Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America

Leonard A. Mermel,[1] Michael Allon,[2] Emilio Bouza,[9] Donald E. Craven,[3] Patricia Flynn,[4] Naomi P. O'Grady,[5] Issam I. Raad,[6] Bart J. A. Rijnders,[10] Robert J. Sherertz,[7] and David K. Warren[8]

[1]Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, Rhode Island; [2]University of Alabama-Birmingham Hospital, Birmingham, Alabama; [3]Tufts University School of Medicine, Lahey Clinic Medical Center, Burlington, Massachusetts; [4]St. Jude Children's Research Hospital, Children's Infection Defense Center, Memphis, Tennessee; [5]National Institutes of Health, Critical Care Medicine Department, Bethesda, Maryland; [6]Section of Infectious Diseases, University of Texas-Cancer Center, Houston; [7]Section of Infectious Diseases, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [8]Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri; [9]Servicio de Microbiología Cliínica y E. Infecciosas Hospital General "Gregorio Marañón," Madrid, Spain; and [10]Internal Medicine and Infectious Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands

These updated guidelines replace the previous management guidelines published in 2001. The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them.

EXECUTIVE SUMMARY

Diagnosis: Intravenous Catheter Cultures

General

1. Catheter cultures should be performed when a catheter is removed for suspected catheter-related bloodstream infection (CRBSI); catheter cultures should not be obtained routinely (A-II).
2. Qualitative broth culture of catheter tips is not recommended (A-II).
3. For central venous catheters (CVCs), the catheter tip should be cultured, rather than the subcutaneous segment (B-III).
4. For cultures of an anti-infective catheter tip, use specific inhibitors in the culture media (A-II).
5. Growth of >15 colony-forming units (cfu) from a 5-cm segment of the catheter tip by semiquantitative (roll-plate) culture or growth of $>10^2$ cfu from a catheter by quantitative (sonication) broth culture reflects catheter colonization (A-I).
6. When catheter infection is suspected and there is a catheter exit site exudate, swab the drainage to collect specimens for culture and Gram staining (B-III).

Short-term catheters, including arterial catheters.

7. For short-term catheter tip cultures, the roll plate technique is recommended for routine clinical microbiological analysis (A-II).
8. For suspected pulmonary artery catheter infection, culture the introducer tip (A-II).

Long-term catheters

9. Semiquantitative growth of <15 cfu/plate of the same microbe from both the insertion site culture and

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Reprints or corresponence: Dr. Leonard Mermel, Div. of Infectious Diseases, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903 (lmermel@lifespan.org).

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the catheter hub culture strongly suggests that the catheter is not the source of a bloodstream infection (A-II).

10. If a venous access subcutaneous port is removed for suspected CRBSI, send the port to the microbiology laboratory for qualitative culture of the port reservoir contents, in addition to the catheter tip (B-II).

Diagnosis: Blood Cultures

11. Obtain samples for blood culture prior to the initiation of antibiotic therapy (figure 1) (A-I).

12. Where available, a phlebotomy team should draw the blood samples (A-II).

13. Skin preparation for obtaining percutaneously drawn blood samples should be performed carefully, with use of either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%), rather than povidone-iodine; allow adequate skin contact and drying times to mitigate blood culture contamination (A-I).

14. If a blood sample is obtained through a catheter, clean the catheter hub with either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%), allowing adequate drying time to mitigate blood culture contamination (A-I).

15. For suspected CRBSI, paired blood samples, drawn from the catheter and a peripheral vein, should be cultured before initiation of antimicrobial therapy, and the bottles should be appropriately marked to reflect the site from which the samples were obtained (A-II).

16. If a blood sample cannot be drawn from a peripheral vein, it is recommended that ⩾2 blood samples should be drawn through different catheter lumens (B-III). It is unclear whether blood cultures should be drawn through all catheter lumens in such circumstances (C-III).

17. A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood culture and from a culture of the catheter tip (A-I), or that 2 blood samples be drawn (one from a catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP) (A-II). Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood

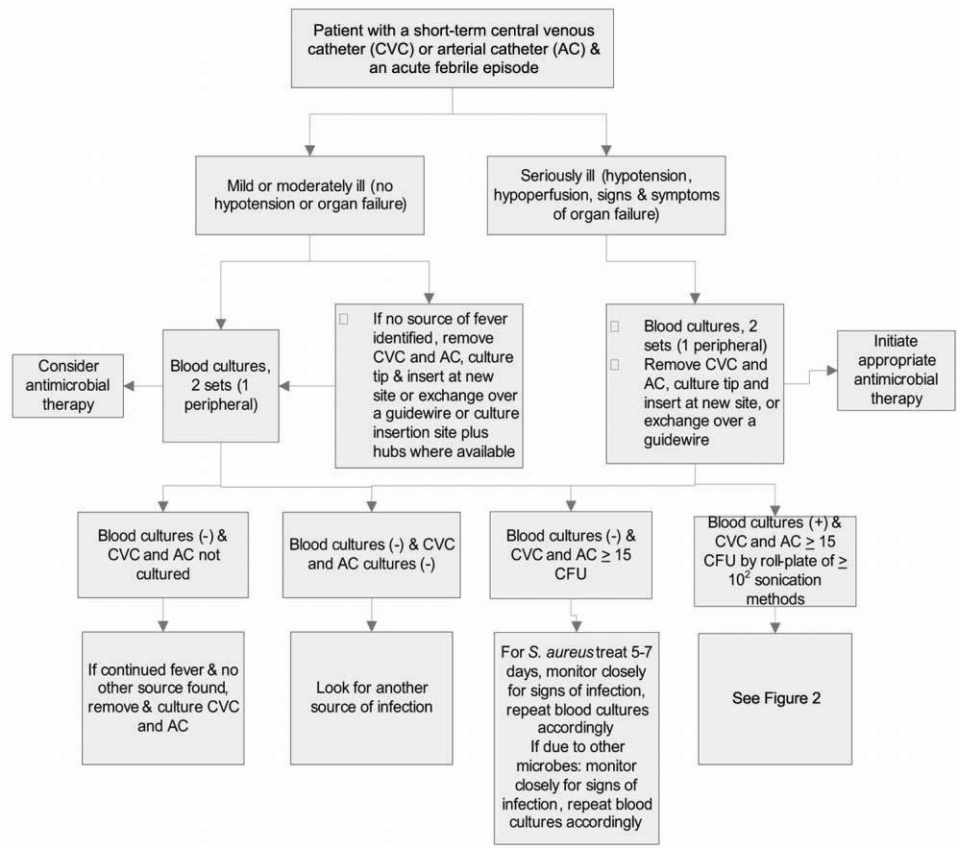

Figure 1. Methods for the diagnosis of acute fever for a patient suspected of having short-term central venous catheter infection or arterial catheter infection. CFU, colony-forming units.

sample obtained from the second lumen should be considered to indicate possible CRBSI (B-II). In this circumstance, the interpretation of blood cultures that meet the DTP criteria is an unresolved issue (C-III).

18. For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI (A-II).

19. For DTP, growth of microbes from a blood sample drawn from a catheter hub at least 2 h before microbial growth is detected in a blood sample obtained from a peripheral vein best defines CRBSI (A-II).

20. Quantitative blood cultures and/or DTP should be performed before initiating antimicrobial therapy and with the same volume of blood per bottle (A-II).

21. Evidence is insufficient to recommend that blood cultures be routinely performed after discontinuation of antimicrobial therapy for CRBSI (C-III).

General Management of Catheter-Related Infection

22. When denoting duration of antimicrobial therapy, day 1 is the first day on which negative blood culture results are obtained (C-III).

23. Vancomycin is recommended for empirical therapy in heath care settings with an elevated prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA); for institutions in which the preponderance of MRSA isolates have vancomycin minimum inhibitory concentration (MIC) values >2 μg/mL, alternative agents, such as daptomycin, should be used (A-II).

24. Linezolid should not be used for empirical therapy (i.e., for patients suspected but not proven to have CRBSI) (A-I).

25. Empirical coverage for gram-negative bacilli should be based on local antimicrobial susceptibility data and the severity of disease (e.g., a fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination, with or without an aminoglycoside) (A-II).

26. Empirical combination antibiotic coverage for multidrug-resistant (MDR) gram-negative bacilli, such as *Pseudomonas aeruginosa,* should be used when CRBSI is suspected in neutropenic patients, severely ill patients with sepsis, or patients known to be colonized with such pathogens, until the culture and susceptibility data are available and de-escalation of the antibiotic regimen can be done (A-II).

27. In addition to coverage for gram-positive pathogens, empirical therapy for suspected CRBSI involving femoral catheters in critically ill patients should include coverage for gram-negative bacilli and *Candida* species (A-II).

28. Empirical therapy for suspected catheter-related candidemia should be used for septic patients with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, femoral catheterization, or colonization due to *Candida* species at multiple sites (B-II).

29. For empirical treatment of suspected catheter-related candidemia, use an echinocandin or, in selected patients, fluconazole (A-II). Fluconazole can be used for patients without azole exposure in the previous 3 months and in health care settings where the risk of *Candida krusei* or *Candida glabrata* infection is very low (A-III).

30. Antibiotic lock therapy should be used for catheter salvage (B-II); however, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter (C-III).

31. Four to 6 weeks of antibiotic therapy should be administered to patients with persistent fungemia or bacteremia after catheter removal (i.e., occurring >72 h after catheter removal) (A-II for *S. aureus* infection; C-III for infection due to other pathogens), to patients who are found to have infective endocarditis or suppurative thrombophlebitis, and to pediatric patients with osteomyelitis; 6–8 weeks of therapy should be used for the treatment of osteomyelitis in adults (figures 2 and 3) (A-II).

32. Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite >72 h of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S. aureus, P. aeruginosa,* fungi, or mycobacteria (A-II). Short-term catheters should be removed from patients with CRBSI due to gram-negative bacilli, *S. aureus,* enterococci, fungi, and mycobacteria (A-II).

33. For patients with CRBSI for whom catheter salvage is attempted, additional blood cultures should be obtained, and the catheter should be removed if blood culture results (e.g., 2 sets of blood cultures obtained on a given day; 1 set of blood cultures is acceptable for neonates) remain positive when blood samples are obtained 72 h after the initiation of appropriate therapy (B-II).

34. For long-term and short-term CRBSI due to less virulent microbes that are difficult to eradicate (e.g., *Bacillus* species, *Micrococcus* species, or Propionibacteria), catheters should generally be removed after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least 1 blood culture sample drawn from a peripheral vein (B-III).

35. In uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus, P. aeruginosa, Bacillus* species, *Micrococcus* species, Propionibacteria, fungi, or mycobacteria, because of the limited access sites in many patients who require long-term intravascular access for survival (e.g., patients undergoing hemodialysis or with short-gut syndrome),

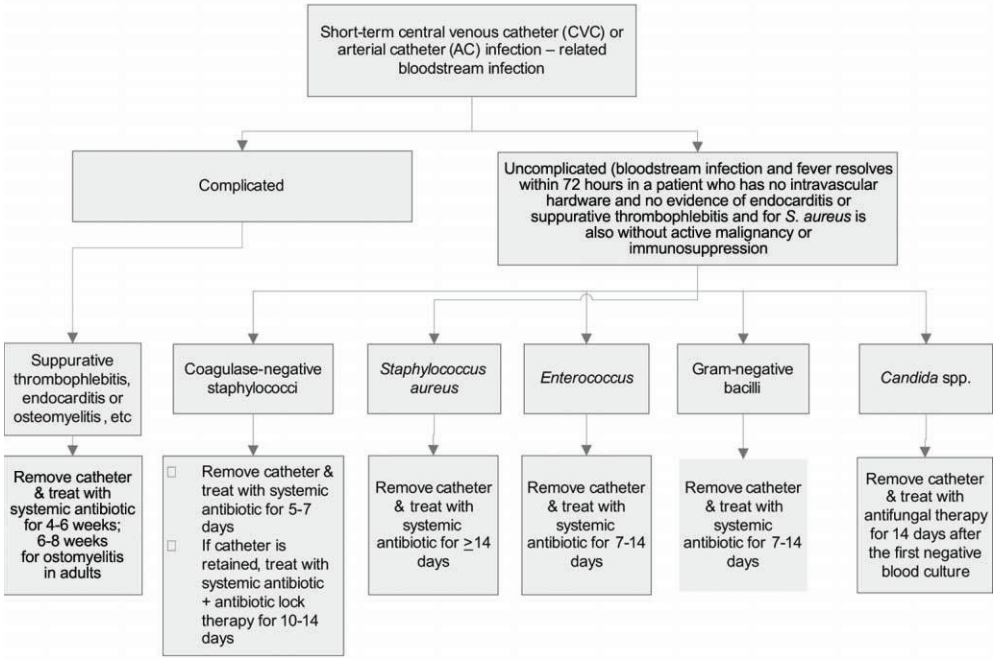

Figure 2. Approach to the management of patients with short-term central venous catheter–related or arterial catheter–related bloodstream infection. CFU, colony-forming units; *S. aureus, Staphylococcus aureus.*

treatment should be attempted without catheter removal, with use of both systemic and antimicrobial lock therapy (B-II).

36. After a positive blood culture result is reported that may represent CRBSI, automated standardized treatment advice can be formulated to improve compliance with Infectious Diseases Society of America (IDSA) guidelines (B-II).

37. Urokinase and other thrombolytic agents are not recommended as adjunctive therapy for patients with CRBSI (B-I).

38. If a catheterized patient has a single positive blood culture that grows coagulase-negative *Staphylococcus* species, then additional cultures of blood samples obtained through the suspected catheter and from a peripheral vein should be performed before the initiation of antimicrobial therapy and/or catheter removal to be certain that the patient has true bloodstream infection and that the catheter is the likely source (A-II).

Recommendations related to the unique aspects of the following subjects may also be found in the text: treating short-term peripheral venous catheters, nontunneled and long-term CVCs, implanted catheter–related infections (other than infections related to hemodialysis catheters), treatment of pediatric patients with catheter-related infections, and treatment of infections related to hemodialysis catheters. Recommendations are also made regarding antibiotic lock therapy, pathogen-specific treatment, management of suppurative thrombophlebitis, management of persistent bloodstream infection, and detection and management of an outbreak of CRBSI. A full listing of all recommendations may be found in table 1.

INTRODUCTION

In 2001, the IDSA published a clinical practice guideline on the management of intravascular catheter-related infection [1]. IDSA updates its guidelines when new data or publications might change a prior recommendation or when the Expert Panel feels clarifications or additional guidance are warranted. For the 2009 Update, the indications for treatment and agents of choice from the 2001 guideline were reviewed [1]. The previous document is a source for a more detailed review of earlier studies.

The Expert Panel addressed the following clinical questions in the 2009 Update:

I. Diagnosis: when and how should catheter cultures and blood cultures be done?

II. How should catheter-related infections generally be managed?

III. What are the unique aspects of treating infections associated with short-term peripheral venous catheters?

IV. What are the unique aspects of treating infections associated with nontunneled CVCs and arterial catheters?

V. What are the unique aspects of treating infections associated with long-term CVCs or implanted catheter–related infections other than those related to hemodialysis catheters?

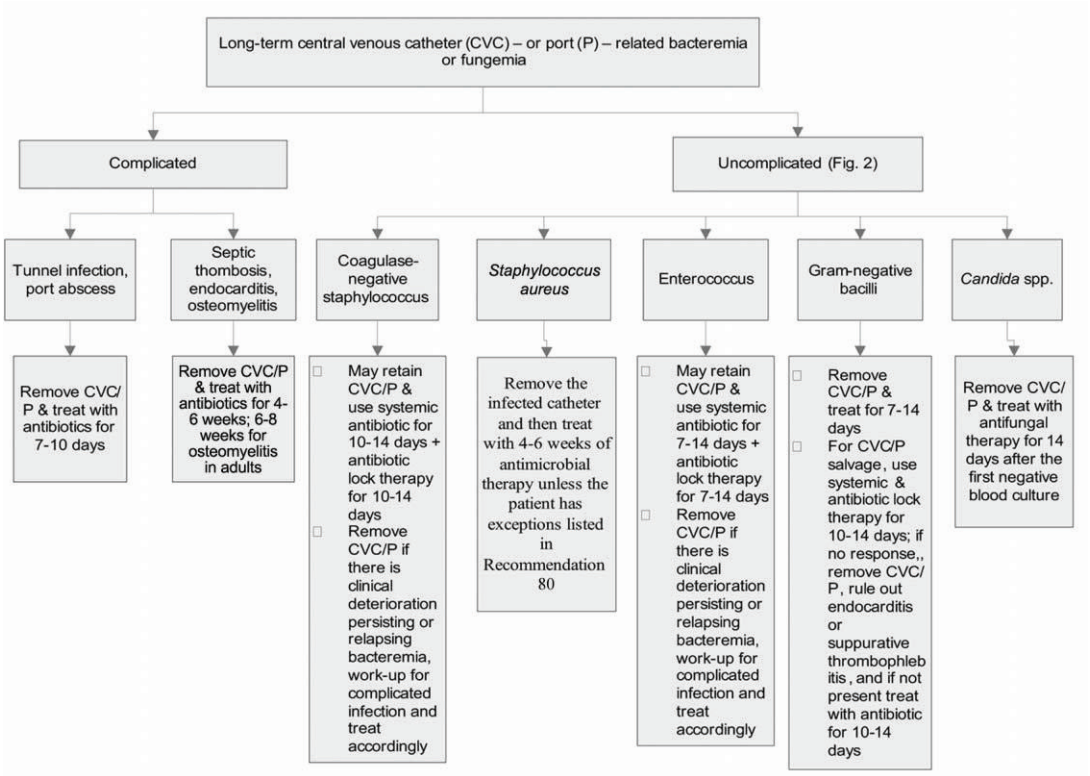

Figure 3. Approach to the treatment of a patient with a long-term central venous catheter (CVC) or a port (P)-related bloodstream infection.

VI. What are the unique aspects of treating pediatric patients who have catheter-related infections?

VII. What are the unique aspects of managing patients who receive hemodialysis through catheters for whom catheter-related infection is suspected or proven?

VIII. What is antibiotic lock therapy, and how is it used to manage patients with catheter-related infection?

IX. Are there pathogen-specific treatment recommendations?

X. How should you manage suppurative thrombophlebitis?

XI. How are persistent bloodstream infection and infective endocarditis managed?

XII. How would you detect and manage a possible outbreak of CRBSI?

Practice guidelines and update methodology. "Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [2, p. 8]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [2].

Expert Panel composition. The IDSA Standards and Practice Guidelines Committee convened a multidisciplinary panel of experts in the management of intravascular catheter-related infections. Expert Panel participants included representatives from the following collaborating organizations: European Society of Clinical Microbiology and Infectious Diseases, Pediatric Infectious Diseases Society, American Society of Nephrology, Society for Critical Care Medicine, and the Society for Healthcare Epidemiology of America.

Literature review and analysis. For the 2009 update, the Expert Panel completed the review and analysis of data published from January 2001 through June 2008. Data published after June 2008 were also considered in the final preparation of the guideline. Computerized literature searches of the PubMed database were performed with combinations of the following search terms: "catheter-related," "infections," "cultures," "management," "treatment," "peripheral," "non-tunneled," "central venous catheter," "arterial catheter," "implanted catheter," "pediatric," "hemodialysis," "antibiotic lock," "bacteremia" "suppurative thrombophlebitis," "endocarditis," and "outbreak."

Process overview. In evaluating the evidence regarding the management of intravascular catheter–related infections, the Expert Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 2) [3].

Consensus development on the basis of evidence. The Expert Panel met face-to-face on 1 occasion and via telecon-

Table 1. Summary of recommendations for the diagnosis and management of intravascular catheter-related bloodstream infection (CRBSI).

Recommendation	Comments	Strength or quality of recommendation	Reference(s)
Diagnosis: when and how should catheter cultures and blood cultures be done?			
Intravenous catheter cultures			
General			
1.	Catheter cultures should be performed when a catheter is removed for suspected CRBSI; catheter cultures should not be obtained routinely	A-II	[22, 26]
2.	Qualitative broth culture of catheter tips is not recommended	A-II	[22, 23]
3.	For central venous catheters (CVCs), the catheter tip should be cultured, rather than the subcutaneous segment	B-III	[20]
4.	For cultures of an anti-infective catheter tip, use specific inhibitors in the culture media	A-II	[31, 32]
5.	Growth of >15 cfu from a 5-cm segment of the catheter tip by semiquantitative (roll-plate) culture or growth of $>10^2$ cfu from a catheter by quantitative (sonication) broth culture reflects catheter colonization	A-I	[22, 23, 27]
6.	When catheter infection is suspected and there is a catheter exit site exudate, swab the drainage to collect specimens for culture and Gram staining	B-III	[1, 33]
Short-term catheters, including arterial catheters			
7.	For short-term catheter tip cultures, the roll plate technique is recommended for routine clinical microbiological analysis	A-II	[27]
8.	For suspected pulmonary artery catheter infection, culture the introducer tip	A-II	[21]
Long-term catheters			
9.	Semiquantitative growth of <15 cfu/plate of the same microbe from both the insertion site culture and the catheter hub culture strongly suggests that the catheter is not the source of a bloodstream infection	A-II	[33]
10.	If a venous access subcutaneous port is removed for suspected CRBSI, send the port to the microbiology laboratory for qualitative culture of the port reservoir contents, in addition to the catheter tip	B-II	[28–30]
Blood cultures			
11.	Obtain samples for blood culture prior to the initiation of antibiotic therapy (figure 1)	A-I	
12.	Where available, a phlebotomy team should draw the blood samples	A-II	[38]
13.	Skin preparation for obtaining percutaneously drawn blood samples should be performed carefully, with use of either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%), rather than povidone-iodine; allow adequate skin contact and drying times to mitigate blood culture contamination	A-I	[39, 40]
14.	If a blood sample is obtained through a catheter, clean the catheter hub with either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%), allowing adequate drying time to mitigate blood culture contamination	A-I	
15.	For suspected CRBSI, paired blood samples, drawn from the catheter and a peripheral vein, should be cultured before initiation of antimicrobial therapy, and the bottles should be appropriately marked to reflect the site from which the samples were obtained	A-II	[33, 44, 45]
16.	If a blood sample cannot be drawn from a peripheral vein, it is recommended that ⩾2 blood samples should be drawn through different catheter lumens	B-III	[36]
	It is unclear whether blood cultures should be drawn through all catheter lumens in such circumstances	C-III	

17.	A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood culture and from a culture of the catheter tip	A-I	
	Or that 2 blood samples be drawn (one from a catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or DTP	A-II	[35, 49]
	Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood sample obtained from the second lumen should be considered to indicate possible CRBSI	B-II	[36]
	In this circumstance, the interpretation of blood cultures that meet the DTP criteria is an unresolved issue	C-III	[36]
18.	For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI	A-II	[35, 72]
19.	For DTP, growth of microbes from a blood sample drawn from a catheter hub at least 2 h before microbial growth is detected in a blood sample obtained from a peripheral vein best defines CRBSI	A-II	[49]
20.	Quantitative blood cultures and/or DTP should be performed before initiating antimicrobial therapy and with the same volume of blood per bottle	A-II	[50]
21.	Evidence is insufficient to recommend that blood cultures be routinely performed after discontinuation of antimicrobial therapy for CRBSI	C-III	
How should catheter-related infections generally be managed?			
22.	When denoting duration of antimicrobial therapy, day 1 is the first day on which negative blood culture results are obtained	C-III	[184]
23.	Vancomycin is recommended for empirical therapy in heath care settings with an elevated prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA); for institutions in which the preponderance of MRSA isolates have vancomycin minimum inhibitory concentration (MIC) values >2 μg/mL, alternative agents, such as daptomycin, should be used	A-II	[55, 56]
24.	Linezolid should not be used for empirical therapy (i.e., for patients suspected but not proven to have CRBSI)	A-I	[52]
25.	Empirical coverage for gram-negative bacilli should be based on local antimicrobial susceptibility data and the severity of disease (e.g., a fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination, with or without an aminoglycoside)	A-II	
26.	Empirical combination antibiotic coverage for multidrug-resistant (MDR) gram-negative bacilli, such as *Pseudomonas aeruginosa,* should be used when CRBSI is suspected in neutropenic patients, severely ill patients with sepsis, or patients known to be colonized with such pathogens, until the culture and susceptibility data are available and de-escalation of the antibiotic regimen can be done	A-II	[13, 258, 259]
27.	In addition to coverage for gram-positive pathogens, empirical therapy for suspected CRBSI involving femoral catheters in critically ill patients should include coverage for gram-negative bacilli and *Candida* species	A-II	[178]
28.	Empirical therapy for suspected catheter-related candidemia should be used for septic patients with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, femoral catheterization, or colonization due to *Candida* species at multiple sites	B-II	[178, 200]
29.	For empirical treatment of suspected catheter-related candidemia, use an echinocandin or, in selected patients, fluconazole	A-II	[186, 187, 194, 260]

