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New Technologies and Advances in Infections Prevention (A Marra, Section Editor)

Innovations in Quality Improvement of Intravascular Catheter-Related Bloodstream Infections

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Abstract

Purpose of review Significant reductions in catheter-related bloodstream infections (CRBSI) have occurred in the United States. Reductions in CRBSIs are attributed to the widespread implementation of the practice-based measures and innovations in the diagnosis, treatment, and prevention of CRBSI.
Recent findings Diagnosis of CRBSI historically required removal of the central venous catheter (CVC) for catheter tip culture. Removing the CVC for CRBSI diagnosis predisposes many patients to potential life-threatening complications. Advances in diagnostic techniques such as culturing catheter hubs, catheter entry site cultures, applying differential time to positivity, molecular diagnostics, biomarkers, and innovative approaches like biosensors on the CVC lumen may provide an alternative to CVC removal. Removal of the CVC is common for the treatment of CRBSI; however, antimicrobial lock therapy is increasingly used as a CVC salvage method. Implementation of newer technology such as antimicrobial coated catheters, chlorhexidine-impregnated dressings, and antiseptic port protectors are crucial for the prevention of CRBSIs. Increasing evidence also support newer sutureless CVC securement devices prevent CRBSIs.
Summary CRBSI remains a significant clinical problem despite advances made in the diagnosis, management, and prevention. Molecular techniques are increasingly being used for pathogen identification in CRBSI, but the optimal diagnostic test remains

debatable. Increasing experience is being gained with antimicrobial lock therapy for CRBSI treatment with catheter salvage. Use and adherence to practice-based measures and technological innovations has significantly reduced CRBSIs. Continued efforts are required to develop a cost-effective and targeted approach for CRBSI prevention.

Introduction

Central line–associated bloodstream infection (CLABSI) is a surveillance term used by the Centers for Disease Control and Prevention (CDC) to identify bloodstream infections (BSIs) in the presence of a central venous catheter (CVC) when no alternative infectious source is identified [1]. Catheter-related bloodstream infection (CRBSI) is the preferred definition of the Infectious Diseases Society of America (IDSA) and requires clinical and microbiological data to confirm BSI due to an intravascular (IV) catheter [2••]. Approximately 30,000 to 40,000 CLABSIs are reported annually in US acute care hospitals, resulting in costs of approximately $30,000–65,000 per case [3]. According to the National Healthcare Safety Network 2013 report, the approximate incidence of CLABSI in the US is 1/1000 CVC days in critical care units and 0.7/1000 CVC days in other inpatient units [4]. The CLABSI rate in Western European countries is comparable to US hospitals [5] and much higher in resource-limited countries (1.6–44.6/1000 CVC days) [6]. In a meta-analysis, CLABSIs were associated with significantly increased odds of in-hospital deaths (odds ratio 2.75 (95% CI, 1.86–4.07)) [7]. Further, patients with CLABSI are more than twice as likely to die when compared to patients with non-CVC BSIs [8]. Additionally, older age and infections with *Staphylococcus aureus* or *Candida* species were independent risk factors for increased mortality [9••]. Considering the high burdens of morbidity, mortality, and healthcare costs, there is concentrated effort on both reporting and reduction of CLABSI. The CDC reported 50% reduction in CLABSIs from 2008 to 2014 among hospitals in the USA [10]. Further decreases in the risk and incidence of CLABSIs demand continued innovation.

Diagnosis of catheter-related bloodstream infections

Although the best method to diagnose CRBSIs remains debatable, IDSA guidelines recommend one of the following criteria for the definitive diagnosis of CRBSIs [2••]:

- Simultaneously collected paired blood cultures from the CVC and peripheral venipuncture, meets criteria for CRBSIs by quantitative blood cultures (>3-fold colony count, CVC versus peripheral) or differential time to positivity (DTP) > 2 h difference in time to positivity (CVC versus peripheral).
- Same microbiological growth from the culture of a catheter segment by semiquantitative roll-plate method (>15 colony-forming units (CFUs)) or quantitative method with sonication fluid culture of catheter (10^2 CFUs) and peripheral blood culture.

OR

- A possible diagnosis of CRBSIs is suggested by paired quantitative blood cultures from two different lumens of a catheter in which at least a 3-fold difference in colony count is noted.

