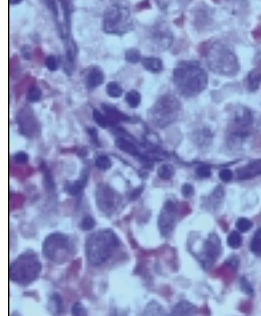


CATHETER-RELATED BLOODSTREAM INFECTIONS, PART I: PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT

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Introduction

Each year in the United States, hospitals and clinics purchase more than 150 million intravascular devices to monitor hemodynamic status, to provide hemodialysis, and to administer intravenous (IV) medications, blood products, and parenteral nutrition fluids.^{1,2} The majority of these devices are peripheral venous catheters, but over 5 million central venous catheters (CVCs) are inserted each year. More than 200,000 nosocomial bloodstream infections occur annually in the United States, most of which are related to different types of intravascular devices, particularly nontunneled CVCs (Table).^{2,4} The risk factors for IV catheter-related infections vary according to the type of catheter, the hospital size, unit, or service, the location of the site of insertion, and the duration of catheter placement.^{2,4,5} Catheter-related bloodstream infections (CRBIs) continue to be a serious problem in critically ill patients.^{4,8} Infections related to IV devices result in significant increases in hospital costs, duration of hospitalization, and patient morbidity. The cost of treating a single episode of CRBI has been estimated to be in excess of \$28,000.⁷

Pathogenesis

Microorganisms gain access to the extraluminal or intraluminal surface of the device by one of the

three following mechanisms: (1) skin organisms invade the percutaneous tract at the time of insertion or afterwards, (2) microorganisms contaminate the catheter hub (and lumen) when the catheter is inserted over a percutaneous guidewire or when it is later manipulated, and (3) organisms are carried hematogenously to the implanted IV device from remote sources of local infection.

For short-term, nontunneled, noncuffed catheters, the skin insertion site is the major source of colonization. Organisms migrate along the external surface of the catheter and the intercutaneous and subcutaneous segments, leading to colonization of the intravascular catheter tip, which may cause bloodstream infection.⁹⁻¹¹ For long-term catheters such as cuffed, tunneled, silicone catheters (Hickman or Broviac; Bard Access Systems, Murray Hill, NJ) or implantable catheters such as ports, the lumen of the hub or the bell of the port is the major source of colonization.^{2,5}

The microorganisms most commonly associated with peripheral vascular and CVC infection are coagulase-negative staphylococci, *Staphylococcus aureus*, different species of aerobic Gram-negative bacilli, and *Candida albicans*. Because colonization on the hands of medical personnel or the skin of the patient is the main source for the contamination of catheters, staphylococci, particularly coagu-

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lase-negative staphylococci, and *S aureus* are the leading causes of CRBIs. Most of the Gram-negative bacilli causing CRBIs are nonenteric organisms acquired from the hospital environment, such as *Stenotrophomonas maltophilia*, *Pseudomonas* organisms, and *Acinetobacter* species. *C albicans* and *C parapsilosis* also colonize on the hands of medical personnel

and are associated with glucose-containing infusions and total parenteral nutrition.

Staphylococci, *Candida*, and some other microbes produce a slimy material rich in exopolysaccharides. This material produces a microbial biofilm that helps these organisms to survive on the surfaces of foreign bodies in the blood-

stream. For this reason, the microorganisms within the biofilm layer are resistant to the activity of antibiotics. Thus, it is often difficult to eradicate a CRBI without removing the catheter. Following catheter insertion, a thrombin layer or sheath covers the external and the internal surfaces of the intravascular segment and promotes adherence of potential microbial patho-

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gens to that surface. This sheath is rich in host-derived proteins, eg, fibrin, fibronectin, thrombospondin, and laminin, that act as adhesins.¹²⁻¹⁵ Adhesins that allow coagulase-negative staphylococci to bind to the polymer composite of catheters have also been identified.¹⁶ Thus, the organisms colonizing the catheter surface are attached to adhesins on the surfaces of the catheter, are covered by a protective layer of biofilm, and are difficult to eradicate.