	Fluconazole can be used for patients without azole exposure in the previous 3 months and in health care settings where the risk of *Candida krusei* or *Candida glabrata* infection is very low	A-III	[184, 260]
30.	Antibiotic lock therapy should be used for catheter salvage	B-II	[114, 124]
	However, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter	C-III	
31.	Four to 6 weeks of antibiotics should be administered in patients with persistent fungemia or bacteremia after catheter removal (i.e., >72 h) and in patients found to have infective endocarditis or suppurative thrombophlebitis and pediatric patients with osteomyelitis	A-II for *S. aureus*; C-III for other pathogens	[143, 146]
	Six to 8 weeks of therapy should be used for the treatment of osteomyelitis in adults (figures 2 and 3) (A-II).		
32.	Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite >72 h of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S. aureus, P. aeruginosa,* fungi, or mycobacteria	A-II	[144, 145]
	Short-term catheters should be removed from patients with CRBSI due to gram-negative bacilli, *S. aureus,* enterococci, fungi, and mycobacteria	A-II	
33.	For patients with CRBSI for whom catheter salvage is attempted, additional blood cultures should be obtained, and the catheter should be removed if blood culture results (e.g., 2 sets of blood cultures obtained on a given day; 1 set of blood cultures is acceptable for neonates) remain positive when blood samples are obtained 72 h after the initiation of appropriate therapy	B-II	
34.	For long-term and short-term CRBSI due to less virulent microbes that are difficult to eradicate (e.g., *Bacillus* species, *Micrococcus* species, or Propionibacteria), catheters should generally be removed after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least 1 blood culture sample drawn from a peripheral vein	B-III	[202, 203, 261]
35.	In uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus, P. aeruginosa, Bacillus* species, *Micrococcus* species, Propionibacteria, fungi, or mycobacteria, because of the limited access sites in many patients who require long-term intravascular access for survival (e.g., patients undergoing hemodialysis or with short-gut syndrome), treatment should be attempted without catheter removal, with use of both systemic and antimicrobial lock therapy	B-II	[114, 124]
36.	After a positive blood culture result is reported that may represent CRBSI, automated standardized treatment advice can be formulated to improve compliance with IDSA guidelines	B-II	[57]
37.	Urokinase and other thrombolytic agents are not recommended as adjunctive therapy for patients with CRBSI	B-I	[58, 59]
38.	If a catheterized patient has a single positive blood culture that grows coagulase-negative *Staphylococcus* species, then additional cultures of blood samples obtained through the suspected catheter and from a peripheral vein should be performed before the initiation of antimicrobial therapy and/or catheter removal to be certain that the patient has true bloodstream infection and that the catheter is the likely source	A-II	[262, 263]
What are the unique aspects of treating short-term peripheral venous catheters?			
39.	Peripheral intravenous catheters with associated pain, induration, erythema, or exudate should be removed	A-I	
40.	Any exudate at the insertion site should be submitted for Gram staining, routine culture, and additional culture for fungi and acid-fast organisms, as indicated, when assessing immunocompromised patients	A-II	

What are the unique aspects of treating nontunneled central venous catheters and arterial catheters?			
41.	For patients who are hospitalized in the intensive care unit with a new onset of fever but without severe sepsis or evidence of bloodstream infection, obtain blood samples for culture from the nontunneled CVC, the arterial catheter (if present), and percutaneously, instead of performing routine catheter removal	B-II	[70]
	Consider culture of samples obtained from the insertion site and catheter hubs, if available, as noted above	A-II	[33]
42.	The CVC and arterial catheter, if present, should be removed and cultured if the patient has unexplained sepsis or erythema overlying the catheter insertion site or purulence at the catheter insertion site	B-II	
43.	For patients with unexplained fever, if blood culture results are positive, the CVC or arterial catheter was exchanged over a guidewire, and the catheter tip has significant growth, then the catheter should be removed and a new catheter placed in a new site	B-II	
What are the unique aspects of treating long-term CVC or implanted catheter-related infections other than hemodialysis catheters?			
44.	Patients with tunnel infection or port abscess require removal of the catheter, incision and drainage if indicated, and 7–10 days of antibiotic therapy in the absence of concomitant bacteremia or candidemia.	A-II	[19, 264]
45.	For patients with suspected exit site infection, obtain cultures of any drainage from the exit site and blood cultures	A-II	[19]
46.	Uncomplicated exit site infections (i.e., those without systemic signs of infection, positive blood culture results, or purulence) should be managed with topical antimicrobial agents on the basis of the exit site culture results (e.g., mupirocin ointment for *S. aureus* infection and ketoconazole or lotrimin ointment for *Candida* infection	B-III	
47.	If an uncomplicated exit site infection fails to resolve with topical therapy or if it is accompanied by purulent drainage, then systemic antibiotics should be administered on the basis of the antimicrobial susceptibility of the causative pathogen; the catheter should be removed if treatment with systemic antibiotics fails	B-II	[19]
48.	If other vascular sites are unavailable and/or the patient is at increased risk for bleeding diathesis in the setting of CRBSI not complicated by an exit site or tunnel infection, then exchange the infected catheter over a guidewire	B-III	[73]
	In such situations, an antimicrobial-impregnated catheter with an anti-infective intraluminal surface should be considered for catheter exchange	B-II	[73]
What are the unique aspects of treating pediatric patients with catheter-related infections?			
49.	Indications for catheter removal for children are similar to those for adults (see recommendations 30–32), unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site). However, the benefits of catheter removal must be weighed against the difficulty of obtaining alternate venous access for an individual patient	A-II	[89]
50.	Children treated without catheter removal should be closely monitored with clinical evaluation and additional blood cultures; the device should be removed if there is clinical deterioration or persistent or recurrent CRBSI	B-III	[89]
51.	In general, empirical antibacterial therapy for children with CRBSI should be similar to that for adults (see recommendations 21–23)	A-II	[89]
52.	Antibiotic lock therapy should be used for catheter salvage	B-II	[93]

	However, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter	C-III	
What are the unique aspects of managing patients receiving hemodialysis through catheters for whom catheter-related infection is suspected or proven?			
53.	Peripheral blood samples should be obtained for culture from vessels that are not intended for future use in creating a dialysis fistula (e.g., hand veins)	A-III	[265]
54.	When a peripheral blood sample cannot be obtained, blood samples may be drawn during hemodialysis from bloodlines connected to the CVC	B-II	[265]
55.	In patients with suspected CRBSI for whom blood cultures have been obtained and for whom antibiotic therapy has been initiated, antibiotic therapy can be discontinued if both sets of blood cultures have negative results and no other source of infection is identified	B-II	[265]
56.	When a peripheral blood sample cannot be obtained, no other catheter is in place from which to obtain an additional blood sample, there is no drainage from the insertion site available for culture, and there is no clinical evidence for an alternate source of infection, then positive results of culture performed on a blood sample obtained from a catheter should lead to continuation of antimicrobial therapy for possible CRBSI in a symptomatic hemodialysis patient	B-II	[100]
57.	The infected catheter should always be removed for patients with hemodialysis CRBSI due to *S. aureus*, *Pseudomonas* species, or *Candida* species and a temporary (nontunneled catheter) should be inserted into another anatomical site	A-II	[115]
	If absolutely no alternative sites are available for catheter insertion, then exchange the infected catheter over a guidewire	B-II	[265]
58.	When a hemodialysis catheter is removed for CRBSI, a long-term hemodialysis catheter can be placed once blood cultures with negative results are obtained	B-III	[265]
59.	For hemodialysis CRBSI due to other pathogens (e.g., gram-negative bacilli other than *Pseudomonas* species or coagulase-negative staphylococci), a patient can initiate empirical intravenous antibiotic therapy without immediate catheter removal. If the symptoms persist or if there is evidence of a metastatic infection, the catheter should be removed	B-II	[265]
	If the symptoms that prompted initiation of antibiotic therapy (fever, chills, hemodynamic instability, or altered mental status) resolve within 2–3 days and there is no metastatic infection, then the infected catheter can be exchanged over a guidewire for a new, long-term hemodialysis catheter	B-II	[111]
60.	Alternatively, for patients for whom catheter removal is not indicated (i.e., those with resolution of symptoms and bacteremia within 2–3 days after initiation of systemic antibiotics and an absence of metastatic infection), the catheter can be retained, and an antibiotic lock can be used as adjunctive therapy after each dialysis session for 10–14 days	B-II	[99]
61.	Empirical antibiotic therapy should include vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (e.g., third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination)	A-II	[265]
62.	Patients who receive empirical vancomycin and who are found to have CRBSI due to methicillin-susceptible *S. aureus* should be switched to cefazolin	A-II	[266]
63.	For cefazolin, use a dosage of 20 mg/kg (actual body weight), rounded to the nearest 500-mg increment, after dialysis	A-II	[104]

64.	A 4–6-week antibiotic course should be administered if there is persistent bacteremia or fungemia (i.e., >72 h in duration) after hemodialysis catheter removal or for patients with endocarditis or suppurative thrombophlebitis, and 6–8 weeks of therapy should be administered for the treatment of osteomyelitis in adults (figures 3 and 4)	B-II	[265]
65.	Patients receiving dialysis who have CRBSI due to vancomycin-resistant enterococci can be treated with either daptomycin (6 mg/kg after each dialysis session) or oral linezolid (600 mg every 12 h)	B-II	[168, 170]
66.	It is not necessary to confirm negative culture results before guidewire exchange of a catheter for a patient with hemodialysis-related CRBSI if the patient is asymptomatic	B-III	[265]
67.	Surveillance blood cultures should be obtained 1 week after completion of an antibiotic course for CRBSI if the catheter has been retained	B-III	[99]
	If the blood cultures have positive results, the catheter should be removed and a new, long-term dialysis catheter should be placed after additional blood cultures are obtained that have negative results	B-III	[265]
What is antibiotic lock therapy and how is it used to manage patients with catheter-related infection?			
Antibiotic lock therapy			
68.	Antibiotic lock is indicated for patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the goal	B-II	[114, 124]
69.	For CRBSI, antibiotic lock should not be used alone; instead, it should be used in conjunction with systemic antimicrobial therapy, with both regimens administered for 7–14 days	B-II	[114, 124]
70.	Dwell times for antibiotic lock solutions should generally not exceed 48 h before reinstallation of lock solution; preferably, reinstallation should take place every 24 h for ambulatory patients with femoral catheters (B-II). However, for patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session	B-II	[128]
	However, for patients who are undergoing hemodialysis the lock solution can be renewed after every dialysis session.	B-II	[128]
71.	Catheter removal is recommended for CRBSI due to *S. aureus* and *Candida* species, instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site)	A-II	[93, 114]
72.	For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or gram-negative bacilli and concurrent negative peripheral blood cultures, antibiotic lock therapy can be given without systemic therapy for 10–14 days	B-III	
73.	For vancomycin, the concentration should be at least 1000 times higher than the MIC (e.g., 5 mg/mL) of the microorganism involved	B-II	[121]
74.	At this time, there are insufficient data to recommend an ethanol lock for the treatment of CRBSI	C-III	[131]
Are there pathogen-specific treatment recommendations?			
Coagulase-negative *Staphylococcus* species			
75.	For uncomplicated CRBSI, treat with antibiotics for 5–7 days if the catheter is removed and for 10–14 days, in combination with antibiotic lock therapy, if the catheter is retained	B-III	
76.	Alternatively, patients with uncomplicated CRBSI can be observed without antibiotics if they have no intravascular or orthopedic hardware, the catheter is removed, and additional blood cultures (performed on samples collected when the patient is not receiving antibiotics) are obtained after catheter withdrawal to confirm the absence of bacteremia	C-III	

77.	Catheter-related bloodstream infection due to *Staphylococcus lugdunensis* should be managed similar to recommendations below for *S. aureus*.	B-II	[132].
Staphylococcus aureus			
78.	Patients with *S. aureus* CRBSI should have the infected catheter removed, and they should receive 4–6 weeks of antimicrobial therapy, unless they have exceptions listed in recommendation 80	B-II	[139, 144]
79.	Patients who are being considered for a shorter duration of therapy should have a transesophageal echocardiograph (TEE) obtained	B-II	[142, 150]
80.	Patients can be considered for a shorter duration of antimicrobial therapy (i.e., a minimum of 14 days of therapy) if the patient is not diabetic; if the patient is not immunosuppressed (i.e., not receiving systemic steroids or other immunosuppressive drugs, such as those used for transplantation, and is nonneutropenic); if the infected catheter is removed; if the patient has no prosthetic intravascular device (e.g., pacemaker or recently placed vascular graft); if there is no evidence of endocarditis or suppurative thrombophlebitis on TEE and ultrasound, respectively; if fever and bacteremia resolve within 72 h after initiation of appropriate antimicrobial therapy; and if there is no evidence of metastatic infection on physical examination and sign- or symptom-directed diagnostic tests	A-II	[135]
81.	If a TEE is performed, it should be done at least 5–7 days after onset of bacteremia to minimize the possibility of false-negative results	B-II	[152]
82.	Short-term catheters should be removed immediately for patients with *S. aureus* CRBSI	A-II	[139, 144]
83.	For *S. aureus* CRBSI involving long-term catheters, the catheters should be removed unless there are major contraindications (e.g., there is no alternative venous access, the patient has significant bleeding diathesis, or quality of life issues take priority over the need for reinsertion of a new catheter at another site)	A-II	[139, 144]
84.	In the rare circumstance that the catheter is retained for a patient with *S. aureus* CRBSI involving a long-term catheter, the patient should receive systemic and antibiotic lock therapy for 4 weeks	B-II	[99, 153]
	Catheter guidewire exchange should be done, if possible, and if it is done, an antimicrobial-impregnated catheter with an anti-infective intraluminal surface should be considered for catheter exchange	B-II	[73]
85.	An additional TEE should be obtained for patients with persistent fever or bloodstream infection >72 h after catheter withdrawal and initiation of appropriate antibiotic therapy if the patient had an earlier TEE obtained and it was without evidence of endocarditis and if there is no evidence of an undrained metastatic infection	A-II	[152]
86.	Patients whose catheter tip grows *S. aureus* but whose initial peripheral blood cultures have negative results should receive a 5–7-day course of antibiotics and close monitoring for signs and symptoms of ongoing infection, including additional blood cultures, as indicated	B-II	[66]
87.	Transthoracic echocardiograph findings are insufficient to rule out infective endocarditis	A-II	[134, 152]
88.	After a catheter has been removed as a result of *S. aureus* CRBSI, placement of a new catheter can proceed when additional blood cultures show no growth	B-II	[144]
Enterococcus species			
89.	Removal of infected short-term intravascular catheters is recommended	B-II	[166, 267]
90.	Removal of infected long-term catheters should be done in cases of insertion site or pocket infection, suppurative thrombophlebitis, sepsis, endocarditis, persistent bacteremia, or metastatic infection	B-II	[162]

91.	Ampicillin is the drug of choice for ampicillin-susceptible enterococci; vancomycin should be used if the pathogen is resistant to ampicillin	A-III	[164, 170]
92.	The role of combination therapy (i.e., a cell wall–active antimicrobial and an aminoglycoside) for treating enterococcal CRBSI without endocarditis is unresolved	C-II	[165] [170]
93.	A 7–14-day course of therapy is recommended for uncomplicated enterococcal CRBSI in which the long-term catheter is retained and antibiotic lock is used or when the short-term catheter is removed	C-III	[159]
94.	For enterococcal CRBSI, a TEE should be done if the patient has signs and symptoms that suggest endocarditis (e.g., new murmur or embolic phenomena); prolonged bacteremia or fever, despite appropriate antimicrobial therapy (e.g., bacteremia or fever >72 h after the onset of appropriate antibiotic therapy); radiographic evidence of septic pulmonary emboli; or the presence of a prosthetic valve or other endovascular foreign bodies	B-III	[160]
95.	Patients with enterococcal CRBSI involving a long-term catheter for whom the catheter is retained should have follow-up blood cultures and catheter removal if persistent bacteremia (>72 h after the initiation of appropriate antibiotic therapy) is detected	B-II	
96.	Antibiotic lock therapy should be used in addition to systemic therapy if the catheter is retained	C-II	[114, 124]
97.	In cases of CRBSI due to ampicillin- and vancomycin-resistant enterococci, linezolid or daptomycin may be used, based on antibiotic susceptibility results	B-II	[168, 170]
Gram-negative bacilli			
98.	Patients with possible CRBSI should receive empirical antibiotic therapy to cover gram-negative bacilli if they are critically ill, if they have sepsis, if they are neutropenic, if they have a femoral catheter in place, or if they have a known focus of gram-negative bacillary infection	A-II	[178]
99.	Patients who are critically ill with suspected CRBSI and who have recent colonization or infection with an MDR gram-negative pathogen should receive 2 antimicrobial agents of different classes with gram-negative activity as initial therapy; de-escalation of the initial regimen to a single appropriate antibiotic is recommended once culture and susceptibility results are available	A-II	[258, 268]
100.	In patients with gram-negative bacillary CRBSI involving a long-term catheter and persistent bacteremia or severe sepsis despite systemic and antibiotic lock therapy, the device should be removed, an evaluation for endovascular infection and metastatic infection should be pursued, and the duration of antibiotic therapy should be extended beyond 7–14 days on the basis of the findings of these studies	C-III	
Candida species			
101.	Catheters should be removed in cases of CRBSI due to *Candida* species	A-II	[188]
102.	For patients with candidemia and a short-term CVC for whom no source of candidemia is obvious, the catheter should be removed and the catheter tip sent for culture	A-II	[190, 193]
	Alternatively, for patients with limited venous access, exchange the catheter over a guidewire and perform catheter cultures	B-II	
	If the catheter is colonized with the same species of *Candida* as found in a percutaneous blood culture, the CVC should be removed	A-II	[190, 193]
103.	Antifungal therapy is recommended for all cases of CRBSI due to *Candida* species, including cases in which clinical manifestations of infection and/or candidemia resolve after catheter withdrawal and before initiation of antifungal therapy	A-II	[192]

Other gram-positive microorganisms			
104.	Diagnosis of CRBSI due to *Corynebacterium*, *Bacillus* and *Micrococcus* species requires at least 2 positive results of blood cultures performed on samples obtained from different sites	A-II	[269]
105.	For the management of these infections, catheter removal is indicated for patients with a short-term CVC, and it is also indicated for patients with an infected long-term catheter or implanted port, unless there are no alternative intravascular access sites	B-III	[202]
How should you manage suppurative thrombophlebitis?			
106.	Suppurative thrombophlebitis should be suspected in patients with persistent bacteremia or fungemia (i.e., patients whose blood culture results remain positive after 3 days of adequate antimicrobial therapy) without another source of intravascular infection (e.g., endocarditis)	A-II	[205, 206, 216]
107.	A diagnosis of suppurative thrombophlebitis requires the presence of positive blood culture results plus the demonstration of a thrombus by radiographic testing (e.g., computed tomography, ultrasonography, or other methods)	A-II	[216, 270]
108.	Surgical resection of the involved vein for patients with suppurative thrombophlebitis should be limited to patients with purulent superficial veins or patients in whom the infection extends beyond the vessel wall, as well as patients who experience failure of conservative therapy with an appropriate antimicrobial regimen	A-II	[208, 220, 271]
109.	The role of heparin use in this setting is unresolved	C-III	[220]
110.	Patients with suppurative thrombophlebitis due to CRBSI should receive a minimum of 3–4 weeks of antimicrobial therapy	B-III	
How are persistent bloodstream infection and infective endocarditis managed?			
111.	Catheter withdrawal is required in the management of catheter-related infective endocarditis	A-II	
112.	TEE should be done for patients with CRBSI who have any of the following: a prosthetic heart valve, pacemaker, or implantable defibrillator; persistent bacteremia or fungemia and/or fever >3 days after initiation of appropriate antibiotic therapy and catheter removal, in addition to a search for metastatic foci of infection, as indicated; and any case of *S. aureus* CRBSI in which duration of therapy less than 4–6 weeks is being considered	A-II	[134, 272, 273]
113.	Unless the clinical condition of the patient dictates otherwise, perform a TEE at least 1 week after the onset of bacteremia or fungemia and consider repeating the TEE for patients with a high index of suspicion for infective endocarditis in whom the initial TEE had negative findings	B-II	[152, 274]
114.	Assess for suppurative thrombophlebitis as noted above	B-II	
115.	Infective endocarditis cannot be ruled out by negative transthoracic echocardiograph findings alone	B-II	[150, 272, 273]
How would you detect and manage an outbreak of CRBSI?			
116.	When extrinsic contamination of infusate or catheter flush or lock solutions is suspected, public health authorities should be alerted and the suspected product should be set aside for culture	A-II	[227, 230]
117.	Establish a case definition for patients who are likely to have been exposed, including a time period, risk factors, and location of the patients	A-II	
118.	A case-control study should be used to establish risk factors for infection and to help elucidate potential sources of contamination	B-II	

119.	Establish relatedness of the suspected organisms by reviewing the antibiotic susceptibility patterns, followed by molecular fingerprinting, such as pulsed-field gel electrophoresis, polymerase chain reaction, or multilocus sequence typing	A-II
120.	Investigation of contamination involves a thorough review of potential breaches in infection control practices in the hospital pharmacy and at the point of delivery of the infusate; this requires interviews with health care personnel and observation of practices in the health care setting	A-II
121.	Cultures of potential point-source contaminants in the environment should be performed, including intravenous medications administered to patients	A-II
122.	During the investigation, heightened surveillance to detect new cases should be instituted	A-II
123.	Following identification of a source, there should be ongoing surveillance to confirm eradication of the source of infection	A-II

NOTE. cfu, colony-forming units; DTP, differential time to positivity; IDSA, Infectious Diseases Society of America.

ference on 8 occasions to complete the work of the guideline. The purpose of the meetings was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the Expert Panel participated in the preparation and review of the draft guideline. Feedback from external peer reviewers was obtained. All collaborating organizations were also asked to provide feedback and endorse the guidelines. The following organizations endorsed the guidelines: American Society of Nephrology, European Society of Clinical Microbiology and Infectious Diseases, Pediatric Infectious Diseases Society, Society for Critical Care Medicine, and the Society for Healthcare Epidemiology of America. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the Board of Directors prior to dissemination.

Guidelines and potential conflicts of interest. All members of the Expert Panel complied with the IDSA policy on potential conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided with the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Expert Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts of interest are listed in the Acknowledgements section.

Revision dates. At annual intervals, the Expert Panel Chair, the Standards and Practice Guidelines Committee liaison advisor, and the Chair of the Standards and Practice Guidelines Committee will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Expert Panel will be reconvened to discuss potential changes. When appropriate, the Expert Panel will recommend revision of the guideline to the Standards and Practice Guidelines Committee and the IDSA Board for review and approval.

EPIDEMIOLOGY AND PATHOGENESIS

Each year in the United States, hospitals and clinics purchase >150 million intravascular devices to administer intravenous fluids, medications, blood products, and parenteral nutrition fluids, to monitor hemodynamic status, and to provide hemodialysis [4]. Different types of intravascular catheters are currently being used (table 3), leading to a myriad of infectious complications (table 4). The focus of these guidelines is on the management of such complications, particularly CRBSI. In the United States, ~80,000 CVC-related bloodstream infections occur in intensive care units each year [5]. In addition, the risk of bloodstream infection varies according to the intravascular device [6], the type of and intended use for the catheter, the insertion site, the experience and education of the individual who installs the catheter, the frequency with which the catheter is accessed, the duration of catheter placement, the characteristics of the catheterized patient, and the use of proven preventative strategies [7, 8]. For the purpose of this guideline, short-term catheters are defined as those devices that are in situ for <14 days.

Most CRBSIs emanate from the insertion site, hub, or both [9]. For long-term catheters—particularly tunneled catheters—the catheter hub is a prominent source of microbes causing bloodstream infection [10]. In order of prevalence, the 4 groups of microbes that most commonly cause CRBSI associated with percutaneously inserted, noncuffed catheters are as follows: coagulase-negative staphylococci, *S. aureus, Candida* species, and enteric gram-negative bacilli. For surgically implanted catheters

Table 2. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.
Quality of Evidence	
I	Evidence from ⩾1 properly randomized, controlled trial.
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

NOTE. Adapted and reproduced with the permission of the Minister of Public Works and Government Services Canada [3].

and peripherally inserted CVCs, they are coagulase-negative staphylococci, enteric gram-negative bacilli, *S. aureus,* and *P. aeruginosa* [8].

