Infections Related to Vascular Access Devices

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Introduction

Single-lumen, tunneled, cuffed silicone elastomer catheters for central venous access were first developed in 1973 by Broviac and Scribner.[1] Subsequently, a larger tunneled catheter was introduced by Hickman et al,[2] and intravenous access is now available via totally implanted venous access devices.

Although the central venous catheter (CVC) reduces the risk of phlebitis, it is 20 to 300 times more expensive and has as much as a 20-fold higher rate of catheter-related bloodstream infection than the peripheral venous catheter.[3] More than 175 million intravascular devices of various types are sold in the United States each year.[3] Of these, five million CVCs are placed annually, with approximately 500,000 catheters associated with infections.[4]

Infection is a leading complication, and catheter-related sepsis represents the most frequent life-threatening complication of vascular catheters.[5] The risk of CVC-related infection depends on several factors such as catheter type, underlying disease of the patient, duration of use, and catheter care and management.[6]

Pathogenesis

Four potential sources for catheter colonization and catheter-related sepsis include the skin insertion site, the catheter hub, hematogenous seeding of the catheter, and infusion contamination. The first two are the most important sources.[5] High-level colonization at the skin insertion site and external catheter colonization are strongly correlated with catheter-related sepsis (ie, in place less than 10 days).[7] Organisms that are present on skin surrounding the catheter wound are frequently the same organisms recovered from CVC-related bacteremia.

Hub contamination is the more likely mechanism of infection for long-term catheters (ie, in place more than 30 days). Catheter-related bacteremia from long-term catheters is the result of contamination of the catheter hub with migration of organisms via the internal lumen.[8]

Diagnosis

Culture of the catheter is considered the “gold standard” for the diagnosis of catheter infection. The semiquantitative roll-plate method is used in most diagnostic laboratories.[8] Other methods used in research settings include quantitative cultures of fluid from catheter flushing or sonication to sample both the luminal and exterior catheter surface.[8] Quantitative catheter culture techniques are limited in that the diagnosis is retrospective and the catheter must be removed for culture. One method to assess for catheter infection without removing the catheter is to obtain quantitative cultures from the catheter and peripheral blood simultaneously. If the number of organisms found in the catheter blood culture is five times (or more) greater than the number found in the peripheral specimen, then catheter-related bacteremia or fungemia is present. Proper management begins with defining the type of catheter-related infection (Table 1).

Choice of Catheter Type

Efforts to prevent skin microorganisms from entering the catheter wound and bloodstream include tunneling of catheters, using catheter cuffs, and totally implanting the catheter. Sterile insertion and meticulous catheter care by a select team are the most effective means to prevent catheter-related infection. In general, subcutaneously implanted ports are associated with fewer infections than externally accessed catheters.[9] Host factors are also important to assess risk of subsequent CVC-related infection. Devices inserted in patients with solid tumors have longer infection-free times than those in patients with hematologic malignancies.[10]

Catheter Location

The placement site of the CVC depends on several factors: the preference of the clinician inserting the catheter (anesthesiologists prefer the jugular vein, while internists and most surgeons prefer the subclavian vein), the need for emergent venous access, and the presence of central venous thrombosis associated with malignancy and its treatment.

Rates of local infections and catheter-related bacteremias are higher when femoral insertion sites are used rather than the subclavian or jugular insertion sites.[11] According to Goetz et al,[11] catheters placed via internal jugular veins are more likely to become infected than catheters placed via subclavian veins.

Management

Exit site infections usually are cured with antibiotics without the need for catheter removal (Fig 1). Tunnel infections occur earlier than device-related bacteremia or fungemia and can be associated with serious local morbidity or death (Figs 2A and 2B). Tunnel infections almost always require CVC removal.

Central venous septic thrombophlebitis is a potentially lethal complication that can be successfully managed with prompt catheter removal and intravenous antimicrobial therapy. Surgery is considered when a suppurative focus is present around the vein.[12] Figs 3A and 3B demonstrate septic pulmonary emboli from hematogenous seeding of infected intravascular clot.
Contaminated infusate given through the CVC is a rare cause of catheter-related sepsis but is the most common identified cause of epididymal nosocomial bacteremia. Several microorganisms, mostly Gram-negative bacilli, are capable of multiplying in parenteral glucose-containing solutions. Parenteral nutrition solutions and lipid emulsions can promote the growth of *Candida* species and *Malassezia furfur*, respectively.

