

Catheter-Related Bloodstream Infection

Matthew R. Goede, MD^a, Craig M. Coopersmith, MD^{b,*}

KEYWORDS

- Central venous catheter • Infection
- Catheter-related bloodstream infection
- Intensive care unit • Bacteremia • Morbidity

Central venous catheters (CVCs) play an essential role in patient care, both in the inpatient and outpatient setting. CVCs can be used to measure central venous pressure, deliver parenteral nutrition, and administer medications that cannot be given safely by a peripheral catheter. The use of CVCs carries a risk of the development of catheter-related bloodstream infection (CR-BSI), however, which can be associated with significant morbidity and mortality. Although a subset of CR-BSIs have historically been believed to be preventable, recent evidence suggests that most, if not all, episodes of CR-BSI are actually preventable. This has recently resulted in CR-BSI being listed as a “never” complication by the Centers for Medicare and Medicaid Services.¹ Based on this designation, hospitals will no longer receive payment when Medicare patients develop CR-BSI, and it is expected that many private insurers also will rapidly adopt this policy. Between its designation as a “never” complication by the federal government and the institution of mandatory public reporting for CR-BSI rates by many states, this complication is rapidly developing a markedly increased public profile.

EPIDEMIOLOGY AND RISK FACTORS

The number of CR-BSIs has been estimated to be 250,000 per year.² CR-BSIs have recently been demonstrated to increase length of stay in the ICU by an average of 2.4 days and increase total hospital length of stay by 7.5 days.³ Its effect on mortality is more controversial. Unadjusted mortality rates have ranged from 16% to 25%; however, this is complicated by the fact that patients with CVCs are likely to be sicker than a typical hospitalized patient.⁴ Recent studies examining adjusted mortality that control for confounders have demonstrated mortality rates ranging from 0% to 17%, with

^a Surgical Critical Care, Barnes-Jewish Hospital/Washington University School of Medicine, St. Louis, MO, USA

^b Department of Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8109, St. Louis, MO 63110, USA

* Corresponding author.

E-mail address: coopersmithc@wustl.edu (C.M. Coopersmith).

rates in hospitalized patients noted to be as high as 23%.^{5,6} The precise economic cost of a CR-BSI can be difficult to quantify, in light of the fact that patients with CVCs tend to have multiple coexisting medical problems. Estimates have varied greater than 10-fold in studies that have been published over the past decade, ranging from \$4888 to \$56,167,^{7,8} although most studies have come up with estimates in the middle of this range.

Risk factors for CR-BSI include length of CVC duration; patient location (outpatient, inpatient floor, ICU); type of catheter; number of lumens; number of manipulations per day; emergent placement; use of catheter for parenteral nutrition; presence of needleless connectors (this increases risk); and whether or not best care practices are followed. CVCs in an ICU setting have a higher infection rate than those in the hospital ward or outpatient setting. According to the 2006 National Healthcare Safety Network report, medical and surgical wards had an incidence rate of 1.5 CR-BSI per 1000 catheter days compared with 2.4 per 1000 catheter days for medical and surgical ICUs.⁹ The risk of infection also varies depending on type of ICU. Cardiothoracic ICUs have the lowest incidence at 1.6 per 1000 catheter days and burn ICUs have the highest rate of 6.8 per 1000 catheter days.⁹ This difference in CR-BSI rates between different types of ICUs may be explained by differing disease processes, severity of illness, and potentially duration of CVC placement. Of note, with continued close scrutiny paid to CR-BSI rates, the incidence of this complication has decreased nearly twofold in under a decade.^{9,10}

Nontunneled catheters are the most commonly inserted CVCs. Because of their prevalence and lack of an infection-suppressing cuff or tunnel, they have historically accounted for approximately 90% of CR-BSIs.¹¹ Several randomized trials have demonstrated that the risk of infection increases with the number of lumens in the catheter.¹² Except in specific clinical situations (ie, long-term parenteral nutrition), however, it may be difficult to predict the number of lumens that are needed, especially in critically ill patients. Because changing a catheter over a guidewire has significant implications for the sterility of the new catheter, most practitioners use multilumen catheters in the inpatient setting.