CRBSIs independently increase hospital cost and length of stay [11–14]. Guidelines for the prevention of these infections have been published [7].

GUIDELINE RECOMMENDATIONS FOR THE MANAGEMENT OF INTRAVASCULAR CATHETER-RELATED INFECTION

DIAGNOSIS: WHEN AND HOW SHOULD CATHETER CULTURES AND BLOOD CULTURES BE DONE?

Intravenous Catheter Cultures: Recommendations

General

1. Catheter cultures should be done when a catheter is removed because of suspected CRBSI; catheter cultures should not be obtained routinely (A-II).
2. Qualitative broth culture of catheter tips is not recommended (A-II).
3. For CVCs, culture the catheter tip, not the subcutaneous segment (B-III).
4. For cultures of an anti-infective catheter tip, use specific inhibitors in the culture media (A-II).
5. Growth of >15 cfu from a 5-cm segment of the catheter tip by semiquantitative (roll-plate) culture or growth of $>10^2$ cfu from a catheter by quantitative (sonication) broth culture reflects catheter colonization (A-I).
6. When catheter-related infection is suspected and there is a catheter exit site exudate, swab the drainage to obtain samples for culture and Gram staining (B-III).

Short-term catheters, including arterial catheters

7. For short-term catheter tip cultures, the roll plate technique is recommended for routine clinical microbiological analysis (A-II).
8. For suspected pulmonary artery catheter-related infection, culture the introducer tip (A-II).

Long-term catheters

9. Semiquantitative growth of <15 cfus/plate of the same microbe from both the insertion site culture and catheter hub culture strongly suggests that the catheter is not the source of a bloodstream infection (A-II).
10. If a venous access subcutaneous port is removed because of suspected CRBSI, send the port to the microbiology laboratory for qualitative culture of the port reservoir contents, in addition to the catheter tip (B-II).

Evidence Summary

Clinical findings are unreliable for establishing the diagnosis of intravascular device–related infection because of their poor sensitivity and specificity. The most sensitive clinical finding, fever, has poor specificity. Inflammation or purulence around the insertion site has greater specificity but poor sensitivity [4, 15]. Blood cultures that are positive for *S. aureus*, coagulase-negative staphylococci, or *Candida* species, in the absence of other identifiable sources of infection, should increase the suspicion for CRBSI [16–18]. Improved symptomatology within 24 h after catheter removal suggests but does not prove that the catheter is the source of infection [19].

Laboratory criteria for diagnosing intravascular catheter-related infections are precise, but differences in definitions and

Table 3. Types of intravascular devices and comments on their use.

Type of intravascular device	Comment
Peripheral venous catheter	Usually inserted into the veins of the forearm or the hand; the most commonly used short-term intravascular device
Peripheral arterial catheter	For short-term use; commonly used to monitor hemodynamic status and to determine blood gas levels of critically ill patients; risk of bloodstream infection may approach that of CVCs
Midline catheter	Peripheral catheter (size, 7.6–20.3 cm) is inserted via the antecubital fossa into the proximal basilic or cephalic veins, but it does not enter central veins; it is associated with lower rates of infection, compared with CVCs
Short-term CVC	Most commonly used CVC; accounts for the majority of all catheter-related bloodstream infections
Pulmonary artery catheter	Inserted through a teflon introducer and typically remains in place for an average duration of only 3 days
Pressure-monitoring system	Used in conjunction with arterial catheter; associated with both epidemic and endemic nosocomial bloodstream infections
Peripherally inserted central catheter	Provides an alternative to subclavian or jugular vein catheterization; is inserted via the peripheral vein into the superior vena cava, usually by way of cephalic and basilar veins; similar risk of infection as CVCs in patients hospitalized in intensive care units
Long-term CVC	Surgically implanted CVC (e.g., Hickman, Broviac, or Groshong catheter) with the tunneled portion exiting the skin and a dacron cuff just inside the exit site; used to provide vascular access to patients who require prolonged chemotherapy, home-infusion therapy, or hemodialysis
Totally implantable device	A subcutaneous port or reservoir with self-sealing septum is tunneled beneath the skin and is accessed by a needle through intact skin; associated with low rates of infection

NOTE. CVC, central venous catheter

methodologies among various studies have made data difficult to compare [4, 18]. When a catheter segment is submitted for culture, it is adequate to culture only the catheter tip and not the subcutaneous portion of the catheter [20]. If a pulmonary artery catheter is removed because of suspected infection, the highest yield is to culture the introducer, rather than the catheter itself [21]. Semiquantitative (roll plate) or quantitative catheter culture techniques (luminal flushing or sonication methods) are the most reliable diagnostic methodologies and have much greater specificity than qualitative broth cultures [22–25]. A recently inserted catheter (i.e., one that had been indwelling for <14 days) is most commonly colonized from a skin microorganism along the external surface of the catheter. Thus, the roll-plate method has high sensitivity. Intraluminal spread of microbes from the catheter hub into the bloodstream is increasingly important for long-term catheters (i.e., those that have been indwelling ⩾14 days). In some studies, the roll-plate method was less sensitive than other methods that also sampled the internal surface of such catheters [10, 26], but other studies have not found this to be the case [27]. For subcutaneous ports, culture of the material inside the port reservoir is more sensitive than catheter tip culture for the diagnosis of CRBSI [28–30].

Antimicrobial coatings may lead to false-negative culture results [31, 32]. For silver sulfadiazine– or chlorhexidine-coated catheters, specific inhibitors can abrogate this effect, but this is not the case for minocycline- or rifampin-coated catheters [31, 32]. The specific components of the inhibitor solution to be used when culturing silver sulfadiazine or chlorhexidine can be found elsewhere [31].

Various methods have been used to diagnose a catheter-related infection without catheter removal. In one method, a moist cotton swab can be used to do a semiquantitative culture of a 3-cm radius around the catheter insertion site, and alginate swabs can be used to sample the inner surface of each catheter hub (1 swab per hub). Swab samples are streaked on blood agar plates. Growth of >15 cfu/plate of the same microbe from the insertion site swab sample and hub swab sample cultures and from a peripheral blood culture suggests CRBSI [33]. This approach also has good negative predictive value for CRBSI when <15 cfu/plate are detected on insertion site and hub swab sample cultures.

Blood Cultures: Recommendations

11. Obtain blood cultures prior to initiation of antibiotic therapy (figure 1) **(A-1)**

Table 4. Commonly used clinical definitions of intravascular catheter-related infections.

Infection	Definition
Catheter colonization	Significant growth of ⩾1 microorganism in a quantitative or semiquantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub
Phlebitis	Induration or erythema, warmth, and pain or tenderness along the tract of a catheterized or recently catheterized vein
Exit site infection	
Microbiological	Exudate at catheter exit site yields a microorganism with or without concomitant bloodstream infection
Clinical	Erythema, induration, and/or tenderness within 2 cm of the catheter exit site; may be associated with other signs and symptoms of infection, such as fever or purulent drainage emerging from the exit site, with or without concomitant bloodstream infection[a]
Tunnel infection	Tenderness, erythema, and/or induration >2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter (e.g., Hickman or Broviac catheter), with or without concomitant bloodstream infection[a]
Pocket infection	Infected fluid in the subcutaneous pocket of a totally implanted intravascular device; often associated with tenderness, erythema, and/or induration over the pocket; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection[a]
Bloodstream infection	
Infusate related	Concordant growth of a microorganism from infusate and cultures of percutaneously obtained blood cultures with no other identifiable source of infection
Catheter related	Bacteremia or fungemia in a patient who has an intravascular device and >1 positive blood culture result obtained from the peripheral vein, clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for bloodstream infection (with the exception of the catheter). One of the following should be present: a positive result of semiquantitative (>15 cfu per catheter segment) or quantitative (>10^2 cfu per catheter segment) catheter culture, whereby the same organism (species) is isolated from a catheter segment and a peripheral blood culture; simultaneous quantitative cultures of blood with a ratio of >3:1 cfu/mL of blood (catheter vs. peripheral blood); differential time to positivity (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 h earlier than a culture of simultaneously drawn peripheral blood of equal volume). Note that this definition differs from the definition of central line–associated bloodstream infection used for infection-control surveillance activities.

NOTE. Adapted in part from Pearson [18]. cfu, colony forming units.

[a] For surveillance purposes, patients with positive results of blood culture would be classified as having central line–associated bloodstream infection.

12. Where available, a phlebotomy team should draw the blood samples for culture (A-II).

13. Skin preparation for percutaneously drawn blood samples should be carefully done with either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%), rather than povidone-iodine; allow adequate skin contact and drying time to mitigate blood culture contamination (A-I).

14. If a blood sample is obtained through a catheter, clean the catheter hub with either alcohol or tincture of iodine or alcoholic chlorhexidine (>0.5%) and allow adequate drying time to mitigate blood culture contamination (A-I).

15. For suspected CRBSI, paired blood samples drawn from the catheter and from a peripheral vein should be cultured before initiation of antimicrobial therapy, and the bottles should be appropriately marked to reflect the site from which the cultures were obtained (A-II).

16. If a blood sample for culture cannot be drawn from a peripheral vein, it is recommended that ⩾2 blood samples should be obtained through different catheter lumens (B-III). It is unclear whether blood samples for culture should be obtained through all catheter lumens in such circumstances (C-III).

17. A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood sample culture and from the catheter tip (A-I) or that 2 blood samples for culture be obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CRBSI criteria for quantitative blood cultures or DTP (A-II). Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood sample obtained from the second lumen should be considered to indicate possible CRBSI (B-II). In this circumstance, the interpretation of blood cultures that meet the DTP criteria is an unresolved issue (C-III).

18. For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood

samples obtained from a peripheral vein best defines CRBSI (A-II).

19. For DTP, growth of microbes from blood drawn from a catheter hub at least 2 h before microbial growth is detected in blood samples obtained from a peripheral vein best defines CRBSI (A-II).

20. Quantitative blood cultures and/or DTP should be done before initiation of antimicrobial therapy and with the same volume of blood per bottle (A-II).

21. Evidence is insufficient to recommend that blood cultures be routinely obtained after discontinuation of antimicrobial therapy for CRBSI (C-III).

Evidence Summary

Blood culture general issues. Although catheter colonization with accompanying systemic signs of infection suggests catheter-related infection, a definitive diagnosis of CRBSI requires positive percutaneous blood culture results with concordant microbial growth from the catheter tip or catheter-drawn cultures that meet the above-described quantitative culture or DTP criteria. The accuracy of all diagnostic microbiologic methods greatly increases with increasing pretest probability. Thus, diagnostic tests for vascular catheter-related infection should not be done unless there is a high index of suspicion. Overall, quantitative blood cultures are the most accurate method by which to diagnose CRBSI [34, 35]. No single test is clearly superior for short-term CRBSI diagnosis. For diagnosis of CRBSI in patients with long-term catheters, quantitative blood cultures are the most accurate test, but DTP also has a high degree of accuracy. Neither method requires catheter removal. If a blood sample for culture cannot be obtained from a peripheral vein, ⩾2 catheter blood samples for culture should be drawn through different catheter lumens [36].

It is important to remember that the definition of CRBSI used in the current document, which deals with management of infections related to intravascular devices, differs from surveillance definitions used to define central line–associated bloodstream infection [37].

Blood culture contamination issues, peripheral blood samples, and paired peripheral and catheter-drawn blood samples. Contamination rates are lower if a dedicated phlebotomy team collects the blood samples for culture [38]. Skin preparation with either alcohol, alcoholic chlorhexidine (>0.5%), or tincture of iodine (10%) leads to lower blood culture contamination rates than does the use of povidone-iodine [39, 40]. Contamination rates among blood samples obtained through newly inserted intravenous catheters are higher than contamination rates among blood samples obtained from peripheral veins [41, 42]. Blood samples obtained through catheters that are in use are associated with a higher rate of false-positive results, compared with cultures of percutaneous blood samples [43]. Thus, there is higher specificity and a greater positive predictive value when blood samples are obtained from a peripheral vein for culture, compared with when blood samples are obtained through catheters for culture [44, 45]. Negative predictive values are excellent for cultures of blood samples obtained from either a peripheral vein or a catheter.

DTP for CVC versus peripheral blood cultures. DTP uses continuous blood culture monitoring for growth (e.g., radiometric methods) and compares the DTP for qualitative blood culture samples obtained from the catheter and from a peripheral vein. The greater the inoculum of microbes inoculated into blood culture bottles, the shorter the incubation required to detect microbial growth [46].

When studied among patients with cancer and patients hospitalized in intensive care units who had both long-term and short-term catheters, this method has been shown to have accuracy comparable to that of quantitative blood cultures, as well as greater cost-effectiveness [35, 47–49]. Most microbiology laboratories do not perform quantitative blood cultures, but many laboratories are able to determine DTP. DTP may not discriminate between CRBSI and non-CRBSI for patients who are already receiving antibiotics [50].

Rapid diagnostic techniques. PCR to target bacterial 16S ribosomal DNA is sensitive and specific for diagnosing catheter-related infection but is not routinely used in clinical microbiology laboratories [51].

HOW SHOULD CATHETER-RELATED INFECTIONS BE MANAGED IN GENERAL?

Recommendations

22. When denoting the duration of antimicrobial therapy, day 1 is the first day on which negative blood culture results are obtained (C-III).

23. Vancomycin is recommended for empirical therapy in heath care settings with an increased prevalence of methicillin-resistant staphylococci; for institutions with a preponderance of MRSA isolates that have vancomycin MIC values >2 μg/mL, alternative agents, such as daptomycin, should be used (A-II).

24. Linezolid should not be used for empirical therapy (i.e., in patients suspected but not proven to have CRBSI) (A-I).

25. Empirical coverage for gram-negative bacilli should be based on local antimicrobial susceptibility data and the severity of disease (e.g., a fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination, with or without an aminoglycoside) (A-II).

26. Empirical combination antibiotic coverage for MDR gram-negative bacilli, such as *P. aeruginosa*, should be used when CRBSI is suspected among neutropenic patients, severely ill patients with sepsis, or patients known to be colonized with such pathogens, until the culture and susceptibility data are

Table 5. Intravenous antimicrobial treatment of intravenous catheter-related bloodstream infection in adults according to the specific pathogen isolated.

Pathogen	Preferred antimicrobial agent	Example, dosage[a]	Alternative antimicrobial agent	Comment
Gram-positive cocci				
Staphylococcus aureus				
Meth susceptible	Penicillinase-resistant Pen[b]	Naf or Oxa, 2 g q4h	Cfaz, 2 g q8h; or Vm, 15 mg/kg q12h	Penicillinase-resistant Pen or Csps are preferred to Vm.[c] For patients receiving hemodialysis, administer Cfaz 20 mg/kg (actual weight), round to nearest 500-mg increment, after dialysis
Meth resistant[e]	Vm	Vm, 15 mg/kg q12h	Dapto, 6–8 mg/kg per day, or linezolid; or Vm plus (Rif or Gm); or TMP-SMZ alone (if susceptible)	Strains of *S. aureus* with reduced susceptibility or resistance to Vm have been reported; strains resistant to linezolid and strains resistant to Dapto have been reported
Coagulase-negative staphylococci				
Meth susceptible	Penicillinase-resistant Pen	Naf or Oxa, 2 g q4h	First-generation Csp or Vm or TMP-SMZ (if susceptible)	Vm has dosing advantages over Naf and Oxa, but the latter are preferred because of concerns about increasing Vm resistance
Meth resistant	Vm	Vm, 15 mg/kg iv q12h	Dapto 6 mg/kg per day, linezolid, or Quin/Dalf	For adults <40 kg, linezolid dose should be 10 mg/kg; strains resistant to linezolid have been reported
Enterococcus faecalis/Enterococcus faecium				
Amp susceptible	Amp or (Amp or Pen) ± aminoglycoside	Amp, 2 g q4h or q6h; or Amp ± Gm, 1 mg/kg q8h	Vm	Vm may have dosing advantages over Amp, but there are concerns about Vm resistance
Amp resistant, Vm susceptible	Vm ± aminoglycoside	Vm, 15 mg/kg iv q12h ± Gm, 1 mg/kg q8h	Linezolid or Dapto 6 mg/kg per day	Quin/Dalf is not effective against *E. faecalis*
Amp resistant, Vm resistant	Linezolid or Dapto	Linezolid, 600 mg q12h; or Dapto 6 mg/kg per day	Quin/Dalf 7.5 mg/kg q8h	Susceptibility of Vm-resistant enterococci isolates varies; Quin/Dalf is not effective against *E. faecalis*
Gram-negative bacilli[d]				
Escherichia coli and *Klebsiella* species				
ESBL negative	Third-generation Csp	Ctri, 1–2 g per day	Cipro or Atm	Susceptibility of strains varies
ESBL positive	Carbapenem	Erta, 1 g per day; Imi, 500 mg q6h; Mero, 1 g q8h; or doripenem, 500 mg q8h	Cipro or Atm	Susceptibility of strains varies
Enterobacter species and *Serratia marcescens*	Carbapenem	Erta, 1 g per day; Imi, 500 mg q6h; Mero, 1 g q8h	Cefepime or Cipro	Susceptibility of strains varies
Acinetobacter species	Amp/Sulb or carbapenem	Amp/Sulb, 3 g q6h; or Imi, 500 mg q6h; Mero, 1 g q8h	…	Susceptibility of strains varies

Stenotrophomonas maltophilia	TMP-SMZ	TMP-SMZ, 3–5 mg/kg q8h	Tic and Clv	…
Pseudomonas aeruginosa	Fourth-generation Csp or carbapenem or Pip and Tazo with or without aminoglycoside	Cefepime, 2 g q8h; or Imi, 500 mg q6h; or Mero, 1 g q8h; or Pip and Tazo, 4.5 g q6h, Amik, 15 mg/kg q24h or Tobra 5–7 mg/kg q24h	…	Susceptibility of strains varies
Burkholderia cepacia	TMP-SMZ or carbapenem	TMP-SMZ, 3–5 mg/kg q8h; or Imi, 500 mg q6h; or Mero, 1 g q8h	…	Other species, such as *B. acidovorans* and *B. pickieii,* may be susceptible to same antimicrobial agents
Fungi				
Candida albicans or other *Candida* species	Echinocandin or fluconazole (if organism is susceptible)	Caspo, 70-mg loading dose, then 50 mg per day; micafungin, 100 mg per day; anidulafungin, 200 mg loading dose followed by 100 mg per day; or fluconazole, 400–600 mg per day	Lipid AmB preparations	Echinocandin should be used to treat critically ill patients until fungal isolate is identified
Uncommon pathogens				
Corynebacterium jeikeium (group JK)	Vm	Vm, 15 mg/kg q12h	Linezolid (based on in vitro activity)	Check susceptibilities for other corynebacteria
Chryseobacterium (Flavobacterium) species	Fluoroquinolone, such as Lvfx	Lvfx 750 mg q24h	TMP-SMZ or Imi or Mero	Based on in vitro activity.
Ochrobacterium anthropi	TMP-SMZ or fluoroquinolone	TMP-SMZ, 3–5 mg/kg q8h; or Cpfx, 400 mg q12h	Imi, Mero, Erta, or Dori plus aminoglycoside	…
Malassezia furfur	AmB	…	Voriconazole	Intravenous lipids should be discontinued; some experts recommend removal of catheter
Mycobacterium species	Susceptibility varies by species	…	…	Different species have wide spectra of susceptibility to antimicrobials [256, 257]

NOTE. See *S. aureus* section of the text regarding important antibiotic management issues concerning linezolid. AmB, amphotericin B; Amp, ampicillin; Atm, aztreonam; Cfaz, cefazolin; cfur, cefuroxime; Clv, clavulanate; Cpfx, ciprofloxacin; Csp, cephalosporin; Ctri, ceftriaxone; Czid, ceftazidime; Erta, ertapenem; Gm, gentamicin; Imi, Imipenem; iv, intravenous; Ket, ketoconazole; Lvfx, levofloxacin; Mero, meropenem; Meth, methicillin; Mez, mezlocillin; Naf, nafcillin; Oxa, oxacillin; Pen, penicillin; PenG, penicillin G; po, by mouth; Pip, piperacillin; Quin/Dalf, quinupristin/dalfopristin; Rif, rifampin; Sulb, sulbactam; Tic, ticarcillin; Tm, tobramycin; TMP-SMZ, trimethoprim-sulfamethoxazole; Vm, vancomycin.

[a] Initial antibiotic dosages for adult patients with normal renal and hepatic function and no known drug interactions. Fluoroquinolones should not be used for patients <18 years of age (see the section of the text devoted to treating pediatric infection [256, 257]).

[b] Pen, if the strain is susceptible.

[c] Some clinicians will add an aminoglycoside for the first 5 days of therapy.

[d] Pending susceptibility results for the isolate.

available and de-escalation of antibiotic therapy can be performed (A-II).

27. In addition to coverage for gram-positive pathogens, empirical therapy for suspected CRBSI involving femoral catheters in critically ill patients should include coverage for gram-negative bacilli and *Candida* species (A-II).

28. Empirical therapy for suspected catheter-related candidemia should be used for septic patients with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, femoral catheterization, or colonization due to *Candida* species at multiple sites (B-II).

29. For empirical treatment of suspected catheter-related candidemia, use an echinocandin or, for selected patients, fluconazole (A-II). Fluconazole can be used for patients without azole exposure in the previous 3 months and in health care settings where the risk of *C. krusei* or *C. glabrata* infection is very low (A-III).

30. Antibiotic lock therapy should be used for catheter salvage (B-II); however, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter (C-III).

31. Four to 6 weeks of antibiotic therapy should be administered to patients with persistent fungemia or bacteremia after catheter removal (i.e., occurring >72 h after catheter removal) (A-II for *S. aureus* infection; C-III for infection due to other pathogens), to patients who are found to have infective endocarditis or suppurative thrombophlebitis, and to pediatric patients with osteomyelitis; 6–8 weeks of therapy should be used for the treatment of osteomyelitis in adults (figures 2 and 3) (A-II).

32. Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite >72 h of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S. aureus, P. aeruginosa,* fungi, or mycobacteria (A-II). Short-term catheters should be removed from patients with CRBSI due to gram-negative bacilli, *S. aureus,* enterococci, fungi, and mycobacteria (A-II).

33. For patients with CRBSI for whom catheter salvage is attempted, additional blood cultures should be obtained, and the catheter should be removed if blood culture results (e.g., 2 sets of blood cultures obtained on a given day; 1 set of blood cultures is acceptable for neonates) remain positive when blood samples are obtained 72 h after the initiation of appropriate therapy (B-II).

34. For long-term and short-term CRBSI due to less virulent microbes that are difficult to eradicate (e.g., *Bacillus* species, *Micrococcus* species, or Propionibacteria), catheters should generally be removed after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least 1 blood culture sample drawn from a peripheral vein (B-III).

35. In uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus, P. aeruginosa, Bacillus* species, *Micrococcus* species, Propionibacteria, fungi, or mycobacteria, because of the limited access sites in many patients who require long-term intravascular access for survival (e.g., patients undergoing hemodialysis or with short-gut syndrome), treatment should be attempted without catheter removal, with use of both systemic and antimicrobial lock therapy (B-II).

36. After a positive blood culture result is reported that may represent CRBSI, automated standardized treatment advice can be formulated to improve compliance with Infectious Diseases Society of America (IDSA) guidelines (B-II).

37. Urokinase and other thrombolytic agents are not recommended as adjunctive therapy for patients with CRBSI (B-I).

38. If a catheterized patient has a single positive blood culture that grows coagulase-negative *Staphylococcus* species, then additional cultures of blood samples obtained through the suspected catheter and from a peripheral vein should be performed before the initiation of antimicrobial therapy and/or catheter removal to be certain that the patient has true bloodstream infection and that the catheter is the likely source (A-II).

Evidence Summary

Antibiotic therapy for catheter-related infection is often initiated empirically. The initial choice of antibiotics will depend on the severity of the patient's clinical disease, the risk factors for infection, and the likely pathogens associated with the specific intravascular device (figure 1 and table 5). In the largest published comparative trial of CRBSI treatment involving antimicrobial therapy and catheter removal, 149 (88%) of 169 patients had a successful microbiologic outcome when evaluated 1–2 weeks after the end of treatment, and there was an 83% microbiologic success rate among 98 cases of CRBSI due to *S. aureus* [52]. Coagulase-negative staphylococci are the most common cause of catheter-related infection. Most of these pathogens exhibit methicillin resistance, and this should be considered when choosing empirical therapy for catheter-related infection [53, 54]. Vancomycin is associated with a lower clinical success rate in treating MRSA bacteremia if the MIC is $\geqslant 2$ μg/mL [55, 56]. Standardized treatment advice can be formulated for each CRBSI on the basis of these guidelines. When such standardized treatment advice is automatically delivered to treating physicians, compliance with the guidelines increases significantly [57].