The administration of blood products through CVCs is a risk factor for CRBI, although thrombocytopenia during catheterization may provide some protection against CRBI, as does CVC insertion under maximal sterile barrier precautions.¹⁷ The prevention of infection associated with continuous IV infusion of factor VIII poses a number of challenges. Assurances of the sterility of the product and proper storage of the product prior to use are of paramount importance. Prevention of infection requires attention to the conditions surrounding insertion of the catheter, including the optimal site of insertion, maximal barrier precautions, and optimal disinfection of the insertion sites. Following insertion, attention must be paid to maintenance issues of the device, including proper disinfection and aseptic techniques when manipulating the catheter hub, daily assessment of the insertion site, and adherence to scheduled changes of the IV tubing. Using proper precautions, the risk of serious infection associated with a continuous infusion of factor VIII can be minimal.¹⁸

Diagnosis

Culture of the catheter is considered the “gold standard” for the diagnosis of catheter infection. Fever with or without chills has poor specificity. Inflammation or purulence around the intravascular device and bloodstream infection has greater specificity but poor sensitivity.² Blood culture results that are positive for *S aureus*, coagulase-negative staphylococci, or *Candida* species, in the absence of any other identifiable source of infection, should increase the suspicion for CRBI.^{3,5,19}

Infected exit sites are usually apparent by the presence of erythema, warmth, tenderness, and swelling. The patient often becomes febrile or develops signs of sepsis while the source remains unknown. Local inflammation is present in less than half of the cases, and the full syndrome of fevers, chills, and hypotension may take days to develop.²⁰ When central veins are involved, diagnosis relies on the combination of positive blood cultures and imaging techniques to detect thrombosis. Endocarditis or septic thrombophlebitis may be suspected if bacteremia persists for more than 48 hours after removal of the infected device. The microbiological tests that may assist in diagnosis can be divided into those that do or do not require removal of the device.

Rapid Diagnostic Techniques

Gram staining of catheter segments may be helpful for the diag-

nosis of local infections but is less sensitive than quantitative methods for the diagnosis of CRBIs.²¹ In one study, use of acridine orange stains for rapid diagnosis resulted in a positive predictive value of 91% and a negative predictive value of 97%.²²

Cultures of Samples of IV Catheters

Vortexing, sonicating, or flushing the catheter lumen with broth catheter culture techniques^{23,24} are the most reliable diagnostic methodologies because they have greater specificity in the identification of catheter-related infection compared with qualitative cultures, where a single contaminating microbe can result in a positive culture result.^{25,26} The most widely used laboratory technique for the clinical diagnosis of catheter-related infection is the semiquantitative method, in which the catheter segment is rolled across the surface of an agar plate and colony-forming units are counted after overnight incubation.²³ Quantitative culture of the catheter segment requires either flushing the segment with broth or vortexing or sonicating it in broth, followed by serial dilutions and surface plating on blood agar.²⁷⁻²⁹ The roll-plate semiquantitative culture method is limited in that it cultures only the external surface of catheters and may not retrieve organisms that are embedded within the biofilm layer on the catheter surface. The limitation of the semiquantitative and quantitative catheter culture methods is that they require removal of the catheter to aid in the diagnosis of

CRBIs.³⁰ This often results in unnecessary removal of noncolonized catheters. At this time, it is unclear whether any of these differences are clinically significant.

Paired Cultures of Blood Drawn Percutaneously and Through the IV Catheter

Patients with suspected IV catheter-related infection have two sets of blood samples drawn for culture, with at least one set drawn percutaneously. The clinical usefulness of cultures of blood samples drawn from an indwelling CVC was assessed in a study of hospitalized patients with cancer.³¹ In these patients, culture of blood drawn through either the central catheter or peripheral vein showed excellent negative predictive value. Culture of blood drawn through an indwelling CVC had low positive predictive value, apparently less than from a peripheral venipuncture. A positive culture result for a blood sample drawn through a catheter requires clinical interpretation, but a negative result is helpful for excluding CRBI.

