Central line infections

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Central venous catheters are commonly used in the critical care setting. Unfortunately, their use is often associated with complications, including fatal infections. Making the diagnosis of central venous catheter infection can be difficult. Additionally, resistance among the more common organisms that cause catheter-related infection is increasing. However, our understanding of the pathogenesis of catheter infection is improving through examination of biofilms. Also, our ability to diagnose catheter-related infections more accurately is improving with new techniques. There is new hope for ruling out catheter-related infection before removal by several methods, including a rapid enzyme-linked immunosorbent assay and the use of time differential for microbial growth between blood cultures obtained from a peripheral site and the catheter itself. Prevention through the use of barrier techniques and antimicrobial-coated catheters has been demonstrated to be of value in reducing catheter-related infection with these devices. Curr Opin Crit Care 2002, 8:441–448

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Abbreviations

CFU	colony-forming units
CR-BSI	catheter-related bloodstream infection
CVC	central venous catheter

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Nosocomial infections are a leading cause of morbidity and mortality in critically ill patients. With an incidence of approximately 80,000 episodes of catheter-related bloodstream infections (CR-BSIs) annually, central venous catheters (CVCs) are the leading cause of nosocomial bloodstream infections in the United States, resulting in 2400 to 20,000 deaths [1••]. Because of the increased length of hospitalization and additional morbidity associated with CVC-related bloodstream infections, related costs have been estimated to be as high as 2 billion dollars annually in the United States [1••,2]. However, because CVCs are used for the administration of essential intravenous fluids, medications, blood products, and nutrition, they are important for optimal care of critically ill patients [1••]. Hence, an understanding of CR-BSIs is important for the implementation of the proper management approach for each patient and to avoid the often preventable adverse outcomes associated with the use of CVCs.

Epidemiology

CR-BSIs are generally caused by coagulase-negative staphylococci, coagulase-positive *Staphylococcus aureus*, *Enterococcus*, aerobic gram-negative bacilli, and *Candida albicans* [2,3]. In a meta-analysis of 2573 patients, the mortality rate for *S. aureus*–related bacteremia was 8.2%, much higher than the mortality rate for other organisms. Coagulase-negative *Staphylococcus*, the most common organism isolated as a cause for infection, has a mortality rate of 0.7%, which is significantly lower than that of most other pathogens [4]. Treatment of these organisms has become increasingly difficult given that more than 50% of *S. aureus* and more than 80% of coagulase-negative *Staphylococcus* isolates are resistant to oxacillin, 25% of enterococci are resistant to vancomycin, and 23% of *Pseudomonas aeruginosa* are resistant to quinolones [5••,6,7].

Pathogenesis of central venous catheter infection

The pathogenesis of CR-BSI often starts with catheter colonization [8•]. Extraluminal colonization of CVCs most commonly occurs because of skin florae that invade the cutaneous tract. Frequently, pathogenic bacteria acquired in the hospital have replaced normal skin florae [8•]. In addition, extraluminal colonization can occur because of hematogenous seeding of the catheter tip from a distant site. Intraluminal colonization can result from frequent manipulations of the catheter hub or over guidewire exchange. When epidemic CR-BSI occurs, intraluminal infection from contaminated infusions should

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be considered. In a recent, preliminary study conducted by Worthington *et al.* [9] of 100 nurses who prepared sterile 0.9% normal saline, it was discovered that 8% of the infusates were contaminated with microorganisms. Thrombus formation either at the site of insertion, where the catheter penetrates the vessel wall, or at the catheter tip can also facilitate intraluminal catheter colonization [10].

When colonization occurs, microorganisms can produce extracellular polymer substances that facilitate adhesion to CVCs. These polymers develop into a matrix, which leads to biofilm formation [11•]. Several biofilm microorganisms have been commonly isolated from CVCs (Table 1). Raad *et al.* [12] discovered that all *in vivo* catheters develop biofilms. Initially, biofilms may not be clinically significant. However, as indwelling time increases, biofilms can become a persistent source of infection, may harbor pathogenic bacteria, and may protect bacteria from host defenses through a measurable decrease in antimicrobial susceptibility. For example, Ceri *et al.* [13] discovered that *Escherichia coli* associated with biofilm required more than 500 times the minimum inhibitory concentration of ampicillin to produce a 3-log reduction. Decreased diffusion of antibiotics, slower growth rates of biofilm-associated organisms, and plasmid exchange among organisms in biofilms account for the decrease in antimicrobial susceptibility [11•].