There are no compelling data to support specific recommendations for the duration of therapy for device-related infection. However, the Expert Panel's recommendations are pre-

sented in figures 1–4. Management of CRBSI should be distinguished on the basis of the removal or retention of the catheter, and a distinction should be made between complicated CRBSI, in which there is suppurative thrombophlebitis, endocarditis, osteomyelitis, or possible metastatic seeding, and uncomplicated CRBSI (figures 1–4). Intravenous administration of thrombolytic agents, such as urokinase, should not be used as adjunctive treatment for CRBSI [58, 59].

WHAT ARE THE UNIQUE ASPECTS OF TREATING PATIENTS WHO HAVE SHORT-TERM PERIPHERAL VENOUS CATHETERS?

Recommendations

39. Peripheral intravenous catheters with associated pain, induration, erythema, or exudate should be removed (A-I).

40. Any exudate at the insertion site should be submitted for Gram staining, routine culture, and additional culture for fungi and acid-fast organisms, as indicated, when assessing immunocompromised patients (A-II).

Evidence Summary

Phlebitis involving short-term, peripheral intravenous catheters is often unrelated to catheter-related infection [60, 61]. The risk of CRBSI, with or without suppurative thrombophlebitis, from such catheters is very low [6].

WHAT ARE THE UNIQUE ASPECTS OF TREATING PATIENTS WITH NONTUNNELED CVCS AND ARTERIAL CATHETERS?

Recommendations

41. For patients who are hospitalized in the intensive care unit with a new onset of fever but without severe sepsis or evidence of bloodstream infection, obtain blood samples for culture from the nontunneled CVC, the arterial catheter (if present), and percutaneously, instead of performing routine catheter removal (B-II). Consider culture of samples obtained from the insertion site and catheter hubs, if available, as noted above (A-II).

42. The CVC and arterial catheter, if present, should be removed and cultured if the patient has unexplained sepsis or erythema overlying the catheter insertion site or purulence at the catheter insertion site (B-II).

43. For patients with unexplained fever, if blood culture results are positive, the CVC or arterial catheter was exchanged over a guidewire, and the catheter tip has significant growth,

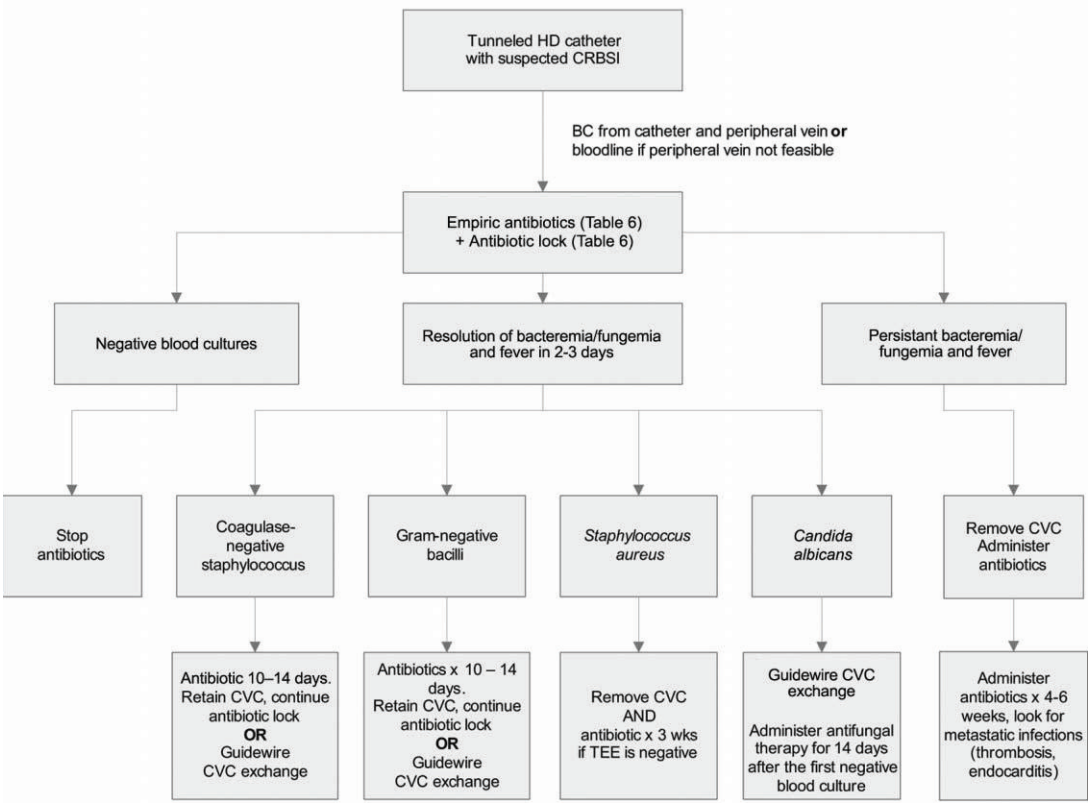

Figure 4. Catheter-related blood stream infection (CRBSI) among patients who are undergoing hemodialysis (HD) with tunneled catheters. BC, blood culture; CVC, central venous catheter; TEE, transesophageal echocardiograph.

then the catheter should be removed and a new catheter placed in a new site (B-II).

Evidence Summary

Diagnosis and management of illness among patients with a nontunneled CVC or arterial catheter and unexplained fever are summarized in table 1 and figures 1 and 2. CVCs in patients with fever and mild-to-moderate disease should not routinely be removed, because the majority of the catheters from patients with suspected catheter-related infection are sterile [62]. Recent studies suggest that the risk of arterial CRBSI approaches that associated with short-term CVCs [63–65].

One study found that 1 in 4 patients with *S. aureus* colonization of an intravascular catheter subsequently developed *S. aureus* bacteremia if they did not receive immediate anti-staphylococcal antibiotics [66]. Similarly, other studies have found that *S. aureus* and *Candida* catheter colonization, compared with catheter colonization due to enterococci or gram-negative bacilli, was more likely to be associated with CRBSI and that CRBSIs due to *S. aureus* and *Candida* species were more likely to be associated with complications than CRBSIs due to enterococci or gram-negative bacilli [26, 67].

The diagnostic evaluation for new onset of fever in patients hospitalized in the intensive care unit is a daily problem for intensive care physicians [68]. New onset of fever often leads to the removal of intravascular catheters and the reinsertion of new catheters over a guidewire or into another site. However, few of these patients have a catheter-related infection [33, 50, 69]. For hemodynamically stable patients without documented bloodstream infection and without a prosthetic valve, pacemaker, or recently placed vascular graft, systematic catheter removal may not be necessary for new onset of fever. Catheter removal only when bloodstream infection is documented or when there is hemodynamic instability reduces unnecessary catheter removal [70]. Nevertheless, if a catheter is to be removed for suspected catheter-related infection and the patient is at high risk for mechanical complications during catheter reinsertion, a guidewire exchange of the catheter can decrease the risk of mechanical complications [71]. The tip of the removed catheter should be sent for culture. If the tip has positive culture results, this newly inserted catheter should be replaced a second time, because bacterial contamination of the newly inserted catheter often occurs.

WHAT ARE THE UNIQUE ASPECTS OF TREATING PATIENTS WITH LONG-TERM CVCS OR IMPLANTED CATHETER-RELATED INFECTIONS THAT ARE NOT ASSOCIATED WITH HEMODIALYSIS CATHETERS?

Recommendations

44. Patients with tunnel infection or port abscess require removal of the catheter, incision and drainage if indicated, and 7–10 days of antibiotic therapy (A-II) in the absence of concomitant bacteremia or candidemia.

45. For patients with suspected exit site infection, obtain cultures of any drainage from the exit site and blood cultures (A-II).

46. Uncomplicated exit site infections (i.e., those without systemic signs of infection, positive blood culture results, or purulence) should be managed with topical antimicrobial agents on the basis of the exit site culture results (e.g., mupirocin ointment for *S. aureus* infection and ketoconazole or lotrimin ointment for *Candida* infection) (B-III).

47. If an uncomplicated exit site infection fails to resolve with topical therapy or if it is accompanied by purulent drainage, then systemic antibiotics should be administered on the basis of the antimicrobial susceptibility of the causative pathogen; the catheter should be removed if treatment with systemic antibiotics fails (B-II).

48. If other vascular sites are unavailable and/or the patient is at increased risk for bleeding diathesis in the setting of CRBSI not complicated by an exit site or tunnel infection, then exchange the infected catheter over a guidewire (B-III). In such situations, an antimicrobial-impregnated catheter with an antiinfective intraluminal surface should be considered for catheter exchange (B-II).

Evidence Summary

Surgically implantable intravascular devices consist of either a tunneled silicone catheter (e.g., Hickman, Broviac, or Groshong catheters; CR Bard) or a subcutaneously implanted port reservoir (e.g., Port-A-Cath; Deltec). Because the removal of such devices is often a management challenge, it is important to be sure that one is dealing with true CRBSI rather than with contaminated blood cultures (e.g., contaminated due to coagulase-negative staphylococci), catheter colonization without concomitant bloodstream infection, or fever from another source (figures 1 and 3). Microbiologic data suggestive of true CRBSI caused by potential skin flora rather than contamination include the following: multiple blood samples with positive culture results obtained from different sites; quantitative blood cultures performed on samples drawn from a catheter with growth of >15 cfu/mL of blood or isolation of the same organism from a catheter culture and a percutaneous blood culture, especially if a culture performed on blood drawn from the catheter shows growth at least 2 h earlier than a culture performed on blood drawn from a peripheral vein [72]. Although several studies suggest that catheter exchange over a guidewire can be used successfully to manage CRBSI associated with long-term catheters [73], most of these were small, uncontrolled studies with poor definitions, and none of these studies used antimicrobial catheters as a replacement for the infected catheter [73–77]. Management of CRBSI for patients

with a long-term CVC or implantable device is summarized in tables 5 and 6 and in figure 3.

WHAT ARE THE UNIQUE ASPECTS OF TREATING PEDIATRIC PATIENTS WITH CATHETER-RELATED INFECTION?

Recommendations

49. Indications for catheter removal for children are similar to those for adults (see recommendations 30–32), unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site). However, the benefits of catheter removal must be weighed against the difficulty of obtaining alternate venous access for an individual patient (A-II).

50. Children treated without catheter removal should be closely monitored with clinical evaluation and additional blood cultures; the device should be removed if there is clinical deterioration or persistent or recurrent CRBSI (B-III).

51. In general, empirical antibacterial therapy for children with CRBSI should be similar to that for adults (see recommendations 21–23) (A-II).

52. Antibiotic lock therapy should be used for catheter salvage (B-II); however, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter (C-III).

Evidence Summary

The pediatric population is diverse, and the probability of infection varies with patient risk factors, the type and location of the device, and the nature of the infusate [78, 79]. Among premature infants, birth weight is inversely proportional to the risk of infection, with infants who have extremely low birth weight (1000–1500 g) having an increased risk, compared with infants who have very low birth weight [80]. Most nosocomial bloodstream infections among pediatric patients are related to the use of an intravascular device [81], and in critically ill neonates, the incidence of CRBSI can be as high as 18 cases per 1000 catheter-days [82]. Most CRBSIs among children are caused by coagulase-negative staphylococci (which account for 34% of cases), followed by *S. aureus* (25%) [83]. Among neonates, coagulase-negative staphylococci account for 51% of CRBSIs, followed by *Candida* species, enterococci, and gram-negative bacilli [78, 84]. Infants with short-gut syndrome, a disorder that is clinically defined by malabsorption, diarrhea, steatorrhea, fluid and electrolyte disturbances, and malnutrition, often resulting from anatomic removal of bowel during the newborn period due to necrotizing enterocolitis, are more likely to have CRBSI due to gram-negative bacilli [85].

Several problems arise when the clinical and laboratory definitions of infection established for adults are applied to children [18, 86]. Although specific pediatric blood culture devices are commercially available, difficulty in obtaining blood samples and concerns about drawing a large volume of blood may result in lower volumes of blood being submitted for culture, which would reduce the negative predictive value of the culture. Often, only results from blood samples obtained via the catheter are available to guide patient management. Peripheral cultures are not often performed when catheter cultures are obtained, because venipuncture can be difficult for infants and young children. A recent study suggests that, among pediatric oncology patients with a double lumen CVC, catheter-related infection can be diagnosed by a ⩾5-fold difference in colony count between the 2 lumens; this method has 62% sensitivity, 93% specificity, and 92% positive predictive value, compared with a comparison between the colony count for 1 lumen and for a peripheral blood sample [87]. However, validation in a prospective study is needed to confirm these findings. In addition, placement of catheters or changing a catheter over a guidewire is difficult for young children, and catheter removal for diagnostic purposes is often not done out of concern over losing access (figure 1). Because of these limitations, definitive CRBSI can often not be diagnosed in children. In these circumstances, many physicians treat their patients as if they had presumed CRBSI.

Although indications for catheter removal among children should follow the recommendations for adults, because of greater vascular access difficulties in children, it is often necessary to attempt CRBSI treatment without catheter removal. Several studies have reported successful CRBSI management among children without catheter removal [88–90]. Such children should be closely monitored, and the device should be removed in the event of clinical deterioration or recurrence of CRBSI. In contrast, treatment of catheter-associated fungemia without removal of the catheter has a low success rate and is associated with higher mortality [91, 92]. Recent reports involving children with *Candida* CRBSI found that the addition of antifungal lock therapy led to a high cure rate without catheter removal, but there are insufficient data to recommend routine catheter salvage using this approach for this infection unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site) [93–95].

Antimicrobial agents that are appropriate for infants and children and the recommended dosages of specific agents, by patient age and weight, are summarized in table 6. Antibiotics should be administered through the involved catheter. In contrast to the recommendation for adults, empirical antifungal coverage in critically ill patients with femoral catheters is not recommended for children. Antifungal therapy should be initiated when yeast is isolated from a blood culture or when the suspicion of fungemia is high [90, 96–98]. The selection of an appropriate antifungal agent depends on the organism that is isolated and the drug characteristics, including available pe-

Table 6. Antibiotic doses for pediatric patients.

Drug	Intravenous dosing	Maximum daily dosage	Comments
Amikacin	Neonates: 0–4 weeks of age and<1200 g, 7.5 mg/kg every 18–24 h; postnatal age ≤7 days and 1200–2000 g, 7.5 mg/kg every 12 h; postnatal age ≤7 days and >2000 g, 7.5–10 mg/kg every 12 h; postnatal age >7 days and 1200–2000 g, 7.5–10 mg/kg every 8–12 h; postnatal age >7 days and >2000 g, 10 mg/kg every 8 h Infants and children: 15–22.5 mg/kg/day divided every 8 h	…	Some consultants recommend initial doses of 30 mg/kg/day divided every 8 h in patients whose serum levels document the need (i.e., cystic fibrosis or febrile neutropenic patients).
Ampicillin	Neonates: postnatal age ≤7 days and ≤2000 g: 50 mg/kg/day divided every 12 h; postnatal age ≤7 days and >2000 g, 75 mg/kg/day divided every 8 h; postnatal age >7 days and <1200 g, 50 mg/kg/day divided every 12 h; postnatal age >7 days and 1200–2000 g, 75 mg/kg/day divided every 8 h; postnatal age >7 days and >2000 g, 100 mg/kg/day divided every 6 h Infants and children: 100–200 mg/kg/day divided every 6 h	12 g	…
Ampicillin-sulbactam	Infants aged ≥1 month: 100–150 mg ampicillin/kg/day divided every 6 h Children: 100–200 mg ampicillin/kg/day divided every 6 h	8 g of ampicillin	…
Anidulafungin	Children 2– 17 years of age[a]: 1.5 mg/kg/day	100 mg	Experience in children is limited.
Caspofungin	Intravenous dosing: infants and children aged 3 months–17 years: loading dose of 70 mg/m^2/day on day 1 followed by 50 mg/m^2/day thereafter	70 mg; may increase to 70 mg/m^2/day if clinical response is inadequate	…
Cefazolin	Intravenous dosing: neonates, postnatal age ≤7 days: 40 mg/kg/day divided every 12 h; postnatal age >7 days and ≤2000 g: 40 mg/kg/day divided every 12 h; postnatal age >7 days and >2000 g: 60 mg/kg/day divided every 8 h Infants and children: 50 mg/kg/day divided every 8 h	…	…
Cefepime	Neonates ≤14 days of age: 30 mg/kg every 12 h Infants > 14 days of age[b] and Children ≤40 kg in weight: 50 mg/kg every 12 h	…	No recommendation available for infants 2 weeks to 2 months of age.
Ceftazidime	Neonates: 0–4 weeks of age and <1200 g, 100 mg/kg/day divided every 12 h; postnatal age ≤7 days and 1200–2000 g, 100 mg/kg/day divided every 12 h; postnatal age ≤7 days and >2000 g: 100–150 mg/kg/day divided every 8–12 h; postnatal age >7 days and ≥1200 g, 150 mg/kg/day divided every 8 h Infants and children ≤12 years of age: 100–150 mg/kg/day divided every 8 h	6 g	
Cefotaxime	Intravenous dosing: neonates aged 0–4 weeks and <1200 g: 100 mg/kg/day divided every 12 h; postnatal age ≤7 days and 1200–2000 g: 100 mg/kg/day divided every 12 h; postnatal age ≤7 days and >2000 g: 100–150 mg/kg/day divided every 8–12 h; postnatal age >7 days and 1200–2000 g: 150 mg/kg/day divided every 8 h; postnatal age >7 days and >2000 g: 150–200 mg/kg/day divided every 6–8 h Infants and children <50 kg: 100–200 mg/kg/day divided every 6–8 h; >12 years and ≥50 kg: 1–2 g every 6–8 h	…	…
Ceftriaxone	Neonates: postnatal age ≤7 days, 50 mg/kg/day given every 24 h; postnatal age >7 days and ≤2000 g, 50 mg/kg/day given every 24 h; postnatal age >7 days and >2000 g, 50–75 mg/kg/day given every 24 h Infants and children: 50–75 mg/kg/day divided every 12–24 h	…	Should not be used in hyperbilirubinemic neonates.
Ciprofloxacin	Neonates: 7–40 mg/kg/day divided every 12 h Infants and children: 20–30 mg/kg/day divided every 12 h	800 mg	Experience in neonates is limited. The risks and benefits of fluoroquinolones in children should be assessed prior to use.
Fluconazole	Neonates aged >14 days, infants, and children: 12 mg/kg/day once daily	…	…
Gentamicin	Neonates: premature neonates and <1000 g, 3.5 mg/kg every 24 h; 0–4 weeks and <1200 g, 2.5 mg/kg every 18–24 h; postnatal age ≤7 days: 2.5 mg/kg every 12 h; postnatal age >7 days and 1200–2000 g, 2.5 mg/kg every 8–12 h; postnatal age >7 days and >2000 g, 2.5 mg/kg every 8 h; once daily dosing for premature neonates with normal renal function, 3.5–4 mg/kg every 24 h; once daily dosing for term neonates with normal renal function, 3.5–5 mg/kg every 24 h Infants and children <5 years of age: 2.5 mg/kg every 8 h; once daily dosing in patients with normal renal function, 5–7.5 mg/kg every 24 h Children ≥5 years of age: 2–2.5 mg/kg every 8 h; once daily dosing in patients with normal renal function, 5–7.5 mg/kg every 24 h	…	Some patients may require larger or more frequent doses (e.g., every 6 h) if serum levels document the need (i.e., cystic fibrosis, patients with major burns, or febrile neutropenic patients).

Imipenem-cilastatin	Neonates: 0–4 weeks of age and <1200 g, 20 mg/kg every 18–24 h; postnatal age ≤7 days, and 1200–1500 g, 40 mg/kg/day divided every 12 h; postnatal age ≤7 days and >1500 g, 50 mg/kg/day divided every 12 h; postnatal age >7 days and 1200–1500 g, 40 mg/kg/day divided every 12 h; postnatal age >7 days and >1500 g, 75 mg/kg/day divided every 8 h Infants <3 months of age: 100 mg/kg/day divided every 6 h Infants ≥3 months of age and children: 60–100 mg/kg/day divided every 6 h	4 g	…
Levofloxacin	Children 6 months to 5 years of age: 10 mg/kg every 12 h Children ≥5 years of age: 10 mg/kg every 24 h with a maximum dose of 500 mg	500 mg	Experience in children is limited. The risks and benefits of fluoroquinolones in children should be assessed prior to use.
Linezolid	Neonates: 0–4 weeks of age and birthweight <1200 g: 10 mg/kg every 8–12 h (note: use every 12 h in patients <34 weeks gestation and <1 week of age); <7 days of age and birthweight ≥1200 g, 10 mg/kg every 8–12 h (note: use every 12 h in patients < 34 weeks gestation and < 1 week of age); ≥7 days and birthweight ≥1200 g, 10 mg/kg every 8 h Infants and children <12 years of age: 10 mg/kg every 8 h Children ≥12 years of age and adolescents: 10 mg/kg every 12 h	600 mg	…
Meropenem	Neonates: postnatal age 0–7 days, 20 mg/kg every 12 h; postnatal age >7 days and 1200–2000 g, 20 mg/kg every 12 h; postnatal age >7 days and >2000 g, 20 mg/kg every 8 h Infants ≥3 months of age and children: 20 mg/kg every 8 h	1 g	…
Micafungin	Children >2 years of age: 1–4 mg/kg/day	150 mg	Younger children, infants, and neonates are likely to require higher doses, but no recommendation is currently available.
Nafcillin	Neonates: 0–4 weeks of age and <1200 g, 50 mg/kg/day in divided doses every 12 h; ≤7 days and 1200–2000 g, 50 mg/kg/day in divided doses every 12 h; ≤7 days of age and >2000 g, 75 mg/kg/day in divided doses every 8 h; >7 days of age and 1200–2000 g, 75 mg/kg/day in divided doses every 8 h; >7 days of age and >2000 g, 100 mg/kg/day in divided doses every 6 h Infants and children: 100–200 mg/kg/day in divided doses every 4–6 h	12 g	…
Oxacillin	Neonates: 0–4 weeks of age and <1200 g, 50 mg/kg/day in divided doses every 12 h; postnatal age <7 days and 1200–2000 g: 50–100 mg/kg/day in divided doses every 12 h; postnatal age <7 days and >2000 g, 75–150 mg/kg/day in divided doses every 8 h; postnatal age ≥7 days and 1200–2000 g: 75–150 mg/kg/day in divided doses every 8 h; postnatal age ≥7 days and >2000 g, 100–200 mg/kg/day in divided doses every 6 h Infants and children: 150–200 mg/kg/day in divided doses every 4–6 h	12 g	…
Quinupristin-dalfopristin	Infants and children: 7.5 mg/kg every 8 h	…	Experience in children is limited. Recommended dosage based on 0.1 to 18 years of age.
Ticarcillin	Neonates: postnatal age ≤7 days and ≤2000 g, 150 mg/kg/day in divided doses every 12 h; postnatal age ≤7 days and >2000 g, 225 mg/kg/day in divided doses every 8 h; postnatal age >7 days and <1200 g, 150 mg/kg/day in divided doses every 12 h; postnatal age >7 days and 1200–2000 g, 225 mg/kg/day in divided doses every 8 h; postnatal age >7 days and >2000 g, 300 mg/kg/day in divided doses every 6–8 h Infants and children: 200–300 mg/kg/day in divided doses every 4–6	24 g	…
Tobramycin	Neonates: preterm neonates <1000 g, 3.5 mg/kg every 24 h; 0–4 weeks of age and <1200 g, 2.5 mg/kg every 18 h; postnatal age ≤7 days and 1200–2000 g, 2.5 mg/kg every 12 h; postnatal age ≤7 days and >2000 g, 2.5 mg/kg every 12 h Infants and children <5 years of age: 2.5 mg/kg every 8 h Children ≥5 years of age: 2–2.5 mg/kg every 8 h	…	Some patients may require larger or more frequent doses (e.g., every 6 h) if serum levels document the need (i.e., cystic fibrosis, patients with major burns, or febrile neutropenic patients).
TMP-SMX	Infants >2 months of age and children: mild-to-moderate infections, 6–12 mg TMP/kg/day in divided doses every 12 h; serious infection, 15–20 mg TMP/kg/day in divided doses every 6–8 h	…	…
Vancomycin	Neonates: postnatal age ≤7 days and <1200 g, 15 mg/kg/day given every 24 h; postnatal age ≤7 days and 1200–2000 g, 10–15 mg/kg given every 12–18 h; postnatal age ≤7 days and >2000 g, 10–15 mg/kg given every 8–12 h; postnatal age >7 days and <1200 g, 15 mg/kg/day given every 24 h; postnatal age >7 days and 1200–2000 g, 10–15 mg/kg given every 8–12 h; postnatal age >7 days and >2000 g, 15–20 mg/kg given every 8 h Infants and children: 40 mg/kg/day in divided doses every 6–8 h	…	…
Voriconazole	Children >2 years of age: 6 mg/kg every 12 h for 2 doses on day 1 (loading dose) followed by 4 mg/kg every 12 h (note: doses as high as 8 mg/kg every 12 h have been reported	…	…

NOTE. Intravenous dosing is given according to Pediatric Lexi-Comp Drugs Web site [279], unless otherwise indicated. Neonates are <4 weeks of age and infants are 4 weeks to 1 year of age, unless otherwise specified. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Benjamin et al. [280].

