Intravascular Catheter–Related Bloodstream Infections

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KEYWORDS

- Catheter-related bloodstream infection
- Central line–associated bloodstream infection • Central venous catheter
- Bacteremia • Health care–associated infection

KEY POINTS

- Approximately 30,000 to 40,000 episodes of catheter-related bloodstream infection (CRBSI) occur in the United States each year, resulting in a significantly increased odds of death and an estimated cost of $45,000 per event.
- Successful prevention of CRBSI requires application of practice-based measures, such as catheter insertion with the use of full sterile barrier precautions, checklists, and maintenance protocols, emphasizing sterile catheter access technique and catheter dressing integrity, as well as judicious application of evidence-based innovative technologic advances, such as antimicrobial-coated catheters, chlorhexidine-impregnated dressings, and passive port protectors.
- A diagnosis of CRBSI can often be made without catheter removal by application of the differential time to positivity blood culture assay.
- Increasing experience is being gained with successful catheter salvage and treatment without catheter removal using antimicrobial lock therapy.

BACKGROUND AND CLINICAL SIGNIFICANCE

Intravascular (IV) catheters, which include peripheral and midline venous catheters, subcutaneously tunneled and nontunneled central venous catheters (CVCs), peripherally inserted central catheters, totally indwelling devices (ie, ports), and arterial catheters (ACs) are essential and ubiquitous in health care. Although great strides have recently been achieved in the prevention of IV catheter–related infection, with an observed 50% reduction in central line–associated bloodstream infections (CLABSIs)

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from 2008 to 2014 in acute-care hospitals in the United States, tens of thousands of patients continue to experience bloodstream infection (BSI) each year, resulting in substantial morbidity and mortality and increased cost.[1] The mean rate of CLABSIs in acute-care hospital units in the United States ranges from zero to 2.9/1000 CVC days depending on the type of unit and is approximately 1/1000 CVC days in critical care units and 0.7/1000 CVC days on other inpatient units.[2]

The rate of CLABSIs in Western European hospitals is generally comparable to that based on data reported by the US National Healthcare Safety Network (NHSN). Among patients in European ICUs, 3.7% develop BSIs (1.9/1000 patient days), with 43.6% of these BSIs attributed to IV catheters.[3] Unfortunately, the incidence of CLABSIs in limited-resource countries is substantially higher (1.6–44.6/1000 CVC days).[4]

An estimated 30,000 to 40,000 episodes of CLABSI continue to occur in US acute-care hospitals yearly, and thousands of additional cases undoubtedly occur in other health care settings (eg, dialysis units, critical access hospitals, long-term acute-care hospitals, and long-term care facilities) that are less well defined.[1,5] CLABSI is associated with significantly increased odds of death (odds ratio 2.75; 95% CI, 1.86–4.07) and an estimated attributable cost of $45,814 (95% CI, $30,919–$65,245).[5,6]

DEFINITIONS AND SURVEILLANCE

Two major designations are used to define BSIs due to vascular catheters: CLABSIs and catheter-related bloodstream infections (CRBSIs). Although the 2 terms are often used interchangeably, they have distinct differences. CLABSI is a surveillance definition that identifies patients with a CVC who experience a BSI that is not attributable to another source.[7] CRBSI is a clinical definition that generally requires specialized microbiologic data (eg, catheter tip culture, quantitative blood cultures, and differential time to positivity [DTP] determination). The CLABSI definition by design is highly sensitive but not as highly specific. The Centers for Medicaid and Medicaid Services requires reporting of CLABSIs and has instituted financial penalties for institutions with CLABSI rates above an arbitrary threshold. Despite improvements, the CLABSI definition over-estimates the true incidence of infection and remains somewhat subjective in assigning the source of infection.[8] Furthermore, many institutions acknowledge use of an adjudication system in defining CLABSI.[9] A more robust means to validate CLABSI data is needed, and consideration should be given to monitoring all-cause BSIs to better avoid systematic under-reporting of CLABSIs or cost shifting to secondary bacteremia designations. In addition, bacteremia due to other vascular catheters (midline catheters [MCs], arterial lines, and peripheral IV catheters) should be captured in any comprehensive surveillance system designed to monitor and diminish BSIs due to IV catheters. Finally, surveillance should be extended to various non–acute-care settings.

IV catheter infections are further defined by the site and extent of infection and can involve the exit site (erythema and/or induration extending no more than 2 cm from the exit site), the tunnel track (evidence of inflammation along the subcutaneous tunnel of an implanted CVC) (**Fig. 1**), or the subcutaneous reservoir of an implanted port (**Fig. 2**). Although purulence at the insertion site (**Fig. 3**) is pathognomonic of an infected IV catheter, most CVCs that are responsible for BSIs are innocuous in appearance, and physical examination findings lack sensitivity.[10,11]

PATHOGENESIS

Fig. 4 illustrates the main routes microbes take to infect a vascular catheter. For short-term, nontunneled catheters, the dermal surface often serves as the source of

Fig. 1. Subcutaneously tunneled CVC tunnel track infection resulting in CRBSI.

microbial contamination. For subcutaneously tunneled catheters and the longer a temporary catheter stays in place, the hub and luminal surface are frequently implicated as the route of inoculation. Also, as efforts to prevent external surface contamination (CVC insertion bundles and chlorhexidine dressings) are increasingly used, hub colonization seems to have become a more prominent route of infection. Catheters are rarely seeded via a hematogenous route or via installation of contaminated infusates. Once microbes gain access to the catheter surface, they quickly adhere, proliferate, aggregate, and elaborate biofilms. The biofilms contain microbes exhibiting a variety of growth and metabolic characteristics, including very quiescent persister cells and small colony variants. Infected vascular catheters exhibiting a mature biofilm-associated infection can be difficult to treat successfully with the catheter in situ,

Fig. 2. Subcutaneous port reservoir infection resulting in CRBSI.

Fig. 3. Obvious purulence at the insertion site of an IV catheter in a patient with CRBSI.

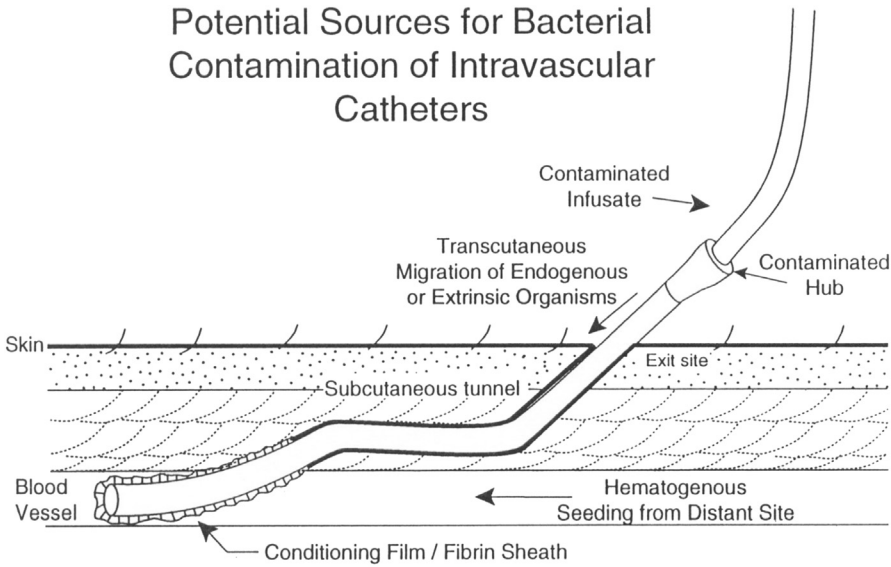

Fig. 4. Pathogenesis of CRBSI. Microbes gain access to the catheter by the following routes: external/dermal surface from transcutaneous migration and internal/luminal surface from contamination of the catheter hub, contamination of the infusate, and hematogenous seeding. (*From* Rupp ME. Infections of intravascular catheters. In: Crossley KB, Archer GL, editors. The staphylococci in human disease. New York: Churchill Livingstone; 1997. p. 381; with permission.)

and most infected catheters are removed to better ensure successful treatment and clinical outcome. Improved means to preserve vascular catheters and treat through infections are needed.

