Central venous catheter (CVC) use now permeates every sector of medicine, spanning the spectrum of both the inpatient and outpatient clinical settings. Their use is primarily directed at securing vascular access for fluids, medications, blood products, total parental nutrition (TPN), and hemodialysis (1). However, these intravascular devices are becoming a ready conduit for bacterial and fungal invasion, resulting in catheter-related bloodstream infection (CRBSI) (Table 110.1) that ultimately can be complicated by septic thrombophlebitis, infective endocarditis, and other metastatic infections, such as lung abscess, brain abscess, and endophthalmitis.

CRBSIs are the most common cause of hospital-acquired infections in the critically ill (2). More than 80,000 CRBSIs are estimated to occur annually in intensive care units (ICUs) in the United States, with an attributable mortality ranging from 12% to 25% (3). Therefore, 9,600 to 20,000 patients die from CRBSI in ICUs annually. The added cost ranges from $28,690 to $56,167 per each individual episode in ICU patients (4). Non-ICU patients, especially the immunocompromised hosts to $56,167 per each individual episode in ICU patients (4). Non-ICU patients, especially the immunocompromised hosts to $56,167 per each individual episode in ICU patients (4). Non-ICU patients, especially the immunocompromised hosts to $56,167 per each individual episode in ICU patients (4). Non-ICU patients, especially the immunocompromised hosts to $56,167 per each individual episode in ICU patients (4).

For long-term catheters—the cuffed, tunneled, silicone catheters, Hickman or Broviac—or implantable devices, the lumen of the hub or belt of the port is the primary source of colonization; organisms migrate along the external surface of the catheter and through the subcutaneous layers and infect the catheter tip (5,6).

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The first step in primary infection is the colonization of the CVC. For short-term, nontunneled, noncuffed, multilumen catheters—which make up 90% of CRBSIs—the skin insertion site is the source of the colonization; organisms migrate along the external surface of the catheter and through the subcutaneous layers and infect the catheter tip (5,6).

The next step in the pathogenesis of CRBSI is the ability of some microbes to form a biofilm of extracellular, polysaccharide-rich, slimy material (20,21), promoting the adherence of the bacteria to the surface of the CVC. Biofilms form on the external surface of short-term catheters and the internal surface of long-term catheters—that is, those with a dwell time of at least 30 days. This biofilm enables bacteria not only to adhere to the surface of the catheter, but also to resist antibiotics, such that “chronic” biofilm eradication becomes a difficult task (22).

Clinical manifestations of CRBSIs can be divided into two categories: local and systemic. Local manifestations include erythema, edema, tenderness, and purulent discharge. These signs and symptoms are neither sensitive nor specific, and cannot be relied on to identify catheter colonization or CVC-related

CLINICAL MANIFESTATIONS

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such as nausea, vomiting, abdominal pain, and diarrhea. Deep-
mental status, and nonspecific gastrointestinal manifestations
may be accompanied by hypotension, hyperventilation, altered
from other foci of infection, and include fever and chills, which
able from those of secondary bloodstream infections arising
Tunnel infection:
3. Exit-site infection
2. Port-pocket infection: Erythema and/or necrosis of the skin
or subcutaneous tissues either over or around the reservoir
of an implanted catheter, and colonization of the catheter if removed
3. Tunnel infection: Erythema, tenderness, and induration of the tissues above the catheter and more than 2 cm from the exit site, and colonization of the catheter if removed

The systemic features of CRBSIs are generally indistinguishable from those of secondary bloodstream infections arising from other foci of infection, and include fever and chills, which may be accompanied by hypotension, hyperventilation, altered mental status, and nonspecific gastrointestinal manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Deep-

| TABLE 110.1 |
| DEFINITIONS OF CATHETER-RELATED BLOODSTREAM INFECTIONS (CRBSIs) |

**PROBABLE CRBSI**
- Clinical manifestations of infection (fever >38°C, chills/rigors, or hypotension)
- No apparent source of the sepsis/bloodstream infection other than the catheter
- Common skin organisms (e.g., coagulase-negative staphylococci) isolated from two blood cultures from patients with intravascular device or a known pathogen (Staphylococcus aureus or Candida) isolated from a single blood culture