PREVENTION

Because of recent regulations suggesting that most if not all CR-BSIs are preventable, a large portion of this article focuses on evidenced-based practices that have been demonstrated to be effective at lowering or eliminating these infections.

Preventing CR-BSIs requires a multipronged strategy ranging from educational to technologic interventions. Attention must also be paid to prevention before a CVC is placed, when it is placed, and every day a catheter remains in place. Although the strategies listed next are applicable to all CVCs, they are focused on short-term access. It should be noted that subcutaneous cuffs and catheter tunneling are effective mechanical methods for preventing extraluminal infection, although both of these mechanisms increase the complexity and invasiveness of the insertion and removal of the catheter, and are not practical for temporary access.

Hand Hygiene

The first step in preventing CR-BSIs is the same as the first step in preventing infection in the operating room: strict adherence to aseptic techniques. This begins with hand hygiene. Although this should be obvious, many health care providers see a bedside procedure as somehow being “different” than even a minor operation, and do not feel the need to wash their hands before placing a CVC, despite the fact that the catheter

can reasonably be expected to be in the central circulation in close proximity to the heart for a week or more, and there is little question that lack of hand hygiene can result in the spread of resistant infections.¹³ Additionally, even if the person inserting a CVC knows that hand hygiene is appropriate, there is extensive literature to support the fact that health care workers repeatedly fail to wash their hands or use alcohol foam. The incidence of this failure has not changed appreciably over the past 30 years despite repeated admonitions from hospital administrators, the lay press, and infection control specialists.^{14,15} Unfortunately, the literature also supports the observation that physicians perform appropriate hand hygiene less frequently than other health care workers, with estimates ranging from one third to one half the time. Of note, alcohol foam is generally as effective as washing hands with soap and water, and there is evidence that hand hygiene usage improves in physicians if alcohol foam is readily available.¹⁶

Skin Antisepsis

Similar to the operating room, thorough skin antisepsis before a procedure is an effective route of preventing infection days later. The use of 2% chlorhexidine (but not 0.5% chlorhexidine) has been shown to result in decreased CR-BSI compared with either 10% povidone iodine or 70% alcohol in a prospective randomized trial of 668 patients.^{17,18} This is also supported by a meta-analysis comparing chlorhexidine with povidone iodine, which revealed a risk reduction of nearly 50%.¹⁹ An economic analysis showed that even though chlorhexidine costs more on a per unit basis, the decreased incidence of CR-BSI (with its associated morbidity and potential mortality) leads to \$113 in savings for each CVC placed.²⁰ It should also be noted that daily baths with 2% chlorhexidine washcloths as opposed to soap and water have been shown to decrease the rate of CR-BSI in a two-arm crossover study of 836 patients in a medical ICU.²¹

Full Barrier Precautions

When placing a CVC, the patient's room needs to be treated similar to an operating room. This means there should be full-sized sterile drapes on the patient and a mask, cap, sterile gown, and gloves on the person placing the CVC (full barrier precautions). An outpatient study of 343 patients demonstrated a sixfold decrease in the rate of CR-BSI when full barrier precautions were used as opposed to when sterile gloves and a small drape alone were used.²² Additionally, a twofold decrease in CR-BSI rates was demonstrated in ICU patients undergoing pulmonary artery catheterization who had full barrier precautions compared with those with less stringent precautions.²³ An economic analysis also showed that even though full barrier precautions cost approximately \$40 per CVC insertion, the decreased incidence of CR-BSI leads to \$252 savings for each CVC placed.²⁴

