnated catheters.

The chlorhexidine/silver sulfadiazine–impregnated catheters have been available for approximately 10 years, and a recent meta-analysis confirmed their effectiveness.[37] In this analysis, the impregnated catheters reduced the risk of catheter-associated bloodstream infection by about 40% when used for less than 14 days in patients who were at high risk for catheter-related bloodstream infection (in an intensive care unit, immunosuppressed, or receiving total parenteral nutrition). Although a chlorhexidine/silver sulfadiazine–impregnated catheter costs approximately $25 more than a standard catheter, cost-benefit analysis favors the use of the antimicrobial-coated catheters because the potential savings accrued by averting catheter-associated bloodstream infections are substantial.[38] Unfortunately, cases of anaphylactic reactions to these catheters have been reported. In Japan, chlorhexidine-containing central venous catheters were withdrawn from the market in 1997 after 13 Japanese patients experienced immediate hypersensitivity reactions to these catheters.[39,40] No anaphylactoid reactions have been reported in the United States, where more than 2.5 million of these catheters have been sold so far.[40]

While the catheters studied in these trials had chlorhexidine/silver sulfadiazine only on the external surface, minocycline/rifampin–impregnated catheters provide antimicrobial activity on both the external and the internal surfaces.[41] Head-to-head comparison of these 2 types of catheters in a prospective, randomized clinical trial in adults at high risk for catheter-related infection found a significant advantage to using the minocycline/rifampin–impregnated catheters.[41] The rate of bloodstream infection with the minocycline/rifampin–impregnated catheters was 0.3% (1 of 356), while the rate of bloodstream infection with the chlorhexidine/silver sulfadiazine–impregnated catheters was 3.4% (13 of 382, $P<.002$). One of the most interesting aspects of these results is that 11 of the 13 bloodstream infections in the chlorhexidine/silver sulfadiazine group occurred when the catheters had been in place for more than 7 days. This finding implies that intraluminal colonization becomes increasingly important in the pathogenesis of catheter-associated infection with increasing time of placement, and the chlorhexidine/silver sulfadiazine–impregnated catheters may have lost their protective ability because they were impregnated only on the external surface. A second-generation catheter is now available that has chlorhexidine on the internal lumen as well as the combined antimicrobials on the outer surface. The amount of chlorhexidine and the extended release activity of the surface antiseptics have also been increased.[42] A new trial comparing the second-generation chlorhexidine/silver sulfadiazine–impregnated catheters with the minocycline/rifampin–impregnated catheters would be useful.

Both the chlorhexidine/silver sulfadiazine– and the minocycline/rifampin–impregnated catheters are approved by the Food and Drug Administration and are currently available for use in the United States. According to recent guidelines from the Centers for Disease Control and Pre-

vention (CDC), the use of an antimicrobial-impregnated central venous catheter is a Category IB recommendation for adults whose catheter is expected to stay in place more than 5 days if the institutional rate of catheter-related bloodstream infection is above benchmark rates despite implementation of a comprehensive infection control strategy.[3] This strategy should include educating health care providers, implementing maximal sterile barrier precautions, and using 2% chlorhexidine skin preparation prior to catheter insertion.

Whether or not widespread use of antimicrobial catheters will induce bacterial resistance is an open question, although no resistant flora have been recovered from these catheters in clinical trials to date.[41,43,44] Several factors may explain why resistant flora have not yet been found. First, these catheters are impregnated with 2 antimicrobial agents that have different mechanisms of activity, thus reducing the likelihood of the emergence of resistance. Indeed, the combination of minocycline and rifampin has been shown to be synergistic in preventing the colonization of catheter surfaces.[43] Second, the immediate environment of an antimicrobial–impregnated vascular catheter has a high concentration of antimicrobial agents and a low density of organisms. Specifically, in the clinical trial comparing the chlorhexidine/silver sulfadiazine–impregnated catheters to the minocycline/rifampin–impregnated catheters, fewer than 25% of the catheters in either arm of the trial had any detectable colonization.[41] This clinical scenario favors the eradication of organisms rather than the development of resistance. Since antimicrobial–impregnated catheters do not cause detectable systemic levels of antimicrobial agents,[45] bacteria residing at distant sites are not exposed to these agents and are thus not under selection pressure to develop resistance. In any case, silver sulfadiazine, chlorhexidine, minocycline, and rifampin are not the drugs of choice to treat catheter-associated infections, and there is little cross-resistance between these agents and first-line agents for catheter-associated infections, such as vancomycin. Therefore, it is unlikely that expanded use of antimicrobial-impregnated catheters will be associated with emergence of clinically significant resistance to therapeutic agents. If the appropriate use of antimicrobial-impregnated catheters decreases the number of catheter-associated infections, the use of systemic antibiotics might decrease as well.[43] However, continued surveillance for resistance as these impregnated catheters are used more widely will provide valuable insights into these issues.

