The Promise of Novel Technology for the Prevention of Intravascular Device–Related Bloodstream Infection. II. Long-Term Devices

Christopher J. Crnich[1] and Dennis G. Maki[1,2]

[1]Section of Infectious Diseases, Department of Medicine, University of Wisconsin Medical School, and [2]Infection Control Department and Center for Trauma and Life Support, University of Wisconsin Hospital and Clinics, Madison

Intravascular devices (IVDs) are widely used for vascular access but are associated with a substantial risk of IVD-related bloodstream infection (BSI). The development of novel technologies based on our understanding of pathogenesis promises a quantum reduction in IVD-related infections in an era of growing nursing shortage. Infections of long-term IVDs (most are in place for ≥10 days), including cuffed and tunneled central venous catheters (CVCs), implanted subcutaneous central venous ports, and peripherally inserted central catheters (PICCs), are primarily due to microorganisms that gain access to the catheter hub and lumen. Novel securement devices and antibiotic lock solutions have been shown to reduce the risk of IVD-related BSI in prospective randomized trials. The challenge for the future will be to identify new preventative technologies and to begin to more-widely adapt those technologies that have already been shown to be efficacious and cost effective.

Long-term intravascular devices (IVDs), such as cuffed Hickman- and Broviac-type catheters, cuffed hemodialysis central venous catheters (CVCs), subcutaneous central venous ports, and peripherally inserted central catheters (PICCs), are indispensable for the care of patients who require prolonged parenteral nutrition or frequent transfusion of blood products or intravenous medications. Historically, the risk of infection associated with the use of these devices has been expressed as the number of BSIs per 100 devices used. However, the Centers for Disease Control and Prevention (CDC) now recommends that rates of IVD-related (IVDR) bloodstream infection (BSI) be expressed per 1000 IVD-days. This recommendation is logical, because it takes into account widely varying risks of IVDR BSI over time for different types of IVDs—for example, in

general, although the rates of IVDR BSI per 100 IVDs used are usually higher for long-term devices, the risk per 1000 IVD-days is usually considerably lower than that for short-term IVDs, such as noncuffed, nontunneled CVCs (table 1) [1, 2].

The risk of IVDR infection, its pathogenesis, general strategies for prevention, and the promise of novel technology engineered to reduce the risk of IVDR BSIs associated with short-term IVDs were reviewed in the first part of this 2-part series [3]. The present article complements and completes our review by examining novel technology for the prevention of IVDR BSIs associated with long-term devices.

PATHOGENESIS

As described in the first part of our review [3], microorganisms usually must first adhere to the intraluminal or extraluminal surface of the IVD before infection of the bloodstream can occur. In contrast to the situation for short-term IVDs, contamination of the catheter hub and lumen appears to be the predominant mode of BSI associated with long-term, permanent IVDs (most of which have been in place for ≥10 days) [4–8]. In general, basic infection-control practices that have been shown to be effective for the prevention of IVDR BSIs

Table 1. Rates of bloodstream infection (BSI) caused by various types of devices used for vascular access.

Device	No. of prospective studies	No. of device-related BSIs			
		Per 100 catheters		Per 1000 catheter-days	
		Pooled mean	95% CI	Pooled mean	95% CI
Peripheral venous catheter	13	0.2	0.1–0.3	0.6	0.3–1.2
Arterial catheter	6	1.5	0.9–2.4	2.9	1.8–4.5
Short-term, nonmedicated CVC	61	3.3	3.3–4.0	2.3	2.0–2.4
Pulmonary-artery catheter	12	1.9	1.1–2.5	5.5	3.2–12.4
Hemodialysis catheter					
Noncuffed	15	16.2	13.5–18.3	2.8	2.3–3.1
Cuffed	5	6.3	4.2–9.2	1.1	0.7–1.6
Peripherally inserted central catheter	8	1.2	0.5–2.2	0.4	0.2–0.7
Long-term tunneled and cuffed CVC	18	20.9	18.2–21.9	1.2	1.0–1.3
Subcutaneous central venous port	13	5.1	4.0–6.3	0.2	0.1–0.2

NOTE. Adapted from Kluger and Maki [2], based on 206 published prospective studies where every device was evaluated for infection. CVC, central venous catheter.

associated with short-term IVDs (most of which have been in place for <10 days) [3, 9] are also likely to be effective for long-term devices—for example, the use of maximal sterile barrier precautions at IVD insertion [10] and use of more-effective cutaneous antisepsis [11–14]. However, technology that reduces intraluminal colonization in addition to extraluminal invasion of the insertion tract should provide additional protection against IVDR BSIs associated with long-term IVDs.