Catheter-related infections: definitions and diagnosis

CR-BSIs are defined as bacteremia or fungemia in a patient with a CVC with the following criteria: (1) clinical signs of infection (fever, chills, tachycardia, hypotension, leukocytosis), (2) no evident source for bloodstream infection other than the CVC, and (3) the same organism growing from the catheter segment as from the peripheral blood [1••,5••]. Obtaining blood cultures from the catheter alone is often inadequate, as a recent retrospective cohort study of 271 critically ill surgical patients demonstrated. In this study, the positive predictive value of culturing the catheter alone was only 63% compared with 78% for peripheral blood [14•].

With the aforementioned definition alone, differentiating between catheter infection and colonization can be difficult. Several techniques have been evaluated to help diagnose an infected CVC. The most common laboratory method to diagnose CR-BSI is the semiquantitative technique. With this method, the catheter tip is rolled across an agar plate. After an overnight incubation, colony-forming units (CFU) are counted. A positive result of a semiquantitative culture requires 15 or more CFU per catheter segment. The quantitative method, which requires vortex or sonicating the catheter in broth or flushing the broth through the catheter and examining serial dilutions and plating on a blood agar, can be used to detect CR-BSI. A quantitative culture requires 10^2 or more CFU per catheter segment or simultaneous quantitative cultures of blood samples with a ratio of 5:1 or more (CVC *vs* peripheral) for a positive catheter culture. Sonication has a sensitivity of approximately 80%, the roll plate method has a sensitivity of 60%, and the flush culture has a sensitivity of 40 to 50%.

Table 1. Biofilm-associated microorganisms commonly isolated from central venous catheters

Coagulase-negative staphylococci
Staphylococcus aureus
Enterococcus faecalis
Klebsiella pneumonia
Pseudomonas aeruginosa
Candida albicans

Adapted with permission [11•].

In a recent analysis of two prospective, randomized trials of 479 patients with CVCs, Raad *et al.* [15] tested the hypothesis that culturing the catheter tip plus the subcutaneous segment by the roll plate and sonication method would increase the diagnostic yield for catheter cultures. For long-term catheter use, the sensitivity of culturing the tip was 83% (95% CI, 35.9–99.6) and culturing the tip plus the subcutaneous segment had a sensitivity of 100% (95% CI, 54.1–100). However, this small improvement in the sensitivity was not statistically significant. For short-term catheters, culturing the catheter tip had a sensitivity of 100%. Hence, adding the subcutaneous catheter segment was not useful. For both catheters, culturing the subcutaneous catheter segment did not significantly alter the low positive predictive value, reflecting the high number of colonized catheters without infection.

Unfortunately, all the aforementioned techniques require removal of the catheter. It has been demonstrated that 80% or more of catheters removed for suspected CR-BSI are not infected [16–18]. Hence, diagnostic tools that do not require initial removal can be helpful in many instances. In a recent case-control study of severe infection caused by coagulase-negative *Staphylococcus*, a rapid enzyme-linked immunosorbent assay for the diagnosis of catheter-related sepsis was evaluated. The investigators found this method to have a sensitivity and specificity of 70% and 100%, respectively, for the diagnosis of catheter-related sepsis without removal of the catheter [19]. Another means of diagnosing CR-BSI without removal of the CVC involves the timing of positive blood culture growth from a CVC versus a peripheral blood sample. This method, known as *differential time to positivity*, uses continuous blood culture monitoring and requires a catheter culture to turn positive 120 minutes before a peripheral blood culture to determine that bacteremia is caused by a central line infection. In one study, the overall sen-

sitivity and specificity for this method were 91% and 94%, respectively [20]. However, many patients in these studies had long-term catheters or implanted devices and had not received extensive antibiotics. In a recent prospective study, the issue of differential time to positivity in patients with short-term catheter use and significant antibiotic use was examined [21•]. The sensitivity for short-term catheter use was only 25% (range, 3–65%) with a positive predictive value of 33% (range, 4–78%).