Anatomic Site of Insertion

In general, the subclavian vein is preferred to either the internal jugular or femoral vein for CVC insertion. Although this is not based on prospective, randomized trials, most studies examining this issue have demonstrated a twofold to threefold increase in CR-BSI when either of the latter approaches is used. This has led expert opinion to support placement of CVCs in the subclavian vein,² although the person performing the insertion should have appropriate expertise because of the increased risk of a pneumothorax when using this insertion site. Potential reasons to use a site other than the subclavian vein include significant coagulopathy, obvious site infection, inaccessibility, or a need for chronic dialysis, because subclavian stenosis and thrombosis

may preclude subsequent use of this site. It should be noted that there is a greater than 10-fold increase in thrombotic complications when using the femoral vein to place a CVC,²⁵ and this site should generally only be used in life-threatening emergencies or when vascular access above the diaphragm is not technically feasible. The role of peripherally inserted central catheters (PICC) is unclear. Some studies have demonstrated that PICC lines may decrease CR-BSI. Some experts, however, believe that infection rates are similar between PICC lines and CVCs placed in the subclavian vein, but less attention may be placed to infection risks in PICC lines, leading to catheters being left in place (with resultant infection risk) longer than might a CVC.

Catheter Care After Insertion

A study comparing changing gauze dressings every other day to transparent dressings changed every 5 days demonstrated no difference in CR-BSI rate in pulmonary artery catheters.²⁶ Either strategy is equally acceptable, although if bleeding occurs, gauze dressings are preferred (and grossly soiled dressings should be changed immediately). Sustained-release chlorhexidine dressings have not been demonstrated to decrease CR-BSI rates but have been associated with a nearly twofold decrease in exit site colonization in a recent meta-analysis,²⁷ so their usefulness is currently unclear. Catheter care teams have been demonstrated to decrease infection rates in multiple trials, including one randomized trial,²⁸ although not all studies support this finding.²⁹ A recent meta-analysis demonstrates that administration sets do not need to be changed more frequently than every 96 hours, although administration sets containing blood or lipids need to be changed every 24 hours.³⁰ There is no role for antibiotic flush solution in routine adult CVCs. Vancomycin lock solution has been demonstrated to have use in highly selected groups including high-risk neonates with PICC lines and oncology patients with long-term tunneled catheters.^{31,32} A recent meta-analysis suggests that antibiotic lock solutions may also prevent CR-BSI in hemodialysis catheters.³³ There is no benefit to prophylactic antibiotics in preventing CR-BSI in adults, and they should not be used. A recent meta-analysis of prophylactic antibiotics in neonates demonstrated reduced rates of documented or suspected bacteremia.³⁴ This was not associated with improved mortality, however, and because of this and concerns about selection of resistant organisms and lack of data on long-term neurodevelopmental outcome, the use of prophylactic antibiotics in neonates is not currently recommended.³⁴

Educational Programs

Multiple studies have shown a significant reduction of CR-BSI when an educational program is initiated.^{35,36} Successful educational programs stressing “best practice” can be targeted at either those placing CVCs or those responsible for maintaining them.

Comprehensive Prevention Programs

Comprehensive prevention programs have also been demonstrated to dramatically decrease CR-BSI rates.^{37,38} These programs include an educational component but also stress specific bedside patterns that may reduce infections. One key component of this is asking whether a CVC is needed on a daily basis. Because the incidence of CR-BSI is proportional to line age, CVCs should be removed as soon as practicable. Although the logic behind this recommendation is clear, it requires a system to ensure that the health care team specifically assesses the need for a CVC each day. Of note, although CVCs should be removed as soon as possible, there is no benefit to routine replacement of CVCs, because studies examining scheduled replacement of

catheters every 3 to 7 days have not been associated with a decrease in CR-BSI rates.^{39,40} There is also no benefit to routine guidewire exchange of CVCs.⁴¹

Another important component of a comprehensive prevention program is empowering the bedside nurse to stop a CVC insertion if breaks in sterile technique are identified. Although it is understood that a scrub nurse is empowered to identify breaks in sterile technique in the operating room, the concept of a bedside nurse doing the equivalent is a cultural change for many institutions. Many experts believe, however, that this is one of the most important components of a prevention program because policies regarding antisepsis are only as good as their implementation.