Several other techniques to prevent intravascular catheter–associated infections are currently being developed. The theory behind the antibiotic lock technique, or leaving an antibiotic solution in the catheter lumen for several hours at a time, is to avoid the use of systemic antibiotics while delivering a high concentration of antibiotics to the catheter-associated pathogens. For example, use of minocycline and ethylenediaminetetraacetate (the anticoagulant EDTA) catheter flushes in 3 adults who had cumulatively had 40 intravascular catheter-related infections eliminated all such infections in 17 months of subsequent observation.[46] Currently, the CDC recommends antibiotic lock solutions only in situations such as these, when the patient has had recurrent catheter-associated infections and still requires an intravascular device.[3] Use of an anticoagulant alone may also be beneficial, perhaps by inhibiting formation of the fibrin sheath to which the colonizing bacteria bind. One small study in 32 patients found that heparinized catheters had lower rates of colonization and associated bloodstream infection than control catheters,[9] but data are insufficient to make a widespread recommendation about surface heparinization or anticoagulation in general as a means to prevent catheter-associated infection. Other novel technologies aimed at preventing catheter-associated infection by impeding catheter colonization include antimicrobial-containing catheter hubs,[47] novel securement devices that limit the in-and-out motion of the catheter at the skin site,[25] and active iontophoresis, or passing a low electrical current through a silver catheter to elute inhibitory silver ions.[48] These promising technologies await evaluation in full-scale clinical trials.

To summarize the techniques for preventing intravascular catheter–associated infections, the cornerstone of preventive strategies is infection control. Good hand hygiene, the use of maximal sterile barriers for insertion of central venous catheters, and specialized IV teams for catheter insertion and maintenance have all shown unequivocal benefits.[3] The antimicrobial-impregnated catheters are a useful adjunct to these infection control measures. However, in clinical practice compliance with even these basic recommendations is low. A survey of 53 hospitals published in 2000 revealed that only 19% had a designated IV team, although establishing a designated IV team was at the time a category IB recommendation and has since been raised to category IA.[49] Obviously, before we seek novel technology to prevent intravascular catheter–associated infections, we should take the time to read and implement established recommendations.

URINARY CATHETERS

Pathogenesis of Infection

Progress in the area of prevention of urinary catheter–associated infections is very limited compared with that in the vascular arena. Comparing and contrasting the pathogenesis of urinary catheter–associated infections to vascular catheter–associated infections elucidates the obstacles to prevention of catheter-associated UTI (CAUTI) (**Table 2**). While blood deposits thrombus on catheters, urine deposits organic molecules such as Tamm-Horsfall glycoprotein, a slimy protein of renal origin. The host proteins deposited from urine may facilitate attachment to the catheter by uropathogens, for *Escherichia coli* and related gram-negative organisms have hairlike projections that bind to the Tamm-Horsfall protein.[50-52] In the bloodstream, flow at the catheter tip is rapid, whereas in a catheterized urinary tract some stasis is usually present. Stasis, of course, predisposes to high levels of bacterial colonization. Additionally, while an intravascular

catheter must pass through a skin wound, urinary catheters pass through a natural orifice. Thus, implementing sterile urinary catheter insertion techniques probably plays a lesser role in prevention of CAUTI, particularly in the case of long-term urinary catheters. In contrast to the relatively low numbers of skin flora present at the insertion site of a vascular catheter, contamination of the periurethral area with high numbers of bowel flora is very common.[53,54] The most frequent causative agents of nosocomial CAUTI derive from the patient's colonic flora or from the hands of health care personnel; these organisms include *E coli*, enterococci, *Pseudomonas*, *Klebsiella*, *Enterobacter*, or *Candida*.[4] The enteric gram-negative organisms found in the catheterized urinary tract are those that are commonly associated with multidrug resistance.[4] Although most intravascular catheters remain in place for days to weeks, many patients wear indwelling urinary catheters for years, even for the duration of their lives. Thus, the difficulties of preventing CAUTI are compounded by catheter location, duration of catheter placement, numbers of organisms, and types of organisms typically contaminating the catheterized urinary tract.

As with vascular catheters, urinary catheters can become colonized through several routes. Extraluminal colonization may occur by direct inoculation when the catheter is inserted, or it may occur later by organisms ascending in the mucus film between the catheter and the urethra. Intraluminal colonization occurs by reflux of organisms from a contaminated drainage bag or by a break in the closed drainage system.[55] Once organisms gain access to the catheterized urinary tract, the level of bacteriuria usually increases to more than 10^5 cfu/mL within 24 to 48 hours in the absence of antimicrobial therapy.[56] Apparently the presence of the urinary catheter alters the physiology of the urinary tract and predisposes the individual to infection, because studies in healthy, noncatheterized women show that introduction of organisms into the bladder rarely leads to high-level bacteriuria.[56] However, in the presence of an indwelling urethral catheter, the rate of acquisition of high-level bacteriuria is approximately 5% per day.[57] Of note, bacteriuria, or the presence of bacteria in the urine, is frequently asymptomatic and is not synonymous with symptomatic UTI.