Management of catheter-related infections

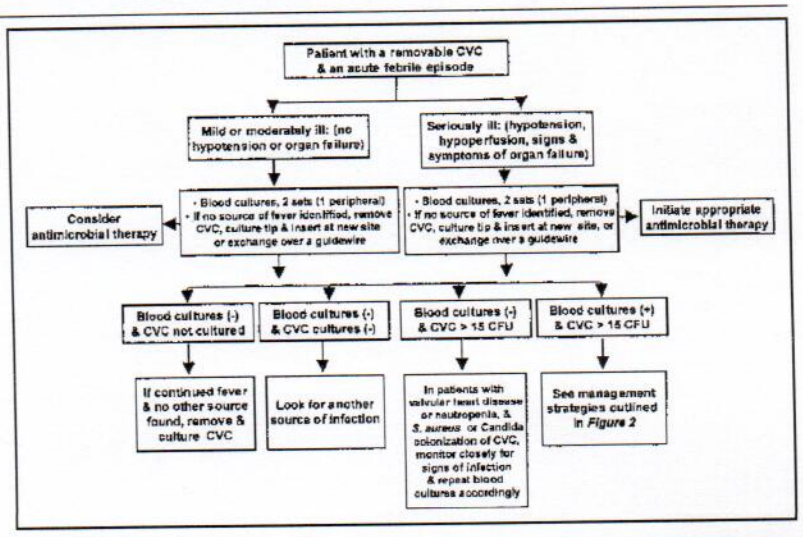
When there is clinical suspicion that a CR-BSI has developed, the clinician is confronted with two choices: (1) removal or nonremoval of the catheter and (2) initiation of antibiotics or observation (Fig. 1). Removal of catheters when a CR-BSI is suspected is a common approach to preventing the excess mortality and morbidity associated with leaving a potential source of infection in place. However, many catheters are removed unnecessarily, and reinsertion of a CVC can be associated with major complications, such as pneumothorax. Flynn *et al.* [22] studied 17 patients with a fivefold greater bacterial concentration difference in blood cultures drawn from a catheter compared with peripheral blood. In 11 patients (65%), the bacteremia was eliminated without removal of the catheter, providing some evidence that catheters do not need to be removed initially, particularly with coagulase-negative *Staphylococcus*. In patients who are mildly to moderately ill (no purulence or erythema overlying the infection site, hypotension, or organ failure), the catheter should not be removed immediately. If the results of the cultures drawn from the catheter are positive, then removal of the catheter is warranted. If there is persistent fever, the results of peripheral blood cultures are negative, and the catheter was not cultured, then it should be removed, and the tip should be sent for culture. If the patient has evidence of serious illness (hypotension, hypoperfusion, signs and symptoms of organ failure), purulence, or erythema at the exit site, then the catheter should be removed. Lastly, if the peripheral blood cultures are negative, and the catheter culture reveals 15 or more CFU, then the patient should be observed, and peripheral blood cultures should be repeated [5••].

Appropriate antibiotic selection can often be difficult. In hospitals where methicillin-resistant staphylococci are present, vancomycin is customarily recommended [5••]. In addition, empiric treatment with a third- or fourth-generation cephalosporin should be considered in immunocompromised or seriously ill patients to cover enteric gram-negative bacteria and *Pseudomonas* species [5••]. When fungemia is suspected, amphotericin B or possibly intravenous fluconazole should be used [5••]. When the antimicrobial sensitivities are known, and the patient's condition has stabilized, then oral agents such as trimethoprim-sulfamethoxazole, ciprofloxacin, or linezolid should be considered because of their superior bioavailability and high tissue penetration [5••].

Currently, definitive data pertaining to the length of therapy for CR-BSI do not exist. Duration of therapy should be dictated by catheter-related complications, surveillance of blood cultures, the organism(s) identified, and the severity of the patient's illness. In a recent publication, the Infectious Disease Society of America provided guidelines for duration of therapy. If a patient has no associated complications, then a 10- to 14-day course should be sufficient for a gram-negative bacillus. If uncomplicated *S. aureus* infection has been identified, then systemic antibiotics should be administered for 14 days. If a *Candida* species is present, then therapy needs to be carried out for 14 days after the last positive blood cul-

Figure 1. Methods for the diagnosis of acute fever in a patient suspected of having nontunneled central venous catheter infection

The patient should be assessed for severity of illness, and two blood samples should be obtained (at least one peripherally and one via a catheter) for culture. If a catheter is the suspected source of infection in a mildly to moderately ill patient, antimicrobial therapy should be considered, and the catheter should either be removed and cultured or exchanged over a guidewire and cultured. Patients with severe disease owing to catheter-related infection should be given appropriate antimicrobial therapy, and the central venous catheter (CVC) should be removed, cultured, and inserted into a different site. Results of catheter and blood cultures help to establish the presence of infection and the infecting organism, which may allow adjustment in antibiotic coverage and management. +, positive; –, negative; CFU, colony-forming units.