Quantitative Cultures of Peripheral and CVC Blood Samples

This technique relies on quantitative culture of paired blood samples, one obtained through the central catheter hub and the other from a peripheral venipuncture site. In most studies, blood obtained from the CVC yields a colony count at least 5- to 10-fold greater than blood obtained from a peripheral vein. This finding is

predictive of CRBI.³² Among tunneled catheters, for which the method is most accurate, a quantitative culture of blood from the CVC that yields at least 100 colony-forming units per microliter may be diagnostic without a companion culture of a peripheral blood sample.³³

Endoluminal Brush Technique

This technique involves brushing the lumen of the catheter and using an acridine orange leukocyte cytospin test on blood drawn through colonized catheters. To determine the accuracy of an endoluminal brush method for the diagnosis of catheter-related sepsis, 230 CVCs in 216 patients were examined prospectively.³⁴ The results were compared with those obtained using methods that require line sacrifice: extraluminal sampling (Maki roll) or endoluminal sampling (modified Cleri flush) of microorganisms. Diagnosis of catheter-related sepsis by the endoluminal brush method could be achieved without line sacrifice and was more sensitive (95%) and specific (84%) than extraluminal sampling of the catheter tip by the Maki roll technique (82% and 66%, respectively).

Differential Time to Positivity for CVC vs Peripheral Blood Cultures

To diagnose catheter-related sepsis without removing the catheter, this method compares the differential time to positivity for qualitative cultures of blood sam-

ples drawn from the catheter and a peripheral vein. It uses continuous blood-culture monitoring for positivity (eg, radiometric methods). An earlier positivity (at least 2 hours) of central vs peripheral simultaneous venous blood cultures suggests catheter-related bacteremia. When used to study tunneled catheters, this method provides accuracy comparable to that of quantitative cultures of blood samples and is cost effective.^{35,36} In a study of differential time to positivity, a definite diagnosis of catheter-related bacteremia could be made in 16 of the 17 patients who had a positive result of culture of a blood sample from the CVC at least 2 hours earlier than they had a positive result of a peripheral blood culture. The overall sensitivity was 91% and specificity was 94%.³⁵ Over a 14-month period in an intensive care unit of a cancer referral center, Blot et al³⁶ obtained simultaneous hub blood and peripheral blood cultures (a mean of 2 per patient) from patients with a suspected CRBI. This prospective study suggested that measurement of the differential time to positivity between hub blood cultures and peripheral blood cultures is a simple and reliable tool for in situ diagnosis of catheter-related sepsis in cancer patients.

Infusate-Related Bloodstream Infection

This is defined as the isolation of the same organism from both infusate and separate percutaneous blood cultures, with no other source of infection. The sudden onset of symptoms of bloodstream

infection soon after the initiation of an infusion, resulting from the administration of contaminated IV fluid, is often diagnostic.²

Venous Access Ports

For port-related infections, catheter-tip culture does not seem to be sufficiently sensitive for the diagnosis of infection since the internal lumen of the port is the source of infection in almost half of the patients.³⁷ The accumulation of infected clots under the silicone septum of the reservoir of venous access ports (VAPs) has been reported. In a study by Douard and colleagues,³⁸ all VAPs removed were prospectively investigated. Before VAP removal, paired quantitative blood cultures were 77% sensitive and 100% specific and had a positive predictive value of 100% and a negative predictive value of 98% for diagnosing VAP bloodstream infections. After VAP removal, tip culture was only 46% sensitive, whereas septum culture was 93.3% sensitive for confirming the diagnosis of VAP bloodstream infections. Therefore, infected deposits that accumulate under the VAP septum are the main source of VAP bloodstream infections.

Management

The most crucial question related to the management of CRBIs is to determine whether the catheter should be removed. A sensible approach is to base the decision on low, moderate, or high risk of CRBIs. Risk depends on the type of the organism (low or high viru-

lence) and whether the CRBI is complicated or uncomplicated.

A low-risk CRBI consists of an uncomplicated CRBI caused by an organism of low virulence usually not associated with deep-seated infections, such as coagulase-negative staphylococci.³⁹⁻⁴¹ For low-risk CRBIs, the infections can be treated without removal of the catheter.⁴² At least 80% of CRBIs caused by coagulase-negative staphylococci respond to antibiotic therapy without the removal of the catheter.⁴³ However, in a patient with a prosthetic heart valve, the catheter should be removed.