STRATEGIES FOR PREVENTION OF IVDR BSIS ASSOCIATED WITH LONG-TERM IVDS

Innovative IVD Design

Subcutaneous cuffs for long-term CVCs. Surgically implanted Hickman and Broviac catheters incorporate a subcutaneous dacron cuff, which becomes ingrown by host tissue, creating a mechanical barrier against invasion of the tract by skin organisms. Rates of BSIs per 1000 IVD-days for these catheters are far lower than those for short-term, percutaneously-inserted, noncuffed CVCs inserted in the intensive care unit (table 1) [1, 2], and cuffed, tunneled CVCs can be considered a quantum advance in the safety of long-term vascular access. The use of dacron cuffs on large, dual-lumen hemodialysis catheters has substantially reduced the risk of IVDR BSI in patients who require long-term central access for dialysis [15, 16].

Subcutaneous central venous ports. Surgically implanted subcutaneous central venous ports, which can be accessed intermittently with a steel needle, have been associated with the lowest rates of IVDR BSI (table 1). A prospective observational study of Hickman catheters and central ports involving patients in an oncology ward showed that, for patients who require intermittent central access, subcutaneous central venous ports appear to be considerably safer with regard to the risk of IVDR BSI [17].

Subcutaneous central venous ports are ideal and preferred when central venous access is intermittently required for short periods (e.g., for periodic chemotherapy). For patients who require prolonged central access (e.g., for parenteral nutrition), a port generally should not be used; for these patients, a cuffed, tunneled catheter or a PICC is preferred [9].

Attachable silver-impregnated cuffs. Studies involving the use of short-term devices have shown some benefit with use of an attachable silver cuff, primarily by preventing deep invasion of cutaneous microorganisms into the insertion tract. Because the cuff cannot prevent luminal colonization, attachable cuffs would not be expected to significantly impact the rates of IVDR BSI associated with long-term dacron-cuffed catheters, and subsequent studies have confirmed this postulate (table 2) [18–20].

PICCs. Studies suggest that PICCs are associated with a substantially lower risk of IVDR BSI than standard, nontunneled, noncuffed CVCs (table 1) [2, 21, 22], perhaps because the bacterial colonization on the arm is less dense than that on the sites used for conventional CVCs (i.e., the neck, the upper chest, and the groin) [23]. However, nearly all of the published data on PICC-related infection are from studies in the outpatient setting, and the prospective studies in which PICCs were used exclusively in hospitalized patients suggest that the risk of IVDR BSI is similar to that seen with cuffed and tunneled CVCs [24, 25].

Table 2. Meta-analyses of prospective, randomized clinical trials of novel technologies for prevention of intravenous device (IVD)–related (IVDR) bloodstream infections (BSIs) involving long-term IVDs.

| Technology | No. of trials | No. of IVDR BSIs/ no. of IVDs studied | | RR (95% CI) | P |
		Study technology	Control device		
Silver-impregnated cuff	3	40/181	43/205	1.05 (0.66–1.71)	.80
Securement device	2	1/144	13/135	0.07 (0.00–0.78)	<.01
Chlorhexidine sponge dressing	1	12/314	11/341	1.18 (0.39–4.06)	.83
Silver-impregnated CVC	1	4/47	6/44	0.62 (0.05–4.12)	.51
Antibiotic lock	6	13/257	40/267	0.34 (0.18–0.62)	<.01
Prophylactic thrombolysis	2	75/396	97/393	0.77 (0.59–1.00)	.06

NOTE. Data are only from prospective, randomized trials that involved long-term, centrally placed IVDs (i.e., cuffed and tunneled central venous catheters [CVCs], peripherally inserted central catheters, and subcutaneous central venous ports) and that reported IVDR BSI as an outcome.