DIAGNOSIS OF CATHETER-RELATED BLOODSTREAM INFECTION

It is important to make an accurate diagnosis of CRBSI because there are grave consequences associated with inaccurate or missed diagnosis, such as unnecessary catheter removal, serious procedural complications, and increased mortality and economic costs. Definitive diagnosis of CRBSI requires clinical signs of sepsis with microbiological evidence. The Infectious Diseases Society of America (IDSA) clinical practice guideline suggests 1 of the following criteria for the definitive diagnosis of CRBSI:[10]

- Growth of the same microorganism from the culture of a catheter segment by semiquantitative roll-plate method (>15 colony-forming units [CFUs]/plate) or quantitative culture by sonication method (10^2 CFUs) and percutaneously obtained peripheral blood culture
- Paired blood cultures obtained simultaneously from a catheter lumen and peripheral blood meets the criteria for CRBSI by quantitative blood cultures ($\geq$3-fold difference in CFU in blood from catheter lumen versus peripheral blood) or DTP ($\geq$2-h difference in time to positivity, catheter lumen vs peripheral)

In situations where peripheral blood cultures or culture of catheter segment cannot be performed, a possible diagnosis of CRBSI is suggested by quantitative blood cultures obtained from 2 different lumens of the catheter in which at least a 3-fold colony count difference is noted.

Catheter Segment Culture for the Diagnosis of Catheter-Related Bloodstream Infection

Maki and colleagues[12] described the utility of the roll-plate semiquantitative culture method in the diagnosis of CRBSI and this remains a frequently used microbiologic test to assess for significant catheter colonization. When a vascular catheter (venous or arterial) is removed for suspicion of CRBSI, the distal 5 cm of the catheter (catheter segment or tip) is sent for roll-plate analysis. If a pulmonary artery catheter is implicated, the introducer tip should be cultured rather than the catheter itself.[10,13] Qualitative culture of the port reservoir is recommended for the diagnosis of a subcutaneous port infection.[14] Because the luminal surface is often involved in infections of long-term catheters, the roll-plate technique (which only samples the external surface of the catheter) is associated with significant false-negative results. Quantitative culture performed after sonication or vortex washing the catheter tip is the preferred method for sampling long-term IV catheters.[15] Unfortunately, these culture techniques require removal of the catheter. Other methods to microbiologically assess the catheter with the device in situ include paired hub and exit site cultures and use of intraluminal brushes.[16–19] A particularly innovative approach to the diagnosis of catheter colonization is the use of biosensors attached to the CVC; however, economic cost of this technology is a limiting factor.[20]

Blood Culture Methods for the Diagnosis of Catheter-Related Bloodstream Infection

Paired quantitative blood cultures

A diagnosis of CRBSI can be made in appropriate clinical settings if the microorganism colony count is at least 3-fold higher in blood cultures obtained from

the CVC versus percutaneously obtained peripheral blood.[10] A meta-analysis by Safdar and colleagues[17] calculated pooled sensitivity and specificity of 8 diagnostic methods to diagnose CRBSI and found paired quantitative blood culture the most accurate, with a sensitivity of 74% to 84% and specificity of 98% to 100%.

Differential time to positivity

The DTP test depends on the use of continuously monitored blood culture systems and is based on the finding that a blood culture with a higher inoculum shows evidence of microbial growth sooner than a blood culture with a lower inoculum. If a vascular catheter is the source of bacteremia, blood sampled through the catheter should have a higher inoculum than peripheral blood and hence should yield evidence of microbial growth more quickly. A cutoff time of 2 hours is generally used for DTP evaluation, and a meta-analysis to assess the utility of DTP for the diagnosis of CRBSI documented a sensitivity of 86% to 92% and a specificity of 79% to 87%.[17,21] Accurate DTP testing requires that an equivalent amount of blood is sampled from both catheter and peripheral sources. A recent study documented, however, that blood cultures drawn from CVCs contain a significantly greater amount of blood than peripheral blood cultures; thus, this requirement for equivalent blood volumes for DTP cultures may not be met in routine practice.[22] The role of DTP for the diagnosis of catheter-related candidemia remains controversial. A retrospective study analyzing the usefulness of DTP for diagnosis of catheter-related candidemia found a DTP greater than 2 hours was 85% sensitive and 82% specific.[23] Other investigators, however, noted poor specificity (40%) associated with DTP testing for CVC-associated candidemia.[16,23]

Multilumen catheters

Current guidelines do not recommend culturing more than 1 lumen of a CVC.[10] A retrospective study noted, however, that up to 37.5% of CRBSIs can be missed if only 1 lumen of a multilumen CVC is cultured.[24] Similarly, a retrospective study by Plane and colleagues[25] found that approximately one-third of CRBSIs are missed if all lumens of the catheter are not cultured. One solution to the added cost associated of sampling all lumens separately is to pool blood drawn from all lumens into a single blood culture bottle.[26] This pooled culture technique does not define which specific lumen is infected and this information may be important if an antimicrobial lock is used in treatment (discussed later).

Molecular-Based Testing and Biomarkers for the Diagnosis of Catheter-Related Bloodstream Infection

Significant time is often required to diagnose CRBSI due to reliance on microbial growth from blood and/or catheter segments. Molecular-based rapid diagnostic testing has evolved recently for the early identification of microorganisms in BSIs, including infections stemming from vascular catheters.[27] The utilization of rapid, non–culture-based diagnostic methods has the potential to supplement conventional microbiologic diagnosis. Non–culture-based systems also may contribute new knowledge regarding microbes, potentially causing CRBSIs that are not recoverable using traditional culture-dependent methods. Biomarkers like interleukin 6, procalcitonin, C-reactive protein, and triggering receptor expressed on myeloid cells 1 (TREM-1) have also been studied for the diagnosis of BSIs. Molecular diagnostic strategies, potentially used together with biomarker identification, may lead to faster and more sensitive means to diagnosis of CRBSI.