A multifaceted prevention program from Johns Hopkins University was described in 2004 that virtually eliminated CR-BSI in the ICU.³⁷ The elements of this prevention program included (1) an educational program, (2) asking health care workers daily about the continued need for a CVC, (3) empowering the bedside nurse to stop a CVC insertion if guidelines were not followed correctly, (4) having a CVC insertion cart to ensure all elements of insertion were kept in one common location, and (5) a CVC checklist performed by the bedside nurse. This study decreased the rate of CR-BSI to 0.54 per 1000 catheter days over the course of 16 months.

Pronovost and colleagues³⁸ then demonstrated that this program could be successful on a large scale. A total of 103 ICUs in Michigan used a modified prevention program that included hand hygiene, full barrier precautions, 2% chlorhexidine as a skin preparation, avoidance of femoral catheters, and removing unnecessary CVCs. The program decreased CR-BSI rates statewide from 7.7 per 1000 catheter days to 1.4 per 1000 catheter days over the course of 18 months. Importantly, although the program was aimed at ICUs, it was not directed toward a specific ICU or hospital type, and included academic and community hospitals of all sizes with all types of ICUs.

Antiseptic- or Antibiotic-Coated Catheters

No area of infection control for the prevention of CR-BSIs has been the subject of as much study or seems to evoke as much passion as the use of antiseptic- or antimicrobial-impregnated catheters. There are currently two commonly used types of catheters: chlorhexidine–silver sulfadiazine (antiseptic impregnated) and minocycline-rifampin (antibiotic impregnated). There have been over 20 randomized, prospective trials evaluating the benefits of these catheters,⁴² and a recent meta-analysis suggests that they are effective in preventing CR-BSIs.⁴³ Most of these studies demonstrate either decreased CR-BSI rates or decreased catheter colonization, and there is no evidence that these catheters increase the selection of resistant organisms. An economic analysis also showed that even though impregnated catheters cost more than uncoated CVCs, the decreased incidence of CR-BSI leads to \$196 savings for each CVC placed.⁴⁴

When to use these catheters is less clear. The Centers for Disease Control and Prevention recommends using an impregnated catheter when (1) a CVC is expected to be in place greater than 5 days; (2) the institution has a comprehensive strategy to prevent CR-BSIs in place, which includes full barrier precaution, 2% chlorhexidine preparation, and an educational program aimed at preventing infections; and (3) CR-BSIs are higher than goal rates set by an institution “based upon bench mark rates.”² Although this sounds simple in theory, it is frequently not clear in advance whether a CVC needs to be in place for greater than 5 days. Similarly, it is not clear what the goal rate for CR-BSI should be in light of the fact that the federal government has indicated this is a “never” complication, suggesting it is preventable 100% of the time. National Healthcare Safety Network data indicate, however, that even though

rates are decreasing, CR-BSI still occurs in most hospitals in the country. Additionally, the usefulness of impregnated catheters in an ICU whose CR-BSI rates are below the national average but are not zero is currently unclear.⁴⁵

What type of catheter to use is also unclear. A meta-analysis of 11 studies comparing chlorhexidine–silver sulfadiazine CVCs with uncoated catheters demonstrates an odds ratio of 0.56 favoring the antiseptic-coated catheters.⁴⁶ A single prospective randomized trial comparing antiseptic-impregnated catheters with minocycline–rifampin–impregnated catheters demonstrated a marked reduction in CR-BSI in the latter (0.3% for the minocycline–rifampin catheters versus 3.4% for the chlorhexidine–silver sulfadiazine catheters).⁴⁷ It should be noted, however, that this study used a first-generation chlorhexidine–silver sulfadiazine catheter, and a newer version with both internal and external coating is now available. An additional type of catheter coated with silver–platinum–carbon has also recently been described. Its benefit versus uncoated catheters has not been clearly documented,⁴⁸ however, and it has been demonstrated to be associated with increased catheter colonization compared with minocycline–rifampin catheters,⁴⁹ so its use cannot be recommended at the current time.