Catheter segment culture

IDSA guidelines recommend roll plate analysis of the distal 5 cm of CVC (catheter segment or tip) for suspected CVC or arterial CRBSIs. In the setting of suspected pulmonary artery catheter–related BSIs, the introducer tip should be cultured rather than the catheter itself [2••]. Long-term CVCs are usually colonized along the internal surface of the catheter lumen and a roll-plate semiquantitative analysis of a long-term CVC tip results in significant false-negative results. Alternatively, a quantitative culture of the fluid obtained by catheter tip sonication is suggested for the diagnosis of CRBSIs in long-term CVCs [2••, 11]. Since the publication of IDSA guidelines, numerous studies have evaluated the performance of quantitative and semiquantitative catheter segment culture methods to diagnose CRBSIs. A randomized controlled trial (RCT) compared semiquantitative roll-plate technique with quantitative sonication sampling and established quantitative sonication was non-superior to roll-plate analysis for the detection of catheter colonization or infection, and the positive predictive value (PPV) of either method was 55% [12].

Peterson and colleagues calculated the PPV of catheter segment culture to diagnose CRBSIs (quantitative and semiquantitative) from three RCTs and reported that the PPV was between 27% and 70% [11–13]. Considering the variability in the PPVs, this study proposed catheter segment cultures should be discarded from future guidelines as the risk of serious life-threatening complications from CVC removal outweighs the diagnostic benefit [14]. Among suspected CRBSIs in which CVC is removed, up to 70% are blood culture negative thus catheter segment culture for all suspected CRBSIs may needlessly predispose many patients to mechanical complications. Similarly, a study using specific quantitative polymerase chain reaction (PCR) assay to detect coagulase-negative *Staphylococcus* (CoNS) DNA from the CVC for suspected CRBSIs demonstrated only 23.5% episodes had a positive catheter segment PCR when conventional cultures were negative [15]. This study further supports that the relative role of CVC in BSIs may be overestimated, rendering routine removal of CVCs for suspected CRBSIs unnecessary.

Diagnosis with catheter in situ

Paired quantitative blood cultures

A meta-analysis compared eight diagnostic methods for CRBSIs and found that paired quantitative blood culture was the most accurate with a sensitivity of 74–84% and specificity 98–100% [16•]. Paired quantitative blood cultures (CVC versus peripheral) showed continued high sensitivity and specificity in different periods (2002 and 2012) [17]. Many have suggested paired quantitative blood cultures are the most accurate diagnostic method; this technique is not widely used due to the cost- and labor-intensive process.

How many lumens of a CVC should be cultured?

Current guidelines recommend against culturing more than one lumen of a CVC, yet approximately one third of CRBSIs are missed if all lumens are not cultured [17, 18]. Given the potential increased cost of culturing all lumens, an alternative approach is to pool blood drawn from all lumens of a CVC and

incubate pooled blood into a single blood culture bottle. This technique is equally sensitive as culturing all lumens of the CVC [19].

Differential time to positivity

Studies have confirmed that a DTP of > 120 min in cultures obtained from the CVC versus from periphery is diagnostic for CRBSI [20, 21]. DTP is 86–93% sensitive and 75–92% specific for CRBSI diagnosis [16•, 22]. Use of DTP for catheter-related candidemia remains controversial. In one study, a DTP of > 120 min for catheter-related candidemia was 85% sensitive and 82% specific [23], whereas in another it was only 40% specific [24]. Notably, for accurate interpretation of DTP, blood volume collected from the CVC and peripheral venipuncture should be equal. The yield of blood cultures significantly improved with increase in collected blood volume [25, 26]. One study indicated the volume of blood collected in blood cultures from CVCs was on an average 2.53 ml higher than the volume collected in peripheral blood cultures [27••]. Thus, indicating DTP may overestimate the role of CVC in BSIs due to unequal blood volumes. Further studies examining DTP in combination with PCR assays are needed to validate the diagnostic performance of DTP.

Newer innovative techniques

CVC entry site and hub culture

Paired semiquantitative cultures from the CVC entry site and CVC hub combined with peripheral blood cultures to diagnose CRBSIs were 78% sensitive and 78% specific [20]. Interestingly, in a prospective study, this method showed a sensitivity of 100% with a negative predictive value of 100% for CRBSIs diagnosis [28].

CVC biosensor

Using a biosensor attached to the CVC, early identification of biofilm formation can be detected by impedance spectrometry. The clinical utility of this technique is limited due to cost concerns [29].

