Editorial

Vascular Catheters Impregnated With Antimicrobial Agents: Present Knowledge and Future Direction

Issam I. Raad, MD, FACP

In 1988, Maki and colleagues predicted the beginning of a new era in the prevention of vascular catheter-related infection. In a concluding statement in their study on an attachable silver-impregnated cuff, Maki et al made the following statement, "Binding of a nontoxic antiseptic or antimicrobial to the entire catheter surface, or incorporation of such substance into the catheter material itself, may ultimately prove to be the most effective technologic innovation for reducing the risk of device-related infections."[1] Studies completed in the late 1980s and early 1990s showed that vascular catheters impregnated with antimicrobials did decrease the risk of catheter colonization and, ultimately, infection.[2-12] Sherertz demonstrated the efficacy of catheters coated with various antimicrobial agents such as dicloxacillin, clindamycin, fusidic acid, and chlorhexidine in vitro and in an animal model.[4,5] Using tridodecylmethyl-ammonium chloride as a bonding cationic surfactant, Kamal et al coated catheters with cefazolin and demonstrated in a prospective trial an almost sevenfold reduction in the incidence of catheter colonization.[8] However, there were no cases of catheter-related bacteremia in either the control or the antibiotic-coated–catheter study arm. The choice of the antimicrobial used (cefazolin) in the coating of catheters raised several questions from an infection control perspective. With the emergence of nosocomial organisms resistant to various antimicrobial agents used in the treatment of bloodstream infections, such as β-lactams, glycopeptides, aminoglycosides, quinolones, and azoles, it is prudent to refrain from using such antimicrobial agents as prophylactic agents in the prevention of catheter-related infections.

As an alternative to therapeutic antibiotics used in the coating of catheters, Maki and colleagues used antiseptic agents such as chlorhexidine and silver sulfadiazine.[7] In a prospective randomized clinical trial that appeared in abstract form, Maki et al showed that catheters coated with chlorhexidine and silver sulfadiazine decreased the risk of catheter-related bloodstream infection by more than fourfold.[7] However, the protective efficacy of these catheters coated with chlorhexidine and silver sulfadiazine could not be demonstrated in two recently reported smaller studies.[13,14]

We recently have coated central venous catheters (CVCs) with a combination of minocycline and rifampin. These catheters were shown to have broad-spectrum in vitro inhibitory activity against staphylococcal organisms, various gram-negative

From the University of Texas, MD Anderson Cancer Center, Section of Infection Control, Houston, Texas.

Patent Disclosure: The patent describing the synergistic and unique activity of minocycline and rifampin in combination in protecting catheter surfaces from slime-producing staphylococcal organisms is the property of the University of Texas MD Anderson Cancer Center and Baylor College of Medicine, with Issam Raad and Rabih Darouiche as inventors. The patent was licensed to Cook Critical Care. Patent no. 5,217,493, June 8, 1993.

Address reprint requests to Issam Raad, MD, FACP, Chief, Section of Infection Control, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

96-ED-236. Raad II. Vascular catheters impregnated with antimicrobial agents: present knowledge and future direction. Infect Control Hosp Epidemiol *1997;18:227-229.*

bacteria, and *Candida albicans*.[10] This was significantly superior to the inhibitory activity of CVC coated with chlorhexidine and silver sulfadiazine and was not associated with the emergence of antibiotic-resistant bacteria.[11,12] This combination significantly decreased the risk of colonization and infection in a rabbit model, as well as in a multicenter prospective clinical trial.[11,12]

Based on the available reported data, CVCs impregnated with antimicrobial agents seem to be safe and efficacious in preventing catheter-related colonization and bloodstream infections.[2,7,8,12] However, several important questions related to this field of investigation need to be addressed and studied.

1. Should all vascular catheters be impregnated with antimicrobial agents? Does that include peripheral catheters?

2. Which patient population would benefit best from the use of such impregnated catheters?

3. What is the impact of using impregnated catheters on the cost of health care? Are these catheters cost-effective?

4. Which agents should be used to impregnate catheters, and which should be avoided to minimize the risk of emergence of organisms resistant to therapeutic antimicrobial agents?