MANAGEMENT OF CATHETER-RELATED BLOODSTREAM INFECTION

Once CRBSI is suspected, empiric antimicrobial therapy should be administered after appropriate cultures are obtained. The choice of empiric antimicrobial agent depends on the following: most likely causative pathogen, type of catheter, host characteristics, local antimicrobial susceptibility patterns, clinical stability of the patient, and presence of complications. Some considerations for appropriate antibiotic therapy are as follows:

- Empiric antibiotics should cover gram-positive organisms; intravascular vancomycin or daptomycin is recommended in health care settings due to the high prevalence of methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci.
- Indications for empiric antibiotics for gram-negative bacilli include the following: neutropenia, critical illness, femoral catheter–related BSI, or known gram-negative bacilli focus of infection at the time of suspected CRBSI. The choice of empiric antibiotics for gram-negative bacilli should be based on the local antimicrobial susceptibility pattern. In general, a fourth-generation cephalosporin, β-lactam/β-lactamase inhibitor combination, or carbapenem, with or without an aminoglycoside, is recommended. In critically ill patients or patients with documented recent colonization with multidrug-resistant (MDR) gram-negative bacilli, combination therapy with 2 different classes of antimicrobials against MDR gram-negative bacilli is indicated. When treating patients with gram-negative bacilli CRBSI, significant consideration should be given for the bacilli to potentially produce AmpC β-lactamase, extended-spectrum β-lactamase (ESBL), metallo-β-lactamase, or a carbapenemase.
- Indications for empiric antifungal therapy for candidemia include critically ill patients, prolonged exposure to broad-spectrum antibiotics, recent gastrointestinal surgery, femoral catheter–related BSI, hematologic malignancies, hematopoietic stem cell transplantation, solid organ transplantion, patients on total parenteral nutrition, and presence of candida colonization at multiple body sites. Echinocandins are preferred antifungal agents for empiric therapy for candidemia, particularly if local prevalence of *Candida krusei* or *Candida glabrata* infection is high or if a patient has received an azole antifungal within the preceding 3 months. **Box 1** offers a summary of treatment considerations for CRBSIs caused by specific pathogens.

Central Venous Catheter Removal

Indications for the removal of an IV catheter in the setting of a CRBSI include the following:

- Severe sepsis, infective endocarditis, septic thrombophlebitis, or persistent bacteremia for greater than 72 hours despite appropriate antimicrobial therapy
- CRBSI due to *S aureus*, MDR gram-negative bacilli, fungi, or mycobacteria
- CRBSIs due to *Micrococcus* spp or *Propionibacterium* once blood culture contamination is ruled out by repeated recovery of the pathogen from blood cultures

A randomized controlled trial in hemodynamically stable ICU patients suspected of having CRBSI compared watchful waiting (catheter removal only after confirmed bacteremia or if new hemodynamic instability) to standard of care (immediate catheter change) and showed a substantial reduction in unnecessary catheter removal without an increase in mortality associated with the watchful waiting strategy.[28] In patients

Box 1
Selected pathogen-specific recommendations for treatment of catheter-related bloodstream infection

Coagulase-negative staphylococci:
- Uncomplicated infection: remove catheter and treat for 5 days to 7 days. If catheter salvage is desired, treat in combination with antibiotic lock therapy for 10 days to 14 days.
- If no IV or orthotic hardware is present, repeat blood cultures after catheter removal are negative, and there is no evidence of complicated infection, observation without antibiotic administration is reasonable alternative.
- *S lugdunensis*: treat as *S aureus.*

S aureus:
- Remove catheter and treat for 2 weeks to 6 weeks.
- TEE indicted if persistent fever or bacteremia greater than 72 hours after removal of catheter. Optimal timing for TEE is 5 days to 7 days after diagnosis of bacteremia to reduce false-negative results.
- Two weeks of parenteral antibiotics is reasonable in uncomplicated CRBSI in appropriate clinical settings.
- A replacement CVC can be inserted if repeat cultures are sterile 48 hours to 72 hours after removal of the infected CVC.

Enterococcus spp:
- Short-term catheter: remove catheter and treat for 7 days to 14 days.
- Long-term catheter: catheter removal is preferred. If catheter salvage is desired, treat for 10 days to 14 days in combination with ALT.
- TEE is indicated if there are clinical or radiographic signs of infective endocarditis or there is persistent fever or bacteremia greater than 72 hours after initiation of appropriate antibiotic therapy or the patient has a prosthetic heart valve.

Other gram-positive bacteria:
- Suspected CRBSIs due to *Micrococcus* spp, *Corynebacterium* spp, *Bacillus* spp, or *Propionibacterium* spp require confirmation of true bacteremia with multiple percutaneous blood cultures.
- Catheter removal is often required as infections are difficult to eradicate

Gram-negative bacilli:
- Empiric gram-negative coverage indication: patient is neutropenic, critically ill, or there is a known focus of gram-negative infection at the time of suspected CRBSI.
- Two empiric gram-negative antibiotics are indicated if a patient is critically ill or previously defined as colonized with an MDR gram-negative bacilli.
- *Pseudomonas* or MDR gram-negative bacilli: remove catheter and treat for 10 days to 14 days.
- Other gram-negative bacilli: remove catheter and treat for 7 days to 14 days. If catheter salvage is attempted, use parenteral antibiotics in combination with ALT for 10 days to 14 days.
- Persistent fever or bacteremia greater than 72 hours despite being on appropriate antimicrobial therapy: remove catheter and look for metastatic infection and infective endocarditis.

Candida spp:
- Remove catheter. Catheter retention is associated with worse outcome.
- Candidemia with a CVC: if no other source, remove CVC and culture tip of the catheter, or exchange catheter over a guide wire and culture tip of the catheter (if CVC is colonized, removed CVC and treat for 14 days).
- Echinocandins: if high prevalence of *Candida krusei* or *Candida glabarata* or recent azole exposure.

Abbreviation: TEE, transesophageal echocardiogram.

with limited venous access, such as hemodialysis catheter (HD) patients with extensive venous thrombosis, catheter exchange over a guide wire should be considered.[29] A systemic review to compare catheter exchange over a guide wire versus new site replacement showed a trend toward increased infections but fewer mechanical complications when the catheter was exchanged over a guide wire.[30] CRBSIs due to low-virulence organisms, particularly in the setting of a high-risk for mechanical complications for new catheter insertion, can be treated with catheter exchange over a guide wire. Many experts recommend use of an antimicrobial impregnated catheter to prevent future colonization and BSIs if the catheter is exchanged over a guide wire.[10] Increasing clinic experience, however, is being accrued regarding preservation of the CVC and treatment with the CVC in situ.[31–33] This CVC preservation strategy involves use of antimicrobial locks, discussed later.

Duration of Antibiotic Therapy

Appropriate duration of antimicrobial therapy in CRBSI is based on the causative pathogen, presence of complications, and host factors. In uncomplicated CRBSI (absence of metastatic infection, endocarditis, suppurative thrombophlebitis, IV hardware, immunosuppression, and resolution of clinical and microbiological signs of infection within 72 hours of initiation of antimicrobial agent) a shorter course of antibiotics should be considered. All complicated CRBSIs require catheter removal. **Box 2** delineates the most common complications associated with CRBSIs.

Antimicrobial Lock Therapy

Often, removal of foreign material is the most desirable approach in the treatment of a foreign body–related infection. Removal of an infected CVC, however, may not be

Box 2
Complications of infections of intravascular catheters

Suppurative thrombophlebitis:
- Suspect suppurative thrombophlebitis if bacteremia persists greater than 72 hours despite being on appropriate antibiotic therapy. Subcutaneous thrombosed vein may present as a cordlike structure.
- Diagnosis made by imaging (ultrasound, CT, or MRI)
- May require surgical intervention and/or anticoagulation
- Remove the catheter and treat for 4 weeks to 6 weeks with parenteral antibiotics.

Persistent bacteremia:
- Persistent bacteremia without an identifiable complication indicates the need for longer courses of antibiotics (consider 4–6 weeks). In the case of *S aureus* bacteremia, if initial TEE is negative, consider repeat TEE in 5 days to 7 days.

Infective endocarditis:
- Longer course of antibiotics (4–6 weeks) and further work-up related to complications of infective endocarditis is required. May need surgical treatment.