**DEFINITE CRBSI**
- Probable CRBSI criteria outlined above with any of the following:
  - Differential quantitative blood cultures with 5:1 ratio of the same organism isolated from blood drawn simultaneously from the central venous catheter (CVC) and peripheral vein
  - Differential positivity time (positive result of culture from a CVC is obtained at least 2 h earlier than positive result of culture from peripheral blood)
  - Positive quantitative skin culture whereby the organism isolated from an infected insertion site is identical to that isolated from blood
  - Isolation of the same organisms from the peripheral blood and from a quantitative or semiquantitative culture of a catheter segment or tip

**DIAGNOSIS**
A clinical diagnosis of CRBSI is frequently inaccurate, as outlined before. Removal of the CVC has previously been mandatory to prove the CRBSI. Microbiologic methods requiring removal of the CVC were studied with the semiquantitative roll plate catheter cultures developed by Maki et al. in 1977 and considered the gold standard. However, the majority of the catheters were removed unnecessarily (32), exposing the patient to the complications related to reinsertion of a new central catheter and adding to the cost as well. To prevent that, techniques allowing accurate diagnosis without removing the line have been elaborated. In the following section, we will review different methods used for the microbiologic diagnosis of CRBSI (Table 110.2).

**Catheter-sparing Diagnostic Methods**
This method consists of obtaining paired quantitative blood cultures (QBCs) simultaneously from the CVC and a peripheral vein. The target is to have both samples drawn <10 minutes apart with the same volume of blood. The hypothesis is that the higher load of organisms on the internal lumen of the CVC signifying CRBSI would translate into a colony count

| TABLE 110.2 |
| SENSITIVITY AND SPECIFICITY OF TESTS USED IN THE DIAGNOSIS OF CRBSI |

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired quantitative blood cultures</td>
<td>75%–93%</td>
<td>97%–100%</td>
</tr>
<tr>
<td>Differential time to positivity</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>Short-term CVCs</td>
<td>90%</td>
<td>72%</td>
</tr>
<tr>
<td>Long-term CVCs</td>
<td>87%</td>
<td>94%</td>
</tr>
<tr>
<td>Acridine orange leukocyte cytospin technique</td>
<td>84%</td>
<td>85%</td>
</tr>
<tr>
<td>Quantitative catheter culture (roll-plate technique)</td>
<td>84%</td>
<td>85%</td>
</tr>
<tr>
<td>Short-term CVCs</td>
<td>45%</td>
<td>75%</td>
</tr>
<tr>
<td>Long-term CVCs</td>
<td>82%</td>
<td>89%</td>
</tr>
<tr>
<td>Long-term CVCs</td>
<td>83%</td>
<td>97%</td>
</tr>
</tbody>
</table>

CRBSI: catheter-related bloodstream infection; CVC, central venous catheter.

from the CVC greater by manyfold than the peripheral stick. A CVC/peripheral ratio of CFU/mL of 5:1 has been chosen by the Infectious Diseases Society of America to represent true infection. However, multiple cutoffs have been used, including 2.1:1 (33), 5:1 (34), 4:1 (35, 36), 5:1 (37), and 10:1 (38).

A recent meta-analysis found that quantitative blood culture is the most accurate, with a pooled sensitivity of 75% to 93% and specificity of 97% to 100% (39). That same study recommended not culturing all catheter tips, but rather culturing only if CRBSI is suspected clinically. Keuten et al. found that a 3:1 ratio has a sensitivity and specificity very close to the 5:1 ratio, and concluded that the latter might be missing true CRBSI episodes (40). This method is limited by the fact that it is expensive and labor intensive, in addition to the difficulty in obtaining samples through the catheter in some cases (41).