DIAGNOSIS

The diagnosis of CR-BSI can be challenging. Physical examination is typically unrevealing, and the diagnosis generally relies on culture data. Positive culture data may be difficult to interpret, however, because clinicians must make the distinction between CR-BSI and catheter colonization. Further, distinctions must be made between CR-BSI and secondary bacteremia, with bloodstream infection resulting from a source other than a CVC (pneumonia, intra-abdominal infection, and so forth).

The first component necessary to the diagnosis of CR-BSI is clinical suspicion. The typical clinical sign that initiates a work-up for CR-BSI is a new fever, not obviously related to a distant infection. Although fever is the most sensitive sign of CR-BSI, it does not have appropriate specificity to make the diagnosis. As in any patient with suspected infection, a history and physical examination should always be performed. The history is generally unrevealing, however, except for the presence or absence of risk factors outlined previously, although it certainly may give clues as to whether another possible source of fever needs to be considered.

Physical examination is also generally unrevealing. Occasionally, it can reveal erythema, induration, or purulence from either the exit site or along the course of the catheter. Although these signs are highly suggestive of a CR-BSI, they are rarely present, however, and the absence of findings on physical examination does not lessen clinical suspicion for the presence of infection. Rarely, a patient with CR-BSI develops endocarditis. In patients with infection and a new murmur on physical examination or a prosthetic heart valve, serial blood cultures should be obtained. If these are positive, this strongly suggests the presence of endocarditis, necessitating a longer course of antibiotic treatment. This should be investigated using an echocardiogram. Although a transthoracic echocardiogram is technically easier, a study of 103 patients with *Staphylococcus aureus* bacteremia (both CR-BSI and non-catheter-related) demonstrated only a 32% sensitivity for transthoracic echocardiogram and 100% sensitivity for transesophageal echocardiogram.⁵⁰

There is no gold standard for how to use blood cultures to assess for CR-BSI. The authors' ICU performs two simultaneous peripheral blood cultures. Another method is to send a simultaneous peripheral blood culture with one drawn through the CVC. A quantitative colony count that is 5- to 10-fold higher in the culture drawn through the CVC is predictive of CR-BSI in tunneled catheters.⁵¹ This method has lower

sensitivity, however, in nontunneled short-term CVCs. If paired cultures are drawn, it is likely that a CR-BSI is present if the catheter culture becomes positive greater than 2 hours before the peripheral culture. The “time to positivity” method has been demonstrated to be 81% sensitive and 92% specific for the diagnosis of CR-BSI.⁵² The latter two techniques, however, put an additional burden on an institution’s microbiology laboratory (quantitative cultures and time of positive culture, respectively) that many are unable to meet. When removing a CVC, some institutions send the catheter tip for quantitative culture. Two techniques for doing so include the sonication method and roll-plating. Of these, sonication better evaluates intra-luminal and extraluminal colonization, whereas roll-plating mostly evaluates extraluminal infection. It should be emphasized that neither a positive catheter tip culture nor a single positive blood culture drawn through a CVC is indicative of CR-BSI. Rather, these are consistent with catheter colonization, which is not equivalent to bacteremia and does not have the same treatment implications. It is this confusion between catheter colonization and infection that is the rationale for why the authors’ ICU does not send either catheter tips or cultures drawn through a CVC. It should be noted that if a patient defervesces after a CVC is removed, this is indirect evidence that a catheter infection may have been present even if peripheral blood cultures are negative.

MICROBIOLOGY

CR-BSIs predominantly come from microorganisms that colonize either catheter hubs or the skin surrounding the insertion site.⁵³ Extraluminal colonization occurs from migration of organisms from the skin along the subcutaneous tract. Intraluminal colonization occurs from contamination by injection ports or hubs.