Osteomyelitis:
- Longer course of antibiotics (6–8 weeks) is required and surgical débridement may be needed.

Local complication:
- Catheter tunnel infection and port pocket infection require catheter removal; 7 days to 10 days of parenteral antibiotics with drainage of abscess.

Abbreviation: TEE, transesophageal echocardiogram.

possible or practical for a variety of reasons, such as extremely limited alternative vascular access or unacceptable complications associated with removal and replacement. ALT is an alternative when catheter removal is not possible, or catheter salvage is desired. Although there is no Food and Drug Administration (FDA)-approved antimicrobial lock solution, ALT is recommended by many experts in adjunct to parenteral antibiotic therapy for catheter salvage.[10] The ALT solution consists of a highly concentrated antibiotic (100–1000 times the minimum inhibitory concentration), which is generally mixed with an anticoagulant.[34] Sufficient volume of the antimicrobial lock solution (usually 2 mL–5 mL) is infused to fill the catheter lumen and it is allowed to dwell in place for hours (the optimum duration of dwell time is unknown, but many institutional ALT protocols suggest a minimum of 2–4 hours). The hallmark of a vascular catheter–associated infection is the presence of a biofilm and, unfortunately, the ability of many antimicrobial agents to kill microorganisms is significantly reduced in a biofilm due to the following: decreased antimicrobial biofilm penetration, presence of inactivating enzymes and efflux pumps in biofilms, and the presence of metabolically quiescent persister cells.[35,36] Citrate and EDTA improve the activity of antimicrobial lock solutions by disrupting biofilm and improving antimicrobial biofilm penetration.[37,38] There are no commercially available ALT solutions. Properties of an ideal ALT solution include the following: intrinsic antimicrobial activity against the offending microorganism, ability to penetrate and disrupt biofilm cells, compatibility with an anticoagulant, prolonged stability, minimal risk for toxicity, low potential for resistance, compatibility with catheter materials, and cost-effectiveness.[34] A randomized double-blind placebo-controlled trial to evaluate the effect of ALT in the treatment of CRBSI in patients with long-term IV devices showed ALT reduced the failure rate from 57% to 33%.[31] Raad and colleagues[39] observed successful salvage of infected CVCs in cancer patients with use of ALT consisting of minocycline, EDTA, and 25% alcohol. A recent systemic review analyzing ALT in CRBSIs suggested that the introduction of components, such as daptomycin, tigecycline, ethanol, and taurolidine, into ALT solutions increased their effectiveness in catheter salvage.[40] **Box 3** summarizes some of the considerations regarding ALT.

PREVENTION

Methods to prevent vascular catheter infections can be broadly grouped into 2 categories: clinical practice–based measures (**Box 4**) and technologic approaches (**Box 5**). Several comprehensive, evidence-based guidelines have been promulgated to steer

Box 3
Summary of considerations regarding antimicrobial lock therapy

- Recommended as adjunct to parenteral antibiotic therapy for catheter salvage
- Antibiotic solution (100–1000 times the MIC) mixed with an anticoagulant installed in the catheter lumen and allowed to dwell for hours
- Higher rate of treatment failure with *S aureus*, *Pseudomonas*, and *Candida* infection
- Concentration of antibiotic can substantially decline over time; antibiotic lock solution should be changed at least every 48 hours.
- Infections occurring shortly after catheter insertion (less than 2 weeks) are often extraluminal; ALT is not likely beneficial.

Abbreviation: MIC, minimum inhibitory concentration.

Box 4
Evidence-based practice interventions (human behavior–oriented interventions) to prevent catheter-related bloodstream infections

Pericatheter insertion
- Appropriate staffing
- Education and training; infusion team
- Use of maximal sterile barriers
- Insertion site selection
- Cutaneous antisepsis with chlorhexidine
- Use of insertion checklist
- Bundle approach

Postcatheter insertion
- Scrub the hub—disinfection of hubs and needleless connectors
- Chlorhexidine patient bathing
- Removal of unneeded catheters
- Catheter dressing maintenance
- Bundle approach

preventive techniques and the main points are summarized in the following discussion.[41–43]

Practice-Based Interventions

Staffing and education

Experience from several CRBSI outbreaks indicates that when units are not staffed with stable and well-trained personnel (nurses and physicians), optimum infection prevention procedures and protocols are not maintained and excess health care–associated infections are the result.[44–46] It is difficult to stipulate minimum staffing requirements from an infection prevention viewpoint because patient acuity and staffing needs vary from unit to unit and from day to day. It suffices to state that units should be staffed with an adequate number of personnel and the personnel must be appropriately educated and trained with regard to vascular catheter selection, proper insertion procedures, catheter care and maintenance, and catheter removal. Some institutions have successfully decreased CLABSI rates by instituting specially trained teams to insert and care for CVCs.[43] There is also a growing recognition that the patient and patient's family should be included in IV catheter education, particularly if they are involved in out-of-hospital care.[42,47]

Box 5
Evidence-based technologic innovation interventions (new devices and technology) to prevent catheter-related bloodstream infections

- Antimicrobial catheter coatings (silver-sulfadiazine/chlorhexidine or minocycline/rifampin)
- Chlorhexidine-impregnated dressings (sponge dressing or gel pad dressing)
- Passive port protectors
- Silver-impregnated connectors
- Sutureless catheter securement
- Antimicrobial catheter locks

Maximal sterile barrier precautions and checklist

Maximal sterile barrier precautions should be used for the insertion of all CVCs and consist of sterile gloves, long-sleeved sterile gown, cap, procedure mask, and a long sterile drape that covers the patient from head to toe.[48,49] To ensure compliance with appropriate insertion procedures, a bedside checklist should be used.[50] A person other than the CVC inserter should complete the checklist and the observer should be empowered to stop the procedure if violations in aseptic technique are noted.

Chlorhexidine cutaneous antiseptic

In patients without contraindications (eg, chlorhexidine allergy), the skin should be disinfected with an alcoholic chlorhexidine solution containing at least 0.5% chlorhexidine.[51] The insertion site should be allowed to dry before catheter insertion. Increasing data indicate that chlorhexidine can be used safely for skin disinfection in some groups of neonates.[52,53]

Insertion site

The femoral site may be more prone to colonization and infection, particularly in obese patients, and should thus be avoided.[54] Although the subclavian site seems the least prone to infectious complications, due to ease of placement with the use of ultrasound guidance, the internal jugular site is often preferred by clinicians.[55–57] In all cases, the CVC insertion site should be individualized and depends on experience of the operator, risk of complications, anticipated duration of catheterization, potential need for dialysis, and other patient factors.[57]

Bundle

A variety of prevention measures can be combined to create a bundle. In many institutions, the bundle consists of use of an all-inclusive insertion kit or catheter cart, hand hygiene, use of alcoholic chlorhexidine for skin disinfection, avoidance of the femoral site, use of maximal sterile barrier precautions, and removal of CVCs as soon as practical.[58,59] The relative contribution of elements of the bundle has not been defined and this approach is most successful when used in a multidisciplinary manner in an institution with a good patient safety foundation.

Postinsertion precautions

As increasing numbers of institutions have instituted peri-insertion checklists and bundles, contamination of the CVC at the time of insertion has become less frequent and a shift in CLABSI etiology away from commensal skin organisms has been evident.[60] This points to the increasing importance of post-CVC insertion preventive measures.