Molecular diagnostics

Significant progress has occurred in the development of rapid molecular diagnostic methods to diagnose BSIs, including CRBSIs [30••]. Rapid pathogen identification with 16S RNA PCR detection, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF), and PNA-FISH are used after a positive culture is detected. A recent meta-analysis demonstrated significant improvement in mortality and time to effective therapy with molecular rapid diagnostics (PCR, MALDI-TOF, and PNA-FISH) [31••]. LightCycler® SeptiFast, Magicplex™ sepsis, SepsiTest®, and T2Candida® are example systems used for rapid identification of microorganisms directly from a blood sample. The clinical utility and cost-effectiveness of these techniques is not yet established [32–34]. The role of 16S RNA detection directly from the CVC has been evaluated in a few

studies [28]. In a prospective study, use of 16S rRNA gene PCR to diagnose port-related BSI improved microorganism detection in 21.1% additional patients when conventional cultures were negative, with a negative predictive value of 97.8% [35].

Biomarkers

The use of procalcitonin as a biomarker of CRBSI was evaluated and found to be significantly elevated in proven CRBSI versus unproven CRBSI [36]. The role of other biomarkers like pro-ADM (proadrenomedullin), interleukin-6, and triggering receptor expressed on myeloid cells 1 (TREM 1) in BSIs appears promising [30••, 37]. Biomarkers, in combination with molecular techniques to diagnose CRBSI, have not been studied; however, this combination has the potential to provide an accurate and efficient diagnosis with the CVC remaining in situ and may further prevent unnecessary removal. Metagenomic shotgun whole-genome sequencing is another emerging technology with the potential to revolutionize the diagnosis of culture-negative infections, including culture-negative CRBSIs [38••].

Updated management approaches to CRBSI

When to administer empiric antimicrobial therapy?

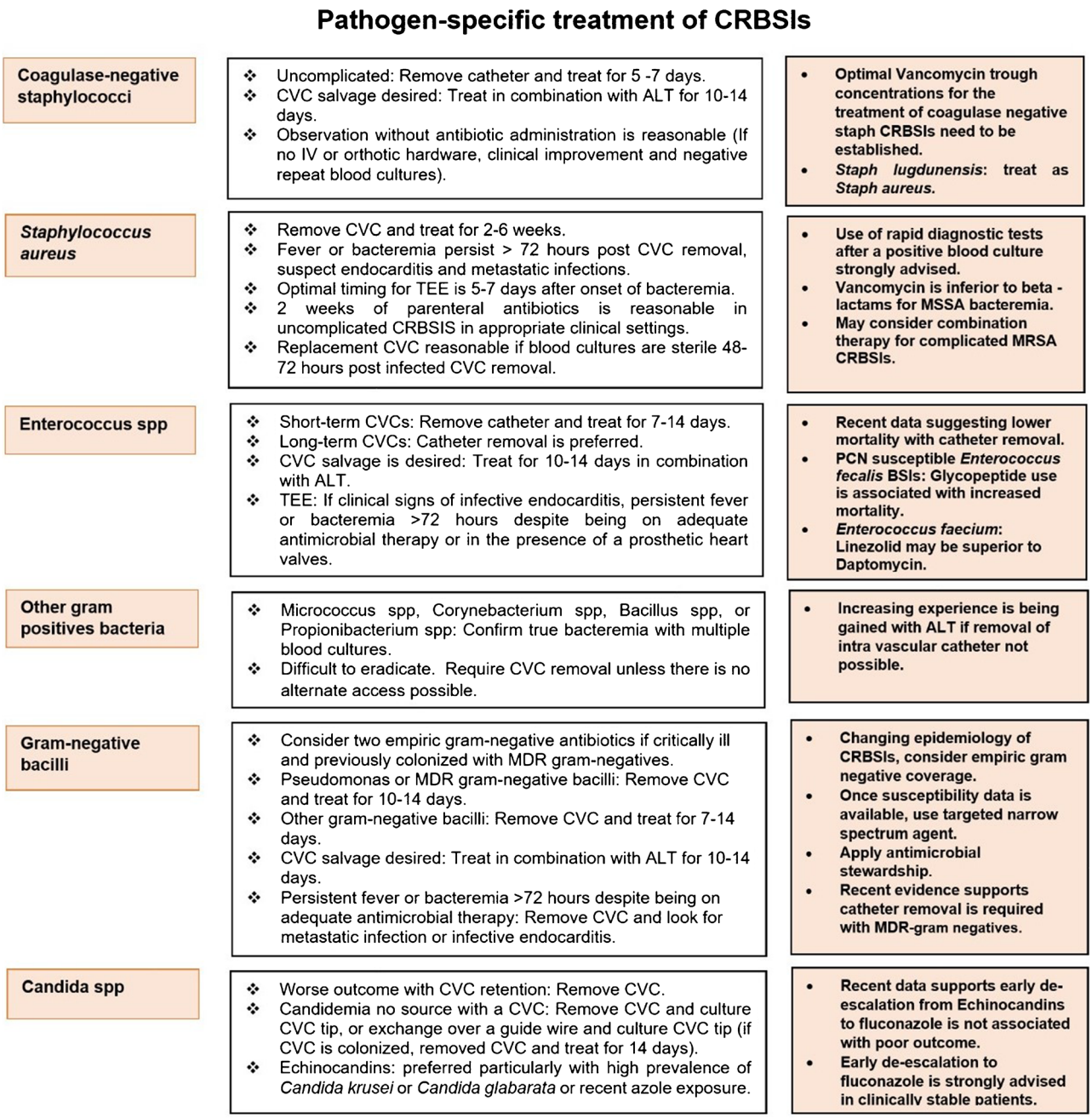
Empiric antimicrobial therapy is indicated for suspected CRBSIs once appropriate cultures are collected. Choice of empiric antimicrobial therapy should be based on the likely pathogens, CVC site, severity of infection, local antibiograms, presence of CRBSI complications (endocarditis, septic thrombosis, osteomyelitis, etc.), and host immune status. The choice of empiric antimicrobial therapy should be individualized, with the following factors taken into consideration:

Empiric gram-positive coverage

Intravenous vancomycin should be initiated to cover *Staphylococcus aureus* and CoNS for suspected CRBSIs. Alternatively, intravenous daptomycin may be considered in institutions with a high local prevalence of MRSA isolates with vancomycin minimum inhibitory concentrations (MIC) of >2 μg/ml [2••].

Empiric gram-negative coverage

The epidemiology of CRBSI has changed with an increase in the incidence of gram-negative bacilli causing CRBSI now up to 40% [39, 40, 41••]. The microbiological etiologies of CRBSIs compared between 1999 to 2000 and 2013 to 2014 showed an increased frequency of gram-negative CRBSIs from 17% to 40% [41••]. A similar European study examined epidemiological changes in CRBSIs from 1991 to 2008 and found an increase in gram-negative CRBSIs from 4.7% to 40.23% [40]. Risk factors for gram-negative CRBSI include neutropenia, spinal cord injury, hematological malignancies, femoral catheter placement, prolonged intensive care unit (ICU) stay, transplantation (hematopoietic stem cell and solid organ), high



Current recommendations for pathogen-specific treatment of CRBSIs. Newer innovative approaches and unresolved issues mentioned in right box. Abbreviation: TEE, transesophageal echocardiogram. MSSA, Methicillin susceptible *Staph aureus.* MRSA, Methicillin resistant *Staph aureus.* ALT, antibiotic lock therapy. IV, intravenous. CVC, Central Venous Catheter. PCN, Penicillin.

Fig. 1. Pathogen-specific treatment of CRBSIs.

index colonization, or concurrent infection with gram-negative bacilli at another body site. No specific antimicrobial agent has been validated in clinical trials for the empiric treatment of gram-negative CRBSI. Choice of

an empiric gram-negative antimicrobial agent should be based on the local antimicrobial susceptibility pattern. Significant consideration should be given to the microorganism's potential to produce AmpC beta-lactamases, extended spectrum beta-lactamases (ESBL), carbapenemases, or metallo-beta-lactamases.

Empiric antifungal coverage

Empiric antifungal coverage should be considered in the presence of risk factors for catheter-related candidemia, e.g., prolonged exposure to broad-spectrum antibiotics, abdominal surgery, femoral catheter, hematopoietic stem cell and solid organ transplant recipients, Candida colonization at multiple body sites, critical illness, and patients receiving total parenteral nutrition. Echinocandins are preferred, especially if the local prevalence of *Candida krusei* or *Candida glabrata* is high or azole exposure is noted within 3 months of suspected catheter-related candidemia. See Fig. 1 showing considerations for pathogen-specific treatment of CRBSI.