A moderate-risk CRBI consists of an uncomplicated CRBI that is caused by organisms of a moderate to high virulence associated with the tendency for deep-seated infections, such as *S aureus* and *Candida* species.⁴⁴⁻⁴⁶ For moderate-risk CRBIs, the short-term catheters should be removed.⁴⁶ In this case, transesophageal echocardiography may aid in the decision to remove the catheters.⁴⁷ In stable patients with long-term tunneled catheters responding to antimicrobial therapy, the use of an antibiotic lock solution without the removal of the catheter may be considered.^{48,49}

A high-risk CRBI is a complicated CRBI, often occurring in a critically ill or immunocompromised patient.⁵⁰⁻⁵³ A complicated CRBI consists of hypotension or organ hypoperfusion, persistence of the fever or positive blood culture for more than 48 hours after the initiation of antimicrobial ther-

apy, presence of septic thrombosis of the great vein, septic emboli, deep-seated infections such as endocarditis^{54,55} and presence of a tunnel or port pocket infection. For these patients, removal of the involved catheter is necessary.⁵⁶⁻⁵⁸ Vancomycin is the drug of choice for the treatment of CRBIs caused by methicillin-resistant staphylococci. However, novel antimicrobial agents, such as linezolid or the combination of quinupristin and dalbapristin with activity against methicillin-resistant staphylococci, may serve as alternative agents to vancomycin, particularly in patients who are either allergic to vancomycin or colonized with vancomycin-resistant enterococci.^{59,60}

The treatment duration for coagulase-negative staphylococci-related CRBIs is usually 5 to 10 days; for uncomplicated *S aureus*-related CRBIs, the range is from 10 to 14 days.^{61,62} However, patients with deep-seated infections (endocarditis or septic thrombosis) associated with the CRBI should receive 4 to 6 weeks of treatment with antimicrobial therapy.⁶³ CRBIs caused by *C albicans* or *C parapsilosis* can be treated with fluconazole.^{64,65} However, resistant organisms, such as *C krusei*, should be treated with high-dose amphotericin B.⁶⁶⁻⁶⁸ A prospective, randomized study of 206 patients, most of whom had suspected catheter-related candidemia, showed that fluconazole given for at least 14 days after catheter removal was as effective as amphotericin B therapy.⁶⁹ Extensive guidelines for the management of catheter-related infections have been recently published.⁷⁰

Antibiotic therapy for CRBI is often initiated empirically. The initial choice of antibiotics depends on the severity of the patient's clinical disease, the risk factors for infection, and the likely pathogens associated with the specific intravascular device. Patients with catheter-related bacteremia should be divided into those with complicated infections, in which there is septic thrombosis, endocarditis, osteomyelitis, or possible metastatic seeding, and those with uncomplicated bacteremia, in which there is no evidence of such complications.

Short-term Peripheral Venous Catheters

If a patient has infection of a short-term peripheral catheter, the catheter should be removed, the tip should be cultured semiquantitatively, and at least 2 separate cultures of blood samples, one of which is drawn percutaneously, should be obtained before initiation of antibiotic therapy.²

Nontunneled CVCs

The diagnosis and management points for patients with a

nontunneled CVC and unexplained fever are summarized in Fig 1. In patients with fever and mild to moderate disease, CVCs should not routinely be removed. The CVC should be removed and cultured if the patient has severe disease or erythema overlying the catheter exit site, purulence at the catheter exit site, or clinical signs of unexplained sepsis.² If the blood culture results are positive or if the CVC is exchanged over a guidewire and has significant colonization by quantitative or semiquantitative cultures, the catheter should be removed and a new catheter

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should be placed in a new site.⁷¹ If there is no evidence of persistent bloodstream infection or if the infecting organism is a coagulase-negative staphylococci and there is no suspicion of local or metastatic complications, the CVC may be retained.⁷² Transesophageal echocardiography should be used to rule out vegetations in patients with *S aureus* CRBIs.⁷³⁻⁷⁵

If bacteremia or fungemia persists or if clinical improvement is lacking, especially if more than 3

days has passed since catheter withdrawal and initiation of appropriate antimicrobial therapy has not been effective, then an aggressive workup for septic thrombosis, infective endocarditis, and other metastatic infections should ensue. A febrile patient with valvular heart disease or a patient with neutropenia (absolute neutrophil count, <1,000 cells/mL) whose catheter tip culture reveals significant growth of *S aureus* or *C albicans* should be followed closely for signs of infection, and some experts

would administer a short course (5 to 7 days) of antibiotics. This is based on the fact that *S aureus* and *Candida* organisms are more likely than enterococci or Gram-negative bacilli to be associated with CRBIs and complications.⁷⁶⁻⁷⁸