There are several microorganisms that cause CR-BSI. The most common are coagulase-negative staphylococci and *S aureus*, gram-negative bacilli, and *Candida albicans*.⁵⁴ The microbiology of CR-BSI is important not only for determining appropriate antibiotic therapy but also in the ultimate outcome from the disease. For instance, *S aureus* bacteremia has been demonstrated to have a mortality rate of 8.2%, whereas mortality from coagulase-negative staphylococci is greater than 10-fold lower (0.7%).⁵⁴ A special concern with *S aureus* is associated venous thrombosis. A recent study demonstrated that a total of 71% of patients with *S aureus* bacteremia from internal jugular, brachial, or subclavian veins had thrombosis on ultrasonography.⁵⁵ Importantly, death or recurrent bacteremia occurred in 32% of these patients. As such, patients with CR-BSI from *S aureus* should undergo ultrasonography even if physical examination is normal.

TREATMENT

The primary treatment of a CR-BSI is to remove the infected catheter. Although adjunctive antibiotic therapy is important, catheter removal represents source control, and there are very few instances (detailed next) where an infected catheter can be left in situ. In the case of nontunneled CVCs, catheter removal is easily accomplished after establishing appropriate access elsewhere. It should be realized that in patients who have a febrile illness in which their CVC is removed for presumed CR-BSI, most have sterile cultures.⁵⁶

Although rare, there are times when the treating physician can consider leaving an infected CVC in place. Patients with coagulase-negative staphylococci may be candidates for catheter salvage if (1) they do not have persistent bacteremia, (2) they do not have evidence of tunnel infection, and (3) they do not have evidence of metastatic complications or severe sepsis.⁵⁴ There is evidence to suggest that

patients recover faster with a higher cure rate if the CVC is removed, however, rather than attempting to salvage the catheter. In patients with tunneled catheters that are risky to remove or replace, antibiotic lock therapy may be used by filling the CVC with a solution containing concentrated antibiotics for a number of hours. Higher antibiotic concentrations must be used because of biofilm formation in these infections. Antibiotic lock solution for tunneled catheters has been demonstrated to result in a catheter salvage rate of 83%, which compares favorably with a salvage rate of 67% in patients treated without this therapy.⁵⁴

As in other suspected infections, broad-spectrum antibiotics should be initiated when CR-BSI is suspected on clinical grounds. Antibiotics should be started before culture and sensitivity results are obtained, because waiting until these are known leaves the patient without antimicrobial therapy and likely increases their mortality if the patient is bacteremic. Once culture and sensitivity results are known, antimicrobial therapy should be narrowed as much as practicable effectively to treat only the causative organism. Generally, a single antimicrobial agent suffices but double coverage can be considered in *Pseudomonas aeruginosa* infections, in neutropenic patients, or in patients with *S aureus* bacteremia when the catheter cannot be safely removed.^{54,57}

There is little level I evidence on length of treatment for CR-BSI, so recommendations are generally based on expert opinion and nonrandomized trials. In general, uncomplicated bacterial or fungal CR-BSIs should be treated for a 10- to 14-day course. Infections with coagulase-negative staphylococci can be treated for 5 to 7 days. Complicated infections with tunneled catheters that cannot be safely removed should be treated for at least 2 to 4 weeks. Patients with endocarditis require at least 6 weeks of therapy. Once a CVC has been removed and therapy initiated, it is appropriate to check follow-up blood cultures to verify the infection is being cleared. Patients with persistent fever, signs of sepsis, or risk factors for distant cardiac infection should have serial blood cultures drawn until these are negative. Patients who do not respond to antibiotic therapy after the suspected catheter has been removed for 3 days need to be evaluated further for possible other sources of infection including the possibility of secondary infections, such as endocarditis, septic thrombophlebitis, or osteomyelitis. Consultation with an infectious disease specialist may also be indicated. It should be noted that in addition to increased risk of thrombotic complications, *S aureus* infections also have an increased incidence of other secondary infections.