Immediate CVC removal versus watchful waiting

Optimal timing for catheter removal in a suspected CRBSI remains unknown. CRBSIs are associated with morbidity and mortality and retaining an infected CVC may further result in unfavorable outcomes. Contrarily, up to 70% of suspected CRBSIs are blood culture negative [15] and removing the CVC in every suspected CRBSI can unnecessarily predispose patients to mechanical complications. In one RCT, watchful waiting (catheter removal only if positive blood culture or hemodynamic instability) demonstrated a significant reduction in unnecessary catheter removals without adding to mortality [42]. A prospective multicenter study in 18 ICUs evaluated immediate versus late CVC removal in suspected CRBSIs and found no difference in mortality between groups [43]. Although routine CVC removal in all suspected CRBSI is not advised, CVC should be promptly removed in patients with confirmed bacteremia/fungemia, hemodynamic instability, transplant recipients, in the presence of an intravascular graft and intracardiac devices (pacers, defibrillators, etc.), or catheter tunnel/port pocket infection.

Indications for CVC removal

Indications for consideration of immediate CVC removal include

- Septic shock, infective endocarditis, or septic thrombophlebitis.
- Persistent bacteremia/candidemia > 72 h despite adequate therapy.
- Infections with *Staphylococcus aureus*, MDR (multidrug resistant) gram-negatives, fungi, or mycobacteria. *Micrococcus* spp. and *Propionibacterium* spp. also require CVC removal once blood culture contamination is ruled out.
- Infection at the CVC tunnel or venous access port pocket.

When to perform catheter exchange over a guidewire?

Routine exchange of CVC over a guidewire is discouraged in confirmed CRBSIs due to associated increased risk of infectious complications [44, 45]. In patients

with extremely limited venous access, extensive venous thrombosis/stenosis, or high risk for mechanical complications, a guidewire exchange may be a reasonable alternative if no CVC entry site or tunnel infection is present [46]. When a CVC is exchanged over the guidewire, antimicrobial lock therapy (ALT) and antimicrobial-impregnated catheters should be considered to prevent future episodes of CRBSIs [2••, 47]. However, in one study, guidewire exchange using an antiseptic silver sulfadiazine/chlorhexidine (SS/CHG)–coated CVC in a microbial colonized site did not prevent re-colonization [48].

Antimicrobial lock therapy

Biofilm formation on the surface of the catheter is the hallmark of CRBSI (Table 1). Extreme resistance to antimicrobial agents is seen in biofilms for various reasons, including reduced antimicrobial penetration, the presence of inactivating enzymes, multidrug resistance gene expression, heterogeneity of microorganisms, and different metabolic activity [47, 50, 51]. ALT is recommended as an adjunct to the parenteral antimicrobials for the treatment of uncomplicated CoNS and gram-negative CRBSIs if catheter salvage is desired [2••]. Antimicrobial lock solution (ALS) is constituted by mixing a highly concentrated antimicrobial agent (100–1000 times the MIC) with an anticoagulant [47]. ALS is infused into the CVC lumen and allowed to remain in place for hours (optimal indwell time is unknown). Both citrate and EDTA disrupt the biofilm and increase the penetration of antimicrobial agents into the

Table 1. Major complications of CRBSI

Suppurative thrombophlebitis:
• Suspect if persistent bacteremia > 72 h despite adequate therapy
• Subcutaneous cord-like structure may be palpable (thrombosed vein)
• Imaging (ultrasound, CT, or MRI) required for diagnosis
• Consider surgical intervention, role of anticoagulation not clear
• Require catheter removal and treat with parenteral antibiotics for 4 to 6 weeks
Persistent bacteremia:
• > 72 h despite adequate therapy, consider metastatic infection
• Require longer course of antimicrobial therapy (4–6 weeks)
• If initial TEE negative, consider repeating TEE 5–7 days
Infective endocarditis:
• Keep high index of suspicion especially with *Staphylococcus aureus* CRBSIs, persistent bacteremia, prosthetic cardiac device, hemodialysis CRBSIs, and new murmur on examination
• Consult AHA/IDSA infective endocarditis guideline for management recommendations [49]
Local complication:
• Catheter tunnel infection: erythema > 2 cm of catheter entry site
• Port pocket infection: culture both port reservoir and catheter tip
• Both require catheter removal; treat with 7–10 days of parenteral antibiotics

TEE, transesophageal echocardiogram

biofilm [52, 53]. Treatment failures have been noted with ALT [54]. A prospective study using minocycline, EDTA, and 25% ethanol for ALS reported successful CVC salvage even with *S. aureus* CRBSIs [55••], and this ALT is now being studied in a multicenter, phase III clinical trial for treatment of CRBSI (NCT02901717). A systematic review suggested the introduction of newer molecules such as daptomycin, tigecycline, ethanol, and taurolidine in an ALS improves the likelihood of catheter salvage [56]. Amphotericin B and other antifungal agents have shown excellent in vitro activity against Candida biofilms, but studies are lacking to determine their clinical utility in ALS [57••, 58••]. Optimal dwell time, volume, duration of therapy, and frequency to change ALS are all unknown. Rare adverse events include systemic toxicity, development of antimicrobial resistance, and corrosion of the catheter material. The usefulness of assessing antimicrobial agents MIC in biofilm cells has not been validated in clinical studies. Anti-quorum sensing is a novel mechanism that targets bacterial communication and has shown promise as an anti-biofilm agent [59]. Table 2 reviews optimal characteristics of antimicrobial lock solution.