Novel Securement Devices

Recently, a novel sutureless device for securing noncuffed vascular catheters became available (StatLock; Venetec International). In a randomized trial of the device, premature loss of pediatric and adult PICCs due to accidental extrusion and PICC-associated thrombosis were significantly reduced [26, 27]. Furthermore, in an adult PICC study population, the incidence of catheter-related BSI was significantly reduced with the use of the novel securement device (table 2) [26]. The potential for this device to reduce infection may derive from the elimination of festering skin suture wounds that are contiguous to the newly inserted catheter and from minimization of the to-and-fro pistoning of the catheter, which may promote invasion of the tract by cutaneous microorganisms through capillary action [28].

Novel Dressings

Garland et al. [29] examined the utility of the chlorhexidine sponge dressing in a multicenter trial that involved 6 neonatal intensive care units; 75% of the catheters studied were PICCs. The study showed that the novel dressing, replaced weekly, yielded results similar to those of gauze and tape combined with periodic cutaneous disinfection with 10% povidone-iodine, with regard to the prevention of cutaneous colonization and catheter-related BSI (table 2). Although they were well tolerated by full-term infants, use of the chlorhexidine dressing in low-birth-weight (i.e., <1000 g) neonates was associated with a 15% incidence of dermatotoxicity. Additional studies are required before the chlorhexidine sponge dressing can be recommended for routine use with long-term IVDs.

Silver-Coated Catheters

In contrast to the extensive research that has gone into the study of novel surfaces for short-term devices, very little data have been published on novel surfaces for long-term devices. In a single study of long-term, tunneled hemodialysis catheters, Trerotola et al. [30] found no difference between silver-coated catheters and control catheters with regard to the rates of BSI (table 2).

Antibiotic Lock Solutions

The prophylactic use of systemic antibiotics at the time of IVD insertion or implantation has not proven to be effective in reducing the incidence of IVDR BSI [31–33] and is strongly discouraged in the new Hospital Infection Control Practices Advisory Committee (HICPAC) draft guideline [9]. However, studies of continuous infusion of vancomycin incorporated into total parenteral nutrition admixtures have shown reduced rates of coagulase-negative staphylococcal BSI in low-birth-weight infants [34, 35]. Unfortunately, this form of prophylaxis results in prolonged low levels of vancomycin in blood and tissue, a milieu conducive to promoting vancomycin resistance.

The antibiotic lock is a novel form of local antibiotic prophylaxis in which an antibiotic solution is instilled into the catheter lumen and allowed to dwell for a defined period of time (usually 6–12 h), after which it is removed. Messing et al. [36] first examined the utility of antibiotic lock solutions for the treatment of device-related BSIs associated with long-term IVDs. Subsequent small, uncontrolled studies involving long-term CVCs that were infected with gram-positive cocci (other than *Staphylococcus aureus*) or gram-negative bacilli have also shown benefit [36–41]. The success of continuous vancomycin infusions in the prevention of IVDR BSIs, as well as uncontrolled studies that have demonstrated that antibiotic lock solutions have a beneficial therapeutic effect on established IVD BSIs, suggests that antibiotic lock solutions may be effective for the prevention of IVDR BSIs associated with long-term devices.

There have been 6 prospective, randomized trials of the use of antibiotic lock solutions for the prevention of BSIs associated with long-term IVDs (table 2) [42–47]. Two of these studies lacked statistical power to detect a significant difference in BSI [43, 44], and the 4 remaining studies found a statistically significant benefit [42, 45–47]. The largest trial, by Henrickson et al. [46], randomized 126 pediatric oncology patients (36,944 IVD-days) who had recently had a tunneled CVC placed to 3 prophylactic lock regimens: heparin (10 U/mL; control), heparin and vancomycin (25 μg/mL), and heparin, vancomycin, and ciprofloxacin (2 μg/mL). Prophylactic use of the vancomycin-ciprofloxacin lock solution was associated with a markedly reduced rate of IVDR infection, compared with heparin alone (0.55 versus 1.72 cases per 1000 IVD-days; $P = .005$). Similarly, the rate of infection for the vancomycin lock solution was significantly reduced (0.37 cases per 1000 IVD-days; $P = .004$).