[b] From [281].

diatric dosing information, toxicities, route of administration, and formulations.

Conventional treatment for CRBSI has not been established to be different from that previously described for adults (table 6 and figures 1–4), but certain procedures may not apply to infants and young children. For example, as noted in figures 3 and 4, echocardiographic examination is not used commonly for small infants and children with CRBSI who do not have other indicators of endocarditis. The optimal duration of therapy has not been established for treating catheter-related infection in children with or without catheter removal [89, 90]. Therefore, recommendations regarding the duration of therapy for pediatric patients with CRBSI should mirror adult recommendations. Lastly, antibiotic lock therapy should also be used, with the recognition that dwell times may be variable, based on limited venous access and the necessity to use the catheter.

WHAT ARE THE UNIQUE ASPECTS OF MANAGING PATIENTS WHO ARE RECEIVING HEMODIALYSIS THROUGH CATHETERS FOR WHOM CATHETER-RELATED INFECTION IS SUSPECTED OR PROVEN?

Recommendations

53. Peripheral blood samples should be obtained for culture from vessels that are not intended for future use in creating a dialysis fistula (e.g., hand veins) (table 7) (A-III).

54. When a peripheral blood sample cannot be obtained, blood samples may be drawn during hemodialysis from bloodlines connected to the CVC (B-II).

55. In patients with suspected CRBSI for whom blood cultures have been obtained and for whom antibiotic therapy has been initiated, antibiotic therapy can be discontinued if both sets of blood cultures have negative results and no other source of infection is identified (B-II).

56. When a peripheral blood sample cannot be obtained, no other catheter is in place from which to obtain an additional blood sample, there is no drainage from the insertion site available for culture, and there is no clinical evidence for an alternate source of infection, then positive results of culture performed on a blood sample obtained from a catheter should lead to continuation of antimicrobial therapy for possible CRBSI in a symptomatic hemodialysis patient (B-II).

57. The infected catheter should always be removed for patients with hemodialysis CRBSI due to *S. aureus*, *Pseudomonas* species, or *Candida* species and a temporary (nontunneled catheter) should be inserted into another anatomical site (A-II). If absolutely no alternative sites are available for catheter insertion, then exchange the infected catheter over a guidewire (B-II).

Table 7. Unique features of catheter-related bloodstream infection among patients who are undergoing hemodialysis.

Usually outpatient status
The ability to provide parenteral antibiotics during hemodialysis sessions
Dialysis units are frequently at geographically remote sites and not adjacent to a hospital
A physician is not usually present
Blood samples for culture are usually sent to a remote laboratory with the potential for delayed incubation of blood culture bottles
Antibiotic drug levels are determined at a remote site and are not available promptly
Peripheral venous access is often unavailable or needs to be avoided
It is unclear if quantitative peripheral blood and catheter cultures differ if samples are obtained during a dialysis session
Catheter removal poses logistical issues, because it may require urgent placement of a new dialysis catheter
Peripherally inserted central venous catheter lines cause venous stenosis that precludes future access in the ipsilateral extremity
Preference is given to antibiotics that can be administered during hemodialysis treatments
Quantitative blood cultures and/or determining differential time to positivity are frequently unable to be done or determined
Limited drug formulary exists in outpatient dialysis units
Pharmacy support is unavailable in outpatient dialysis units

58. When a hemodialysis catheter is removed for CRBSI, a long-term hemodialysis catheter can be placed once blood cultures with negative results are obtained (B-III).

59. For hemodialysis CRBSI due to other pathogens (e.g., gram-negative bacilli other than *Pseudomonas* species or coagulase-negative staphylococci), a patient can initiate empirical intravenous antibiotic therapy without immediate catheter removal. If the symptoms persist or if there is evidence of a metastatic infection, the catheter should be removed (B-II). If the symptoms that prompted initiation of antibiotic therapy (fever, chills, hemodynamic instability, or altered mental status) resolve within 2–3 days and there is no metastatic infection, then the infected catheter can be exchanged over a guidewire for a new, long-term hemodialysis catheter (B-II).

60. Alternatively, for patients for whom catheter removal is not indicated (i.e., those with resolution of symptoms and bacteremia within 2–3 days after initiation of systemic antibiotics and an absence of metastatic infection), the catheter can be retained, and an antibiotic lock can be used as adjunctive therapy after each dialysis session for 10–14 days (B-II).

61. Empirical antibiotic therapy should include vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (e.g., third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination) (A-II).

62. Patients who receive empirical vancomycin and who are found to have CRBSI due to methicillin-susceptible *S. aureus* should be switched to cefazolin (A-II).

63. For cefazolin, use a dosage of 20 mg/kg (actual body weight), rounded to the nearest 500-mg increment, after dialysis (A-II).

64. A 4–6-week antibiotic course should be administered if there is persistent bacteremia or fungemia (i.e., >72 h in duration) after hemodialysis catheter removal or for patients with endocarditis or suppurative thrombophlebitis, and 6–8 weeks of therapy should be administered for the treatment of osteomyelitis in adults (figures 3 and 4) (B-II).

65. Patients receiving dialysis who have CRBSI due to vancomycin-resistant enterococci can be treated with either daptomycin (6 mg/kg after each dialysis session) or oral linezolid (600 mg every 12 h) (B-II).

66. It is not necessary to confirm negative culture results before guidewire exchange of a catheter for a patient with hemodialysis-related CRBSI if the patient is asymptomatic (B-III).

67. Surveillance blood cultures should be obtained 1 week after completion of an antibiotic course for CRBSI if the catheter has been retained (B-III). If the blood cultures have positive results, the catheter should be removed and a new, long-term dialysis catheter should be placed after additional blood cultures are obtained that have negative results (B-III).

Table 8. Antibiotic dosing for patients who are undergoing hemodialysis.

Empirical dosing pending culture results
Vancomycin plus empirical gram-negative rod coverage based on local antibiogram data
OR
Vancomycin plus gentamicin
(Cefazolin may be used in place of vancomycin in units with a low prevalence of methicillin-resistant staphylococci)
Vancomycin: 20-mg/kg loading dose infused during the last hour of the dialysis session, and then 500 mg during the last 30 min of each subsequent dialysis session
Gentamicin (or tobramycin:) 1 mg/kg, not to exceed 100 mg after each dialysis session
Ceftazidime: 1 g iv after each dialysis session
Cefazolin: 20 mg/kg iv after each dialysis session
For *Candida* infection
An echinocandin (caspofungin 70 mg iv loading dose followed by 50 mg iv daily; intravenous micafungin 100 mg iv daily; or anidulafungin 200 mg iv loading dose, followed by 100 mg iv daily); fluconazole (200 mg orally daily); or amphotericin-B

NOTE. iv, intravenous.

Evidence Summary

It is frequently not feasible to obtain a peripheral blood sample for culture from patients who are receiving dialysis [99]. In some patients, the peripheral veins have been exhausted as a result of multiple failed dialysis fistulas or grafts. Moreover, it is important to avoid drawing blood from peripheral veins that will be used for future creation of a fistula or graft, because venipuncture may injure the vein.

A substantial proportion of patients who receive dialysis who have CRBSI are treated successfully in the outpatient setting. Hospitalization is only indicated for patients with severe sepsis or metastatic infection. CRBSI in patients who are undergoing hemodialysis has several unique features that may dictate differences in their management, compared with that of other patients (tables 7 and 8 and figure 4).

CRBSI in patients who are undergoing hemodialysis may be caused by several different pathogens, but such cases are most often due to coagulase-negative staphylococci or *S. aureus* [99–101]. If possible, antibiotic selection should be made on the basis of pharmacokinetic characteristics that permit dosing after each dialysis session (e.g., vancomycin, ceftazidime, or cefazolin) [102], or antibiotics that are unaffected by dialysis (e.g., ceftriaxone) should be used. The majority of gram-negative organisms causing CRBSI in patients who are undergoing hemodialysis are susceptible to aminoglycosides and third- or fourth-generation cephalosporins [99, 100], but cephalosporins are preferred, because aminoglycosides carry a substantial risk of inducing irreversible ototoxicity [103]. Validated dosing schedules for cefazolin and vancomycin to ensure therapeutic concentrations have been published (table 8) [104, 105].

Among patients who are undergoing hemodialysis who have CRBSI involving long-term catheters, not only is the catheter the source of the infection, but it is also the vascular access for providing ongoing dialysis. The 4 potential treatment options for such patients are (1) intravenous antibiotics alone, (2) prompt catheter removal with delayed placement of a new long-term catheter, (3) exchange of the infected catheter with a new one over a guidewire, or (4) use of systemic antibiotics and an antibiotic lock in the existing catheter (figure 4 and table 9) [102]. Administration of intravenous antibiotics alone is not a satisfactory approach, because bloodstream infection recurs in the majority of patients once the course of antibiotics has been completed [101, 106–109]. Moreover, the risk of treatment failure among patients who are undergoing hemodialysis whose CRBSI is treated with antibiotics alone is a 5-fold higher, compared with the risk among patients who undergo catheter removal [110]. For patients whose symptoms resolve after 2–3 days of intravenous antibiotic therapy and who do not have evidence of metastatic infection, guidewire exchange of the catheter is associated with cure rates that are comparable to those associated with immediate removal and delayed placement of a new catheter [74–76, 111, 112]. Patients with hemodialysis-associated CRBSI due to gram-negative pathogens or CRBSI due to coagulase-negative staphylococci may have the catheter retained and be treated with adjunctive antibiotic lock therapy for 3 weeks, or they may have the catheter exchanged over a guidewire and then receive the same antibiotic course (figure 4).

Table 9. Final concentrations of antibiotic lock solutions used for the treatment of catheter-related bloodstream infection.

Antibiotic and dosage	Heparin or saline, IU/mL	Reference(s)
Vancomycin, 2.5 mg/mL	2500 or 5000	[100, 275]
Vancomycin, 2.0 mg/mL	10	[275]
Vancomycin, 5.0 mg/mL[a]	0 or 5000	[276, 277]
Ceftazidime, 0.5 mg/mL	100	[123]
Cefazolin, 5.0 mg/mL	2500 or 5000	[100, 277]
Ciprofloxacin, 0.2 mg/mL[b]	5000	[130]
Gentamicin, 1.0 mg/mL	2500	[100]
Ampicillin, 10.0 mg/mL	10 or 5000	[275]
Ethanol, 70%[c]	0	[131]

NOTE. These antibiotic lock solutions will not precipitate at the given concentrations. Cefazolin is the preferred agent for treatment of methicillin-susceptible staphylococci, and vancomycin is the preferred agent for treatment of methicillin-resistant staphylococci. Ceftazidime, gentamicin, or ciprofloxacin can be used for treatment of gram-negative microorganisms. Ampicillin is the preferred agent for infections due to ampicillin-sensitive *Enterococcus* species, and vancomycin is the preferred agent for treatment of ampicillin-resistant enterococci other than vancomycin-resistant enterococci. The use of an ethanol lock can be considered for the treatment of a mixed gram-positive and gram-negative infection. NA, not applicable.

[a] Vancomycin at 5 mg/mL is more efficacious than at 1 mg/mL in eradicating staphylococci embedded within biofilm [276]. A precipitate appears when mixing a 10 mg/mL of vancomycin with 10,000 IU/mL of heparin; however, by agitating the solution for ~10 s, the precipitation resolves and the solution remains precipitate-free for 72 h at 37°C [277]. The lock solution in 2500 IU/mL heparin can be made as follows: using vials containing 50 mg/mL of vancomycin in water, remove 2 mL and dilute in 8 mL 0.9% NaCl, resulting in 10 mg/mL of vancomycin. Place 1 mL of 5000 IU/mL heparin in a glass test tube and mix with 1 mL of the 10-mg/mL vancomycin solution (B. J. Rijnders and R. Mathot, personal communication).

[b] The maximum concentration of ciprofloxacin is limited because of precipitation at higher concentrations.

[c] An in-vitro study demonstrated the compatibility of ethanol 70% and silicone or polyetherurethane catheters [278].

For antibiotic lock therapy, the antibiotic is combined with heparin and instilled into each catheter lumen at the end of each dialysis session (table 9) [99, 113, 114]. The success rate is 87%–100% for infection due to gram-negative pathogens and 75%– 84% for infection due to *Staphylococcus epidermidis*, but it is only 40%–55% for hemodialysis-associated CRBSI due to *S. aureus* [100, 114, 115].

WHAT IS ANTIBIOTIC LOCK THERAPY AND HOW IS IT USED TO TREAT PATIENTS WITH CATHETER-RELATED INFECTION?

Recommendations

68. Antibiotic lock is indicated for patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the goal (B-II).

69. For CRBSI, antibiotic lock should not be used alone; instead, it should be used in conjunction with systemic antimicrobial therapy, with both regimens administered for 7–14 days (B-II).

70. Dwell times for antibiotic lock solutions should generally not exceed 48 h before reinstallation of lock solution; preferably, reinstallation should take place every 24 h for ambulatory patients with femoral catheters (B-II). However, for patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session (B-II).

71. Catheter removal is recommended for CRBSI due to *S. aureus* and *Candida* species, instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site) (A-II).

72. For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or gram-negative bacilli and concurrent negative peripheral blood cultures, antibiotic lock therapy can be given without systemic therapy for 10–14 days (B-III).

73. For vancomycin, the concentration should be at least 1000 times higher than the MIC (e.g., 5 mg/mL) of the microorganism involved (B-II).

74. At this time, there are insufficient data to recommend an ethanol lock for the treatment of CRBSI (C-III).

Evidence Summary

Antibiotic lock therapy for CRBSI is used in conjunction with systemic antibiotic therapy and involves installing a high concentration of an antibiotic to which the causative microbe is susceptible in the catheter lumen. In 14 open trials of CRBSI involving long-term catheters with catheter retention and administration of standard parenteral therapy without the adjunctive use of antibiotic lock therapy, the mean success rate was 67%. The likelihood of success varies with the site of infection (e.g., tunnel or pocket infection are unresponsive to salvage) and with the microbe causing the infection (e.g., coagulase-negative staphylococci are likely to respond; *S. aureus* is not). Recurrent bacteremia after parenteral therapy is more likely to occur if that therapy is administered through a retained catheter than if the catheter is removed [116]. This likely reflects the inability of most antibiotics to achieve therapeutic concentrations needed to kill microbes growing in a biofilm [117–122]. Antibiotic concentrations must be 100 to 1000 times greater to kill sessile bacteria within a biofilm than to kill planktonic bacteria [117–122]. Because the majority of infections involving long-term catheters or totally implanted catheters are intraluminal, eradication of such infections is attempted by filling the catheter lumen with supratherapeutic concentrations of antibiotics and leaving them indwelling for hours or days, thereby creating an antibiotic lock. In 21 open trials of antibiotic lock therapy for CRBSI involving long-term catheters, with or without concomitant parenteral therapy, catheter salvage without relapse occurred in 77% of episodes. Two con-

trolled clinical trials of the use of antibiotic lock therapy together included only 92 patients, and treatment was successful in 58% of the control subjects and 75% of the patients treated with an antibiotic lock [123, 124]. Compared with bacterial infection, *Candida* CRBSI is more difficult to eradicate with antibiotic lock therapy [93, 125–127]. In the largest published series on the use of antibiotic lock for CRBSI due to *S. aureus*, treatment failure was observed in one-half of the cases [114]. Antibiotic lock solutions contain the desired antimicrobial concentration (table 9), and they are usually mixed with 50–100 units of heparin or normal saline in sufficient volume to fill the catheter lumen (usually 2–5 mL). Rapidly decreasing antibiotic concentrations may occur over time in the distal lumen of catheters instilled with an antibiotic lock, especially among ambulatory patients with femoral catheters [128]. Thus, to maintain a concentration of vancomycin that is >1000 times the MIC_{90} of staphylococci during the entire dwell time, a concentration of 5 mg/mL is preferred, and the antibiotic lock fluid should be changed at least every 48 h.

Although the duration of antibiotic lock therapy has varied substantially among different studies (3–30 days), most studies have used a 2-week duration. Vancomycin, cefazolin, and ceftazidime remain stable in heparin solutions at 25°C and 37°C for several days [129]. Not all antibiotic-heparin combinations can be used, because precipitation occurs when some antibiotics are mixed with heparin, especially with increasing antibiotic concentrations [130]. Table 9 lists antibiotic lock solutions that can be used without the risk of precipitation.

The use of an antibiotic lock does not obviate the need for systemic antimicrobial therapy. However, when blood cultures have become negative and signs of sepsis have resolved, systemic antimicrobial therapy can be given orally in some patients. The combination of an orally administered, well-absorbed antibiotic (e.g., a fluoroquinolone or linezolid) and an antibiotic lock that can be left in place for 24–48 h may be more practical in some cases of outpatient management of CRBSI with coagulase-negative staphylococci [129].

Catheters that are in place for <2 weeks are most often infected extraluminally, and patients with catheters in place for longer periods may also have evidence of extraluminal infection [10]. Antibiotic lock therapy is unlikely to have any impact on extraluminal infection.

Other antimicrobial locks are being evaluated for the treatment of CRBSI. One pediatric CRBSI study had a high success rate using a 70% ethanol antimicrobial lock [131].

On occasion, symptomatic patients with catheters have multiple catheter-drawn blood cultures that are positive for coagulase-negative staphylococci or, more rarely, gram-negative bacilli, but also have concurrent percutaneous blood cultures with negative results. Such patients can be considered to have an intraluminally colonized catheter. If these colonized catheters are left in place, patients may go on to develop a true CRBSI. Therefore, if such catheters cannot be removed, antibiotic lock therapy without systemic therapy can be given through the retained catheter.

ARE THERE PATHOGEN-SPECIFIC TREATMENT RECOMMENDATIONS?

Coagulase-Negative *Staphylococcus* Species

Recommendations

75. For uncomplicated CRBSI, treat with antibiotics for 5–7 days if the catheter is removed and for 10–14 days, in combination with antibiotic lock therapy, if the catheter is retained (B-III).
76. Alternatively, patients with uncomplicated CRBSI can be observed without antibiotics if they have no intravascular or orthopedic hardware, the catheter is removed, and additional blood cultures (performed on samples collected when the patient is not receiving antibiotics) are obtained after catheter withdrawal to confirm the absence of bacteremia (C-III).
77. CRBSI due to *Staphylococcus lugdunensis* should be managed in a manner similar to CRBSI due to *S. aureus* (B-II).

Evidence summary. Coagulase-negative staphylococci are the most common cause of catheter-related infection. Most patients have a benign clinical course; rarely, patients develop sepsis with a poor outcome. For example, *S. lugdunensis* is an uncommon cause of catheter-related infection; however, it can cause endocarditis and metastatic infections similar to those caused by *S. aureus* [132].

The interpretation of blood cultures positive for coagulase-negative staphylococci remains problematic, because they are the most common contaminant and, at the same time, they are the most common cause of CRBSI. A high proportion of positive blood cultures performed on samples drawn from multiple sites remains the best indication for true CRBSI due to coagulase-negative staphylococci [17, 133].

No randomized trials have evaluated the treatment of coagulase-negative staphylococcal CRBSI. Such infections may resolve with removal of the catheter without antibiotic therapy, and some experts recommend that no antibiotic therapy be administered to patients without endovascular hardware unless fever and/or bacteremia persist after catheter withdrawal. Other experts recommend that such infections be treated with antibiotics. Specific management strategies for coagulase-negative staphylococcal infection associated with different catheters and devices are summarized in table 5 and figures 2–4.

S. aureus

Recommendations

78. Patients with *S. aureus* CRBSI should have the infected catheter removed, and they should receive 4–6 weeks of antimicrobial therapy (B-II), unless they have exceptions listed in recommendation 80.

79. Patients who are being considered for a shorter duration of therapy should have a transesophageal echocardiograph (TEE) obtained (B-II).

80. Patients can be considered for a shorter duration of antimicrobial therapy (i.e., a minimum of 14 days of therapy) if the patient is not diabetic; if the patient is not immunosuppressed (i.e., not receiving systemic steroids or other immunosuppressive drugs, such as those used for transplantation, and is nonneutropenic); if the infected catheter is removed; if the patient has no prosthetic intravascular device (e.g., pacemaker or recently placed vascular graft); if there is no evidence of endocarditis or suppurative thrombophlebitis on TEE and ultrasound, respectively; if fever and bacteremia resolve within 72 h after initiation of appropriate antimicrobial therapy; and if there is no evidence of metastatic infection on physical examination and sign- or symptom-directed diagnostic tests (A-II).

81. If a TEE is performed, it should be done at least 5–7 days after onset of bacteremia to minimize the possibility of false-negative results (B-II).

82. Short-term catheters should be removed immediately for patients with *S. aureus* CRBSI (A-II).

83. For *S. aureus* CRBSI involving long-term catheters, the catheters should be removed unless there are major contraindications (e.g., there is no alternative venous access, the patient has significant bleeding diathesis, or quality of life issues take priority over the need for reinsertion of a new catheter at another site) (A-II).

84. In the rare circumstance that the catheter is retained for a patient with *S. aureus* CRBSI involving a long-term catheter, the patient should receive systemic and antibiotic lock therapy for 4 weeks (B-II). Catheter guidewire exchange should be done, if possible, and if it is done, an antimicrobial-impregnated catheter with an anti-infective intraluminal surface should be considered for catheter exchange (B-II).

85. An additional TEE should be obtained for patients with persistent fever or bloodstream infection >72 h after catheter withdrawal and initiation of appropriate antibiotic therapy if the patient had an earlier TEE obtained and it was without evidence of endocarditis and if there is no evidence of an undrained metastatic infection (A-II).

86. Patients whose catheter tip grows *S. aureus* but whose initial peripheral blood cultures have negative results should receive a 5–7-day course of antibiotics and close monitoring for signs and symptoms of ongoing infection, including additional blood cultures, as indicated (B-II).

87. Transthoracic echocardiograph findings are insufficient to rule out infective endocarditis (A-II).

88. After a catheter has been removed as a result of *S. aureus* CRBSI, placement of a new catheter can proceed when additional blood cultures show no growth (B-II).

Evidence summary. There are no data from randomized trials with adequate sample size to determine the optimal duration for the treatment of *S. aureus* CRBSI. Traditionally, *S. aureus* bacteremia has been treated with a 4-week course of therapy because of concern about the risk of infective endocarditis [134, 135]. However, several studies have suggested that the risk of infective endocarditis or other deep tissue infection related to *S. aureus* bacteremia may be sufficiently low among selected patients with uncomplicated CRBSI to recommend a shorter course of therapy (i.e., a minimum of 14 days of therapy) [136–140]. Identifying patients without risk factors for hematogenous complications and pursing an aggressive evaluation which may include TEE is important before proceeding to short-course therapy [141].

Many patients (25%–30%) with *S. aureus* bacteremia will have hematogenous complications, including cardiac or musculoskeletal involvement [142–146]. Clinical identifiers can be helpful in determining which patients with *S. aureus* bacteremia have a complicated infection [143, 144, 146]. One of the most consistent predictors of hematogenous complications is positive blood culture results 72 h after initiation of appropriate antimicrobial therapy and catheter removal [143–146]. Additional predictors of hematogenous complications include community-acquired infection and skin changes consistent with septic emboli [143, 144]. Failure or delay in removing the catheter increases the risk for hematogenous complications [144]. In addition, removal of vascular catheters infected with *S. aureus* has been associated with a more rapid response to therapy and/or a higher cure rate, compared with catheter retention [139, 144, 147, 148].