Prevention of CRBSIs

Annually in the USA, CLABSIs cause an estimated 25,000 preventable deaths and cost up to $21 billion [60]. Approximately 65–70% of CLABSIs are preventable [60]. The widespread implementation of guidelines [61••] combined with new approaches have significantly reduced CLABSIs. A targeted approach for implementation of new technology is crucial due to the cost concerns. New scoring systems, such as the Michigan PICC-CLABSI (MPC) score, may identify patients at high risk for CLABSI, allowing for targeted interventions. A higher MPC score predicted increased risk for CLABSIs ($p < 0.0001$), and every point increase raised the hazard ratio by 1.63 (95% CI, 1.56–1.71) [62••]. Considerations for the prevention of CRBSIs are noted below.

Site of CVC insertion

Multiple studies suggest femoral CVCs are at higher risk for infections compared to jugular or subclavians. A meta-analysis demonstrated the relative risk (RR) of CLABSI among femoral versus subclavian catheters was 2.44 (95% CI, 1.25–4.75). Among internal jugular versus femoral catheters, the RR was 0.55 (95% CI, 0.34–0.89) [63]. Due to the higher risk of CLABSI, the authors recommended avoidance of femoral CVCs, particularly among obese patients [63, 64].

Table 2 . Optimal characteristics of antimicrobial lock solution

- Ability to penetrate and disrupt biofilm cells
- Compatibility with an anticoagulant
- Prolonged stability at room temperature
- Minimal risk for systemic toxicity
- Low potential for resistance
- Compatibility with catheter material
- Cost-effectiveness

CVC insertion technique and use of ultrasonography

Aseptic insertion technique using full sterile barriers consisting of a cap, mask, gloves, long sleeve gown, and full drape are indicated for the prevention of CLABSI [65]. Skin disinfection at the insertion site with chlorhexidine (CHG) solution (> 0.5%) with alcohol should be performed prior to insertion [66, 67••]. Multiple skin punctures from repeated attempts may provide an entry site for microorganisms leading to increased risk of BSIs. Use of ultrasonography (USG) significantly reduces the number of failed attempts to cannulate a CVC and substantially reduces mechanical complications, thus is recommended [68]. A checklist to safeguard compliance with appropriate sterile technique and USG is recommended [69].

The central line bundle

The Institute of Healthcare Improvement recommends the use of a "central line bundle" that includes the implementation of five recommended practices: hand hygiene, maximum barrier precautions, chlorhexidine skin antisepsis, optimal catheter site selection, and daily review of line necessity [70]. However, compliance with the central line bundle recommended practices remains questionable [71]. The use of checklists to improve compliance with recommended practices in healthcare settings has been advocated [72]. One innovative approach is to integrate the central line insertion bundle with post-CVC insertion recommendations noted below.

CVC maintenance care

Adherence to the recommended practices in CVC maintenance including hub cleaning, dressing care, and prompt removal when indicated are crucial for CLABSI prevention [73]. The majority of CLABSIs occur more than 5 days after insertion, suggesting lapses in CVC maintenance [74]. Similarly, higher CLABSI rates are reported when the majority of CVC maintenance care is performed by inexperienced providers, indicating the need for education and training of the personnel involved in CVC care. There is abundant evidence indicating that appropriate staffing of personnel trained for CVC care significantly reduces CLABSI [75].

CVC dressing care

The integrity of CVC dressing is vital for the prevention of CLABSI and dressings should be changed promptly if loose, soiled, or damp [61••]. Similarly, routine changing of the CVC dressing and catheter tubing should be performed at recommended intervals (Table 3 CVC maintenance care) [61••, 76]. Other innovative approaches such as human factor engineering–based interventions to improve adherence to the recommended practices in CVC maintenance have been evaluated. A prospective observational study compared the use of a CVC maintenance kit and a procedural guide (how to perform central line maintenance) to standard maintenance care. The maintenance kit significantly improved protocol compliance and reduced the CLABSI rate from 2.21/1000 CVC days to 0/1000 CVC days (95% CI, 0–0.81) [77••]. Table 3 describes CVC maintenance bundles for the prevention of CLABSIs.