### Differential Time to Positivity

The differential time to positivity (DTP) of qualitative paired CVC and peripheral blood culture has been a more practical test for centers that lack the logistics for QBCs, especially with the introduction of automated radiometric blood culture systems that record the time at which a culture turns positive. The hypothesis suggests that time to positivity of a culture is closely related to the inoculum size of micro-organisms. The technique involves measuring the difference between the time required for culture positivity in simultaneously drawn samples of catheter blood and peripheral blood. In a single center trial of CRBSI, a DTP of 120 minutes was associated with 81% sensitivity and 92% specificity for short-term catheters and 93% sensitivity and 75% specificity for long-term catheters (42). A meta-analysis showed that the DTP of 120 minutes predicts CRBSI, with a pooled sensitivity and specificity of 89% and 87% for short-term catheters and 90% and 72% for long-term catheters, respectively (39). This technique also demands a simultaneous blood draw (within 10 minutes) from the line and the peripheral vein with the same amount of blood. One limitation of this study is that its sensitivity could be compromised when antibiotics are given intraluminally at the time of drawing the blood cultures through the catheters (42).

### Acridine Orange Cytospin Technique

This test involves 1 mL of ethylenediaminetetraacetic acid (EDTA) blood aspirated through the CVC. The sample is added to 10% formalin saline solution for 2 minutes. The sample is then centrifuged, the supernatant decanted, and the cellular deposit homogenized and cytospun. A monolayer is stained with 1 in 10,000 acridine orange staining and viewed by ultraviolet light. A positive test is indicated by the presence of any bacteria (43). This method is expensive but takes 30 minutes, with a sensitivity of 87% and specificity of 94% (44). It should be noted that this technique has only been tested by a small group of investigators and is not easy to perform correctly in order to reproduce the Kite method (45).

### Catheter-drawn Quantitative Blood Culture

This method includes a single quantitative blood culture drawn through the CVC. The cutoff of 100 CFU/mL establishes the diagnosis with a pooled sensitivity of 81% to 86% and pooled specificity of 45% to 96% (39). In a retrospective study in a pediatric cancer population (46), this technique showed a sensitivity of 75%, specificity of 69%, positive predictive value of 79%, and likelihood ratio of 2.44—that is, the odds of having a true CRBSI with the >100 CFU/mL cutoff increase by 2.44 when compared to <100 CFU/mL. One major drawback to this technique is that it cannot distinguish between CRBSI and high-grade bacteremia, especially in immunocompromised patients.

### Diagnostic Methods Requiring Catheter Removal

#### Semiquantitative Roll-plate Catheter Culture

This method was described by Maki et al. in 1977 and remains the international reference diagnostic method (47). It consists of rolling a 3- to 3-cm section of the distal tip of the CVC at least four times back and forth over an agar plate surface and leaving it to incubate overnight. A cutoff of ≥15 CFU defines catheter colonization; if at the same time a peripheral culture grows with the same organism, then a CRBSI is diagnosed. However, this method does not sample the internal lumen of a CVC that is the source of the infection in long-term catheters. Nevertheless, pooled sensitivity and specificity in 14 trials involving short-term catheters was 84% and 85%, respectively (39); this number decreased to 45% and 75%, respectively, with long-term CVCs (i.e., those with more than 30 days of dwell time) (6,48).

#### Quantitative Catheter Cultures

This type of culture involves flushing or sonication a catheter segment in broth with the target of retrieving organisms from both surfaces of the line. A threshold of ≥1,000 CFU correlated best with colonization; CRBSI would be defined by the same cutoff accompanied by a high clinical suspicion and absence of evidence of other sites of infection. As would be expected, the sonication method had a higher sensitivity than the roll-plate method for long-term CVCs (6); however, both sonication and vortexing had the same sensitivity and specificity of the roll-plate method for short-term CVCs (49). A recent meta-analysis revealed a pooled sensitivity and specificity of 82% and 89% for short-term catheters and 83% and 97% for long-term catheters, respectively (39).

#### Stain and Microscopy Rapid Diagnostic Techniques

This method suggests staining of the removed catheter segments and subsequent microscopy testing. The cutoff value of 1 organism per 20 oil immersion fields indicates that the catheter is colonized. Cooper and Hopkins (50) reported 100% sensitivity, 97% specificity, a positive predictive value of 84%, and a negative predictive value of 100%, but the results were not reproduced in another study (51). In a similar technique, acridine orange staining has been used for diagnosis, in which fluorescence is indicative of positivity (52). In addition to achieving a sensitivity of 84% and a specificity of 99%, acridine orange staining may be more easily performed than Gram staining, though microscopic techniques as a whole are labor intensive.