SUMMARY

CR-BSIs are a common complication of central venous catheterization, resulting in substantial morbidity. A large percentage of them are preventable, leading the Centers for Medicare and Medicaid Services recently to define this as a “never” complication. CR-BSIs can be prevented by use of appropriate hand hygiene, 2% chlorhexidine as a skin preparation, full barrier precautions, avoidance of femoral catheters, empowering the bedside nurse to halt a CVC insertion if sterile technique is not followed, removing unneeded catheters as soon as possible, and comprehensive educational programs. If all of these are unsuccessful, antiseptic- or antibiotic-impregnated catheters are an effective tool to prevent infections. The diagnosis of CR-BSI is made largely based on culture results, and broad-spectrum antibiotics should be initiated as soon as an infection is suspected. Antimicrobial therapy can subsequently be narrowed once the causative organism is known. Except in rare circumstances, patients with CR-BSI need to have their infected CVC removed.

REFERENCES

1. Medicare program: changes to the hospital inpatient prospective payment systems and fiscal year 2008 rates. *Fed Regist* 2007;72:47379–428.
2. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2002;51:1–29.
3. Warren DK, Quadir WW, Hollenbeak CS, et al. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34:2084–9.
4. Higuera F, Rosenthal VD, Duarte P, et al. The effect of process control on the incidence of central venous catheter-associated bloodstream infections and mortality in intensive care units in Mexico. *Crit Care Med* 2005;33:2022–7.
5. Digiovine B, Chenoweth C, Watts C, et al. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med* 1999;160:976–81.
6. Diekema DJ, Beekmann SE, Chapin KC, et al. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *J Clin Microbiol* 2003;41:3655–60.
7. Rosenthal VD, Guzman S, Orellano PW. Nosocomial infections in medical-surgical intensive care units in Argentina: attributable mortality and length of stay. *Am J Infect Control* 2003;31:291–5.
8. Dimick JB, Pelz RK, Consunji R, et al. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. *Arch Surg* 2001;136:229–34.
9. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. *Am J Infect Control* 2007;35:290–301.
10. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control* 1999;27:520–32.
11. Pearson ML. Guideline for prevention of intravascular device-related infections. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;17:438–73.
12. Farkas JC, Liu N, Bleriot JP, et al. Single- versus triple-lumen central catheter-related sepsis: a prospective randomized study in a critically ill population. *Am J Med* 1992;93:277–82.
13. Goldmann D. System failure versus personal accountability: the case for clean hands. *N Engl J Med* 2006;355:121–3.
14. Albert RK, Condie F. Hand-washing patterns in medical intensive-care units. *N Engl J Med* 1981;304:1465–6.
15. Jenner EA, Fletcher BC, Watson P, et al. Discrepancy between self-reported and observed hand hygiene behaviour in healthcare professionals. *J Hosp Infect* 2006;63:418–22.
16. Maury E, Alzieu M, Baudel JL, et al. Availability of an alcohol solution can improve hand disinfection compliance in an intensive care unit. *Am J Respir Crit Care Med* 2000;162:324–7.
17. Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991;338:339–43.
18. Humar A, Ostromecki A, Drenfeld 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.
19. Chaiyakunapruk N, Veenstra DL, Lipsky BA, et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. *Ann Intern Med* 2002;136:792–801.
 20. Chaiyakunapruk N, Veenstra DL, Lipsky BA, et al. Vascular catheter site care: the clinical and economic benefits of chlorhexidine gluconate compared with povidone iodine. *Clin Infect Dis* 2003;37:764–71.
 21. Bleasdale SC, Trick WE, Gonzalez IM, et al. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. *Arch Intern Med* 2007;167:2073–9.
 22. 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.
 23. Mermel LA, McCormick RD, Springman SR, et al. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. *Am J Med* 1991;91:197S–205S.
 24. Hu KK, Veenstra DL, Lipsky BA, et al. Use of maximal sterile barriers during central venous catheter insertion: clinical and economic outcomes. *Clin Infect Dis* 2004;39:1441–5.
 25. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;286:700–7.
 26. Maki DG, Stolz SS, Wheeler S, et al. 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.
 27. Ho KM, Litton E. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother* 2006;58:281–7.
 28. Sherertz R. Look before you leap: discontinuation of an infusion therapy team. *Infect Control Hosp Epidemiol* 1999;20:99–100.
 29. bi-Said D, Raad I, Umphrey J, et al. Infusion therapy team and dressing changes of central venous catheters. *Infect Control Hosp Epidemiol* 1999;20:101–5.
 30. Gillies D, O’Riordan L, Wallen M, et al. Optimal timing for intravenous administration set replacement *Cochrane Database Syst Rev* 2005;CD003588.
 31. Garland JS, Alex CP, Henrickson KJ, et al. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics* 2005;116:e198–205.
 32. van DW, van Woensel JB. Prophylactic antibiotics for preventing early central venous catheter gram positive infections in oncology patients *Cochrane Database Syst Rev* 2007;CD003295.
 33. Jaffer Y, Selby NM, Taal MW. Meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *Am J Kidney Dis* 2008;51:233–41.
 34. Jardine LA, Inglis GD, Davies MW, et al. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. *Cochrane Database Syst Rev* 2008;CD006179.
 35. Coopersmith CM, Rebmann TL, Zack JE, et al. Effect of an education program on decreasing catheter-related bloodstream infections in the surgical intensive care unit. *Crit Care Med* 2002;30:59–64.