**Catheter Removal**

Indications for catheter removal are summarized in Table 2. Infection eventually occurs in nearly 25% of central venous access devices. The catheter is not the cause of every fever, and the presence or persistence of fever does not mean that the catheter either is infected or needs to be removed.[13] Generally, a catheter does not need to be removed unless the blood culture has remained persistently positive after 72 hours of appropriate antibiotics or the patient has evidence of a tunnel infection.

More than 95% of patients with chemotherapy-induced neutropenic fever or bacteremia will not require CVC removal.[14] Catheters should not be removed empirically for persistent fever in neutropenic patients since catheter removal does not affect resolution of fever.[15]

**Coagulase-Negative Staphylococci**

Bacteremias in neutropenic patients shifted from Gram-negative bacilli to Gram-positive organisms during the 1980s. Currently, the most frequent cause of bacteremia in neutropenic patients is coagulase-negative staphylococci (CNS). One half to two thirds of the bacteremias due to CNS in these patients are of unknown origin.[8]

CNS organisms are common, usually avulent, commensal organisms of human skin that have become pathogens of medical progress. The dramatic increase in CNS bacteremia parallels the use of long-term intravascular catheters.[8] The organisms account for half of the 60,000 cases of nosocomial bacteremia caused each year by intravascular catheters, with *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* being most common.

Although CNS organisms are the predominant cause of nosocomial bacteremia and infect a wide variety of prosthetic medical devices, they also commonly cause blood culture contamination.[8] The positive predictive value of blood cultures from which CNS bacteremia were isolated was 4.1% to 11.7%. However, in a high-risk population, 26% of blood cultures that were positive for CNS represented infections.[16] The ability of CNS to produce "slime" or an exopolysaccharide when in contact with a prosthetic device allows for persistence of infection that necessitates catheter removal in some instances.[8]

Vancomycin given for seven days for coagulase-negative staphylococci CVC-related bacteremia is effective if defervescence and sterilization of the blood occur within 48 to 72 hours. A shorter duration may be used if the CVC is removed.[7]

*S. haemolyticus* represents approximately 10% of clinical CNS isolates[17] and is characterized by resistance to multiple antimicrobial agents including vancomycin. Due to its antimicrobial resistance profile, *S. haemolyticus* bacteremia may require catheter removal for cure more often than other CNS.

**Staphylococcus Aureus**

Vascular catheters are the most common source of *Staphylococcus aureus* bacteremia, especially in hospitalized patients. Serious complications characterized by deep-seated infection or fatal sepsis occur in 20% to 30% of cases following catheter-related *S. aureus* bacteremia.[18] Fever and/or bacteremia that persists for more than three days after catheter removal and initiation of antibiotic therapy were associated with an acutely complicated course requiring prolonged treatment.[18] A delayed response to catheter removal and antibiotic therapy characterize the clinical course of the patients with early complications.

Uncomplicated CVC-related bacteremia should be treated for 10 to 14 days with a semisynthetic penicillin (oxacillin, nafcillin) or vancomycin. *S. aureus* bacteremia complicated by a deep-seated infection such as septic thrombosis, endocarditis, osteomyelitis, septic emboli, abscesses, and septic arthritis should be treated with four to six weeks of the aforementioned antibiotics.[5] Addition of gentamicin for the first one to two weeks may improve eradication of *S. aureus* infection. When *S. aureus* endocarditis is suspected, echocardiography is performed to rule out a valve ring abscess, large vegetations, and incompetent valves.

**Enterococci**

Enterococci accounted for 8% of nosocomial bloodstream infections reported to the National Nosocomial Infection Surveillance during 1986 to 1989.[19] During 1989 to 1993, 3.8% of the bloodstream infections reported were vancomycin resistant. Risk factors for vancomycin-resistant enterococci (VRE) bacteremia include receipt of antimicrobials (including vancomycin), gastrointestinal colonization with VRE, use of indwelling devices, prolonged hospital stay, and patients with cancer or posttransplantation. VRE bacteremia was associated with a higher mortality (36.6%) than vancomycin-susceptible strains (16.4%).[20] However, attributable mortality to antimicrobial resistance was not assessed. At our center, 10 VRE bacteremias in neutropenic patients required catheter removal for cure in addition to ampicillin/sulbactam, gentamicin, imipenem/cilastatin, and vancomycin in various combinations.