### PREVENTIVE STRATEGIES

It should go without saying—but obviously does not—that CVCs should only be used when medically necessary, and...
PREVENTIVE MEASURES TO DECREASE THE RISK OF COLONIZATION OF CENTRAL VENOUS CATHETERS

- Hand hygiene
- Avoiding femoral site insertion if possible
- Removing unnecessary catheters
- Cutaneous antiseptic agents (2% chlorhexidine-based preparations)
- Maximal sterile barrier (handwashing, sterile gloves, large drape, and sterile gown, mask, and cap)
- Antimicrobial catheter lock solutions (a combination of an antibiotic like heparin or ethylendiaminetetraacetic acid plus an antimicrobial agent, such as vancomycin, minocycline, or ciprofloxacin)
- Antimicrobial coating of catheter (with minocycline retapam or chlorhexidine/silver sulfadiazine)


cutaneous antiseptics with chlorhexidine, avoidance of femoral site, and removal of CVCs determined to be unnecessary were associated with a significant decrease in CRBSI rate—from 7.7 per 1,100 catheter-days to 1.4 per 1,000 catheter-days (p < 0.001) over 18 months of follow-up (53). In 1992, Cobb et al., in an attempt to reduce catheter-related infection, conducted a controlled study whereby CVCs or pulmonary artery catheters were changed or exchanged over guidewire every 3 days. The former procedure resulted actually in an increase in the risk of mechanical complications, whereas the latter technique increased the risk of bloodstream infection (9). Table 110.3 provides a listing of preventive strategies to decrease the risk of colonization of central venous catheters. We review below the novel strategies implemented by the Healthcare Infection Control Practices Advisory Committee (HICPAC) and other professional organizations, including the Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), and American Society of Critical Care Anesthesiologists (ASCCA) aiming at controlling all factors that could lead to colonization of the CVC, and hence decreasing the rate of CRBSI.

Maximal Sterile Barrier

This involves wearing a sterile gown, gloves, and a cap and using a large drape similar to those used in the operating room during the insertion of catheters as opposed to the regular precautions consisting of sterile gloves and a small drape only. The HICPAC/CDC guidelines recommend this technique while inserting CVCs, PICC lines, and pulmonary artery catheters (54) (category 1A) based on a number of studies (58–60).

A prospective study conducted by Raad et al. with long-term, nontunneled silicone CVCs and PICC lines in a cancer patient population demonstrated not only a reduction of CRBSIs (p = 0.03), but also that this practice was cost effective (58). Merrel et al., in another prospective study with Swan-Ganz pulmonary artery (PA) catheters, found that less stringent barrier precautions were associated with a significantly increased risk of catheter-related infection (relative risk = 2.1, p = 0.03) (59). Of note is that this technique failed to reduce the colonization of CRBSIs associated with arterial catheters (60).

Antimicrobial Catheter Lock Solutions

Antimicrobial catheter lock involves flushing the catheter lumens and then filling it with 2 to 3 mL of a combination of an antibiotic plus an antimicrobial agent. The dwell (lock) time varies between clinicians, but 20 to 24 hours is the most preferred. However, this might not be possible if the catheter has to be used (61). This intervention has often been used in long-term CVCs that remain in place longer than 30 days. Hendrickson et al. showed that a combination of vancomycin and heparin, with or without ciprofloxacin, was equivalent, but each was superior to heparin alone (62). Heparin prevents the formation of the fibrin sheath on the inner surface of the line. Of six studies, four revealed a significant reduction in CRBSI with the above lock solution (63–65), and two demonstrated no benefit (66,67). Vancomycin-heparin lock solutions did not promote vancomycin resistance (66), but the risk of superinfection with Gram-negative bacilli and Candida is present since the vancomycin spectrum is limited to Gram-positive bacteria. A recent meta-analysis concluded that the use of a vancomycin lock solution in high-risk patient populations being treated with long-term central intravascular devices (IVDs) reduces the risk of bloodstream infection with a risk ratio of 0.34 (95% confidence interval [CI], 0.12–0.98; p = 0.04) (68).