Table 2. Differences in Pathogenesis of Infection of Vascular and Urinary Catheters

	Vascular Catheters	Urinary Catheters
Surrounding media	Blood	Urine
State of media	Flow	Stasis
Entry site	Skin wound	Urethral orifice
Numbers of local flora	Few	Many
Result of colonization	Bacteremia	Bacteriuria
Duration of placement	Days to months	Years

In the normal, noncatheterized bladder, the 2 main host defense mechanisms against UTI are mechanical clearance of organisms by voiding and the intrinsic antibacterial activity of the bladder wall itself.[58] Proposed mechanisms for the increased risk of bacteriuria in catheterized individuals include the presence of residual urine in the bladder,[59-61] ischemic damage to the bladder mucosa through overdistention,[62] mechanical irritation from the presence of the catheter, and the presence of a foreign body to support biofilm formation.[15] Not surprisingly, a systematic evaluation of urine specimens from chronically catheterized patients revealed that 98% of weekly urine specimens from such patients contained more than 10^5 cfu/mL of bacteria, and over 77% of the specimens were polymicrobial.[63] All of these mechanisms involved in the pathogenesis of colonization and infection of the colonized urinary tract combine to make CAUTI very difficult to prevent in individuals wearing urinary catheters for longer than 2 weeks.

Prevention of Infections

Few effective preventive strategies are available for prevention of CAUTI, and what preventive strategies exist are chiefly applicable to patients with temporary urinary catheters. As with vascular catheters, preventive strategies for CAUTI can be divided into categories such as "what works" and "what might work," but by far the largest category is "what does not work" (Table 1). The category of "what does not work" includes almost all preventive strategies utilizing antimicrobial agents or antibiotics in persons with long-term, indwelling urethral catheters. Numerous trials of oral antibiotics and urinary acidifying agents,[64-68] antimicrobial bladder washes,[69,70] antimicrobial drainage bag solutions,[71] and topical disinfectants[72-75] all point to the same conclusion: bacteriuria and UTI can be suppressed temporarily, but resistant flora eventually appear. For example, frequent use of the antiseptic agent chlorhexidine in a particular hospital for perineal cleaning, catheter lubrication, and drainage bag cleaning led to an outbreak in which more than 90 patients became colonized with chlorhexidine-resistant bacteria.[76] The reasons for the inevitable failure to suppress bacteriuria in chronically catheterized individuals are directly related to the pathogenesis of bladder infections in these individuals: the nearby bowel flora are numerous, diverse, and frequently resistant to one or more antimicrobial agents. The catheter provides a route for organisms to enter the bladder and also serves as a foreign body for colonization. Opportunities for the exchange of DNA encoding drug resistance abound. Thus, trying to rid the catheterized bladder of all microbial flora is futile and promotes the growth of resistant organisms. Furthermore, frequent courses of antibiotics subject patients to possible adverse drug effects and suprainfections, such as *Clostridium difficile* colitis.[77]

In terms of "what works" to prevent CAUTI, the situation parallels that with vascular catheter infections in that the simplest strategies are the most effective. Use of a closed drainage system, or catheter drainage into a connected bag rather than into an open container, reduces the incidence of bacteriuria to approximately 50% at 14 days of continuous catheterization.[78] This finding contrasts favorably with the

documentation of significant bacteriuria in 95% of patients receiving open catheter drainage for 96 hours.[79] Another very effective strategy is to avoid prolonged catheterization, or even to avoid catheterization at all. Clean, nonsterile, intermittent catheterization can lead to bladder colonization rates as low as 20% to 40% over more than a year of follow-up.[80] Although randomized comparisons are lacking, the rates of bacteriuria and UTI are lower with suprapubic catheterization, condom catheters, and intermittent catheterization than with chronic indwelling urethral catheters.[57,81] Some argue very convincingly that indwelling catheters are a form of "one-point restraint" for hospitalized patients, and their use should be curtailed.[82] Finally, effort should be made to ensure dependent drainage at all times, because having the drainage tube above the level of the bladder or below the level of the collection bag is associated with an increased risk of CAUTI.[4]