**Viridans Streptococci**

Bacteremia due to viridans streptococci in neutropenic patients has been associated with mucosal colonization with streptococci in the setting of high-dose cytobrine arabinoside-related epithelial damage in the gut.[21] High doses of cytobrine arabinoside, the presence of mucositis, and the absence of previous therapy with parenteral antibiotics are independent risk factors. Adult respiratory distress syndrome, shock, and death have been reported in neutropenic patients with viridans streptococci bacteremia. However, catheter removal has not been required to cure viridans streptococci bacteremia.

**Bacillus and Other Gram-Positive Organisms**

Although mortality due to *Bacillus* species bacteremia in cancer patients is low, recurrent bacteremia usually necessitates removal of the catheter.[22]

Micrococcus and Stomatococcus species are other Gram-positive organisms that may cause catheter-related infections in cancer patients. Vancomycin or ampicillin without catheter removal usually is effective.[23]

**Polymicrobial Infections**

Polymicrobial infections in neutropenic patients with mucositis are common but generally not associated with catheter infection. Multiple-pathogen episodes usually involve enteric Gram-negative bacilli or enterococci.[24] However, when the catheter is the source of polymicrobial bacteremia, catheter removal usually is required for cure.
Candida Infection

The incidence of invasive Candida infection is estimated to be 10% to 30% in patients with hematologic malignancies and 22% to 25% in bone marrow transplant recipients.[25] During 1980 to 1990, hospitals participating in the National Nosocomial Infection Surveillance reported a nearly fivefold increase in the rate of nosocomial fungal bloodstream infections and a nearly twofold increase in the proportion of bloodstream infections due to fungal pathogens.[19] A vascular catheter was the important portal of entry for candidemia in one third of cases. Although catheter-related fungemia was associated with a better outcome than other portals of entry, a mortality rate of approximately 20% is expected.[26] Candidemia occurs predominantly in severely debilitated patients and may be a marker for impending death.

The likelihood of hematogenously disseminated candidiasis is high, even if one blood culture yields a Candida species, regardless of whether the blood sample is obtained through an indwelling venous catheter or indirectly from a peripheral vein.[27] The detection of Candida species in the bloodstream was considered the therapeutic equivalent of the isolation of S. epidermidis from blood, such that two or more cultures should be positive in order to warrant therapy.[28] However, because of the high complication rate of candidemia, a single positive blood culture for Candida species should be considered the therapeutic equivalent of S. aureus bacteremia and warrants prompt antifungal therapy and removal of any CVC.[28] Fluconazole and amphotericin B do not differ significantly as therapy for candidemia in patients without neutropenia who are not severely immunocompromised.[29]

The mean interval to development of candidemia sepsis is nine to 11 days after the onset of granulocytopenia.[30] Risk factors for candidemia include the number of prior antibiotics, isolation of Candida species from sites other than blood, prior hemodialysis, prior use of a Hickman catheter, corticosteroids, chemotherapy, radiotherapy, multiple blood transfusions, and central venous nutrition.[31]

In oncology patients and bone marrow transplant recipients, the presence or absence of neutrophils dictates the course of deep-seated candidal infection. Approximately one third of patients with candidemia will die of the direct effects of the fungal infection, one third will die of underlying disease, and the remaining third will survive hospitalization and their infection.[32]

Mortality from candidemia was associated with sustained positivity of blood cultures and severity of underlying illness. In cases of sustained candidemia, the isolation of non-albicans Candida species also correlated with increased mortality.[33]

Candidemia remains a difficult entity to treat, and not all candidiasis are equal. Whether candidiasis is disseminated and whether late complications are likely to occur is difficult to establish at the bedside. Since more than 80% of neutropenic patients with fungemia due to C. albicans or C. tropicalis had disseminated disease at autopsy, fungemic patients are appropriate candidates for early empiric antifungal therapy.[34] Approximately 50% of patients with disseminated candidiasis have negative blood cultures. This emphasizes the importance of early empiric antifungal therapy among neutropenic leukemic patients.