Minocycline and EDTA (M-EDTA), another lock solution, was reported in a prospective randomized trial to significantly reduce the risk of catheter colonization and infection when compared with heparin in long-term hemodialysis CVCs (69). This solution was superior in an in vitro biofilm model and in an animal model to vancomycin-heparin lock solution (70,71). A clinical study of pediatric cancer populations showed that M-EDTA significantly reduced the risk of catheter infection and colonization when compared to heparin (72).

In a prospective nonrandomized study of tunneled CVCs in a pediatric cancer population, ethanol as a lock solution of eight randomized trials found an overall reduction of 49% in catheter-associated bloodstream infections when a disinfectant containing chlorhexidine was used (57).
Antimicrobial Impregnation of Catheters

This technique consists of the impregnation of the external and/or internal surface of the catheter with an antiseptic or antibiotic; the slow release of antimicrobials would prevent initial bacterial adherence and biofilm formation, with virtually undetectable serum levels. The HCPAC/CDC, with a category 1B, recommends use of the coated CVCs described herein. The first-generation catheters were impregnated on the external surface with CHX and silver sulfadiazine (CHX/SSD; Arrow Gard and Arrow Gard Plus, Arrow International, Inc.). That technique lowered the rate of CRBSI from 7.6 cases per 1,000 catheter-days to 1.6 cases per 1,000 catheter-days ($p = 0.03$), with a decrease in the rate of colonization (relative risk, 0.36 [95% CI, 0.36–0.89]; $p = 0.003$) (75); the estimated cost savings per CVC insertion was $196 (76). However, three subsequent studies failed to show that difference (77–79). This was explained by the fact that short-term catheter infection is due to external colonization, whereas long-term CRBSIs due to internal colonization are not prevented by external coating. Moreover, Mermel showed that these catheters do not protect if the CVC dwell time is more than 3 weeks, secondary to wearing off of the antimicrobial activity (3). The second-generation CHX/SSD-coated catheters were impregnated on both surfaces. In a multicenter, randomized double-blind prospective study from 14 French ICUs, second-generation catheters failed to decrease the rate of CRBSI (80,81) when compared to noncoated catheters, although they significantly decreased the rate of colonization (11/1,000 catheter-days to 3.6/1,000 catheter-days; $p = 0.03$), with a decrease in the rate of colonization (relative risk, 0.56 [95% CI, 0.36–0.89]; $p = 0.002$) (82). However, the CRBSI rates were low and similar between the two groups (83). In another prospective randomized study compared these catheters to the M/R-coated type; the latter was more efficacious in reducing, to a significant degree, CVC colonization with Gram-positive and Gram-negative bacteria ($p = 0.039$). However, the CRBSI rates were low and similar between the two groups (84). Another prospective randomized study compared the skin disinfection of antibiotic-coated catheters and failed to detect any emergence of resistance (81,82,85,86). A retrospective review of the M/R-coated CVC experience in bone marrow transplant patients also detected no emergence of resistance of staphylococci to either component (87). Through prospective randomized studies, the M/R-coated CVCs were shown to bring the risk of CRBSI to a level ≤0.3 per 1,000 catheter-days in nontunneled, noncuffed CVCs (81,82,86), which is lower than the 1.4 per 1,000 catheter-days achieved with multiple other aseptic measures applied collectively (such as the maximal sterile barrier, chlorhexidine cutaneous antiseptic, and hand hygiene).

Silver-impregnated Catheters

Other catheters incorporate silver, platinum, and carbon (SPC) into the polyurethane, allowing topical silver ion release (Vanxive CVC with oligan, Edwards Life Sciences, Irvine, CA). A recent prospective randomized study compared these catheters to the M/R-coated type; the latter was more efficacious in reducing, to a significant degree, CVC colonization with Gram-positive and Gram-negative bacteria ($p = 0.039$). However, the CRBSI rates were low and similar between the two groups (88). In another prospective, randomized, controlled, open-label, multicenter clinical trial, the SPC CVCs failed to show any benefit in reducing CRBSI or colonization (89). Management of CRBSI is based on the organisms causing such an infection, and is described below.