Patients with *S. aureus* CRBSI have a significantly higher risk of hematogenous complications if they have a retained foreign body, if they are hemodialysis-dependent, if they have AIDS, or if they are diabetic or receiving immunosuppressive medications [144]. For this reason, a longer course of therapy is prudent for immunosuppressed patients with *S. aureus* CRBSI.

Many cases of infective endocarditis are not suspected clinically and are therefore not detected [149]. Studies using TEE to identify infective endocarditis among patients with *S. aureus* bacteremia have shown high rates of valvular vegetations (25%–32%) [142, 150, 151]. TEE is superior to transthoracic echocardiography in detecting valvular vegetations [134]. Additionally, TEE is most sensitive when performed 5–7 days after the onset of bacteremia [152].

A combination of antibiotic lock therapy and systemic therapy has been used to salvage infected ports and long-term (e.g., hemodialysis) catheters for some patients with *S. aureus* CRBSI [99, 107, 153]. Although some catheters without evidence of exit site infection or tunnel infection may be salvaged, most patients with *S. aureus* CRBSIs eventually experience relapse and require removal of the catheter [99, 107].

Patients with catheters that are colonized with *S. aureus* who are not bacteremic are at risk for subsequent *S. aureus* bacteremia [66, 154], and administering antistaphylococcal therapy within 24 h after removal of the catheter may reduce the likelihood that the patient will develop bacteremia.

In the largest randomized, published study assessing treatment of CRBSI in adults, a group of patients who received linezolid was compared with a control group that received non–weight-based vancomycin (for MRSA infection) or oxacillin (2 g every 6 h) or dicloxacillin (500 mg orally every 6 h); for suspected gram-negative bacteremia, aztreonam or amikacin was recommended [52]. The rate of successful microbiologic outcome at test of cure for patients with methicillin-susceptible *S. aureus* CRBSI was 82% for the linezolid group and 83% for the control group (95% confidence interval [CI], −16 to 14); for patients with MRSA CRBSI, it was 81% for the linezolid group and 86% for the control group (95% CI, −26 to 16). A successful clinical outcome at test of cure for patients with methicillin-susceptible *S. aureus* CRBSI was achieved in 67% in the linezolid group and 67% in the control group (95% CI, −19 to 19); for patients with MRSA CRBSI, it was 79% in the linezolid group and 76% in the control group (95% CI, −21 to 27). Kaplan-Meier survival curves for intention-to-treat populations found that there was no statistically significant difference between the 2 treatment groups among patients with *S. aureus* bacteremia (hazard ratio [HR], 0.70; 95% CI, 0.34–1.44) or among patients who had gram-negative bacteremia (HR, 1.94; 95% CI, 0.78–4.81). However, patients without bacteremia at baseline were less likely to survive in the linezolid group than in the control group (HR, 2.20; 95% CI, 1.07–4.50). Thus, linezolid has not been recommended for empirical therapy in this guideline (i.e., for patients in whom CRBSI is suspected but not confirmed). Specific management strategies for *S. aureus* CRBSI are summarized in table 5 and figures 2–4.

Enterococcus Species

Recommendations

89. Removal of infected short-term intravascular catheters is recommended (B-II).

90. Removal of infected long-term catheters should be done in cases of insertion site or pocket infection, suppurative thrombophlebitis, sepsis, endocarditis, persistent bacteremia, or metastatic infection (B-II).

91. Ampicillin is the drug of choice for ampicillin-susceptible enterococci; vancomycin should be used if the pathogen is resistant to ampicillin (A-III).

92. The role of combination therapy (i.e., a cell wall–active antimicrobial and an aminoglycoside) for treating enterococcal CRBSI without endocarditis is unresolved **(C-II)**.

93. A 7–14-day course of therapy is recommended for uncomplicated enterococcal CRBSI in which the long-term catheter is retained and antibiotic lock is used or when the short-term catheter is removed (C-III).

94. For enterococcal CRBSI, a TEE should be done if the patient has signs and symptoms that suggest endocarditis (e.g., new murmur or embolic phenomena); prolonged bacteremia or fever, despite appropriate antimicrobial therapy (e.g., bacteremia or fever >72 h after the onset of appropriate antibiotic therapy); radiographic evidence of septic pulmonary emboli; or the presence of a prosthetic valve or other endovascular foreign bodies (B-III).

95. Patients with enterococcal CRBSI involving a long-term catheter for whom the catheter is retained should have follow-up blood cultures and catheter removal if persistent bacteremia (>72 h after the initiation of appropriate antibiotic therapy) is detected (B-II).

96. Antibiotic lock therapy should be used in addition to systemic therapy if the catheter is retained **(C-II)**.

97. In cases of CRBSI due to ampicillin- and vancomycin-resistant enterococci, linezolid or daptomycin may be used, based on antibiotic susceptibility results (B-II).

Evidence summary. Enterococci account for 10% of all nosocomial bloodstream infections [155, 156], many of which are caused by intravascular catheters. Sixty percent of *Enterococcus faecium* and 2% of *Enterococcus faecalis* nosocomial bloodstream infections are resistant to vancomycin [156]. Antimicrobial resistance to newer agents, such as linezolid, has been reported [157, 158].

The risk of endocarditis as a complication of enterococcal CRBSI is relatively low. In a multicenter study involving >205 cases of CRBSI due to vancomycin-resistant enterococci, only 1.5% had definitive evidence of endocarditis [159]. However, signs and symptoms of endocarditis, persistent bacteremia, or enterococcal bacteremia in the presence of a prosthetic valve warrant further evaluation with TEE [160, 161]. Enterococcal bacteremia that persists for >4 days is independently associated with mortality [162, 163].

There are no data from randomized trials with adequate statistical power to determine the role of combination antimicrobial therapy or the optimal treatment duration for enterococcal CRBSI. Several retrospective cohort studies found no statistically significant differences in outcomes among patients with uncomplicated enterococcal bloodstream infection treated with combination therapy versus monotherapy [164,

165]. However, one large series found that combination therapy with gentamicin and ampicillin was more effective than monotherapy when the catheter was retained in cases of enterococcal CRBSI [166]. The combination of ampicillin and high-dose ceftriaxone was used successfully in a nonrandomized study of enterococcal endocarditis for patients in which use of an aminoglycoside was precluded because of either antimicrobial resistance or nephrotoxicity [167].

An open-label clinical trial among solid-organ transplant recipients reported a 63% success rate in treating vancomycin-resistant enterococci bloodstream infections with linezolid [168]. Quinupristin-dalfopristin has been reported for use in treating bloodstream infections due to *E. faecium,* with an overall clinical response rate of 69% in the small subset of patients with CRBSI [169]. An open-label study of neutropenic patients found a 44% cure rate in an intention-to-treat analysis of enterococcal bacteremia treated with daptomycin [170]. In a retrospective cohort study, chloramphenicol treatment of vancomycin-resistant enterococci bloodstream infections had a clinical response rate of 61% [171]. Specific management strategies for enterococcal CRBSI are summarized in table 5 and figures 2–4.

Gram-Negative Bacilli

Recommendations

98. Patients with possible CRBSI should receive empirical antibiotic therapy to cover gram-negative bacilli if they are critically ill, if they have sepsis, if they are neutropenic, if they have a femoral catheter in place, or if they have a known focus of gram-negative bacillary infection (A-II).

99. Patients who are critically ill with suspected CRBSI and who have recent colonization or infection with an MDR gram-negative pathogen should receive 2 antimicrobial agents of different classes with gram-negative activity as initial therapy (A-II). De-escalation of the initial regimen to a single appropriate antibiotic is recommended once culture and susceptibility results are available (A-II).

100. In patients with gram-negative bacillary CRBSI involving a long-term catheter and persistent bacteremia or severe sepsis despite systemic and antibiotic lock therapy, the device should be removed, an evaluation for endovascular infection and metastatic infection should be pursued, and the duration of antibiotic therapy should be extended beyond 7–14 days on the basis of the findings of these studies (C-III).

Evidence summary. During the past 2 decades, rates of gram-negative bacillary intravascular device infection and secondary bacteremia among adults have decreased, supplanted by infections due to coagulase-negative staphylococci, *S. aureus* (often MRSA), and *Candida* species [172]. The incidence of infections due to antibiotic-resistant gram-negative pathogens has increased over the past decade [86, 173], and patients with CRBSI due to MDR gram-negative pathogens are at greater risk for inappropriate initial antibiotic therapy, which results in increased morbidity and mortality [172–177]. Risk factors for infection due to MDR gram-negative bacilli include being critically ill, being neutropenic, having received prior antibiotic therapy, and having a femoral catheter [172, 178–180].

Over the past decade, the incidence of gram-negative bacilli resistant to third- and fourth-generation cephalosporins has increased [15, 86, 173]. MDR *Klebsiella pneumoniae* and *Escherichia coli* expressing extended-spectrum β-lactamases have been associated with poor clinical outcomes when treated with cephalosporins or piperacillin-tazobactam versus carbapenems, even when the organisms appear to be susceptible in vitro [173, 177]. In addition, there is increasing concern over the evolution of MDR gram-negative bacilli having carbapenemases that confer resistance to carbapenems, and many of these enzymes are active against cephalosporins [173]. No randomized, controlled trials have evaluated various treatments for gram-negative bacilli that produce these β-lactamases or carbapenemases and require therapy with polymyxin (colistin) or an aminoglycoside [181]. Treatment failure among patients with *Enterobacter* bacteremia who are administered cephalosporins has also been observed [172].

Most of the recommendations for the management of CRBSI due to MDR gram-negative bacilli have been limited by small numbers of cases derived from outbreaks or small clusters of infections, concerns over the accuracy and interpretation of in vitro susceptibility data, and confounding by concurrent use of combinations of antibiotics. When culture and susceptibility data are available, the initial antibiotic regimen can be adjusted to a single agent for the remainder of the therapeutic course, usually for 7–14 days [182]. Recommendations and guidelines for the management of sepsis have been recently published [176]. Recommendations for antimicrobial therapy for specific gram-negative pathogens are shown in table 5.

Several studies have advocated the removal of an infected catheter for patients with CRBSI due to MDR gram-negative bacilli that have a propensity for biofilm production, such as *Acinetobacter baumannii, Pseudomonas* species, and *Stenotrophomonas maltophilia* [172, 179, 180, 183]. However, these studies are limited by small numbers of patients and lack data on the efficacy of combination therapy with an antibiotic lock and systemic antibiotics. Recent studies in which antibiotic lock and systemic antibiotics were used to treat gram-negative rod CRBSI have found high success rates [99, 114]. Specific management strategies for gram-negative bacillary CRBSI are summarized in table 5 and figures 2–4.

Candida Species

Recommendations

101. Catheters should be removed in cases of CRBSI due to *Candida* species (A-II).

102. For patients with candidemia and a short-term CVC for whom no source of candidemia is obvious, the catheter should be removed and the catheter tip sent for culture (A-II). Alternatively, for patients with limited venous access, exchange the catheter over a guidewire and perform catheter cultures (B-II). If the catheter is colonized with the same species of *Candida* as found in a percutaneous blood culture, the CVC should be removed (A-II).

103. Antifungal therapy is recommended for all cases of CRBSI due to *Candida* species, including cases in which clinical manifestations of infection and/or candidemia resolve after catheter withdrawal and before initiation of antifungal therapy (A-II).

Evidence summary. Fluconazole administered at a dosage of 400 mg daily for 14 days after the first negative blood culture result is obtained is equivalent to amphotericin B in the treatment of candidemia caused by *Candida albicans* and azole-susceptible strains [184]. For *Candida* species with decreased susceptibility to azoles (e.g., *C. glabrata* and *C. krusei*), echinocandins (caspofungin administered with a 70-mg intravenous loading dose, followed by 50 mg daily administered intravenously; micafungin at a dosage of 100 mg daily administered intravenously or anidulafungin with a 200-mg intravenous loading dose followed by 100 mg daily administered intravenously) or lipid formulations of amphotericin B (ambisome or amphotericin B lipid complex) administered intravenously at a dosage of 3–5 mg/kg daily are highly effective [185–187]. Conventional amphotericin B therapy is also effective but is associated with more adverse effects.

The impact of CVC removal on the outcome of candidemia has been evaluated in 6 prospective studies [188–193]. All 6 prospective studies showed that CVC retention worsened outcome [188–193].

There are limited clinical data to suggest that antifungal lock therapy with amphotericin B may result in catheter salvage for patients with candidemia [93, 127]. Echinocandins [194], lipid formulations of amphotericin B [194, 195], or ethanol-based lock solutions [196, 197] eradicate biofilm-containing *Candida* in vitro, but catheter retention in combination with antifungal lock therapy is still investigational at the present time.

If *Candida* is grown from blood samples obtained from a patient with a long-term catheter or implantable port, the decision regarding catheter removal should be based on predictors of a catheter-related candidemia versus another source of infection (e.g., the gastrointestinal tract). Predictors of CRBSI involving long-term catheters include the following: a >3:1 quantity of *Candida* growing from the catheter-drawn blood cultures, compared with percutaneous blood cultures; catheter-drawn blood cultures growing >2 h before percutaneous blood cultures [36, 48, 49, 198]; candidemia in a patient who has not received chemotherapy or steroid therapy within 1 month before the onset of infection and who has no dissemination or other apparent source for the bloodstream infection except the intravascular catheter; candidemia in a patient receiving hyperalimentation through the catheter; and persistent candidemia unresponsive to systemic antifungal therapy [199, 200]. Any of these conditions should raise suspicion for *Candida*-related CRBSI and the need to remove the catheter. Management of candidemia and other fungal infections is summarized in table 5 and figures 2–4, and in the recent IDSA guidelines for the management of candidiasis [201].

Other Gram-Positive Microorganisms

Recommendations

104. Diagnosis of CRBSI due to *Corynebacterium*, *Bacillus* and *Micrococcus* species requires at least 2 positive results of blood cultures performed on samples obtained from different sites (A-II).

105. For the management of these infections, catheter removal is indicated for patients with a short-term CVC, and it is also indicated for patients with an infected long-term catheter or implanted port, unless there are no alternative intravascular access sites (B-III).

Evidence summary. Isolation of these microorganisms from a single blood culture set does not prove true bloodstream infection. Confirmation by multiple percutaneous blood culture results positive for the same organism is required before meaningful conclusions can be drawn as to the significance of the culture results. CRBSIs due to *Micrococcus* and *Bacillus* species are difficult to treat successfully unless the infected catheter is removed [202, 203]. A high incidence of CRBSI due to *Micrococcus* species has been reported among patients treated for pulmonary arterial hypertension with continuous epoprostenol [204]. Specific management strategies for treating CRBSI due to these pathogens are summarized in table 5.

HOW SHOULD YOU MANAGE SUPPURATIVE THROMBOPHLEBITIS?

Recommendations

106. Suppurative thrombophlebitis should be suspected in patients with persistent bacteremia or fungemia (i.e., patients

whose blood culture results remain positive after 72 h of adequate antimicrobial therapy) without another source of intravascular infection (e.g., endocarditis) (A-II).

107. A diagnosis of suppurative thrombophlebitis requires the presence of positive blood culture results plus the demonstration of a thrombus by radiographic testing (e.g., computed tomography, ultrasonography, or other methods) (A-II).

108. Surgical resection of the involved vein for patients with suppurative thrombophlebitis should be limited to patients with purulent superficial veins or patients in whom the infection extends beyond the vessel wall, as well as patients who experience failure of conservative therapy with an appropriate antimicrobial regimen (A-II).

109. The role of heparin use in this setting is unresolved (C-III).

110. Patients with suppurative thrombophlebitis due to CRBSI should receive a minimum of 3–4 weeks of antimicrobial therapy (B-III).

Evidence Summary

Suppurative thrombophlebitis may involve central or peripheral veins or arteries and result in high-grade and persistent bacteremia or fungemia [205–210]. Patients who undergo chemotherapy for malignancy and patients with solid tumors who develop *S. aureus* CRBSI may be at increased risk for suppurative thrombophlebitis, because *S. aureus* is the most common offending organism [207, 211–214]. Septic pulmonary emboli and other metastatic infections may complicate this condition [207, 215]. Patients may remain febrile and bacteremic or fungemic for prolonged periods of time despite the initiation of appropriate antimicrobial therapy; however, few patients have physical examination findings that suggest the diagnosis of suppurative thrombophlebitis [216]. Only a minority of patients require surgery for the definite resolution of suppurative thrombophlebitis.

Because infected intravascular thrombus and intraluminal abscess may remain intact after catheter removal, this infection may become manifest after catheter removal [209]. When peripheral veins are involved, many older children and adult patients have localized pain, erythema, and edema, and a smaller subset of patients demonstrate an abscess, palpable cord, or purulent drainage [206, 217, 218]. A patient with suppurative thrombophlebitis caused by a peripheral arterial catheter may present with a pseudoaneurysm or embolic lesions of the involved hand [205, 210]. Patients with suppurative thrombophlebitis of the great central veins may have ipsilateral neck, chest, or upper extremity swelling [208, 209, 219]. There are no randomized studies to guide the optimal choice or duration of antibiotics, use of anticoagulants, thrombolytic agents, or excision of the involved vessel, but anticoagulation with heparin should be considered [220]. Specific management strategies for suppurative thrombophlebitis are summarized in figures 2 and 3.

HOW IS PERSISTENT BLOODSTREAM INFECTION AND INFECTIVE ENDOCARDITIS MANAGED?

Recommendations

111. Catheter withdrawal is required in the management of catheter-related infective endocarditis (A-II).

112. TEE should be done for patients with CRBSI who have any of the following: a prosthetic heart valve, pacemaker, or implantable defibrillator; persistent bacteremia or fungemia and/or fever >72 h after initiation of appropriate antibiotic therapy and catheter removal, in addition to a search for metastatic foci of infection, as indicated; and any case of *S. aureus* CRBSI in which duration of therapy less than 4–6 weeks is being considered (A-II).

113. Unless the clinical condition of the patient dictates otherwise, perform a TEE at least 5–7 days after the onset of bacteremia or fungemia and consider repeating the TEE for patients with a high index of suspicion for infective endocarditis in whom the initial TEE had negative findings (B-II).

114. Assess for suppurative thrombophlebitis as noted above (B-II).

115. Infective endocarditis cannot be ruled out by negative transthoracic echocardiograph findings alone (B-II).

Evidence Summary

Colonized intravascular catheters are the most commonly identified source of nosocomial endocarditis and account for one- to two-thirds of reported cases [24, 25, 34, 221–224]. Staphylococci are the main etiologic agents, followed by *Enterococcus* and *Candida* species [24, 25]. The risk of nosocomial endocarditis is greatest among patients with *S. aureus* bacteremia who have prosthetic heart valves, pacemakers, malignancy, or who are receiving dialysis through a catheter [24, 25, 34, 44, 225, 226].

There are no data from randomized clinical trials to establish the indications for TEE, but clinical examination has a low sensitivity for diagnosing infective endocarditis. A TEE should be offered to all patients with *S. aureus* bacteremia, with the possible exception of patients whose fever and bacteremia resolve within 72 h after catheter removal who have no underlying cardiac predisposing conditions for endocarditis and no clinical signs of endocarditis [135].

Repeatedly positive blood culture results and/or unchanged clinical status for 72 h after catheter removal usually reflects serious sequelae of CRBSI, such as suppurative thrombophlebitis, endocarditis, or metastatic foci of infection. Specific management strategies for infective endocarditis due to CRBSI are

summarized in figures 2 and 3, and general guidelines can be found elsewhere [272].

HOW WOULD YOU DETECT AND MANAGE AN OUTBREAK OF CRBSI?

Recommendations

116. When extrinsic contamination of infusate or catheter flush or lock solutions is suspected, public health authorities should be alerted and the suspected product should be set aside for culture (A-II).

117. Establish a case definition for patients who are likely to have been exposed, including a time period, risk factors, and location of the patients (A-II).

118. A case-control study should be used to establish risk factors for infection and to help elucidate potential sources of contamination (B-II).

119. Establish relatedness of the suspected organisms by reviewing the antibiotic susceptibility patterns, followed by molecular fingerprinting, such as pulsed-field gel electrophoresis, polymerase chain reaction, or multilocus sequence typing (A-II).

120. Investigation of contamination involves a thorough review of potential breaches in infection control practices in the hospital pharmacy and at the point of delivery of the infusate. This requires interviews with health care personnel and observation of practices in the health care setting (A-II).

121. Cultures of potential point-source contaminants in the environment should be performed, including intravenous medications administered to patients (A-II).

122. During the investigation, heightened surveillance to detect new cases should be instituted (A-II).

123. Following identification of a source, there should be ongoing surveillance to confirm eradication of the source of infection (A-II).

Evidence Summary

Outbreaks of CRBSI occur infrequently and are most commonly caused by contaminated infusate [4]. These infections can be difficult to recognize and are sufficiently uncommon that they may go unnoticed by clinicians. Any fluids administered through an intravenous catheter can become contaminated, either during the manufacturing process or while being prepared or administered in the health care setting. Numerous outbreaks of bloodstream infection related to contaminated, intravenously administered products have been reported [227–237]. In addition, medical equipment can become contaminated because of inadequate infection-control practices [238–254]. In some instances, health care workers have adulterated intravenous narcotics for illicit use and have contaminated the narcotics in the process [255].

Bacteria that are most often implicated in contamination of infusate include gram-negative bacilli capable of reproducing at room temperature, such as *Klebsiella* species, *Enterobacter* species, *Serratia* species, *Burkholdaria cepacia, Ralstonia pickettii,* and *Citrobacter freundii* [4]. Gram-negative bacilli that are unusual human pathogens or that are frequently found in the environment should alert the clinician to the possibility of contaminated infusate.

Because the clinical picture of contaminated infusate is the same as that of bloodstream infection due to other causes, contamination of infusate often will not be detected unless there is a cluster of unusual bloodstream infections or several patients develop a bloodstream infection due to the same organism. Contaminated infusate should be suspected when no other infection is present that would account for a bloodstream infection or when the abrupt onset of shock occurs in association with infusion of parenteral medication or fluid.

Contamination in the hospital pharmacy should be suspected if an increase in bloodstream infection due to the same microorganism occurs among patients on different hospital units. Suspected contamination should prompt an immediate and thorough investigation. Assistance from public health authorities may be required, especially if related outbreaks occur in multiple health care settings.

UNRESOLVED ISSUES

- Prior guidelines call for negative TEE findings for all patients with *S. aureus* CRBSI to allow for a treatment duration of only 2 weeks [1]. However, some experts believe that a TEE is not needed for patients without intravascular hardware who have rapid resolution of bacteremia and signs and symptoms of acute infection.
- The true value and optimal duration of antimicrobial lock solutions as an adjunctive to systemic antibiotic therapy administered through the catheter remains unknown.
- Can antimicrobial therapy for CRBSI due to coagulase-negative staphylococci be safely omitted for patients who are at low risk for complications (i.e., those who no intravascular foreign body) when clinical signs and symptoms have resolved promptly after catheter removal?
- The clinical impact of culturing and reporting colonized catheters for patients without bacteremia or fungemia is unclear.
- What is the optimal duration of therapy for *S. lugdunensis* CRBSI?
- It remains unclear which strategy—CVC change over a guidewire, insertion of a new CVC at a new site, or watchful waiting—is preferred among patients with suspected but unconfirmed catheter-related infection, pending blood culture results.
- How should patients be treated who have positive catheter-drawn blood culture results and negative percutaneous blood culture results?

- What is the optimal duration of antimicrobial use when an infected CVC is not removed?
- Is the roll-plate method or the sonication method preferred for the diagnosis of long-term catheter–related infection?
- Should blood cultures be routinely obtained after completing a course of antibiotics for CRBSI?

PERFORMANCE MEASURES

1. Determine whether patients with CRBSI due to *S. aureus* or *Candida* species are treated with prompt catheter removal.
2. Determine how often catheters are removed from patients with CRBSI who have >72 h of bacteremia or fungemia despite administration of antimicrobial agents to which the pathogens are susceptible.
3. Determine how often patients with *S. aureus* bacteremia for >72 h after catheter removal and appropriate antibiotic therapy receive antibiotic treatment for at least 4 weeks.
4. For adult patients assessed for possible CRBSI who are not receiving hemodialysis through a catheter, determine whether 2 sets of blood cultures are obtained, one of percutaneous blood samples and the other of blood samples obtained through a catheter.
5. Determine whether blood culture bottles are labeled regarding the anatomic site or catheter used to obtain the blood sample for culture.
6. Determine how often a β-lactam antibiotic is used instead of vancomycin for β-lactam–susceptible staphylococcal CRBSI among patients without a β-lactam allergy.