Table 3. Practice-based interventions for CVC maintenance

- Assess catheter necessity every day
- Perform CVC site care with chlorhexidine whenever dressing is changed
- Change gauze dressing every 2 days
- Routine dressings change every 7 days or if visibly soiled, damp, or loose
- Replacement of intravenous administration sets no more often than every 96 h, unless contaminated
- Change parenteral nutrition administration sets every 24 h
- Tubing to administer blood, blood products after the completion of each unit or every 4 h
- Tubing for propofol infusions change every 6 to 12 h
- Optimal time period for a needle used to access implanted ports can stay in place is unknown
- Minimize disconnection/reconnection of infusion sets

CVC hub disinfection

Manipulations of catheter hubs for drug administration or blood sampling provides an opportunity for the introduction of microorganisms and may lead to CVC colonization/infection. Every time a hub is manipulated, it should be scrubbed with an appropriate antiseptic solution (70% alcohol, CHG, or povidone iodine) [61••]. Simmons and colleagues compared the antiseptic scrub time of 3, 10, and 15 s for catheter hubs contaminated with *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Pseudomonas aeruginosa*. A nearly 20-fold decrease in bacterial CFU/ml was noted with 15 s versus 3 s scrub time; however, this difference in bacterial load was not statically significant [78]. Some experts suggest optimal scrub time may depend on the design of the catheter connector and degree of hub contamination [79, 80].

Chlorhexidine bathing

In a RCT, daily chlorhexidine bathing significantly reduced total BSIs (CLABSI + non-CVC) 9.2 vs. 22.6 infections/1000 patient-days ($p = 0.027$) [81••]. Similarly, two recent meta-analyses noted a significant reduction in CLABSI with daily CHG bathing [82••, 83••]. Although CHG bathing is associated with reduction in CLABSIs, there is growing concern regarding acquired CHG resistance [84••]. The clinical impact of antiseptic resistance remains unknown.

Removal of unnecessary CVCs

Several studies consistently demonstrate that removing unnecessary CVCs decreases CVC utilization and CLABSI in hospitals [85, 86••, 87••]. Similarly, in a long-term acute care facility, a multidisciplinary infection prevention team performed weekly reviews of CVC necessity and reduced CLABSIs by 73% [88]. A systematic review also noted interventions to remove unneeded CVCs significantly decreased CLABSI [89••]. Organizations should strongly consider multidisciplinary team interventions for daily assessment of continued CVC need and removal of non-essential CVCs.

Technological innovations to prevent CRBSIs

Antimicrobial-impregnated CVC

Antimicrobial (minocycline/rifampin) or antiseptic (CHG/silver sulfadiazine) impregnated CVCs can cost-effectively reduce CLABSIs [90••, 91••]. Minocycline/rifampin or CHG/silver sulfadiazine are the most common antimicrobial coatings used; less data is available regarding other CVC coatings such as heparin, silver, platinum/carbon, and teicoplanin impregnation [92••]. A meta-analysis noted 2% absolute risk reduction (95% CI, 3% to 1%) in CLABSI with the use of antimicrobial-coated CVCs and the number needed to treat to prevent one CABSI was 50 [92••]. Another meta-analysis evaluating the effect of CVC antimicrobial impregnation on clinically diagnosed sepsis, CLABSIs, and all-cause mortality indicated minocycline–rifampin impregnated catheters were most effective in preventing CLABSI, and the effect on sepsis and mortality was unclear. Miconazole/rifampin impregnation was most effective in preventing CVC colonization [93••]. CVC antimicrobial impregnation did not increase antimicrobial resistance [94]. Antimicrobial-impregnated CVCs should be strongly considered in the institutions with high CLABSI rate, especially when other measures have failed.

Chlorhexidine-impregnated dressings

CHG-impregnated dressings elute chlorhexidine directly to the external surface of the CVC and around the entry site. Several studies have reported a reduction in CLABSIs with the use of CHG-impregnated dressings [95–97]. CHG-impregnated dressings should be routinely used in CVC care.