Management

The management of CRBSIs involves confirming the source of infection, determining the choice of antimicrobials, determining the duration of therapy, and deciding whether to remove the catheters. Confirmation of the infection is dependent on the diagnostic measures outlined above. The duration of therapy depends on whether the infection is complicated (i.e., by a septic phlebitis or endocarditis) or uncomplicated.

Coagulase-negative Staphylococcus (CNS)

Coagulase-negative staphylococci are the primary organisms involved in CRBSIs because they are the most common skin organisms. However, and for the same reason, they are the most frequent blood contaminants. A recent study indicated that QBC collected through CVC, with a cutoff point of 15 CFU/mL, could be a useful laboratory criterion, together with positive clinical findings for differentiating true bacteremia from false-positive contaminated blood cultures, with a sensitivity of 96%, specificity of 94%, positive predictive value of 86%, and negative predictive value of 98% (90). The IDSA guidelines recommend removing the CVC and treating for
Gram-negative Bacilli

G. N. bacteraemia is rarely due to a CVC; rather, it generally arises from a visceral source of infection such as the genitourinary, pulmonary, or gastrointestinal tracts. However, CRBSIs caused by such organisms as K. pneumoniae, Enterobacter spp., P. aeruginosa spp., Acinetobacter spp., and Stenotrophomonas maltophilia have been reported (103, 104). Elting and Bodey reported a 15-year experience of 149 episodes of sepsisemia caused by Xanthomonas maltophilia and Pseudomonas spp. in cancer patients where the CVC was the most common source (103). Hanna et al. demonstrated that catheter removal within 72 hours of the onset of the catheter-related GNB was the only independent protective factor against the relapse of infection (odds ratio, 0.13; 95% confidence interval, 0.02–0.75; p = 0.02) (104). IDSA guidelines (91) recommend removing nontunneled CVCs and treating for 10 to 14 days; there are no data to guide the use of intravenous versus oral antibiotics. It is considered appropriate to attempt to salvage the CVC in certain situations (e.g., when unable to access other vascular sites due to anatomic challenges or if there is a high risk of hemorrhagic complications because of thrombocytopenia or elevated prothrombin time) using systemic and lock solution therapies. However, lock therapy for GNB CRBSIs is anecdotal; successful cases were salvaged using gentamicin, amikacin, or ceftazidime (91, 101).

Candida

Five large prospective studies proved that catheter retention was associated with increased mortality and an increase in the mean duration of candidemia in cases of Candida CRBSI (105–109). Hung et al. investigated the predisposing factors and prognostic determinants of Candida bacteraemia in a Taiwan hospital and concluded that higher severity scores, nonremoval of the catheter, persistent candidemia, and lack of antifungal therapy adversely affect the outcome (107). Raad et al., in a retrospective study of 408 patients with candidemia and an indwelling CVC, using a multivariate analysis, demonstrated that catheter removal 72 hours or sooner after onset of candidemia improved the response to antifungal therapy exclusively in patients with catheter-related candidemia (p = 0.04) (110). IDSA guidelines recommend removing the CVC and treating for 14 days after the last positive blood culture in uncomplicated cases. Endophthalmitis merits 6 weeks of therapy (91). Further studies are needed to define the role of antifungal lock solution in these cases. Fluconazole and caspofungin were equivalent to amphotericin B in candidemia, but with a better safety profile (109, 110); therefore, fluconazole or caspofungin should be considered in documented cases of catheter-related candidemia. If the rates of fluconazole-resistant Candida glabrata and Candida krusei in the hospital are high, an echinocandin (caspofungin, micafungin, or anidulafungin) would be the best alternative to amphotericin B.

SUMMARY

Central venous catheters are as much a part of modern ICU practice as are mechanical ventilators and antibiotics. When CVCs are placed with the appropriate technique, accessed, and cared for, it is possible to use these devices while approximating a zero incidence of infection. As is true in the majority of the practice of critical care medicine, it is in the details that the battle is won or lost.
Chapter 110: Catheter-Related Bloodstream Infections

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1187. A randomized, controlled trial.

1226. A randomized, controlled trial.

1265. A randomized, controlled trial.