Removal of unneeded or potentially contaminated central venous catheters

The need for CVCs should be assessed daily and unnecessary CVCs should be removed. Programmatic approaches to CVC assessment and removal are most effective if they use a standardized procedure and use checklists, audits, and electronic monitoring and reminders.[54,61] Also, in instances in which compliance with CVC insertion precautions cannot be assured (emergent CVC insertion in the field or code blue situations), the CVC should be removed and replaced at a new site as soon as a patient's condition allows (within 24–48 hours).[41,43]

Catheter hub and needleless connector disinfection—"scrub the hub"

An appropriate antiseptic (70% alcohol, alcoholic chlorhexidine, and povidone iodine) should be used to scrub the catheter hub or needleless connector before accessing the catheter. The minimum scrub time to adequately disinfect needleless connectors is not defined and depends on the connector design and degree of contamination.[62] It

seems that some connector designs are associated with a greater risk of BSI and this probably relates to features, such as transparency, displacement, fluid pathway and flow dynamics, and, perhaps most important, the ease of cleaning of the interface between the diaphragm and the plastic housing (smooth, easy-to-clean interface without cracks or crevices).[63–65]

Chlorhexidine patient bathing

Chlorhexidine is believed a more effective disinfectant to prevent CLABSI due to its long residual activity and resistance to inactivation.[66] As discussed previously, chlorhexidine should be used for skin disinfection for initial CVC insertion and then routinely during dressing changes.[41–43] In addition, a growing body of literature indicates that routine patient bathing with chlorhexidine or universal decolonization protocols results in CLABSI prevention.[67–70] There is concern, however, that widespread or indiscriminate use of chlorhexidine will promote the emergence of chlorhexidine resistance.[71]

Catheter dressing integrity and administration set replacement

CVC dressings should be changed at weekly intervals for transparent semipermeable dressings and every 2 days for gauze dressings.[41–43] Dressing integrity seems to be an important risk factor for the development of CLABSIs, and CVC dressings should be changed whenever they become loose, damp, or soiled.[41–43,72] Because frequent administration set change does not decrease CLABSIs, administration sets should be routinely changed no more frequently than every 96 hours.[43] Administration sets for parenteral nutrition should be changed every 24 hours, whereas those used to administer blood and blood products should be changed after the completion of each unit or every 4 hours.[43] Tubing for propofol infusions should be changed every 6 hours to 12 hours.[43] Disconnection/reconnection of infusion sets should be minimized.

Postinsertion bundles

Many institutions have combined postinsertion measures to prevent CLABSIs into bundles consisting of reminders to remove CVCs and compliance with scrub-the-hub and dressing integrity recommendations.[73,74]

Technologic Innovations to Prevent Catheter-Related Bloodstream Infection

In recent years, a variety of innovative devices designed to prevent CRBSIs have been brought to market (see **Box 5**). In some instances, because human behavior can be difficult to change, the introduction of a device that protects against lapses in human practices (hand hygiene, scrub the hub, appropriate CVC dressing changes, and so forth) may be particularly useful and cost effective. The following section briefly covers commercially available products.

Antimicrobial coated intravascular catheters

There is extensive experience and a large body of evidence to indicate that CVCs coated with antimicrobial agents are associated with a decreased risk of CRBSI.[75–78] The catheters with the greatest amount of supporting data are coated with either silver sulfadiazine/chlorhexidine or minocycline/rifampin. Fewer data are available to support use of CVCs with other coatings.[75,78] Available data suggest that use of antimicrobial coated CVCs does not result in an emergence of antibiotic resistance.[79] Guidelines suggest that antimicrobial coated CVCs be used in patients in whom the catheter is expected to stay in place at least 5 days and when routine practice measures (ie, insertion bundle and postinsertion care) have not eliminated preventable

CRBSI.[41–43] These considerations, however, are appropriate for all technologic approaches to CRBSI prevention.

Chlorhexidine-impregnated dressings

Chlorhexidine-impregnated dressings prevent microorganisms present at the skin and the insertion site from proliferating and gaining access to the external surface of the CVC. Extensive data exist supporting their use to prevent CRBSIs.[72,80]

Antibiotic-impregnated needleless connectors

Needleless connectors may be prone to microbial colonization resulting in BSIs. To decrease this risk, connectors impregnated with silver have been introduced. Silver-impregnated connectors are less prone to microbial colonization, and their use may decrease CRBSIs.[81,82]

Passive port protectors

As discussed previously, the widespread use of insertion precautions to prevent contamination and chlorhexidine skin disinfection with dressing changes or patient bathing regimens has resulted in a shift in the most prominent route of inoculation from the external/dermal surface of the CVC to the hub/luminal surface. Because it is difficult to maintain strict aseptic technique with all CVC access events, some institutions have introduced passive port protectors that bathe the catheter connector hub with alcohol when it is not in use. There are increasing data that this is an effective means to prevent CRBSIs.[83,84]

Catheter lock solutions

Although there are no FDA-approved catheter lock solutions for the prevention or treatment of CRBSIs, there is a great amount of data to indicate that antibiotic or antiseptic solutions can be used to prevent CRBSIs.[85–88] A variety of antibiotics and antiseptics have been used in solutions to lock catheters, and antimicrobial locks are increasingly used to prevent infections in patients with long-term need for vascular access (hemodialysis, total parenteral nutrition dependence, and so forth) or in patients with a history of recurrent CRBSI.

Catheter securement

Sutures used to secure CVCs result in trauma to the skin and provide a foreign body nidus for microbial colonization.[89] Therefore, sutureless securement systems have been developed and are supported by some clinical data.[90,91]

CONSIDERATIONS REGARDING OTHER VASCULAR CATHETERS

Peripheral Intravascular Catheters

Peripheral intravascular catheters (PIVCs) are nearly ubiquitous in hospitalized patients, and approximately 330 million PIVCs are purchased in the United States yearly.[92–94] The incidence of PIVC-BSI is approximately 0.2% and approximately 20% of *S aureus* BSIs are due to infected PIVCs.[94] At present, because of their widespread use and limited appreciation of risk, as well as successful programs to prevent CRBSIs, there may be more patients experiencing BSIs due to PIVCs than due to CVCs.[94] Prolonged PIVC dwell time seems directly related to the risk of colonization and infection.[94] At present, many institutions recommend that PIVCs are replaced every 3 days to 4 days.[41] There is a growing body of evidence, however, that PIVCs can be changed based on clinical indications rather than on a set schedule and the PIVC dwell time will most likely increase.[95,96] Therefore, it will become increasingly important for institutions to develop standardized programs to ensure that personnel

inserting PIVCs are competent and that PIVCs are inspected daily and removed with evidence of phlebitis or exudate. In addition, similar to CVCs, PVICs that are inserted emergently or without appropriate aseptic technique should be replaced as soon as practical.

Midline Catheters

MCs, generally composed of polyurethane or silicone and 8 cm to 20 cm in length, are usually placed proximal to the antecubital fossa with the tip terminating below the axillary vein. MCs are FDA approved for short-term vascular access of less than 30 days. Adverse reactions and hypersensitivity due to catheter materials resulted in a decline in use of MCs in the 1990s.[97,98] In more recent years, however, with changes in catheter materials and design, a resurgence in use of MCs is evident. Besides their longer duration of use compared with PIVCs, MCs have the advantage of being compatible with power injection and can be multilumen. Because they are located in the peripheral vein, they do not require radiographic confirmation regarding placement location. MCs are not compatible with infusates of high osmolality or pH outside the 5 to 9 range.[99] Increasing experience indicates, however, that medications outside these parameters can be safely administered via MCs.[99,100]

There are few data regarding complications of MCs. It seems they are less likely to result in BSIs than CVCs, and available studies report BSI rates less than 0.5/1000 MC days.[99,101,102] Other complications, however, such as phlebitis and thrombosis, seem more common in MCs than CVCs.[92,99,101] Because BSIs due to PIVCs and MCs do not count as a CLABSIs and because mechanical complications are generally not tracked or reported to regulatory agencies, some institutions are relying heavily on MCs to limit the use of CVCs and thus decrease CLABSIs.