The 2 lock solutions (heparin-vancomycin and heparin-vancomycin-ciprofloxacin) studied by Henrickson et al. [46] showed comparable protection against gram-positive and gram-negative IVDR infections. Unfortunately, the investigators failed to distinguish local infections from true IVDR BSIs in the final data, which limits one's ability to fully analyze the results of this study. Furthermore, although the rates of nosocomial colonization or infection with vancomycin-resistant enterococci (as detected by clinical cultures ordered by patient's physicians) were similar in the 3 groups, no effort was made to proactively assess the impact of an antibiotic lock solution on nosocomial colonization with vancomycin-resistant enterococci, methicillin-resistant *S. aureus,* and fluoroquinolone-resistant gram-negative bacilli in the study population.

A subsequent randomized trial involving a neonatal population showed an 80% reduction in PICC-related BSIs (RR, 0.20; $P = .03$) [47]. This study used a vancomycin lock solution for 20 or 60 min twice per day and prospectively screened for colonization and infection with vancomycin-resistant organisms in exposed infants; no such colonization or infection was found.

The effectiveness of a vancomycin lock solution for the prevention of BSIs involving subcutaneous central ports has also been reported in a historical-control study [48]. In that study, the rates of *Staphylococcus epidermidis* bacteremia decreased from 0.80 cases per 1000 IVD-days before the vancomycin lock solution was used routinely to 0.17 cases per 1000 IVD-days during the 3 years that the vancomycin lock solution was used routinely ($P < .0001$).

A novel lock solution containing minocycline and ethylenediaminetetraacetate (M-EDTA) was recently reported to have prevented recurrent BSIs in 3 patients with long-term IVDs in place who had experienced numerous IVDR BSIs before use of the anti-infective lock solution [49]. In a randomized trial involving patients with long-term hemodialysis CVCs, use of an M-EDTA flush solution resulted in significantly reduced rates of explanted catheter colonization (8% versus 69% of catheters; $P = .005$); however, the rates of IVDR BSI were not reported [50].

Taurolidine, a derivative of the aminosulfonic acid taurine, is a biologically well-tolerated antiseptic with broad-spectrum antimicrobial activity [51]. In uncontrolled trials, the use of a taurolidine lock solution appeared to substantially reduce the rate of catheter-related BSI associated with hemodialysis catheters [52] and other long-term IVDs [53].

Many of the aforementioned studies used a lock solution that contained vancomycin. It seems unlikely that microorganisms in the exposed patient's flora could develop resistance to vancomycin from the minute quantities of drug in a catheter lumen (<15 μg), yet there is justified concern about the possible effect of wide prophylactic use of antibiotic lock solutions. Much more data are needed—specifically, data from randomized studies that prospectively assess the impact on nosocomial colonization by vancomycin-resistant enterococci, methicillin-resistant *S. aureus,* and other antibiotic-resistant microorganisms—before their routine use can be recommended. However, because antibiotic lock solutions clearly reduce the risk of IVDR BSI associated with long-term IVDs, the new HICPAC draft guideline [9] considers their use acceptable *in individual cases* in which a patient who requires indefinite vascular access (e.g., a patient with short-bowel syndrome or who is undergoing hemodialysis) continues to experience IVDR BSIs despite stringent compliance with infection-control guidelines.

Prophylactic Thrombolysis

Prophylactic use of anticoagulation agents, including mini-dose heparin [54] and warfarin [55, 56], has been shown to reduce catheter thrombosis associated with CVCs in randomized trials, but the effect on IVDR infection has not been reported. Three recent randomized trials of prophylactic installation of urokinase (5000 IU/mL every 1–2 or 3–4 weeks) into long-term IVDs have shown a reduced incidence of thrombosis and premature IVD loss [57–59]. Of more importance, 2 of these trials also showed a reduction in IVDR BSIs (table 2) [57, 58]. Prophylactic thrombolysis appears to be well tolerated, but a cost-benefit analysis of this novel but expensive practice needs to be performed.