In contrast to the scenario with vascular catheters, antimicrobial-impregnated urinary catheters fit best into the "what probably works" category. Most research in this area has studied silver-coated urinary catheters, but unfortunately most of these studies used bacteriuria rather than symptomatic UTI as a surrogate end point. Thus, meta-analysis of 8 trials of silver-coated urinary catheters found that the summary odds ratio for bacteriuria with use of silver-coated catheters was 0.59 (95% confidence interval, 0.42-0.84).[83] However, the studies differed in important aspects of their designs (use of systemic antibiotics, patient populations), and their odds ratios also had significant heterogeneity. Examination of the single study performed in patients with acute spinal cord injury, who receive long-term urinary catheters, showed that the silver-coated catheters delayed but did not prevent the onset of bacteriuria.[84] Minocycline/rifampin–impregnated urinary catheters have been demonstrated to delay the onset of gram-positive but not gram-negative bacteriuria.[85] Since minocycline and rifampin are less active against gram-negative organisms, the higher numbers of gram-negative organisms at the urethral meatus than on the skin at the site of vascular catheter insertion may have overwhelmed the gram-negative antibacterial activity of these bladder catheters. Nitrofurazone-containing urinary catheters have been effective in vitro against multidrug-resistant strains of bacteria, and a single clinical trial found a lower rate of bacteriuria in patients who received nitrofurazone-impregnated urinary catheters compared with a control group.[86,87] In general, antimicrobial-coated urinary catheters may offer significant benefit for hospitalized patients undergoing short-term bladder colonization, but a firm recommendation cannot yet be made for their use. A problem common to all antimicrobial-impregnated urinary catheters is that elution of subinhibitory levels of the antimicrobial agent into the urine may induce resistance in the resident organisms with prolonged catheter use.[76]

Although systemic antibiotics are not recommended in general for patients with asymptomatic bacteriuria, in certain situations treatment of asymptomatic bacteriuria is warranted. Treatment of asymptomatic bacteriuria in pregnant women is recommended because the incidence of preterm labor, symptomatic UTI, and pyelonephritis is higher in bacteriuric pregnant women, but whether treating the bacteriuria improves the outcome of pregnancy is unclear.[88] Men with bacteriuria who are about to undergo urologic surgery should be treated to reduce the risk of postoperative bacteremia.[57,89] Since postoperative UTI is very common in renal transplant patients and is a frequent source of bacteremia, asymptomatic bacteriuria should be treated in recent renal transplant patients as well.[89]

However, in other immunocompetent populations, treatment of asymptomatic bacteria is not recommended and might even be harmful. For example, a recent study of antimicrobial treatment of diabetic women with asymptomatic bacteriuria found no difference in the incidence of symptomatic UTI or episodes of hospitalization for UTI between the treated and untreated groups.[90] However, treated women did experience significantly more treatment-related adverse effects. These findings mirror those of an earlier study of girls with asymptomatic bacteriuria, in which effective treatment of the organisms the girls had in their bladders increased their subsequent risk of contracting acute pyelonephritis with a different strain.[91] Other studies support nontreatment of asymptomatic bacteriuria in institutionalized elderly persons,[90] persons with spinal cord injury,[65] and healthy nonpregnant women.[92] Thus, screening for the presence of asymptomatic bacteriuria as well as treatment of asymptomatic bacteriuria in catheterized patients should be discouraged.

Bacterial interference is one of the leading contenders in the category of "what might work" to prevent CAUTI. Bacterial interference, or the use of benign bacteria to prevent colonization and symptomatic infection with pathogenic organisms, avoids the use of antimicrobial agents and the attendant potential problems of resistance. Deliberate vaginal colonization with *Lactobacillus* of women who had recurrent, non–catheter-associated UTI reduced the prevalence of vaginal coliforms and symptomatic UTI.[93-95] However, *Lactobacillus* colonizes the female urogenital epithelium but not the bladder, and thus it is not an ideal agent to prevent CAUTI. On the other hand, *E coli* 83972, a nonpathogenic strain, does readily colonize the abnormal urinary tracts of persons with neurogenic bladders.[96] Deliberate inoculation of the bladders of persons with spinal cord injury with this strain of *E coli* reduced the incidence of symptomatic UTI in comparison with the patients' baseline rates of UTI.[97] Furthermore, in vitro data suggest that *E coli* 83972–coated bladder catheters impede catheter colonization by uropathogens.[98] A prospective trial of direct bladder inoculation with *E coli* 83972 in spinal cord–injured patients is under way.

CONCLUSIONS

Considerable progress has been made in the prevention of intravascular catheter–associated infections. Recent studies have brought

better understanding of the risk factors for intravascular catheter infections, have clarified preventive infection control strategies, and have introduced novel technologies such as antimicrobial-impregnated vascular catheters. While vascular catheters are a relatively new phenomenon in the medical field, urinary catheters have been in use for more than a century. Recent years have not contributed substantially to our ability to prevent CAUTI, as the closed drainage system developed in 1928[78] is still the most effective strategy available. Unfortunately, many aspects of the pathogenesis of CAUTI render the preventive strategies that work well with vascular catheters ineffective in the bladder. However, these difficulties should not discourage research in this area but rather should be regarded as a challenge for the future.

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