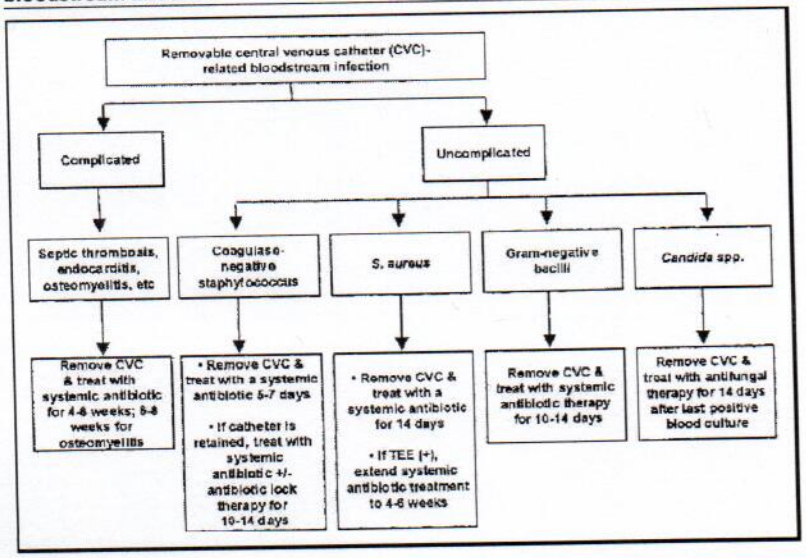
ture result. If endocarditis or persistent fungemia and bacteremia are complicating factors, then 4 to 6 weeks of antimicrobial therapy should be implemented. A prolonged course of therapy for 6 to 8 weeks should be considered if osteomyelitis is a complicating factor [5••] (Fig. 2).

With *S. aureus*–associated bacteremia, endocarditis should be ruled out with transesophageal echocardiography. Although the exact time to request that transesophageal echocardiography be performed has yet to be determined, some researchers have advocated the value of transesophageal echocardiography evaluation if there is persistent bacteremia, fungemia, or a lack of clinical improvement after 3 days of appropriate therapy and catheter withdrawal. If the results of transesophageal echocardiography are negative, then workup for septic thrombosis versus other metastatic infections should be considered.

Central venous catheters are an important risk factor for candidemia. In a recent prospective study assessing the incidence of nosocomial bloodstream infection in patients infected with HIV, *Candida* was the third most common cause of nosocomial bloodstream infection and, with an incidence of 72 cases per 10,000 admissions, accounted for 20% of CR-BSI. Additionally, in this same study, the mortality rate was highest in patients with candidemia [23]. When candidemia is confirmed, patients should receive a dilated funduscopic examination for possible endophthalmitis [24]. All patients with fungemia require antifungal therapy (Table 2). In addition, there are data to suggest that patients would benefit from catheter removal. One review of 21 episodes of catheter removal found that of 13 patients in whom the catheter was removed and appropriate antimicrobials were initiated, only two patients had persistent candidemia. This was in contrast to six of eight patients with persistent candidemia who had the catheter left in place while antifungal therapy was initiated ($P = 0.018$) [25]. Nguyen *et al.* [26] examined 427 consecutive patients with candidemia in a prospective, observational study and reported that the mortality rate for patients in whom the catheter was removed was less than that for those patients in whom the catheter remained in place (21% *vs* 41%, $P < 0.001$). Because of its association with CR-BSI, one should strongly consider removal of a CVC when isolation of *Candida parapsilosis* from the blood occurs. However, some experts argue against the removal of CVCs in patients with other forms of candidemia. This is largely a result of the gastrointestinal origin in a significant number of cases of candidemia and the cost and complications associated with removal [27,28].