Sherertz et al, as reported in this issue of the journal, have investigated in a prospective, randomized, double-blind study the role of chlorhexidine-coated peripheral venous catheters in preventing the risks of phlebitis and catheter colonization.[15] Catheters covered with chlorhexidine decreased the risk of phlebitis when compared with uncoated control catheters, but this decrease was not statistically significant. In addition, coated catheters did not decrease the risk of colonization as compared to control uncoated catheters. However, among catheters that were colonized with microorganisms, coating with chlorhexidine substantially decreased the risk of phlebitis (P=.07). Survival analysis showed that chlorhexidine-coated catheters decreased the risk of phlebitis only during the first 3 days of placement (P=.06). Because most peripheral catheters are removed within 3 days of placement, the decrease in the risk of phlebitis during the first 3 days will not have an impact on prolonging the duration of placement of short-term peripheral venous catheters. However, the study by Sherertz and colleagues is important in demonstrating the safety of catheters coated with chlorhexidine and the fact that they may decrease the risk of phlebitis during the first 3 days of placement. These data are consistent with previous data that have demonstrated that catheters coated with chlorhexidine alone do not increase the risk of inflammation compared with uncoated polyurethane catheters in a rabbit model.[16] Kamal et al studied a peripheral arterial catheter as part of a prospective, randomized study of catheters impregnated with cefazolin and demonstrated a decrease in the risk of colonization; however, this difference was not statistically significant.[8] Hence, at the present time, there is no firm evidence that antiseptic or antimicrobial coating of peripheral vascular catheters significantly decreases the risk of phlebitis or catheter-related bloodstream infections. Given the low risk of bloodstream infections associated with peripheral vascular catheters, the use of coated peripheral catheters might not be cost-effective.

The patient population that might benefit the most from antiseptic-coated or antimicrobial-coated vascular catheters would be those at the highest risk of bloodstream infection and those in whom the bloodstream infection would result in the highest risk for morbidity and mortality. This patient population includes critically ill patients with CVCs, for whom at least 4% of the CVCs are associated with a bloodstream infection resulting in 6.5 additional days in the intensive-care unit and an additional cost of $28,690 per survivor.[17,18] The attributable mortality of CVC-related bloodstream infections in that patient population is 25%.[18] Immunocompromised patients, such as cancer or human immunodeficiency virus patients receiving interleukin-2 or hyperalimentation therapy, may benefit from such devices. The role of antiseptic or antimicrobial impregnation of pulmonary artery catheters in critically ill patients also should be considered. Given the high cost of surgically placing subcutaneous ports and tunneled catheters in immunocompromised patients, silicone catheters coated with antimicrobial agents should be considered as a potentially cost-effective alternative that would eliminate the need for surgical implantation. To serve as a cost-effective alternative, silicone catheters should maintain an antimicrobial preservative in the silicone of the catheter for a long period of time and be inserted on an outpatient basis without the need for a surgical procedure requiring the operating room.

The risk of emerging multidrug-resistant nosocomial pathogens exists in any situation where antimicrobial agents are used. However, the concern related to antimicrobial resistance should not deter the medical community from using antimicrobial agents in a judicious prophylactic manner. To win the prophylactic war against emerging multidrug-resistant organisms, one should use the strategy of "divide and conquer." Therapeutic agents, such as glycopeptides, β-lactams, quinolones, and aminoglycoside antibiotics, used in the

treatment of bloodstream infections should not be used to coat vascular catheters or in a prophylactic manner. Antiseptic agents such as chlorhexidine and silver sulfadiazine, or antimicrobial agents such as fusidic acid, novobiocin, minocycline, rifampin, and polymyxin, could be considered for impregnating vascular catheters. The fact that vascular catheters impregnated with antimicrobial agents decreased the risk of colonization could have an impact on the excessive and unnecessary use of some antimicrobial agents. In many hospitals, vancomycin often is given to treat a febrile patient with a single positive blood culture for coagulase-negative staphylococci drawn through the CVC. The positive predictive value of a single blood culture positive for coagulase-negative staphylococci ranges from 4.1% to 26.4%.[19-22] Such positive cultures drawn through the CVC often are a byproduct of intraluminal or hub colonization of the catheter rather than a bloodstream infection associated with a skin organism. CVCs in which both the internal and external surfaces are coated with antimicrobial agents are less prone to luminal colonization and hence might result in a lower frequency of false-positive blood cultures for coagulase-negative staphylococci. This, in turn, might decrease the unnecessary use of vancomycin and therefore may decrease the risk of emergence of vancomycin-resistant antibiotics. It is important to realize that resistance is most likely to emerge in the setting of high bacterial colonization of a specific area (such as the gastrointestinal tract) or in patients with infections characterized by a high concentration of organisms (such as endocarditis). CVCs rarely are colonized with a high concentration of organisms, and hence the resistance to a synergistic combination of antimicrobial agents would be relatively low. However, to minimize the risk of antimicrobial resistance, the following principles should be considered: (1) Impregnate the external and internal surface of catheters with antimicrobials that are not used routinely as therapeutic agents in the treatment of bloodstream infections. (2) The antimicrobial agents should be used in combinations that are not antagonistic and, preferably, that are synergistic. (3) The antimicrobial combination should have broad-spectrum inhibitory activity against methicillin-resistant staphylococci, resistant gram-negative bacilli (such as *Stenotrophomonas maltophilia)*, and *Candida* species.