THE FUTURE OF PREVENTION WITH ALL TYPES OF IVDS

The new HICPAC draft guideline [9] now recommends the use of chlorhexidine for cutaneous antisepsis with all forms of vascular access. Anti-infective–impregnated CVCs are recom-

mended if institutional rates of infection are >3.3 BSIs per 1000 IVD-days despite full adherence to maximal barrier precautions, especially for patients at high risk for IVDR BSI (e.g., patients receiving total parenteral nutrition, those who are neutropenic, or those who have a CVC that is likely to remain in place for >4 days). Moreover, the Agency for Healthcare Research and Quality has also recently recommended wide-scale use of chlorhexidine–silver-sulfadiazine–impregnated CVCs and minocycline-rifampin–coated CVCs to prevent catheter-related BSIs [60].

Unfortunately, based on informal surveys of infection-control practitioners (D.G.M., unpublished data), it appears that adoption of novel technologies for the prevention of IVDR infection by health care institutions has been disappointingly slow, primarily because administrators and purchasing agents see only a premium acquisition cost and are oblivious to the benefit gained in the reduction of morbidity rates, mortality rates, and length of stay in the hospital. The published trials involving new technologies show that many of these items are not only effective, but they are also cost effective [61–66] and warrant adoption by hospitals and other health care groups.

Future research must strive to improve our understanding of the biological forces governing cutaneous colonization in order to develop more-effective strategies to suppress it, to find new antiseptics that exhibit greater and more-prolonged levels of surface activity, to better delineate the molecular mechanisms of microbial adherence to prosthetic surfaces in order to develop new materials intrinsically resistant to colonization, and to design IVDs that more-effectively deny microbial access.

It is essential that future trials have adequate power to conclusively determine the efficacy or lack of efficacy of novel technologies for the prevention of IVDR BSIs and utilize molecular subtyping techniques [14, 62–64, 67, 68] to identify the source of *every* IVDR BSI. Moreover, if novel technologies use anti-infective materials, trials evaluating their effectiveness must seek to assure clinicians that the technology does not promote resistance to the anti-infective agent. Finally, it is essential to ensure that the innovation does not result in a paradoxically increased risk of other, unexpected complications in exposed patients [69, 70] or health care providers.