Given the lack of guidelines pertaining to the management of catheters in the context of candidemia, it is not surprising that a large group of patients with candidemia continue to be treated without removal of all catheters. To determine the best course of action, Nucci and Anaissie [29••] conducted a literature review of studies that examined CVC removal and the outcome of patients with candidemia. One study showed benefit, one showed no benefit, and two showed a marginal benefit with removal of the catheter. Thus, the investigators concluded that catheters in patients with candidemia should be removed. However, in each case, removal must be weighed against the risk of reinsertion of central venous access (*ie*, thrombocytopenia, marginal lung function, and risk of pneumothorax), particularly in patients with cancer with neutropenia and mucositis in whom a

Figure 2. Approach to the management of patients with nontunneled central venous catheter–related bloodstream infection



Duration of treatment depends on whether the infection is complicated or uncomplicated. The catheter should be removed, and systemic antimicrobial therapy should be initiated, except in some cases of uncomplicated catheter-related infection owing to coagulase-negative staphylococci. For infections owing to *Staphylococcus aureus*, transesophageal echocardiography may reveal the presence of endocarditis and help to determine the duration of treatment. +, positive; –, negative; CVC, central venous catheter; TEE, transesophageal echochardiography.

Table 2. *Candida* species associated with central venous catheters and therapy

Species	Therapy	Comments
C. parapsilosis	Amphotericin B, 0.6 mg/kg/d, *or* Fluconazole, 6.0 mg/kg/d	Very frequently associated with catheters Can use either therapy
C. albicans	Amphotericin B, 0.6 mg/kg/d, *or* Fluconazole, 6.0 mg/kg/d	Can use either therapy
C. tropicalis	Amphotericin B, 0.6 mg/kg/d, *or* Fluconazole, 6.0 mg/kg/d	Can use either therapy
C. glabrata	Amphotericin B ≥0.7 mg/kg/d Fluconazole, 6.0 mg/kg/d	Often has reduced susceptibility to both azoles and amphotericin. Most recommend amphotericin B.
C. krusei	Amphotericin, 1.0 mg/kg/d	Available data suggest that amphotericin is the best choice.
C. lusitaniae	Fluconazole	Many isolates are resistant to amphotericin.

Adapted with permission [24].

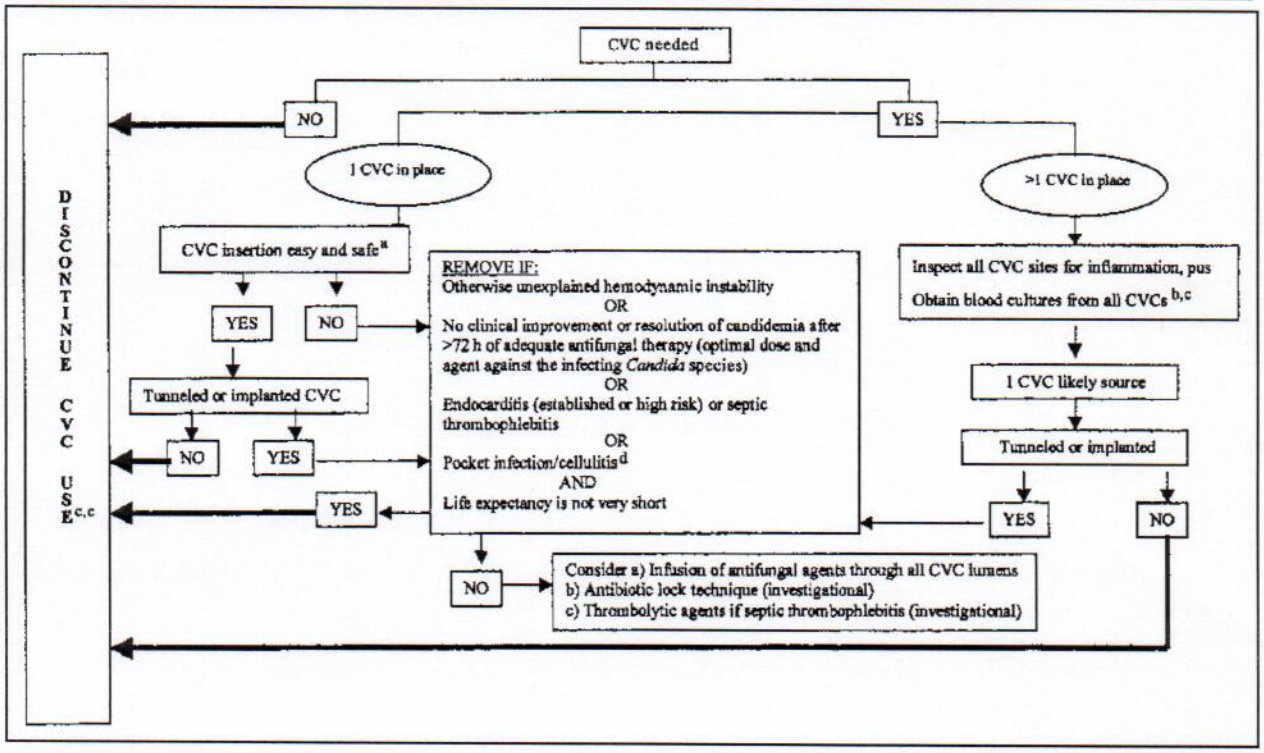
gastrointestinal source is more probable and removal is unlikely to make a significant difference [29••] (Fig. 3).