Port protectors and antiseptic-impregnated connectors

Antiseptic-impregnated port protectors release continuous antiseptic agent to the catheter hubs when CVC is not in use; although data from RCTs are limited, quasi-experimental studies indicate a beneficial effect. Alcohol-impregnated CVC port protectors reduced CLABSI from 2.3 infections/1000 CVCs days to 0.3 infections/1000 CVC days (RR 0.14; 95%, CI 0.02–1.07; $p = 0.03$) [98]. SwabCap (Excelsior Medical Corporation, Neptune, NJ) contains 70% isopropyl alcohol, and was designed to passively protect and disinfect the catheter hubs. The use of port protectors compared with standard antiseptic scrubbing of catheter hubs resulted in a 34% reduction in CLABSIs [99]. Silver-impregnated needleless connectors are designed to reduce microbial colonization and have been effectively used in the prevention of CLABSIs [100, 101]. Passive port protectors and antimicrobial-impregnated needleless connectors are attractive options for CLABSI prevention as these methods minimize the risk of human error.

Antimicrobial lock solutions

ALS were discussed earlier in this review with regard to treatment of CRBSI, which may also have a role in primary prevention. Many ALS have shown excellent ability to eradicate biofilm formed on inert surfaces, including highly resistant microorganism biofilms [102••]. A recent RCT compared trimethoprim, ethanol, and Ca-EDTA lock solution to heparin lock solution for CLABSI prevention and demonstrated a 4.56-fold reduction in CLABSI (0.41 to 0.09/1000 CVC days, $p < 0.03$) with the use of trimethoprim, ethanol, and Ca-EDTA lock solution [103••]. Various antimicrobial agents have been used in ALS; however, there is no single FDA-approved ALS available at present [104–106]. ALS are a novel approach for the prevention of CLABSI and should be considered for prevention of recurrent CLABSIs.

CVC securement devices

Disadvantages of CVC securement through sutures include an increased risk of BSI through microorganism entry sites via skin punctures and a foreign nidus for bacterial colonization. Additionally, sutures may result in pain and skin trauma. Multiple sutureless CVC securement devices (CSDs) are commercially available such as SecurAcath (Interrad Medical), StatLock (Bard Access Systems), and Grip-Lok™ (TIDI Products, LLC). Multiple studies have evaluated CSDs, and there is increasing evidence supporting sutureless CSDs as effective in reducing CLABSI [96, 107, 108]. The optimal sutureless CSD is unknown as higher mechanical failure rates are seen with some sutureless CSDs.

In summary, several technological innovations such as antimicrobial-impregnated CVCs, antiseptic-impregnated port protectors, antimicrobial-impregnated needleless connectors, CHG-impregnated dressings, and sutureless CVC securement devices have been shown to reduce CLABSIs effectively, but the higher cost of these innovative techniques may limit their use. It is crucial to use cost-effective, targeted interventions to prevent CLABSIs (for a summary of all the above strategies, please see Table 4).

Table 4 . Technological innovation for the prevention of CRBSI

- Antimicrobial-impregnated CVCs
- Chlorhexidine-impregnated dressings
- Antiseptic-impregnated port protectors
- Antimicrobial-impregnated needleless connectors
- Antimicrobial lock solutions
- CVC sutureless securement devices (CSDs)

Conclusion

CRBSI results in thousands of deaths annually. Continued efforts are required to address challenges in the diagnosis, management, and prevention of CRBSIs. Due to changing epidemiology and emerging antimicrobial resistance, use of rapid diagnostic techniques and application of antimicrobial stewardship should be strongly encouraged in the management of CRBSIs. There is also increasing evidence to support the use of antimicrobial lock therapy for the treatment and prevention of CRBSIs. Although several practice-based and technological innovations are available for the prevention of CRBSIs, these do not supplant the need for adherence with evidence-based practices such as high-quality training of the staff regarding CVC insertion and maintenance.

Compliance with ethical standards

Conflicts of interest

1. Rajendra Karnatak: Dr. Karnatak declares no conflicts of interests.
2. Mark E Rupp: Dr. Rupp reports personal fees from 3M, personal fees from Citius, personal fees from Teleflex.
3. Kelly Cawcutt: Dr. Cawcutt declares paid for lecture on vascular access and attendance at an advisory board meeting for BD.

Human and animal rights informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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In vitro study demonstrated antimicrobial lock solution with nitroglycerine + Citrate + Ethanol (NiCE) completely eradicated biofilms of MRSA, VISA, VRE, MDR *Pseudomonas aeruginosa*, MDR *Klebsiella pneumoniae*, MDR *Enterobacter cloacae*, and *Candida glabrata* isolates.

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