Tunneled CVCs or Implantable Devices

Surgically implantable vascular devices consist of either surgically implantable catheters, such as a tunneled silicone catheter (eg, a

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Hickman, Broviac, or Groshong catheter), or implantable devices, such as a Port-a-Cath (Deltec Inc, St. Paul, Minn).⁵ Because removal of a surgically implantable vascular device is often a management challenge, it is important to ensure that the patient has a true CRBI rather than skin contamination, catheter colonization, or infection from another source (Fig 2). For a patient who has a tunneled CVC and a single blood culture result that is positive for coagulase-negative staphylococci, the clinician should repeat the blood cultures and not remove the catheter or initiate antimicrobial therapy before determining that the positive result reflects a true CRBI and that the catheter is the source of the bloodstream infection.⁷⁹ Microbiological data suggestive of bloodstream infection caused by coagulase-negative staphylococci, rather than contamination, include multiple positive blood culture results, quantitative cultures of blood samples drawn from a catheter with 100 colony-forming units per microliter, and isolation of the same organism from quantitative catheter cultures and percutaneous blood cultures.⁸⁰ A differential growth time of more than 2 hours for cultures of blood samples obtained through the CVC, compared with cultures of peripheral blood samples, is also predictive of CRBI.

Patients with complicated device infections, such as tunnel infection or port abscess, require removal of the catheter and 7 to 10 days of antibiotic therapy; patients with septic thrombosis or endocarditis require removal of the

catheter or device and antibiotic treatment for 4 to 6 weeks; and patients with osteomyelitis require removal of the catheter and antibiotic treatment for 6 to 8 weeks.⁵ In the presence of uncomplicated infection due to coagulase-negative staphylococci, the CVC may be retained if there is no evidence of persisting or relapsing bacteremia.⁷² For catheter-related bacteremia caused by organisms other than coagulase-negative staphylococci, some investigators would retain the CVC, depending on the patient's clinical status, and would use systemic and antibiotic lock therapy.

Complications

Septic Thrombosis

Septic thrombosis is a serious complication of intravascular catheterization and may involve central veins or arteries after prolonged dwell times. Patients often have high-grade and persistent bacteremia or fungemia. Continued positive blood culture results following catheter withdrawal suggest a diagnosis of septic thrombosis or endocarditis. Septic pulmonary emboli and other metastatic infections may complicate this condition.^{44,81} Because an infected intravascular thrombus and intraluminal abscess may remain intact until after catheter removal, this infection may not become apparent until after catheter removal.^{82,83} Septic thrombosis due to a peripheral arterial catheter may present with a pseudoaneurysm or embolic lesions of the involved hand.^{84,85} Patients with septic thrombosis of the great

central veins may have ipsilateral neck, chest, or upper extremity swelling. In general, *S aureus* is the most common infecting organism. Less common pathogens include *Candida* species⁸⁶ and Gram-negative bacilli.⁷⁹ There are no randomized studies to guide the optimal choice or duration of antibiotics, the use of anticoagulants such as heparin, or possible excision of the involved vessel.

Persistent Bloodstream Infection and Infective Endocarditis

Colonized intravascular catheters are the most common identified source of nosocomial endocarditis, accounting for one to two thirds of reported cases. Staphylococci are the most common causative pathogens in these cases. For nontunneled catheters, and in most instances involving tunneled catheters, persistent bacteremia or fungemia warrants removal of the device, especially in patients with sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Repeatedly positive blood cultures, unchanged clinical status, or both for 3 days after catheter removal usually reflect serious sequelae such as septic thrombosis, endocarditis, or metastatic foci of infection. Such patients should be treated presumptively for an endovascular infection by use of antimicrobial therapy for >4 weeks (in most cases) and surgical intervention when indicated unless septic thrombosis has been ruled out radiographically and endocarditis has been excluded by transesophageal echocardiography.^{87,88}

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