References

1. Maki D, Mermel L. Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. Hospital Infections. 4th ed. Philadelphia: Lippincott-Raven, **1998**:689–724.
2. Kluger D, Maki D. The relative risk of intravascular device–related bloodstream infections with different types of intravascular devices in adults: a meta-analysis of 206 published studies [abstract]. Infect Control Hosp Epidemiol **1999**; 21:95–6.
3. Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device–related bloodstream infection. I. Pathogenesis and short-term devices. Clin Infect Dis **2001**; 34:1232–42.
4. Cheesbrough JS, Finch RG, Burden RP. A prospective study of the mechanisms of infection associated with hemodialysis catheters. J Infect Dis **1986**; 154:579–89.
5. Flynn PM, Shenep JL, Stokes DC, Barrett FF. In situ management of confirmed central venous catheter–related bacteremia. Pediatr Infect Dis J **1987**; 6:729–34.
6. Weightman NC, Simpson EM, Speller DC, Mott MG, Oakhill A. Bacteraemia related to indwelling central venous catheters: prevention, diagnosis and treatment. Eur J Clin Microbiol Infect Dis **1988**; 7:125–9.
7. Maki DG, Stolz SM, McCormick RD, Spiegel C. Possible association of a commercial needleless system with central venous catheter–related bacteremia [abstract J201]. In: Programs and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy (Orlando, FL). American Society for Microbiology, **1994**:215.
8. Maki DG, Narans LL, Banton J. A prospective study of the pathogenesis of PICC-related BSI [abstract K-10]. In: Programs and abstracts of the 38th Interscience Conference of Antimicrobial Agents and Chemotherapy (San Diego). American Society of Microbiology, **1998**:502.
9. O'Grady NP, Alexander M, Dellinger EP, et al. Draft guideline for the prevention of intravascular catheter–related infections. Available for download at: http://www.cdc.gov/ncidod/hip/Ivguide.htm. Accessed 15 October **2001**.
10. Raad, II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter–related infections by using maximal sterile barrier precautions during insertion. Infect Control Hosp Epidemiol **1994**; 15:231–8.
11. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. Lancet **1991**; 338: 339–43.
12. Mimoz O, Karim A, Mercat A, et al. Chlorhexidine compared with povidone-iodine as skin preparation before blood culture: a randomized, controlled trial. Ann Intern Med **1999**; 131:834–7.
13. Humar A, Ostromecki A, Direnfeld J, et al. Prospective randomized trial of 10% povidone-iodine versus 0.5% tincture of chlorhexidine as cutaneous antisepsis for prevention of central venous catheter infection. Clin Infect Dis **2000**; 31:1001–7.
14. Maki DG, Knasinski V, Narans LL, Gordon BJ. A randomized trial of a novel 1% chlorhexidine–75% alcohol tincture versus 10% povidone-iodine for cutaneous disinfection with vascular catheters [abstract 142]. In: Programs and abstracts of the 31st Annual Meeting of the Society for Hospital Epidemiology of America (Toronto). Society for Hospital Epidemiology of America, **2001**:70.
15. Cappello M, De Pauw L, Bastin G, et al. Central venous access for haemodialysis using the Hickman catheter. Nephrol Dial Transplant **1989**; 4:988–92.
16. Dryden MS, Samson A, Ludlam HA, Wing AJ, Phillips I. Infective complications associated with the use of the Quinton "Permcath" for long-term central vascular access in haemodialysis. J Hosp Infect **1991**; 19:257–62.
17. Groeger JS, Lucas AB, Thaler HT, et al. Infectious morbidity associated with long-term use of venous access devices in patients with cancer. Ann Intern Med **1993**; 119:1168–74.
18. Clementi E, Marie O, Arlet G, Villers S, Boudaoud S, Falkman H. Usefulness of an attachable silver-impregnated cuff for prevention of catheter-related sepsis (CRS) [abstract]? In: Programs and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). American Society of Microbiology, **1991**.
19. Groeger JS, Lucas AB, Coit D, et al. A prospective, randomized evaluation of the effect of silver impregnated subcutaneous cuffs for preventing tunneled chronic venous access catheter infections in cancer patients. Ann Surg **1993**; 218:206–10.
20. Dahlberg PJ, Agger WA, Singer JR, et al. Subclavian hemodialysis catheter infections: a prospective, randomized trial of an attachable silver-impregnated cuff for prevention of catheter-related infections. Infect Control Hosp Epidemiol **1995**; 16:506–11.
21. Graham DR, Keldermans MM, Klemm LW, Semenza NJ, Shafer ML.

Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. Am J Med **1991**; 91:95S–100S.

22. Duerksen DR, Papineau N, Siemens J, Yaffe C. Peripherally inserted central catheters for parenteral nutrition: a comparison with centrally inserted catheters. JPEN J Parenter Enteral Nutr **1999**; 23:85–9.

23. Maki DG. Marked differences in skin colonization of the insertion site for central venous, arterial and peripheral IV catheters: the major reason for differing risks of catheter related infection [abstract 712]? In: Programs and abstracts of the 30th Interscience Conference of Antimicrobial Agents and Chemotherapy (Atlanta). American Society for Microbiology, **1990**:205.

24. Cowl CT, Weinstock JV, Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr **2000**; 19:237–43.

25. Janes M, Kalyn A, Pinelli J, Paes B. A randomized trial comparing peripherally inserted central venous catheters and peripheral intravenous catheters in infants with very low birth weight. J Pediatr Surg **2000**; 35:1040–4.

26. Schears GJ, Liebeig C, Frey AM, et al. StatLock catheter securement device significantly reduces central venous catheter complications [abstract]. In: National patient safety foundation compendium on best practice. Chicago: Joint Commission on Accreditation of Healthcare Organization, **2001**.

27. Yamamoto AJ, Solomon JA, Soulen MC, et al. Sutureless securement device reduces complications of peripherally inserted central venous catheters [abstract]. In: Programs and abstracts of the 26th Annual Scientific Meeting of the Society of Cardiovascular and Interventional Radiologists. (San Antonio, TX). **2001**:125.

28. Cooper GL, Schiller AL, Hopkins CC. Possible role of capillary action in pathogenesis of experimental catheter-associated dermal tunnel infections. J Clin Microbiol **1988**; 26:8–12.

29. Garland JS, Harris MC, Alex CP, et al. A randomized trial comparing povidone-iodine to chlorhexidine gluconate impregnated dressing for prevention of central venous catheter infections in neonates. Pediatrics **2001**; 107:1431–7.