REFERENCES

1. Maki DG, Garman JK, Shapiro JM, Ringer M, Helgerson RB. An attachable silver-impregnated cuff for prevention of infection with central venous catheters: a prospective randomized multicenter trial. *Am J Med* 1988;85:307-314.
2. Trooskin SZ, Donetz AP, Harvey RA, Greco RS. Prevention of catheter sepsis by antibiotic bonding. *Surgery* 1985;97:547-551.
3. Bach A, Bohrer H, Motsch J, Martin E, Geiss HK, Sonntag HG. Prevention of bacterial colonization of intravenous catheters by antiseptic impregnation of polyurethane polymers. *J Antimicrob Chemother* 1994;33:969-978.
4. Sherertz RJ, Forman DM, Solomon DD. Efficacy of dicloxacillin-coated polyurethane catheters in preventing subcutaneous *Staphylococcus aureus* infection in mice. *Antimicrob Agents Chemother* 1989;33:1174-1178.
5. Sherertz RJ, Carruth A, Hampton AA, Byron MP, Solomon DD. Efficacy of antibiotic-coated catheters in preventing subcutaneous *Staphylococcus aureus* infection in rabbits. *J Infect Dis* 1993;167:98-106.
6. Greenfeld JI, Sampath L, Popilskis SJ, Brunnert SR, Stylianos S, Modak S. Decreased bacterial adherence and biofilm formation on chlorhexidine and silver sulfadiazine-impregnated central venous catheters implanted in swine. *Crit Care Med* 1995; 23:894-900.
7. Maki DG, Wheeler SJ, Stolz SM. Study of a novel antiseptic-coated central venous catheter. *Crit Care Med* 1991; 19(suppl):99S. Abstract.
8. Kamal GD, Pfaller MA, Rempe LE, Jebson PJR. Reduced intravascular catheter infection by antibiotic bonding: a prospective, randomized, controlled trial. *JAMA* 1991;265:2364-2368.
9. Mermel LA, Stolz SM, Maki DG. Surface antimicrobial activity of heparin-bonded and antiseptic impregnated vascular catheters. *J Infect Dis* 1993;167:920-924.
10. Raad I, Darouiche R, Hachem R, Sacilowski M, Bodey GP. Antibiotics and prevention of microbial colonization of catheters. *Antimicrob Agents Chemother* 1995;39:2397-2400.
11. Raad I, Darouiche R, Hachem R, Mansouri M, Bodey GP. The broad spectrum activity and efficacy of catheters coated with minocycline and rifampin. *J Infect Dis* 1996;173:418-424.
12. Raad I, Darouiche R. Central venous catheters (CVC) coated with minocycline and rifampin (M/R) for the prevention of catheter-related bacteremia (CRB). In: 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco, CA; September 1995. Abstract J7.
13. Ciresi DL, Albrecht RM, Volkers PA, Scholten DJ. Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. *Am Surg* 1996;62:641-646.
14. Pemberton LB, Ross V, Cuddy P, Kremer H, Fessler T, McGurk E. No difference in catheter sepsis between standard and antiseptic central venous catheters. *Arch Surg* 1996;131:986-989.
15. Sherertz RJ, Stephens JL, Marosok RD, et al. The risk of peripheral vein phlebitis associated with chlorhexidine-coated catheters. A randomized, double-blind trial. *Infect Control Hosp Epidemiol* 1997;18:230-236.
16. Carruth WA, Byron MP, Solomon DD, White WL, Stoddard GJ, Sherertz RJ. Subcutaneous catheter-related inflammation in a rabbit model is predictive of peripheral vein phlebitis in human volunteers. *J Biomed Mater Res* 1994;28:259-267.
17. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271:1598-1601.
18. Heiselman D. Nosocomial bloodstream infection in the critically ill. *JAMA* 1994;272:1819-1820. Letter.
19. Kirchoff LV, Sheagren JN. Epidemiology and clinical significance of blood cultures positive for coagulase-negative staphylococcus. *Infect Control* 1985;6:479-486.
20. Fidalgo S, Vasquez F, Mendoza MC, Perez F, Mendez FJ. Bacteremia due to *Staphylococcus epidermidis:* microbiologic, epidemiologic, clinical, and prognostic features. *Rev Infect Dis* 1990;12:520-528.
21. Ringberg H, Thoren A, Bredberg A. Evaluation of coagulase-negative staphylococci in blood cultures: a prospective clinical and microbiological study. *Scand J Infect Dis* 1991;23:315-323.
22. Herwaldt LA, Geiss M, Kao C, Pfaller MA. The positive predictive value of isolating coagulase-negative staphylococci from blood cultures. *Clin Infect Dis* 1996;22:14-20.