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References

1. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis **2001**; 32:1249–72.
2. Field MJ, Lohr KN, eds. Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Clinical practice guidelines: directions for a new program. Washington, DC: National Academy Press, **1990**.
3. The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J **1979**; 121:1193–254.
4. Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. Hospital infections. Philidelphia, PA: Lippincott-Raven, **1998**:689–724.
5. Mermel LA. Prevention of intravascular catheter-related infections. Ann Intern Med **2000**; 132:391–402.
6. 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**; 81:1159–71.
7. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep **2002**; 51:1–29.
8. Safdar N, Mermel LA, Maki DG. The epidemiology of catheter-related infection in the critically ill. In: O'Grady N, Pittet D, eds. Catheter-related infections in the critically ill. New York, NY: Kluwer, **2004**: 1–23.
9. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. Ann Intern Med **1997**; 127:257–66.
10. Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis **1993**; 168:400–7.
11. Renaud B, Brun-Buisson C. Outcomes of primary and catheter-related bacteremia: a cohort and case-control study in critically ill patients. Am J Respir Crit Care Med **2001**; 163:1584–90.
12. Dimick JB, Pelz RK, Consunji R, Swoboda SM, Hendrix CW, Lipsett PA. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. Arch Surg **2001**; 136:229–34.
13. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis **2005**; 41:1591–8.
14. Warren DK, Quadir WW, Hollenbeak CS, Elward AM, Cox MJ, Fraser VJ. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. Crit Care Med **2006**; 34:2084–9.
15. 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**; 30:2632–5.
16. Shukrallah B, Hanna H, Hachem R, Ghannam D, Chatzinikolaou I, Raad I. Correlation between early clinical response after catheter removal and diagnosis of catheter-related bloodstream infection. Diagn Microbiol Infect Dis **2007**; 58:453–7.
17. Kiehn TE, Armstrong D. Changes in the spectrum of organisms causing bacteremia and fungemia in immunocompromised patients due to venous access devices. Eur J Clin Microbiol Infect Dis **1990**; 9: 869–72.
18. Pearson ML. Guideline for prevention of intravascular device-related infections. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol **1996**; 17:438–73.
19. Mayhall CG. Diagnosis and management of infections of implantable

devices used for prolonged venous access. Curr Clin Top Infect Dis **1992**; 12:83–110.
20. Raad, II, Hanna HA, Darouiche RO. Diagnosis of catheter-related bloodstream infections: is it necessary to culture the subcutaneous catheter segment? Eur J Clin Microbiol Infect Dis **2001**; 20:566–8.
21. Mermel LA, McCormick RD, Springman SR, Maki DG. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. Am J Med **1991**; 91:197S-205S.
22. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis: critical level of quantitative tip cultures. Arch Intern Med **1987**; 147:873–7.
23. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter–related infection. N Engl J Med **1977**; 296:1305–9.
24. Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis **1980**; 141:781–6.
25. Sherertz RJ, Raad, II, Belani A, et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol **1990**; 28:76–82.
26. Sherertz RJ, Heard SO, Raad II. Diagnosis of triple-lumen catheter infection: comparison of roll plate, sonication, and flushing methodologies. J Clin Microbiol **1997**; 35:641–6.
27. 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**; 40:1096–100.
28. Douard MC, Arlet G, Longuet P, et al. Diagnosis of venous access port-related infections. Clin Infect Dis **1999**; 29:1197–202.
29. Longuet P, Douard MC, Arlet G, Molina JM, Benoit C, Leport C. Venous access port–related bacteremia in patients with acquired immunodeficiency syndrome or cancer: the reservoir as a diagnostic and therapeutic tool. Clin Infect Dis **2001**; 32:1776–83.
30. Whitman ED, Boatman AM. Comparison of diagnostic specimens and methods to evaluate infected venous access ports. Am J Surg **1995**; 170:665–9; discussion 69–70.
31. Schmitt SK, Knapp C, Hall GS, Longworth DL, McMahon JT, Washington JA. Impact of chlorhexidine-silver sulfadiazine-impregnated central venous catheters on in vitro quantitation of catheter-associated bacteria. J Clin Microbiol **1996**; 34:508–11.
32. Schierholz JM, Bach A, Fleck C, Beuth J, Konig D, Pulverer G. Measurement of ultrasonic-induced chlorhexidine liberation: correlation of the activity of chlorhexidine-silver-sulfadiazine-impregnated catheters to agar roll technique and broth culture. J Hosp Infect **2000**; 44:141–5.
33. Bouza E, Alvarado N, Alcala L, Perez MJ, Rincon C, Munoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis **2007**; 44:820–6.
34. Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med **1994**; 120:667–76.
35. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med **2005**; 142:451–66.
36. Gaur AH, Flynn PM, Heine DJ, Giannini MA, Shenep JL, Hayden RT. Diagnosis of catheter-related bloodstream infections among pediatric oncology patients lacking a peripheral culture, using differential time to detection. Pediatr Infect Dis J **2005**; 24:445–9.
37. National Healthcare Safety Network, Centers for Disease Control and Prevention. The National Healthcare Safety Network [NHSN] manual: patient safety component protocol. January 2008. Available at: http://www.cdc.gov/ncidod/dhqp/pdf/nhsn/NHSN_ManualPatientSafetyProtocol_CURRENT.pdf. Accessed 30 July 2008.
38. Bekeris LG, Tworek JA, Walsh MK, Valenstein PN. Trends in blood culture contamination: a College of American Pathologists Q-Tracks study of 356 institutions. Arch Pathol Lab Med **2005**; 129:1222–5.
39. Little JR, Murray PR, Traynor PS, Spitznagel E. A randomized trial of povidone-iodine compared with iodine tincture for venipuncture site disinfection: effects on rates of blood culture contamination. Am J Med **1999**; 107:119–25.
40. Mimoz O, Karim A, Mercat A, et al. Chlorhexidine compared with povidone-iodine as skin preparation before blood culture: a randomized, controlled trial. Ann Intern Med **1999**; 131:834–7.
41. Ramsook C, Childers K, Cron SG, Nirken M. Comparison of blood-culture contamination rates in a pediatric emergency room: newly inserted intravenous catheters versus venipuncture. Infect Control Hosp Epidemiol **2000**; 21:649–51.
42. Norberg A, Christopher NC, Ramundo ML, Bower JR, Berman SA. Contamination rates of blood cultures obtained by dedicated phlebotomy vs intravenous catheter. JAMA **2003**; 289:726–9.
43. Everts RJ, Vinson EN, Adholla PO, Reller LB. Contamination of catheter-drawn blood cultures. J Clin Microbiol **2001**; 39:3393–4.
44. DesJardin JA, Falagas ME, Ruthazer R, et al. Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. Ann Intern Med **1999**; 131:641–7.
45. Martinez JA, DesJardin JA, Aronoff M, Supran S, Nasraway SA, Snydman DR. Clinical utility of blood cultures drawn from central venous or arterial catheters in critically ill surgical patients. Crit Care Med **2002**; 30:7–13.
46. Haimi-Cohen Y, Vellozzi EM, Rubin LG. Initial concentration of *Staphylococcus epidermidis* in simulated pediatric blood cultures correlates with time to positive results with the automated, continuously monitored BACTEC blood culture system. J Clin Microbiol **2002**; 40: 898–901.
47. Blot F, Schmidt E, Nitenberg G, et al. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. J Clin Microbiol **1998**; 36:105–9.
48. Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. Lancet **1999**; 354:1071–7.
49. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med **2004**; 140: 18–25.
50. Rijnders BJ, Verwaest C, Peetermans WE, et al. Difference in time to positivity of hub-blood versus nonhub-blood cultures is not useful for the diagnosis of catheter-related bloodstream infection in critically ill patients. Crit Care Med **2001**; 29:1399–403.
51. Warwick S, Wilks M, Hennessy E, et al. Use of quantitative 16S ribosomal DNA detection for diagnosis of central vascular catheter-associated bacterial infection. J Clin Microbiol **2004**; 42:1402–8.
52. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis **2009**; 48: 203–12.
53. Miragaia M, Couto I, Pereira SF, et al. Molecular characterization of methicillin-resistant *Staphylococcus epidermidis* clones: evidence of geographic dissemination. J Clin Microbiol **2002**; 40:430–8.
54. Pottumarthy S, Fritsche TR, Jones RN. Evaluation of alternative disk diffusion methods for detecting mecA-mediated oxacillin resistance in an international collection of staphylococci: validation report from the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis **2005**; 51:57–62.
55. Moise PA, Sakoulas G, Forrest A, Schentag JJ. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2007**; 51:2582–6.
56. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol **2004**; 42:2398–402.
57. Rijnders BJ, Vandecasteele SJ, Van Wijngaerden E, De Munter P, Pee-

termans WE. Use of semiautomatic treatment advice to improve compliance with Infectious Diseases Society of America guidelines for treatment of intravascular catheter-related infection: a before-after study. Clin Infect Dis **2003**; 37:980–3.
58. Atkinson JB, Chamberlin K, Boody BA. A prospective randomized trial of urokinase as an adjuvant in the treatment of proven Hickman catheter sepsis. J Pediatr Surg **1998**; 33:714–6.
59. La Quaglia MP, Caldwell C, Lucas A, et al. A prospective randomized double-blind trial of bolus urokinase in the treatment of established Hickman catheter sepsis in children. J Pediatr Surg **1994**; 29:742–5.
60. Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters: a randomized controlled trial. Ann Intern Med **1991**; 114:845–54.
61. Bregenzer T, Conen D, Sakmann P, Widmer AF. Is routine replacement of peripheral intravenous catheters necessary? Arch Intern Med **1998**; 158:151–6.
62. Rello J, Coll P, Prats G. Evaluation of culture techniques for diagnosis of catheter-related sepsis in critically ill patients. Eur J Clin Microbiol Infect Dis **1992**; 11:1192–3.
63. Esteve F, Pujol M, Limon E, et al. Bloodstream infection related to catheter connections: a prospective trial of two connection systems. J Hosp Infect **2007**; 67:30–4.
64. Koh DB, Gowardman JR, Rickard CM, Robertson IK, Brown A. Prospective study of peripheral arterial catheter infection and comparison with concurrently sited central venous catheters. Crit Care Med **2008**; 36:397–402.
65. Mermel LA, Maki DG. Infectious complications of Swan-Ganz pulmonary artery catheters: pathogenesis, epidemiology, prevention, and management. Am J Respir Crit Care Med **1994**; 149:1020–36.
66. Ekkelenkamp MB, van der Bruggen T, van de Vijver DA, Wolfs TF, Bonten MJ. Bacteremic complications of intravascular catheters colonized with *Staphylococcus aureus.* Clin Infect Dis **2008**; 46:114–8.
67. Peacock SJ, Eddleston M, Emptage A, King A, Crook DW. Positive intravenous line tip cultures as predictors of bacteraemia. J Hosp Infect **1998**; 40:35–8.
68. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med **2008**; 36:1330–49.
69. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. Jama **2001**; 286:700–7.
70. Rijnders BJ, Peetermans WE, Verwaest C, Wilmer A, Van Wijngaerden E. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med **2004**; 30:1073–80.
71. Pettigrew RA, Lang SD, Haydock DA, Parry BR, Bremner DA, Hill GL. Catheter-related sepsis in patients on intravenous nutrition: a prospective study of quantitative catheter cultures and guidewire changes for suspected sepsis. Br J Surg **1985**; 72:52–5.
72. Chatzinikolaou I, Hanna H, Hachem R, Alakech B, Tarrand J, Raad I. Differential quantitative blood cultures for the diagnosis of catheter-related bloodstream infections associated with short- and long-term catheters: a prospective study. Diagn Microbiol Infect Dis **2004**; 50: 167–72.
73. Martinez E, Mensa J, Rovira M, et al. Central venous catheter exchange by guidewire for treatment of catheter-related bacteraemia in patients undergoing BMT or intensive chemotherapy. Bone Marrow Transplant **1999**; 23:41–4.
74. Carlisle EJ, Blake P, McCarthy F, Vas S, Uldall R. Septicemia in long-term jugular hemodialysis catheters; eradicating infection by changing the catheter over a guidewire. Int J Artif Organs **1991**; 14:150–3.
75. Shaffer D. Catheter-related sepsis complicating long-term, tunnelled central venous dialysis catheters: management by guidewire exchange. Am J Kidney Dis **1995**; 25:593–6.
76. Robinson D, Suhocki P, Schwab SJ. Treatment of infected tunneled venous access hemodialysis catheters with guidewire exchange. Kidney Int **1998**; 53:1792–4.
77. Porter KA, Bistrian BR, Blackburn GL. Guidewire catheter exchange with triple culture technique in the management of catheter sepsis. JPEN J Parenter Enteral Nutr **1988**; 12:628–32.
78. Baltimore RS. Neonatal nosocomial infections. Semin Perinatol **1998**; 22:25–32.
79. Almuneef MA, Memish ZA, Balkhy HH, Hijazi O, Cunningham G, Francis C. Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. J Hosp Infect **2006**; 62:207–13.
80. Gilad J, Borer A. Prevention of catheter-related bloodstream infections in the neonatal intensive care setting. Expert Rev Anti Infect Ther **2006**; 4:861–73.
81. Jarvis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Am J Med **1991**; 91:185S-91S.
82. Garland JS, Alex CP, Henrickson KJ, McAuliffe TL, Maki DG. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. Pediatrics **2005**; 116:e198–205.
83. Wiener ES, McGuire P, Stolar CJ, et al. The CCSG prospective study of venous access devices: an analysis of insertions and causes for removal. J Pediatr Surg **1992**; 27:155–63; discussion 63–4.
84. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. Pediatrics **1996**; 98:357–61.
85. Piedra PA, Dryja DM, LaScolea LJ Jr. Incidence of catheter-associated gram-negative bacteremia in children with short bowel syndrome. J Clin Microbiol **1989**; 27:1317–9.
86. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control **2004**; 32:470–85.
87. Franklin JA, Gaur AH, Shenep JL, Hu XJ, Flynn PM. In situ diagnosis of central venous catheter-related bloodstream infection without peripheral blood culture. Pediatr Infect Dis J **2004**; 23:614–8.
88. Hartman GE, Shochat SJ. Management of septic complications associated with Silastic catheters in childhood malignancy. Pediatr Infect Dis J **1987**; 6:1042–7.
89. Flynn PM, Shenep JL, Stokes DC, Barrett FF. In situ management of confirmed central venous catheter-related bacteremia. Pediatr Infect Dis J **1987**; 6:729–34.
90. Wiener ES. Catheter sepsis: the central venous line Achilles' heel. Semin Pediatr Surg **1995**; 4:207–14.
91. Dato VM, Dajani AS. Candidemia in children with central venous catheters: role of catheter removal and amphotericin B therapy. Pediatr Infect Dis J **1990**; 9:309–14.
92. Jones GR, Konsler GK, Dunaway RP, Lacey SR, Azizkhan RG. Prospective analysis of urokinase in the treatment of catheter sepsis in pediatric hematology-oncology patients. J Pediatr Surg **1993**; 28: 350–5; discussion 55–7.
93. Johnson DC, Johnson FL, Goldman S. Preliminary results treating persistent central venous catheter infections with the antibiotic lock technique in pediatric patients. Pediatr Infect Dis J **1994**; 13:930–1.
94. Castagnola E, Marazzi MG, Tacchella A, Giacchino R. Broviac catheter-related candidemia. Pediatr Infect Dis J **2005**; 24:747.
95. Buckler BS, Sams RN, Goei VL, et al. Treatment of central venous catheter fungal infection using liposomal amphotericin-B lock therapy. Pediatr Infect Dis J **2008**; 27:762–4.
96. Stovroff M, Teague WG. Intravenous access in infants and children. Pediatr Clin North Am **1998**; 45:1373–93, viii.
97. Huskins WC, Goldmann DA. Nosocomial infections. In: Feigin RD, Cherry JD, eds. Textbook of pediatric infectious diseases. Philadelphia, PA: WB Saunders, **1998**:2545–85.

98. Decker MD, Edwards KM. Central venous catheter infections. Pediatr Clin North Am **1988**; 35:579–612.
99. Poole CV, Carlton D, Bimbo L, Allon M. Treatment of catheter-related bacteraemia with an antibiotic lock protocol: effect of bacterial pathogen. Nephrol Dial Transplant **2004**; 19:1237–44.
100. Krishnasami Z, Carlton D, Bimbo L, et al. Management of hemodialysis catheter-related bacteremia with an adjunctive antibiotic lock solution. Kidney Int **2002**; 61:1136–42.
101. Saad TF. Bacteremia associated with tunneled, cuffed hemodialysis catheters. Am J Kidney Dis **1999**; 34:1114–24.
102. Allon M. Dialysis catheter-related bacteremia: treatment and prophylaxis. Am J Kidney Dis **2004**; 44:779–91.
103. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis **1997**; 24:796–809.
104. Fogel MA, Nussbaum PB, Feintzeig ID, Hunt WA, Gavin JP, Kim RC. Cefazolin in chronic hemodialysis patients: a safe, effective alternative to vancomycin. Am J Kidney Dis **1998**; 32:401–9.
105. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. Kidney Int **1996**; 50: 929–36.
106. Lund GB, Trerotola SO, Scheel PF Jr, et al. Outcome of tunneled hemodialysis catheters placed by radiologists. Radiology **1996**; 198: 467–72.
107. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med **1997**; 127: 275–80.
108. Pourchez T, Moriniere P, Fournier A, Pietri J. Use of Permcath (Quinton) catheter in uraemic patients in whom the creation of conventional vascular access for haemodialysis is difficult. Nephron **1989**; 53:297–302.
109. Swartz RD, Messana JM, Boyer CJ, Lunde NM, Weitzel WF, Hartman TL. Successful use of cuffed central venous hemodialysis catheters inserted percutaneously. J Am Soc Nephrol **1994**; 4:1719–25.
110. Mokrzycki MH, Zhang M, Cohen H, Golestaneh L, Laut JM, Rosenberg SO. Tunnelled haemodialysis catheter bacteraemia: risk factors for bacteraemia recurrence, infectious complications and mortality. Nephrol Dial Transplant **2006**; 21:1024–31.
111. Tanriover B, Carlton D, Saddekni S, et al. Bacteremia associated with tunneled dialysis catheters: comparison of two treatment strategies. Kidney Int **2000**; 57:2151–5.
112. Beathard GA. Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. J Am Soc Nephrol **1999**; 10:1045–9.
113. Capdevila JA, Segarra A, Planes AM, et al. Successful treatment of haemodialysis catheter-related sepsis without catheter removal. Nephrol Dial Transplant **1993**; 8:231–4.
114. Fernandez-Hidalgo N, Almirante B, Calleja R, et al. Antibiotic-lock therapy for long-term intravascular catheter-related bacteraemia: results of an open, non-comparative study. J Antimicrob Chemother **2006**; 57:1172–80.
115. Maya ID, Carlton D, Estrada E, Allon M. Treatment of dialysis catheter-related *Staphylococcus aureus* bacteremia with an antibiotic lock: a quality improvement report. Am J Kidney Dis **2007**; 50:289–95.
116. Raad I, Davis S, Khan A, Tarrand J, Elting L, Bodey GP. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol **1992**; 13:215–21.
117. Gaillard JL, Merlino R, Pajot N, et al. Conventional and nonconventional modes of vancomycin administration to decontaminate the internal surface of catheters colonized with coagulase-negative staphylococci. JPEN J Parenter Enteral Nutr **1990**; 14:593–7.
118. Simon VC, Simon M. Antibacterial activity of teicoplanin and vancomycin in combination with rifampicin, fusidic acid or fosfomycin against staphylococci on vein catheters. Scand J Infect Dis Suppl **1990**; 72:14–9.
119. Guggenbichler JP, Berchtold D, Allerberger F, et al. In vitro and in vivo effect of antibiotics on catheters colonized by staphylococci. Eur J Clin Microbiol Infect Dis **1992**; 11:408–15.
120. Ramirez de Arellano E, Pascual A, Martinez-Martinez L, Perea EJ. Activity of eight antibacterial agents on *Staphylococcus epidermidis* attached to Teflon catheters. J Med Microbiol **1994**; 40:43–7.
121. Kropec A, Huebner J, Wursthorn M, Daschner FD. In vitro activity of vancomycin and teicoplanin against *Staphylococcus aureus* and *Staphylococcus epidermidis* colonizing catheters. Eur J Clin Microbiol Infect Dis **1993**; 12:545–8.
122. Pascual A, Ramirez de Arellano E, Martinez Martinez L, Perea EJ. Effect of polyurethane catheters and bacterial biofilms on the in-vitro activity of antimicrobials against *Staphylococcus epidermidis*. J Hosp Infect **1993**; 24:211–8.
123. Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. J Antimicrob Chemother **2005**; 55:90–4.
124. 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**; 58:816–21.
125. Krzywda EA, Andris DA, Edmiston CE Jr, Quebbeman EJ. Treatment of Hickman catheter sepsis using antibiotic lock technique. Infect Control Hosp Epidemiol **1995**; 16:596–8.
126. Benoit JL, Carandang G, Sitrin M, Arnow PM. Intraluminal antibiotic treatment of central venous catheter infections in patients receiving parenteral nutrition at home. Clin Infect Dis **1995**; 21:1286–8.
127. Arnow PM, Kushner R. Malassezia furfur catheter infection cured with antibiotic lock therapy. Am J Med **1991**; 90:128–30.
128. Soriano A, Bregada E, Marques JM, et al. Decreasing gradient of antibiotic concentration in the lumen of catheters locked with vancomycin. Eur J Clin Microbiol Infect Dis **2007**; 26:659–61.
129. Anthony TU, Rubin LG. Stability of antibiotics used for antibiotic-lock treatment of infections of implantable venous devices (ports). Antimicrob Agents Chemother **1999**; 43:2074–6.
130. Droste JC, Jeraj HA, MacDonald A, Farrington K. Stability and in vitro efficacy of antibiotic-heparin lock solutions potentially useful for treatment of central venous catheter-related sepsis. J Antimicrob Chemother **2003**; 51:849–55.
131. Onland W, Shin CE, Fustar S, Rushing T, Wong WY. Ethanol-lock technique for persistent bacteremia of long-term intravascular devices in pediatric patients. Arch Pediatr Adolesc Med **2006**; 160:1049–53.
132. Zinkernagel AS, Zinkernagel MS, Elzi MV, et al. Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. Infection **2008**; 36:314–21.
133. Byers K, Anglim A, al. E. Case fatality rate for catheter-related bloodstream infections (CRSBI): a meta-analysis [abstract 43]. In: Program and abstracts of the Fifth Annual Meeting of the Society for Hospital Epidemiology of America (San Diego). **1995**:23.
134. Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated *Staphylococcus aureus* bacteremia. Ann Intern Med **1999**; 130:810–20.
135. Pigrau C, Rodriguez D, Planes AM, et al. Management of catheter-related *Staphylococcus aureus* bacteremia: when may sonographic study be unnecessary? Eur J Clin Microbiol Infect Dis **2003**; 22:713–9.
136. Iannini PB, Crossley K. Therapy of *Staphylococcus aureus* bacteremia associated with a removable focus of infection. Ann Intern Med **1976**; 84:558–60.
137. Mylotte JM, McDermott C, Spooner JA. Prospective study of 114 consecutive episodes of *Staphylococcus aureus* bacteremia. Rev Infect Dis **1987**; 9:891–907.
138. Raad, II, Sabbagh MF. Optimal duration of therapy for catheter-related *Staphylococcus aureus* bacteremia: a study of 55 cases and review. Clin Infect Dis **1992**; 14:75–82.
139. Malanoski GJ, Samore MH, Pefanis A, Karchmer AW. *Staphylococcus aureus* catheter-associated bacteremia. Minimal effective therapy and