30. Trerotola SO, Johnson MS, Shah H, et al. Tunneled hemodialysis catheters: use of a silver-coated catheter for prevention of infection—a randomized study. Radiology **1998**; 207:491–6.

31. McKee R, Dunsmuir R, Whitby M, Garden OJ. Does antibiotic prophylaxis at the time of catheter insertion reduce the incidence of catheter-related sepsis in intravenous nutrition? J Hosp Infect **1985**; 6:419–25.

32. Ranson MR, Oppenheim BA, Jackson A, Kamthan AG, Scarffe JH. Double-blind placebo controlled study of vancomycin prophylaxis for central venous catheter insertion in cancer patients. J Hosp Infect **1990**; 15:95–102.

33. Ljungman P, Hagglund H, Bjorkstrand B, Lonnqvist B, Ringden O. Peroperative teicoplanin for prevention of gram-positive infections in neutropenic patients with indwelling central venous catheters: a randomized, controlled study. Support Care Cancer **1997**; 5:485–8.

34. Kacica MA, Horgan MJ, Ochoa L, Sandler R, Lepow ML, Venezia RA. Prevention of gram-positive sepsis in neonates weighing less than 1500 grams. J Pediatr **1994**; 125:253–8.

35. Spafford PS, Sinkin RA, Cox C, Reubens L, Powell KR. Prevention of central venous catheter–related coagulase-negative staphylococcal sepsis in neonates. J Pediatr **1994**; 125:259–63.

36. Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier JJ. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. JPEN J Parenter Enteral Nutr **1988**; 12:185–9.

37. Messing B, Man F, Colimon R, Thuillier F, Beliah M. Antibiotic lock technique is an effective treatment of bacterial catheter-related sepsis during parenteral nutrition. Clin Nutr **1990**; 9:220–4.

38. Rao JS, O'Meara A, Harvey T, Breatnach F. A new approach to the management of Broviac catheter infection. J Hosp Infect **1992**; 22:109–16.

39. Johnson DC, Johnson FL, Goldman S. Preliminary results treating persistent central venous catheter infections with the antibiotic lock technique in pediatric patients. Pediatr Infect Dis J **1994**; 13:930–1.

40. Krzywda EA, Andris DA, Edmiston CE Jr, Quebbeman EJ. Treatment of Hickman catheter sepsis using antibiotic lock technique. Infect Control Hosp Epidemiol **1995**; 16:596–8.

41. Benoit JL, Carandang G, Sitrin M, Arnow PM. Intraluminal antibiotic treatment of central venous catheter infections in patients receiving parenteral nutrition at home. Clin Infect Dis **1995**; 21:1286–8.

42. Schwartz C, Henrickson KJ, Roghmann K, Powell K. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin-susceptible organisms. J Clin Oncol **1990**; 8:1591–7.

43. Rackoff WR, Weiman M, Jakobowski D, et al. A randomized, controlled trial of the efficacy of a heparin and vancomycin solution in preventing central venous catheter infections in children. J Pediatr **1995**; 127:147–51.

44. Daghistani D, Horn M, Rodriguez Z, Schoenike S, Toledano S. Prevention of indwelling central venous catheter sepsis. Med Pediatr Oncol **1996**; 26:405–8.

45. Carratala J, Niubo J, Fernandez-Sevilla A, et al. Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter–related infection in neutropenic patients with cancer. Antimicrob Agents Chemother **1999**; 43:2200–4.

46. Henrickson KJ, Axtell RA, Hoover SM, et al. Prevention of central venous catheter–related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. J Clin Oncol **2000**; 18:1269–78.

47. Garland JS, Henrickson KJ, Maki DG. A prospective randomized trial of vancomycin-heparin lock for prevention of catheter-related bloodstream infection in an NNICU [abstract 1734]. In: Programs and abstracts of the 2002 Annual Meeting of the Pediatric Academic Societies (Baltimore). Pediatric Academic Societies, **2002**:235.

48. Rubie H, Juricic M, Claeyssens S, et al. Morbidity using subcutaneous ports and efficacy of vancomycin flushing in cancer. Arch Dis Child **1995**; 72:325–9.