Prevention of catheter-related infections

Several factors increase the risk of CVC-related infection, including neutropenia, malignancy, parenteral feeding, ICU admission, mechanical ventilation, hyperalimentation, multilumen catheter, and any type of shock. Many of these risk factors cannot be altered. However, some risk factors can be controlled, including the choice of catheter insertion site, use of maximum sterile barriers during catheter placement, indwelling time, insertion procedure, catheter care, and biofilm prevention.

The possibility of infection is highest where there is the largest concentration of skin florae independent of the cleansing technique. This risk is greatest when a CVC is inserted into the femoral vein compared with the subclavian vein (19.8% *vs* 4.5%, $P < 0.001$) [30••]. The risk is less with the jugular site compared with the femoral site and even lower at the subclavian site [31–33]. The types of organisms differ depending on the

Figure 3. Proposed management of central venous catheters in nonneutropenic patients with candidemia



[a]High risk of bleeding or pneumothorax; serious complication with bleeding or pneumothorax (such as patients with limited lung function). [b]Value of quantitative blood cultures not established. [c]Especially in patients with *Candida parapsilosis* (typically associated with central venous catheter [CVC]–related candidemia). [d]Most cases of cellulitis at the CVC site are not infectious and occur within a few days of CVC insertion. Patients with severe neutropenia and mucositis are unlikely to benefit from CVC removal. [e]Candidemia caused by contaminated intravenous fluids and total parenteral nutrition may occur. Removal of CVC recommended in addition to elimination of the source of contamination.

site where the CVC is placed. With the femoral site, *Enterococcus*, *Enterobacteriaceae*, and *Pseudomonas* species have a greater incidence of occurrence, comparatively speaking [34].

There is a significant positive relation between the risk of infection and the length of catheter indwelling time. After 3 days, the risk of infection increases to 3 to 5%. After 7 days, the cumulative risk increases to 5 to 10% [35,36]. The route of infection is time dependent. Extraluminal infection occurs more often with short-term use, and intraluminal infection develops more often with long-term use. To reduce the length of catheter indwelling time, some clinicians have adopted the strategy of routine replacement of CVCs without signs of clinical infection. With routine catheter replacement, the physician has two choices: catheter replacement at a new site or catheter replacement using the Seldinger technique of guidewire exchange [37]. In a recent, systematic review of the literature, Cook *et al.* [38] examined 12 published randomized trials to evaluate guidewire exchange versus new site replacement techniques on the incidence of catheter colonization, infection, bacteremia, and mechanical complications. They also examined scheduled catheter replacement compared with as-needed catheter changes. In cases of scheduled guidewire exchange, they found a trend ($P > 0.5$) toward increased colonization (relative risk, 1.29; 95% CI, 0.87–1.84) and a trend toward catheter-related bacteremia (relative risk, 1.69; 95% CI, 0.27–11.07). When all noninfectious adverse outcomes were pooled, there was a trend toward a decreased incidence of mechanical complications compared with new site replacement for catheters that were indwelling for the same length of time. When patients were randomly selected to have their catheter changed via guidewire exchange because of a suspected catheter-related infection, sensitivity analysis showed a trend toward increased frequency of catheter colonization. Interestingly, no difference in the frequency of catheter-related bacteremia was detected when patients were randomized to guidewire exchange versus new site placement when catheters were changed because of suspected catheter-related infection. Lastly, the researchers discovered that prophylactic catheter changes every 3 days versus every 7 days did not decrease the incidence of catheter-related colonization or bacteremia (relative risk, 0.87; 95% CI, 0.65–1.16). However, given the increased incidence of infection and thrombosis at the femoral site recently demonstrated in a randomized trial in France [39], changing from a femoral to a subclavian or an internal jugular site may be justified, even if there is no sign of infection at the femoral site.