36. Eggimann P, Harbarth S, Constantin MN, et al. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet* 2000;355:1864–8.
37. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32:2014–20.
38. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725–32.
39. Eyer S, Brummitt C, Crossley K, et al. Catheter-related sepsis: prospective, randomized study of three methods of long-term catheter maintenance. *Crit Care Med* 1990;18:1073–9.
40. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;327:1062–8.
41. Cook D, Randolph A, Kernerman P, et al. Central venous catheter replacement strategies: a systematic review of the literature. *Crit Care Med* 1997;25:1417–24.
42. Crnich CJ, Maki DG. Are antimicrobial-impregnated catheters effective? When does repetition reach the point of exhaustion? *Clin Infect Dis* 2005;41:681–5.
43. Hockenhull JC, Dwan K, Boland A, et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Assess* 2008;12:1–154.
44. 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.
45. Schuerer DJ, Zack JE, Thomas J, et al. Effect of chlorhexidine/silver sulfadiazine-impregnated central venous catheters in an intensive care unit with a low bloodstream infection rate after implementation of an educational program: a before-after trial. *Surg Infect (Larchmt)* 2007;8:445–54.
46. Veenstra DL, Saint S, Saha S, et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;281:261–7.
47. Darouiche RO, Raad I, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. *N Engl J Med* 1999;340:1–8.
48. Kalfon P, de VC, Samba D, et al. Comparison of silver-impregnated with standard multi-lumen central venous catheters in critically ill patients. *Crit Care Med* 2007;35:1032–9.
49. Fraenkel D, Rickard C, Thomas P, et al. A prospective, randomized trial of rifampicin-minocycline-coated and silver-platinum-carbon-impregnated central venous catheters. *Crit Care Med* 2006;34:668–75.
50. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol* 1997;30:1072–8.
51. Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative blood culture. *Eur J Clin Microbiol Infect Dis* 1989;8:142–4.
52. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med* 2004;140:18–25.

53. Mermel LA, Eggimann P, Harbarth S, et al. Prevention of intravascular catheter-related infections Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet* 2000;355:1864–8.
54. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249–72.
55. Crowley AL, Peterson GE, Benjamin DK Jr, et al. Venous thrombosis in patients with short- and long-term central venous catheter-associated *Staphylococcus aureus* bacteremia. *Crit Care Med* 2008;36:385–90.
56. Rello J, Coll P, Prats G. Evaluation of culture techniques for diagnosis of catheter-related sepsis in critically ill patients. *Eur J Clin Microbiol Infect Dis* 1992;11: 1192–3.
57. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. *Antimicrob Agents Chemother* 1997;41:1127–33.