Arterial Catheters

Most studies conclude that ACs are associated with about the same risk of BSIs as nontunneled CVCs.[103–109] ACs, however, are often regarded as less infection prone and they are generally not included in surveillance programs that track CLABSIs. Femoral ACs may be more prone to BSIs than other sites and the femoral site should be avoided if possible.[106,109] ACs should be inserted and cared for with the same level of concern as CVCs. Unfortunately, surveys suggest that aseptic technique and appropriate barrier precautions are often violated when ACs are inserted.[110]

Hemodialysis Catheters

Compared with patients receiving HD via an arteriovenous fistula or graft, those undergoing HD via an IV catheter are more likely to experience CRBSI. Tunneled HD catheters are less prone to infection than nontunneled HD catheters. In the 2014 Centers for Disease Control and Prevention NHSN Dialysis Event Surveillance Report,[111] 6005 outpatient dialysis facilities in the United States reported a total of 22,576 dialysis access–related BSIs, of which 69.8% were associated with CVCs. HD catheter–associated BSIs can be prevented by application of antimicrobial ointment at the catheter exit site as well as weekly administration of recombinant tissue plasminogen activating factor.[112–114] In diagnosis of HD catheter–associated BSIs, poor peripheral access may preclude collection of peripheral blood cultures and thus blood cultures from HD bloodline are often relied on. Specific recommendations regarding the treatment of HD catheter–associated BSIs follow:

- HD catheter removal is indicated when infection is due to *S aureus, Pseudomonas* spp, or *Candida* spp.

- BSIs due to gram-negative bacilli (other than *Pseudomonas* spp) and coagulase-negative staphylococci can be empirically treated with systemic antibiotics without immediate removal of HD catheter. If significant clinical improvement within 48 hours to 72 hours is not observed, catheter exchange over a guide wire is appropriate.
- HD catheters should be removed in the presence of metastatic infections, persistent fever, or bacteremia for greater than 72 hours despite appropriate antimicrobial treatment.
- Treatment with parenteral antibiotics in combination with ALT can be done if there is clinical improvement within 48 hours to 72 hours and there is no absolute indication to remove the HD catheter, as discussed previously.

SUMMARY

Despite the great strides that have been made in recent years to prevent CRBSI, it remains a significant clinical problem. Emphasis should continue to be placed on practice-based measures, such as education, training, and application of insertion and maintenance bundles. Elimination of preventable CRBSIs, however, also requires judicious use of technologic innovations, such as coated catheters and impregnated dressings. It is evident that many catheter infections can be successfully treated with the catheter in situ through the application of antimicrobial locks—however, patient selection remains undefined and an approved catheter lock solution is lacking. Important questions remain regarding all facets of CRBSI—including pathogenesis, diagnosis and surveillance, prevention, and treatment.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). National and state healthcare associated infections progress report. Available at: http://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf. Accessed July 26, 2018.
2. Dudeck MA, Edwards JR, Allen-Bridson K, et al. National healthcare safety network report, data summary for 2013, device-associated module. Am J Infect Control 2015;43(3):206–21.
3. European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC, editor. Annual epidemiological report for 2016. Stockholm: ECDC; 2018.
4. Rosenthal VD. Central line-associated bloodstream infections in limited-resource countries: a review of the literature. Clin Infect Dis 2009;49(12):1899–907.
5. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173(22):2039–46.
6. Ziegler MJ, Pellegrini DC, Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. Infection 2015;43(1):29–36.
7. Centers for Disease Control and Prevention. National healthcare safety network (NHSN) patient safety component manual. Chapter 4: Bloodstream infection

event (central line-associated bloodstream infection and non-central line associated bloodstream infection). 2018. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanualcurrent.pdf. Accessed July 26, 2018.
8. Mayer J, Greene T, Howell J, et al. Agreement in classifying bloodstream infections among multiple reviewers conducting surveillance. Clin Infect Dis 2012; 55(3):364–70.
9. Beekmann SE, Diekema DJ, Huskins WC, et al. Diagnosing and reporting of central line-associated bloodstream infections. Infect Control Hosp Epidemiol 2012;33(9):875–82.
10. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of america. Clin Infect Dis 2009;49(1):1–45.
11. Safdar N, Maki DG. Inflammation at the insertion site is not predictive of catheter-related bloodstream infection with short-term, noncuffed central venous catheters. Crit Care Med 2002;30(12):2632–5.
12. Maki D, Weise C, Sarafin H. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977;296:1305–9.
13. 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(3B):197S–205S.
14. Douard MC, Arlet G, Longuet P, et al. Diagnosis of venous access port-related infections. Clin Infect Dis 1999;29(5):1197–202.
15. Slobbe L, El Barzouhi A, Boersma E, et al. Comparison of the roll plate method to the sonication method to diagnose catheter colonization and bacteremia in patients with long-term tunnelled catheters: a randomized prospective study. J Clin Microbiol 2009;47(4):885–8.
16. Bouza E, Alvarado N, Alcala L, et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis 2005;40(8):1096–100.
17. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 2005;142(6): 451–66.
18. Cercenado E, Ena J, Rodriguez-Creixems M, et al. A conservative procedure for the diagnosis of catheter-related infections. Arch Intern Med 1990;150(7): 1417–20.
19. Catton JA, Dobbins BM, Kite P, et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. Crit Care Med 2005;33(4):787–91.
20. Paredes J, Alonso-Arce M, Schmidt C, et al. Smart central venous port for early detection of bacterial biofilm related infections. Biomed Microdevices 2014; 16(3):365–74.
21. 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(1):18–25.
22. Jones RL, Sayles HR, Fey PD, et al. Effect of clinical variables on the volume of blood collected for blood cultures in an adult patient population. Infect Control Hosp Epidemiol 2017;38(12):1493–7.
23. Park KH, Lee MS, Lee SO, et al. Diagnostic usefulness of differential time to positivity for catheter-related candidemia. J Clin Microbiol 2014;52(7): 2566–72.