Silver-coated or antibiotic-coated catheters

Catheters coated with silver ions are one of several options used to prevent CR-BSI. Silver ions attach to the sulfhydryl group of cellular membranes, which decreases adherence of microorganisms to the catheters. In a recent study of 97 patients randomized to conventional polyurethane catheter or silver-impregnated catheters, there was a tendency toward a reduced rate of infection with silver-impregnated catheters [40•]. In a randomized trial of 233 patients to evaluate the development of thrombosis of silver-coated catheters, Christoph *et al.* [41••] found that silver-coated catheters did not develop thrombosis at a greater frequency than uncoated catheters. In addition, these investigators found that catheter-related infection occurred in 21.2% of the control group versus 10.2% in the silver-coated group ($P = 0.011$). Catheter-related septicemia was observed in 5% of patients with silver-coated catheters versus 8.8% with standard catheters. Thus, silver-coated catheters may decrease the incidence of colonization and CR-BSI.

When catheters coated with chlorhexidine/silver sulfadiazine were compared with noncoated catheters, chlorhexidine/silver sulfadiazine catheters decreased the incidence of CR-BSI by approximately 40%. Chlorhexidine/silver sulfadiazine catheters are economically beneficial for critically ill or immunocompromised patients [42]. When chlorhexidine/silver sulfadiazine catheters were compared with minocycline- and rifampin-coated catheters in a prospective, randomized trial, minocycline- and rifampin-coated catheters were less likely to be colonized compared with catheters impregnated with chlorhexidine and silver sulfadiazine ($P < 0.001$). In catheters impregnated with minocycline and rifampin, CR-BSI was significantly reduced compared with catheters coated with chlorhexidine and silver sulfadiazine [43]. However, there is some concern that minocycline- and rifampin-coated catheters can induce the development of resistant organisms based on animal studies. Therefore, at some institutions, chlorhexidine and silver sulfadiazine catheters are preferred [1••]. Recent guidelines suggest that antimicrobial catheters should be used in patients who are at high risk for CR-BSI (those who are immunocompromised or receiving total parenteral nutrition) and who will need the catheter for more than 4 days.

In the future, arresting biofilm formation could serve as a means of preventing CR-BSI. Low-voltage electric current and antibiotic prophylaxis against the establishment of *Staphylococcus epidermis* biofilms has become a potential method to prevent catheter-related infections in animal studies [44,45]. This method involves silver catheters wrapped helically with electrically charged wires resulting in continuous release of silver ions inhibiting bacterial growth. Coating catheters with specific antiadhesion molecules could also prevent biofilm formation. These methods require clinical evaluation. In addition, the future may include routine vaccinations against the common causes of infections in high-risk patients. The capsular polysaccharides of *S. aureus* play a role in the

pathogenesis of this organism. These polysaccharides, when bound to recombinant exoprotein A, can cause an immunologic stimulant against *Staphylococcus*. Recently, in a double-blind trial of patients on hemodialysis with end-stage renal disease, Shinefield *et al.* [46••] evaluated a vaccine of *S. aureus* type 5 and eight capsular polysaccharides conjugated to a benign *P. aeruginosa* exotoxin A. In patients receiving the vaccine, *S. aureus* bacteremia developed in 11 of 892 compared with 26 of 906 in the control group (estimate of efficacy, 57%; 95% CI, 10–81%; $P = 0.02$).

Conclusions

CR-BSIs are an important cause of morbidity and mortality. When a CR-BSI is suspected, management decisions regarding the removal of the catheter and the choice of antibiotics should be based on a careful clinical evaluation combined with systematic efforts to diagnose CR-BSI by catheter tip culture and peripheral blood culture. Several methods have been developed that clearly decrease the rate of infection in patients requiring CVCs, including sterile precautions during catheter insertion and the use of antibiotic-coated catheters. In the future, the physician may have additional options with the potential of vaccines against bacteria, especially *S. aureus*, and the use of antiadhesion molecules against biofilms on the catheters.

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