49. Raad I, Buzaid A, Rhyne J, et al. Minocycline and ethylenediaminetetraacetate for the prevention of recurrent vascular catheter infections. Clin Infect Dis **1997**; 25:149–51.

50. Bleyer A, Mason L, Raad I, Sherertz RJ. A randomized, double-blind trial comparing minocycline/EDTA vs. heparin as flush solution for hemodialysis catheters [abstract]. Infect Control Hosp Epidemiol **1999**; 21:100.

51. Torres-Viera C, Thauvin-Eliopoulos C, Souli M, et al. Activities of taurolidine in vitro and in experimental enterococcal endocarditis. Antimicrob Agents Chemother **2000**; 44:1720–4.

52. Sodemann K, Polaschegg HD, Feldmer B. Two years' experience with Dialock and CLS (a new antimicrobial lock solution). Blood Purification **2001**; 19:251–4.

53. Jurewitsch B, Lee T, Park J, Jeejeebhoy K. Taurolidine 2% as an antimicrobial lock solution for prevention of recurrent catheter-related bloodstream infections. JPEN J Parenter Enteral Nutr **1998**; 22:242–4.

54. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. Chest **1998**; 113:165–71.

55. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. Ann Intern Med **1990**; 112:423–8.

56. Boraks P, Seale J, Price J, et al. Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. Br J Haematol **1998**; 101:483–6.

57. Fraschini G, Becker M, Bruso P, Wang Z, Ruber M. Comparative trial of urokinase (uk) vs. heparin (h) as prophylaxis for central venous

ports [abstract]. In: Programs and abstracts of the 27th Annual Meeting of the American Society of Clinical Oncology (ASCO; Orlando, FL). ASCO, **1991**:337.

58. Ray CE, Jr., Shenoy SS, McCarthy PL, Broderick KA, Kaufman JA. Weekly prophylactic urokinase instillation in tunneled central venous access devices. J Vasc Interv Radiol **1999**; 10:1330–4.

59. Jones GR, Dillon PW, Bagnall-Reeb H, Buckley J, Haase GM. Urokinase for prevention of central venous catheter occlusions and infections [abstract]. J Pediatr Hematol Oncol **2001**; 23:A26.

60. Saint S. Prevention of intravascular catehter-associated infections. AHRQ evidence report. Making health care safer: a critical analysis of patient safety practices. Available at: http://www.ahrq.gov/clinic/ptsafety/spotlight.htm. Accessed 15 October **2001**.

61. Booth F, Cohen I, Kerins R, Lawler D. Are antibacterially impregnated catheters cost effective [abstract 7]? Crit Care Med **1996**; 24(Suppl 1): A45.

62. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter–related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. Ann Intern Med **1997**; 127:257–66.

63. Maki DG, Mermel LA, Kluger DM, et al. The efficacy of a chlorhexidine-impregnated sponge (biopatch) for the prevention of intravascular catheter–related infection—a prospective, randomized, controlled, multicenter trial [abstract J64]. In: Programs and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (Toronto). American Society for Microbiology, **2000**:230.

64. Raad I, Darouiche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. The Texas Medical Center Catheter Study Group. Ann Intern Med **1997**; 127:267–74.

65. Saint S, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter–related infection: are antimicrobial catheters useful? Infect Control Hosp Epidemiol **2000**; 21:375–80.

66. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. JAMA **1999**; 282:554–60.

67. Maki DG, Stolz SS, Wheeler S, Mermel LA. A prospective, randomized trial of gauze and two polyurethane dressings for site care of pulmonary artery catheters: implications for catheter management. Crit Care Med **1994**; 22:1729–37.

68. Darouiche RO, Raad, II, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. N Engl J Med **1999**; 340:1–8.

69. Cookson ST, Ihrig M, O'Mara EM, et al. Increased bloodstream infection rates in surgical patients associated with variation from recommended use and care following implementation of a needleless device. Infect Control Hosp Epidemiol **1998**; 19:23–7.

70. Danzig LE, Short LJ, Collins K, et al. Bloodstream infections associated with a needleless intravenous infusion system in patients receiving home infusion therapy. JAMA **1995**; 273:1862–4.