24. Guembe M, Rodriguez-Creixems M, Sanchez-Carrillo C, et al. How many lumens should be cultured in the conservative diagnosis of catheter-related bloodstream infections? Clin Infect Dis 2010;50(12):1575–9.
25. Planes AM, Calleja R, Bernet A, et al. Evaluation of the usefulness of a quantitative blood culture in the diagnosis of catheter-related bloodstream infection: comparative analysis of two periods (2002 and 2012). Enferm Infecc Microbiol Clin 2016;34(8):484–9.
26. Herrera-Guerra AS, Garza-Gonzalez E, Martinez-Resendez MF, et al. Individual versus pooled multiple-lumen blood cultures for the diagnosis of intravascular catheter-related infections. Am J Infect Control 2015;43(7):715–8.
27. Zhang L, Rickard CM. Non-culture based diagnostics for intravascular catheter related bloodstream infections. Expert Rev Mol Diagn 2017;17(2):181–8.
28. Rijnders BJ, Peetermans WE, Verwaest C, et al. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med 2004;30(6):1073–80.
29. Casey J, Davies J, Balshaw-Greer A, et al. Inserting tunnelled hemodialysis catheters using elective guidewire exchange from nontunnelled catheters: is there a greater risk of infection when compared with new-site replacement? Hemodial Int 2008;12(1):52–4.
30. Cook D, Randolph A, Kernerman P, et al. Central venous catheter replacement strategies: a systematic review of the literature. Crit Care Med 1997;25(8):1417–24.
31. Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, et al. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. J Antimicrob Chemother 2005;55(1):90–4.
32. Fortun J, Grill F, Martin-Davila P, et al. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic-lock therapy. J Antimicrob Chemother 2006;58(4):816–21.
33. Sanchez-Munoz A, Aguado JM, Lopez-Martin A, et al. Usefulness of antibiotic-lock technique in management of oncology patients with uncomplicated bacteremia related to tunneled catheters. Eur J Clin Microbiol Infect Dis 2005;24(4):291–3.
34. Justo JA, Bookstaver PB. Antibiotic lock therapy: review of technique and logistical challenges. Infect Drug Resist 2014;7:343–63.
35. Lewis K, Spoering A, Kaldalu N, et al. Persisters: specialized cells responsible for biofilm tolerance to antimicrobial agents [Chapter: 12]. In: Pace JL, Rupp ME, Finch RG, editors. Biofilms, infection, and antimicrobial therapy. Boca Raton (FL): Taylor & Francis; 2006. p. 241–53.
36. Georgopapadakou N. Antibiotic resistance in biofilms [Chapter: 21]. In: Pace JL, Rupp ME, Finch RG, editors. Biofilms, infection, and antimicrobial therapy. Boca Raton (FL): Taylor & Francis; 2006. p. 401–5.
37. Banin E, Brady KM, Greenberg EP. Chelator-induced dispersal and killing of pseudomonas aeruginosa cells in a biofilm. Appl Environ Microbiol 2006;72(3):2064–9.
38. Raad II, Fang X, Keutgen XM, et al. The role of chelators in preventing biofilm formation and catheter-related bloodstream infections. Curr Opin Infect Dis 2008;21(4):385–92.
39. Raad I, Chaftari AM, Zakhour R, et al. Successful salvage of central venous catheters in patients with catheter-related or central line-associated bloodstream infections by using a catheter lock solution consisting of

minocycline, EDTA, and 25% ethanol. Antimicrob Agents Chemother 2016; 60(6):3426–32.
40. Vassallo M, Dunais B, Roger PM. Antimicrobial lock therapy in central-line associated bloodstream infections: a systematic review. Infection 2015;43(4): 389–98.
41. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 2011;39(4 Suppl 1): S1–34.
42. Marschall J, Mermel LA, Fakih M, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(Suppl 2):S89–107.
43. Gorski L, Hadaway L, Hagle M, et al. Infusion therapy. Standards of practice. J Infus Nurs 2016;39(15):S17–8.
44. Fridkin SK, Pear SM, Williamson TH, et al. The role of understaffing in central venous catheter-associated bloodstream infections. Infect Control Hosp Epidemiol 1996;17(3):150–8.
45. Stone PW, Pogorzelska M, Kunches L, et al. Hospital staffing and health care-associated infections: a systematic review of the literature. Clin Infect Dis 2008;47(7):937–44.
46. Leistner R, Thurnagel S, Schwab F, et al. The impact of staffing on central venous catheter-associated bloodstream infections in preterm neonates - results of nation-wide cohort study in germany. Antimicrob Resist Infect Control 2013;2(1):11.
47. Nailon R, Rupp ME. A community collaborative to develop consensus guidelines to standardize out-of-hospital maintenance care of central venous catheters. J Infus Nurs 2015;38(2):115–21.
48. 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(4 Pt 1):231–8.
49. 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(10):1441–5.
50. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med 2004;32(10): 2014–20.
51. 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(11):792–801.
52. Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. J Perinatol 2012;32(1):4–9.
53. Sathiyamurthy S, Banerjee J, Godambe SV. Antiseptic use in the neonatal intensive care unit - a dilemma in clinical practice: an evidence based review. World J Clin Pediatr 2016;5(2):159–71.
54. Parenti CM, Lederle FA, Impola CL, et al. Reduction of unnecessary intravenous catheter use. internal medicine house staff participate in a successful quality improvement project. Arch Intern Med 1994;154(16):1829–32.
55. 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(6):700–7.

56. Randolph AG, Cook DJ, Gonzales CA, et al. Ultrasound guidance for placement of central venous catheters: a meta-analysis of the literature. Crit Care Med 1996;24(12):2053–8.
57. Marik PE, Flemmer M, Harrison W. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. Crit Care Med 2012;40(8):2479–85.
58. 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(26):2725–32.
59. Blot K, Bergs J, Vogelaers D, et al. Prevention of central line-associated bloodstream infections through quality improvement interventions: a systematic review and meta-analysis. Clin Infect Dis 2014;59(1):96–105.
60. Zakhour R, Chaftari AM, Raad II. Catheter-related infections in patients with haematological malignancies: novel preventive and therapeutic strategies. Lancet Infect Dis 2016;16(11):e241–50.
61. Seguin P, Laviolle B, Isslame S, et al. Effectiveness of simple daily sensitization of physicians to the duration of central venous and urinary tract catheterization. Intensive Care Med 2010;36(7):1202–6.
62. Rupp ME, Yu S, Huerta T, et al. Adequate disinfection of a split-septum needleless intravascular connector with a 5-second alcohol scrub. Infect Control Hosp Epidemiol 2012;33(7):661–5.
63. Rupp ME, Sholtz LA, Jourdan DR, et al. Outbreak of bloodstream infection temporally associated with the use of an intravascular needleless valve. Clin Infect Dis 2007;44(11):1408–14.
64. Jarvis WR, Murphy C, Hall KK, et al. Health care-associated bloodstream infections associated with negative- or positive-pressure or displacement mechanical valve needleless connectors. Clin Infect Dis 2009;49(12):1821–7.
65. Tabak YP, Jarvis WR, Sun X, et al. Meta-analysis on central line-associated bloodstream infections associated with a needleless intravenous connector with a new engineering design. Am J Infect Control 2014;42(12):1278–84.
66. Denton G. Chlorhexidine. In: Block SS, editor. Disinfection, sterilization, and preservation. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 321–33.
67. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med 2013;368(24):2255–65.
68. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med 2013;368(6):533–42.
69. Kim HY, Lee WK, Na S, et al. The effects of chlorhexidine gluconate bathing on health care-associated infection in intensive care units: a meta-analysis. J Crit Care 2016;32:126–37.
70. Frost SA, Alogso MC, Metcalfe L, et al. Chlorhexidine bathing and health care-associated infections among adult intensive care patients: a systematic review and meta-analysis. Crit Care 2016;20(1):379.
71. Kampf G. Acquired resistance to chlorhexidine - is it time to establish an 'antiseptic stewardship' initiative? J Hosp Infect 2016;94(3):213–27.
72. Timsit JF, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. Am J Respir Crit Care Med 2012;186(12):1272–8.