unusual infectious complications associated with arterial sheath catheters. Arch Intern Med **1995**; 155:1161–6.
140. Ehni WF, Reller LB. Short-course therapy for catheter-associated *Staphylococcus aureus* bacteremia. Arch Intern Med **1989**; 149:533–6.
141. Cabell CH, Fowler VG Jr. Importance of aggressive evaluation in patients with *Staphylococcus aureus* bacteremia. Am Heart J **2004**; 147: 379–80.
142. Abraham J, Mansour C, Veledar E, Khan B, Lerakis S. *Staphylococcus aureus* bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* bacteremia. Am Heart J **2004**; 147:536–9.
143. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med **2003**; 163: 2066–72.
144. Fowler VG Jr, Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. Clin Infect Dis **2005**; 40:695–703.
145. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. Jama **2005**; 293:3012–21.
146. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) **2003**; 82:322–32.
147. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis **1998**; 27:478–86.
148. Reilly JJ Jr, Steed DL, Ritter PS. Indwelling venous access catheters in patients with acute leukemia. Cancer **1984**; 53:219–23.
149. Roder BL, Wandall DA, Frimodt-Moller N, Espersen F, Skinhoj P, Rosdahl VT. Clinical features of *Staphylococcus aureus* endocarditis: a 10-year experience in Denmark. Arch Intern Med **1999**; 159:462–9.
150. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. J Am Coll Cardiol **1997**; 30:1072–8.
151. Sullenberger AL, Avedissian LS, Kent SM. Importance of transesophageal echocardiography in the evaluation of *Staphylococcus aureus* bacteremia. J Heart Valve Dis **2005**; 14:23–8.
152. Sochowski RA, Chan KL. Implication of negative results on a monoplane transesophageal echocardiographic study in patients with suspected infective endocarditis. J Am Coll Cardiol **1993**; 21:216–21.
153. Kuizon D, Gordon SM, Dolmatch BL. Single-lumen subcutaneous ports inserted by interventional radiologists in patients undergoing chemotherapy: incidence of infection and outcome of attempted catheter salvage. Arch Intern Med **2001**; 161:406–10.
154. Ruhe JJ, Menon A. Clinical significance of isolated *Staphylococcus aureus* central venous catheter tip cultures. Clin Microbiol Infect **2006**; 12: 933–6.
155. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
156. Jones RN, Marshall SA, Pfaller MA, et al. Nosocomial enterococcal blood stream infections in the SCOPE Program: antimicrobial resistance, species occurrence, molecular testing results, and laboratory testing accuracy. SCOPE Hospital Study Group. Diagn Microbiol Infect Dis **1997**; 29:95–102.
157. Gonzales RD, Schreckenberger PC, Graham MB, Kelkar S, DenBesten K, Quinn JP. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. Lancet **2001**; 357:1179.
158. Kanafani ZA, Federspiel JJ, Fowler VG Jr. Infective endocarditis caused by daptomycin-resistant *Enterococcus faecalis*: a case report. Scand J Infect Dis **2007**; 39:75–7.
159. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. Ann Intern Med **2001**; 135:484–92.
160. Anderson DJ, Murdoch DR, Sexton DJ, et al. Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. Infection **2004**; 32:72–7.
161. Fernandez-Guerrero ML, Herrero L, Bellver M, Gadea I, Roblas RF, de Gorgolas M. Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteraemia. J Intern Med **2002**; 252:510–5.
162. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis **2005**; 191:588–95.
163. Bhavnani SM, Drake JA, Forrest A, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. Diagn Microbiol Infect Dis **2000**; 36:145–58.
164. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore) **1988**; 67:248–69.
165. Gray J, Marsh PJ, Stewart D, Pedler SJ. Enterococcal bacteraemia: a prospective study of 125 episodes. J Hosp Infect **1994**; 27:179–86.
166. Sandoe JA, Witherden IR, Au-Yeung HK, Kite P, Kerr KG, Wilcox MH. Enterococcal intravascular catheter-related bloodstream infection: management and outcome of 61 consecutive cases. J Antimicrob Chemother **2002**; 50:577–82.
167. Gavalda J, Len O, Miro JM, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. Ann Intern Med **2007**; 146:574–9.
168. El-Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* in solid organ transplant recipients: report of a multicenter compassionate-use trial. Transpl Infect Dis **2003**; 5:121–5.
169. Linden PK, Moellering RC Jr, Wood CA, et al. Treatment of vancomycin-resistant *Enterococcus faecium* infections with quinupristin/dalfopristin. Clin Infect Dis **2001**; 33:1816–23.
170. Poutsiaka DD, Skiffington S, Miller KB, Hadley S, Snydman DR. Daptomycin in the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia in neutropenic patients. J Infect **2007**; 54:567–71.
171. Lautenbach E, Schuster MG, Bilker WB, Brennan PJ. The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant Enterococcus. Clin Infect Dis **1998**; 27:1259–65.
172. Seifert H. Catheter-related infections due to gram-negative bacilli. In: Seifert H, Jansen B, Farr BM, eds. Catheter-Related Infections. New York, NY: Marcel Drekker, **1997**:111–38.
173. Jacoby GA, Munoz-Price LS. The new β-lactamases. N Engl J Med **2005**; 352:380–91.
174. Raymond DP, Pelletier SJ, Crabtree TD, Evans HL, Pruett TL, Sawyer RG. Impact of antibiotic-resistant gram-negative bacilli infections on outcome in hospitalized patients. Crit Care Med **2003**; 31:1035–41.
175. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **2000**; 118:146–55.
176. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: **2008**. Crit Care Med **2008**; 36:296–327.
177. Paterson DL, Ko WC, Von Gottberg A, et al. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol **2001**; 39:2206–12.
178. Lorente L, Jimenez A, Santana M, et al. Microorganisms responsible for intravascular catheter-related bloodstream infection according to the catheter site. Crit Care Med **2007**; 35:2424–7.
179. Seifert H, Strate A, Pulverer G. Nosocomial bacteremia due to *Acinetobacter baumannii.* Clinical features, epidemiology, and predictors of mortality. Medicine (Baltimore) **1995**; 74:340–9.
180. Friedman ND, Korman TM, Fairley CK, Franklin JC, Spelman DW. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. J Infect **2002**; 45:47–53.
181. Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic

for multidrug-resistant gram-negative bacterial infections. Lancet Infect Dis **2006**; 6:589–601.
182. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis **2004**; 4:519–27.
183. Elting LS, Bodey GP. Septicemia due to *Xanthomonas* species and non-aeruginosa *Pseudomonas* species: increasing incidence of catheter-related infections. Medicine (Baltimore) **1990**; 69:296–306.
184. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med **1994**; 331:1325–30.
185. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med **2002**; 347: 2020–9.
186. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med **2007**; 356:2472–82.
187. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet **2007**; 369:1519–27.
188. Nguyen MH, Peacock JE Jr, Tanner DC, et al. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, prospective, observational study. Arch Intern Med **1995**; 155:2429–35.
189. Hung CC, Chen YC, Chang SC, Luh KT, Hsieh WC. Nosocomial candidemia in a university hospital in Taiwan. J Formos Med Assoc **1996**; 95:19–28.
190. Rex JH, Bennett JE, Sugar AM, et al. Intravascular catheter exchange and duration of candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. Clin Infect Dis **1995**; 21:994–6.
191. Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics **2000**; 106:E63.
192. Nucci M, Colombo AL, Silveira F, et al. Risk factors for death in patients with candidemia. Infect Control Hosp Epidemiol **1998**; 19: 846–50.
193. Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of *Candida* bloodstream infection: results from population-based surveillance, barcelona, Spain, from 2002 to 2003. J Clin Microbiol **2005**; 43:1829–35.
194. Kuhn DM, George T, Chandra J, Mukherjee PK, Ghannoum MA. Antifungal susceptibility of *Candida* biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. Antimicrob Agents Chemother **2002**; 46:1773–80.
195. Schinabeck MK, Long LA, Hossain MA, et al. Rabbit model of *Candida albicans* biofilm infection: liposomal amphotericin B antifungal lock therapy. Antimicrob Agents Chemother **2004**; 48:1727–32.
196. Mukherjee PK, Mohamed S, Chandra J, et al. Alcohol dehydrogenase restricts the ability of the pathogen *Candida albicans* to form a biofilm on catheter surfaces through an ethanol-based mechanism. Infect Immun **2006**; 74:3804–16.
197. Raad I, Hanna H, Dvorak T, Chaiban G, Hachem R. Optimal antimicrobial catheter lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol, rapidly eradicates organisms embedded in biofilm. Antimicrob Agents Chemother **2007**; 51:78–83.
198. Seifert H, Cornely O, Seggewiss K, et al. Bloodstream infection in neutropenic cancer patients related to short-term nontunnelled catheters determined by quantitative blood cultures, differential time to positivity, and molecular epidemiological typing with pulsed-field gel electrophoresis. J Clin Microbiol **2003**; 41:118–23.
199. Raad I, Hanna H, Maki DG. Intravascular-catheter-related infections: advances in diagnosis, prevention and mangement. Lancet Infect Dis **2007**; 7:645–57.
200. Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in patients with cancer and candidemia. Clin Infect Dis **2004**; 38:1119–27.
201. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis **2009**; 48:503–35.
202. Cotton DJ, Gill VJ, Marshall DJ, Gress J, Thaler M, Pizzo PA. Clinical features and therapeutic interventions in 17 cases of *Bacillus* bacteremia in an immunosuppressed patient population. J Clin Microbiol **1987**; 25:672–4.
203. Peces R, Gago E, Tejada F, Laures AS, Alvarez-Grande J. Relapsing bacteraemia due to *Micrococcus luteus* in a haemodialysis patient with a Perm-Cath catheter. Nephrol Dial Transplant **1997**; 12:2428–9.
204. Oudiz RJ, Widlitz A, Beckmann XJ, et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest **2004**; 126:90–4.
205. Maki DG, McCormick RD, Uman SJ, Wirtanen GW. Septic endarteritis due to intra-arterial catheters for cancer chemotherapy. I. Evaluation of an outbreak. II. Risk factors, clinical features and management, III. Guidelines for prevention. Cancer **1979**; 44:1228–40.
206. Khan EA, Correa AG, Baker CJ. Suppurative thrombophlebitis in children: a ten-year experience. Pediatr Infect Dis J **1997**; 16:63–7.
207. Verghese A, Widrich WC, Arbeit RD. Central venous septic thrombophlebitis: the role of medical therapy. Medicine (Baltimore) **1985**; 64: 394–400.
208. Strinden WD, Helgerson RB, Maki DG. *Candida* septic thrombosis of the great central veins associated with central catheters: clinical features and management. Ann Surg **1985**; 202:653–8.
209. Kaufman J, Demas C, Stark K, Flancbaum L. Catheter-related septic central venous thrombosis: current therapeutic options. West J Med **1986**; 145:200–3.
210. Falk PS, Scuderi PE, Sherertz RJ, Motsinger SM. Infected radial artery pseudoaneurysms occurring after percutaneous cannulation. Chest **1992**; 101:490–5.
211. Torres-Rojas JR, Stratton CW, Sanders CV, et al. Candidal suppurative peripheral thrombophlebitis. Ann Intern Med **1982**; 96:431–5.
212. Fry DE, Fry RV, Borzotta AP. Nosocomial blood-borne infection secondary to intravascular devices. Am J Surg **1994**; 167:268–72.
213. van Rooden CJ, Schippers EF, Barge RM, et al. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol **2005**; 23:2655–60.
214. Ghanem GA, Boktour M, Warneke C, et al. Catheter-related *Staphylococcus aureus* bacteremia in cancer patients: high rate of complications with therapeutic implications. Medicine (Baltimore) **2007**; 86: 54–60.
215. Raad I, Narro J, Khan A, Tarrand J, Vartivarian S, Bodey GP. Serious complications of vascular catheter-related *Staphylococcus aureus* bacteremia in cancer patients. Eur J Clin Microbiol Infect Dis **1992**; 11: 675–82.
216. Crowley AL, Peterson GE, Benjamin DK Jr, et al. Venous thrombosis in patients with short- and long-term central venous catheter-associated *Staphylococcus aureus* bacteremia. Crit Care Med **2008**; 36: 385–90.
217. Garrison RN, Richardson JD, Fry DE. Catheter-associated septic thrombophlebitis. South Med J **1982**; 75:917–9.
218. Walsh TJ, Bustamente CI, Vlahov D, Standiford HC. Candidal suppurative peripheral thrombophlebitis: recognition, prevention, and management. Infect Control **1986**; 7:16–22.
219. Gressianu MT, Dhruva VN, Arora RR, et al. Massive septic thrombus formation on a superior vena cava indwelling catheter following *Torulopsis (Candida) glabrata* fungemia. Intensive Care Med **2002**; 28: 379–80.
220. Falagas ME, Vardakas KZ, Athanasiou S. Intravenous heparin in combination with antibiotics for the treatment of deep vein septic thrombophlebitis: a systematic review. Eur J Pharmacol **2007**; 557:93–8.
221. Lamas CC, Eykyn SJ. Hospital acquired native valve endocarditis: analysis of 22 cases presenting over 11 years. Heart **1998**; 79:442–7.
222. Fernandez-Guerrero ML, Verdejo C, Azofra J, de Gorgolas M. Hospital-acquired infectious endocarditis not associated with cardiac surgery: an emerging problem. Clin Infect Dis **1995**; 20:16–23.

223. Terpenning MS, Buggy BP, Kauffman CA. Hospital-acquired infective endocarditis. Arch Intern Med **1988**; 148:1601–3.
224. Eggimann P, Harbarth S, Constantin MN, Touveneau S, Chevrolet JC, Pittet D. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet **2000**; 355:1864–8.
225. Siegman-Igra Y, Anglim AM, Shapiro DE, Adal KA, Strain BA, Farr BM. Diagnosis of vascular catheter-related bloodstream infection: a meta-analysis. J Clin Microbiol **1997**; 35:928–36.
226. Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative blood culture. Eur J Clin Microbiol Infect Dis **1989**; 8:142–4.
227. Maki DG, Martin WT. Nationwide epidemic of septicemia caused by contaminated infusion products. IV. Growth of microbial pathogens in fluids for intravenous infusions. J Infect Dis **1975**; 131:267–72.
228. Centers for Disease Control and Prevention. Epidemiologic notes and reports: nosocomial bacteremias associated with intravenous fluid therapy—USA. 1971. MMWR Morb Mortal Wkly Rep **1997**; 46:1227–33.
229. Garrett DO, McDonald LC, Wanderley A, et al. An outbreak of neonatal deaths in Brazil associated with contaminated intravenous fluids. J Infect Dis **2002**; 186:81–6.
230. Sunenshine RH, Tan ET, Terashita DM, et al. A multistate outbreak of *Serratia marcescens* bloodstream infection associated with contaminated intravenous magnesium sulfate from a compounding pharmacy. Clin Infect Dis **2007**; 45:527–33.
231. Centers for Disease Control and Prevention. Update: delayed onset *Pseudomonas fluorescens* bloodstream infections after exposure to contaminated heparin flush—Michigan and South Dakota, 2005–2006. MMWR Morb Mortal Wkly Rep **2006**; 55:961–3.
232. Centers for Disease Control and Prevention. *Pseudomonas* bloodstream infections associated with a heparin/saline flush—Missouri, New York, Texas, and Michigan, 2004–2005. MMWR Morb Mortal Wkly Rep **2005**; 54:269–72.
233. Centers for Disease Control and Prevention. Update: *Yersinia enterocolitica* bacteremia and endotoxin shock associated with red blood cell transfusions—United States, 1991. MMWR Morb Mortal Wkly Rep **1991**; 40:176–8.
234. Tresoldi AT, Padoveze MC, Trabasso P, et al. *Enterobacter cloacae* sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution. Am J Infect Control **2000**; 28:258–61.
235. Dixon RE, Kaslow RA, Mackel DC, Fulkerson CC, Mallison GF. Aqueous quaternary ammonium antiseptics and disinfectants: use and misuse. JAMA **1976**; 236:2415–7.
236. Frank MJ, Schaffner W. Contaminated aqueous benzalkonium chloride: an unnecessary hospital infection hazard. JAMA **1976**; 236: 2418–9.
237. Grohskopf LA, Roth VR, Feikin DR, et al. *Serratia liquefaciens* bloodstream infections from contamination of epoetin alfa at a hemodialysis center. N Engl J Med **2001**; 344:1491–7.
238. Macias AE, Munoz JM, Herrera LE, et al. Nosocomial pediatric bacteremia: the role of intravenous set contamination in developing countries. Infect Control Hosp Epidemiol **2004**; 25:226–30.
239. Richards C, Alonso-Echanove J, Caicedo Y, Jarvis WR. *Klebsiella pneumoniae* bloodstream infections among neonates in a high-risk nursery in Cali, Colombia. Infect Control Hosp Epidemiol **2004**; 25: 221–5.
240. Archibald LK, Ramos M, Arduino MJ, et al. *Enterobacter cloacae* and *Pseudomonas aeruginosa* polymicrobial bloodstream infections traced to extrinsic contamination of a dextrose multidose vial. J Pediatr **1998**; 133:640–4.
241. Sardan YC, Zarakolu P, Altun B, et al. A cluster of nosocomial *Klebsiella oxytoca* bloodstream infections in a university hospital. Infect Control Hosp Epidemiol **2004**; 25:878–82.
242. Prospero E, Barbadoro P, Savini S, Manso E, Annino I, D'Errico MM. Cluster of *Pseudomonas aeruginosa* catheter-related bloodstream infections traced to contaminated multidose heparinized saline solutions in a medical ward. Int J Hyg Environ Health **2006**; 209:553–6.
243. Takahashi H, Kramer MH, Yasui Y, et al. Nosocomial *Serratia marcescens* outbreak in Osaka, Japan, from 1999 to 2000. Infect Control Hosp Epidemiol **2004**; 25:156–61.
244. *Enterobacter cloacae* bloodstream infections associated with contaminated prefilled saline syringes—California, November 1998. MMWR Morb Mortal Wkly Rep **1998**; 47:959–60.
245. Watson JT, Jones RC, Siston AM, et al. Outbreak of catheter-associated *Klebsiella oxytoca* and *Enterobacter cloacae* bloodstream infections in an oncology chemotherapy center. Arch Intern Med **2005**; 165:2639–43.
246. Pan A, Dolcetti L, Barosi C, et al. An outbreak of *Serratia marcescens* bloodstream infections associated with misuse of drug vials in a surgical ward. Infect Control Hosp Epidemiol **2006**; 27:79–82.
247. Perz JF, Craig AS, Stratton CW, Bodner SJ, Phillips WE Jr, Schaffner W. *Pseudomonas putida* septicemia in a special care nursery due to contaminated flush solutions prepared in a hospital pharmacy. J Clin Microbiol **2005**; 43:5316–8.
248. Selenic D, Dodson DR, Jensen B, Arduino MJ, Panlilio A, Archibald LK. *Enterobacter cloacae* bloodstream infections in pediatric patients traced to a hospital pharmacy. Am J Health Syst Pharm **2003**; 60: 1440–6.
249. Civen R, Vugia DJ, Alexander R, et al. Outbreak of *Serratia marcescens* infections following injection of betamethasone compounded at a community pharmacy. Clin Infect Dis **2006**; 43:831–7.
250. Siegman-Igra Y, Jacobi E, Lang R, Schwartz D, Carmeli Y. Unexpected hospital-acquired bacteraemia in patients at low risk of bloodstream infection: the role of a heparin drip. J Hosp Infect **2005**; 60:122–8.
251. Moreira BM, Leobons MB, Pellegrino FL, et al. *Ralstonia pickettii* and *Burkholderia cepacia* complex bloodstream infections related to infusion of contaminated water for injection. J Hosp Infect **2005**; 60: 51–5.
252. Tanaka T, Takahashi H, Kobayashi JM, Ohyama T, Okabe N. A nosocomial outbreak of febrile bloodstream infection caused by heparinized-saline contaminated with *Serratia marcescens,* Tokyo, 2002. Jpn J Infect Dis **2004**; 57:189–92.
253. Nasser RM, Rahi AC, Haddad MF, Daoud Z, Irani-Hakime N, Almawi WY. Outbreak of *Burkholderia cepacia* bacteremia traced to contaminated hospital water used for dilution of an alcohol skin antiseptic. Infect Control Hosp Epidemiol **2004**; 25:231–9.
254. Sebert ME, Manning ML, McGowan KL, Alpern ER, Bell LM. An outbreak of *Serratia marcescens* bacteremia after general anesthesia. Infect Control Hosp Epidemiol **2002**; 23:733–9.
255. Ostrowsky BE, Whitener C, Bredenberg HK, et al. *Serratia marcescens* bacteremia traced to an infused narcotic. N Engl J Med **2002**; 346: 1529–37.
256. American Academy of Pediatrics. In: Pickering LK, ed. Redbook: 2003 report on the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, **2003**.
257. Nelson JD. 2000 Pocketbook of pediatric antimicrobial therapy. 14th ed. Baltimore, MD: Lippincott, Williams & Wilkins, **2000**.
258. Chee L, Brown M, Sasadeusz J, MacGregor L, Grigg AP. Gram-negative organisms predominate in Hickman line-related infections in non-neutropenic patients with hematological malignancies. J Infect **2008**; 56:227–33.
259. Rodriguez-Creixems M, Alcala L, Munoz P, Cercenado E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985–2006. Medicine (Baltimore) **2008**; 87:234–49.
260. Blot S, Janssens R, Claeys G, et al. Effect of fluconazole consumption on long-term trends in candidal ecology. J Antimicrob Chemother **2006**; 58:474–7.
261. Blue SR, Singh VR, Saubolle MA. *Bacillus licheniformis* bacteremia: five cases associated with indwelling central venous catheters. Clin Infect Dis **1995**; 20:629–33.
262. Ruhe J, Menon A, Mushatt D, Dejace P, Hasbun R. Non-epidermidis coagulase-negative staphylococcal bacteremia: clinical predictors of true bacteremia. Eur J Clin Microbiol Infect Dis **2004**; 23:495–8.

263. Finkelstein R, Fusman R, Oren I, Kassis I, Hashman N. Clinical and epidemiologic significance of coagulase-negative staphylococci bacteremia in a tertiary care university Israeli hospital. Am J Infect Control **2002**; 30:21–5.
264. Ingram J, Weitzman S, Greenberg ML, Parkin P, Filler R. Complications of indwelling venous access lines in the pediatric hematology patient: a prospective comparison of external venous catheters and subcutaneous ports. Am J Pediatr Hematol Oncol **1991**; 13:130–6.
265. Allon M, Daugirdas J, Depner TA, Greene T, Ornt D, Schwab SJ. Effect of change in vascular access on patient mortality in hemodialysis patients. Am J Kidney Dis **2006**; 47:469–77.
266. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin Infect Dis **2007**; 44:190–6.
267. Benjamin DK Jr, Miller W, Garges H, et al. Bacteremia, central catheters, and neonates: when to pull the line. Pediatrics **2001**; 107:1272–6.
268. Bouza E, Burillo A, Munoz P. Empiric therapy for intravenous central line infections and nosocomially-acquired acute bacterial endocarditis. Crit Care Clin **2008**; 24:293–312, viii-ix.
269. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis **1997**; 24:584–602.
270. Chirinos JA, Garcia J, Alcaide ML, Toledo G, Baracco GJ, Lichtstein DM. Septic thrombophlebitis: diagnosis and management. Am J Cardiovasc Drugs **2006**; 6:9–14.
271. Garcia J, Aboujaoude R, Apuzzio J, Alvarez JR. Septic pelvic thrombophlebitis: diagnosis and management. Infect Dis Obstet Gynecol **2006**; 2006:15614.
272. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation **2005**; 111:e394–434.
273. Chu VH, Bayer AS. Use of echocardiography in the diagnosis and management of infective endocarditis. Curr Infect Dis Rep **2007**; 9: 283–90.
274. Vieira ML, Grinberg M, Pomerantzeff PM, Andrade JL, Mansur AJ. Repeated echocardiographic examinations of patients with suspected infective endocarditis. Heart **2004**; 90:1020–4.
275. Robinson JL, Tawfik G, Saxinger L, Stang L, Etches W, Lee B. Stability of heparin and physical compatibility of heparin/antibiotic solutions in concentrations appropriate for antibiotic lock therapy. J Antimicrob Chemother **2005**; 56:951–3.
276. Lee JY, Ko KS, Peck KR, Oh WS, Song JH. In vitro evaluation of the antibiotic lock technique (ALT) for the treatment of catheter-related infections caused by staphylococci. J Antimicrob Chemother **2006**; 57:1110–5.
277. Vercaigne LM, Sitar DS, Penner SB, Bernstein K, Wang GQ, Burczynski FJ. Antibiotic-heparin lock: in vitro antibiotic stability combined with heparin in a central venous catheter. Pharmacotherapy **2000**; 20:394–9.
278. Crnich CJ, Halfmann JA, Crone WC, Maki DG. The effects of prolonged ethanol exposure on the mechanical properties of polyurethane and silicone catheters used for intravascular access. Infect Control Hosp Epidemiol **2005**; 26:708–14.
279. Pediatric Lexi-Comp Drugs. Available at: http://www.lexi.com. Accessed 12 May 2009.
280. Benjamin DK Jr, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. Antimicrob Agents Chemother **2006**; 50:632–8.
281. 2008 Neofax: a manual of drugs used in neonatal care. 21st ed. Physician's Desk Reference, **2008**.