73. Exline MC, Ali NA, Zikri N, et al. Beyond the bundle–journey of a tertiary care medical intensive care unit to zero central line-associated bloodstream infections. Crit Care 2013;17(2):R41.
74. Guerin K, Wagner J, Rains K, et al. Reduction in central line-associated bloodstream infections by implementation of a postinsertion care bundle. Am J Infect Control 2010;38(6):430–3.
75. Casey AL, Mermel LA, Nightingale P, et al. Antimicrobial central venous catheters in adults: a systematic review and meta-analysis. Lancet Infect Dis 2008; 8(12):763–76.
76. Lai NM, Chaiyakunapruk N, Lai NA, et al. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. Cochrane Database Syst Rev 2016;(3):CD007878.
77. Ramritu P, Halton K, Collignon P, et al. A systematic review comparing the relative effectiveness of antimicrobial-coated catheters in intensive care units. Am J Infect Control 2008;36(2):104–17.
78. Wang H, Huang T, Jing J, et al. Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. J Hosp Infect 2010; 76(1):1–11.
79. Ramos ER, Reitzel R, Jiang Y, et al. Clinical effectiveness and risk of emerging resistance associated with prolonged use of antibiotic-impregnated catheters: more than 0.5 million catheter days and 7 years of clinical experience. Crit Care Med 2011;39(2):245–51.
80. Timsit JF, Bouadma L, Ruckly S, et al. Dressing disruption is a major risk factor for catheter-related infections. Crit Care Med 2012;40(6):1707–14.
81. Casey AL, Karpanen TJ, Nightingale P, et al. Microbiological comparison of a silver-coated and a non-coated needleless intravascular connector in clinical use. J Hosp Infect 2012;80(4):299–303.
82. Jacob JT, Chernetsky Tejedor S, Dent Reyes M, et al. Comparison of a silver-coated needleless connector and a standard needleless connector for the prevention of central line-associated bloodstream infections. Infect Control Hosp Epidemiol 2015;36(3):294–301.
83. Wright MO, Tropp J, Schora DM, et al. Continuous passive disinfection of catheter hubs prevents contamination and bloodstream infection. Am J Infect Control 2013;41(1):33–8.
84. Kamboj M, Blair R, Bell N, et al. Use of disinfection cap to reduce central-line-associated bloodstream infection and blood culture contamination among hematology-oncology patients. Infect Control Hosp Epidemiol 2015;36(12): 1401–8.
85. Zacharioudakis IM, Zervou FN, Arvanitis M, et al. Antimicrobial lock solutions as a method to prevent central line-associated bloodstream infections: a meta-analysis of randomized controlled trials. Clin Infect Dis 2014;59(12):1741–9.
86. Snaterse M, Ruger W, Scholte Op Reimer WJ, et al. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. J Hosp Infect 2010;75(1):1–11.
87. Oliveira C, Nasr A, Brindle M, et al. Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. Pediatrics 2012;129(2):318–29.
88. Maiefski M, Rupp ME, Hermsen ED. Ethanol lock technique: review of the literature. Infect Control Hosp Epidemiol 2009;30(11):1096–108.

89. Karpanen TJ, Casey AL, Whitehouse T, et al. Clinical evaluation of a chlorhexidine intravascular catheter gel dressing on short-term central venous catheters. Am J Infect Control 2016;44(1):54–60.
90. Yamamoto AJ, Solomon JA, Soulen MC, et al. Sutureless securement device reduces complications of peripherally inserted central venous catheters. J Vasc Interv Radiol 2002;13(1):77–81.
91. Ullman AJ, Cooke ML, Mitchell M, et al. Dressings and securement devices for central venous catheters (CVC). Cochrane Database Syst Rev 2015;(9):CD010367.
92. Mushtaq A, Navalkele B, Kaur M, et al. Comparison of midline *vs.* central venous catheter-related bloodstream infections: are midlines safer than central venous lines? Open Forum Infect Dis 2017;4(1):S637. Available at: https://academic.oup.com/ofid/article/4/suppl_1/S637/4295469.
93. Hadaway L. Short peripheral intravenous catheters and infections. J Infus Nurs 2012;35(4):230–40.
94. Mermel LA. Short-term peripheral venous catheter-related bloodstream infections: a systematic review. Clin Infect Dis 2017;65(10):1757–62.
95. Rickard CM, Webster J, Wallis MC, et al. Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomised controlled equivalence trial. Lancet 2012;380(9847):1066–74.
96. Webster J, Osborne S, Rickard CM, et al. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. Cochrane Database Syst Rev 2015;(8):CD007798.
97. Mermel LA, Parenteau S, Tow SM. The risk of midline catheterization in hospitalized patients. A prospective study. Ann Intern Med 1995;123(11):841–4.
98. Centers for Disease Control and Prevention (CDC). Adverse reactions associated with midline catheters–united states, 1992-1995. MMWR Morb Mortal Wkly Rep 1996;45(5):101–3.
99. Adams DZ, Little A, Vinsant C, et al. The midline catheter: a clinical review. J Emerg Med 2016;51(3):252–8.
100. Caparas JV, Hu JP. Safe administration of long-term vancomycin through a novel midline catheter: a response to letter to the editor. J Vasc Access 2016;17(4):e92.
101. Xu T, Kingsley L, DiNucci S, et al. Safety and utilization of peripherally inserted central catheters versus midline catheters at a large academic medical center. Am J Infect Control 2016;44(12):1458–61.
102. Sharp R, Esterman A, McCutcheon H, et al. The safety and efficacy of midlines compared to peripherally inserted central catheters for adult cystic fibrosis patients: a retrospective, observational study. Int J Nurs Stud 2014;51(5):694–702.
103. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 2006;81(9):1159–71.
104. Koh DB, Gowardman JR, Rickard CM, et al. Prospective study of peripheral arterial catheter infection and comparison with concurrently sited central venous catheters. Crit Care Med 2008;36(2):397–402.
105. Lucet JC, Bouadma L, Zahar JR, et al. Infectious risk associated with arterial catheters compared with central venous catheters. Crit Care Med 2010;38(4):1030–5.
106. Safdar N, O'Horo JC, Maki DG. Arterial catheter-related bloodstream infection: incidence, pathogenesis, risk factors and prevention. J Hosp Infect 2013;85(3):189–95.

107. Pirracchio R, Legrand M, Rigon MR, et al. Arterial catheter-related bloodstream infections: results of an 8-year survey in a surgical intensive care unit. Crit Care Med 2011;39(6):1372–6.
108. Esteve F, Pujol M, Perez XL, et al. Bacteremia related with arterial catheter in critically ill patients. J Infect 2011;63(2):139–43.
109. Gowardman JR, Lipman J, Rickard CM. Assessment of peripheral arterial catheters as a source of sepsis in the critically ill: a narrative review. J Hosp Infect 2010;75(1):12–8.
110. Cohen DM, Carino GP, Heffernan DS, et al. Arterial catheter use in the ICU: a national survey of antiseptic technique and perceived infectious risk. Crit Care Med 2015;43(11):2346–53.
111. Nguyen DB, Shugart A, Lines C, et al. National Healthcare Safety Network (NHSN) Dialysis Event Surveillance Report for 2014. Clin JAm Soc Nephrol 2017;12:1–8.
112. Levin A, Mason AJ, Jindal KK, et al. Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. Kidney Int 1991;40(5):934–8.
113. Lok CE, Stanley KE, Hux JE, et al. Hemodialysis infection prevention with polysporin ointment. J Am Soc Nephrol 2003;14(1):169–79.
114. Hemmelgarn BR, Moist LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med 2011; 364(4):303–12.