Neutropenia predisposes patients with candidemia to microbiologic failure despite appropriate antifungal therapy.[26] In a study of bacteremia or fungemia in neutropenic patients, mortality was 36% with adequate therapy but 88% with inadequate therapy.[35] The mortality rate for patients with catheter-related candidemia in whom the catheters were retained was significantly higher than that of patients in whom the catheters were removed (41% vs 21%, respectively).[26] The growth of Candida species in blood obtained from either a catheter or a peripheral vein should be considered indicative of hematogenously disseminated candidiasis, and the patient should receive appropriate antifungal therapy.[36] Treatment is indicated for all episodes of candidemia since it is impossible to predict who has a benign infection, even with a relatively avirulent organism such as C. parapsilosis.[34]

A retrospective study of 155 cases of catheter-associated fungemia showed that patients who received amphotericin B within one day of onset of fungemia had a 38% mortality rate compared to a 69% mortality rate for those patients who did not receive therapy until two or more days after the onset of fungemia.[37] However, the significant mortality associated with most episodes of candidemia underscores the need to diagnose and treat all candidemic patients quickly. The total dose and duration of antifungal therapy should be determined several days into therapy, after the patient's candidemia has been identified as either transient or sustained.[33]

The cytoreductive regimens used to induce remissions in acute leukemia and to prepare for bone marrow transplant produce severe and long-lasting neutropenia as well as profound damage to mucosal barriers. In general, solid tumors are treated with regimens that cause only mild and transient myelosuppression and little damage to mucosal barriers. The chemotherapy regimens for lymphomas are typically intermediate in dose intensity, producing moderately severe myelosuppression and mucosal barrier damage. Cytotoxic therapy-related epithelial damage in the gut, such as that seen with high-dose cytarabine, correlates with invasive fungal disease.[38]

The pathogenesis of fungemia in bone marrow transplant recipients is probably the result of colonization of the gastrointestinal tract followed by invasion of the bloodstream.[25] The catheter may or may not become colonized during a period of fungemia. Among 665 patients who underwent bone marrow transplantation, systemic candidal infection was diagnosed in 76 patients (11.4%), with one third of these patients' deaths attributable to the infection.[39] The reduction in colonization of Candida species may have been important in preventing systemic infections, since colonization has been shown to be related to the development of systemic candidiasis. Prophylaxis with fluconazole may be useful.[40]

In addition to being the most common colonizing Candida species, C. albicans is generally the most virulent.[41] However, in the setting of neutropenia following chemotherapy, C. tropicalis is the most virulent. The key host determinants associated with susceptibility to C. tropicalis are neutropenia, antibiotic suppression of the bacterial flora, and damage to the gastrointestinal mucosa.[41] C. tropicalis has been less problematic in patients with solid tumors than with the more intensive regimes required for leukemia. Patients treated for acute leukemia or recipients of bone marrow transplantation that were colonized with C. tropicalis had an attack rate for C. tropicalis infection of 60%, much higher than that for C. albicans (5%) or other Candida species.[41] Although C. albicans remains the most frequent cause of fungemia and hematogenously disseminated candidiasis, there has been an increase in the frequency of infections caused by C. krusei, C. lusitaniae, C. parapsilosis, C. tropicalis, and Torulopsis (Candida) glabrata.[32]

Candidemia tends to originate from the catheter in the nonneutropenic patient and from the gastrointestinal tract in the neutropenic patient. The assumption is that primary candidal CVC infection is difficult to eradicate without catheter removal, whereas secondary hematogenous seeding of the catheter frequently may be cured without catheter removal. Management of candidal bloodstream infections in neutropenic cancer patients at M.D. Anderson Cancer Center usually does not include removal of the CVC unless septic thrombophlebitis is suspected in the setting of persistent candidemia.[42] At our institution, we recommend that the catheter be removed for nonneutropenic patients in cases of fungemia and that treatment be given with intravenous amphotericin B or intravenous fluconazole. If neutropenia is present with fungemia, we treat with amphotericin B without catheter removal. If the patient is septic or has 72 hours of fungemia while on antifungal treatment, all CVCs are removed.

Prevention

Recommendations to lower the risk of catheter-related infection that are simple and inexpensive include using maximal barrier precautions at catheter insertion, choosing the subclavian vein rather than the internal jugular or femoral vein for insertion, using tincture of iodine or chlorhexidine-based preparations for cutaneous antiseptis,
maintaining a protocol for decontamination of catheter ports and hubs, and employing an intravenous catheter team.[43] In a prospective, randomized trial, the use of maximal sterile barrier precautions (consisting of mask, cap, sterile gloves, gown, and large drape) when inserting CVCs resulted in a 6.3-fold lower catheter-related sepsis rate than when using only sterile gloves and a small drape.[44] Maximal sterile barrier precautions at the time of insertion significantly decreased the rate of catheter-related infections, particularly staphylococci and *Candida* species. Early contamination of catheters during insertion is an important cause of subsequent catheter-related colonization and infections. Skin organisms caused 83% of catheter infections with minimal sterile barrier precautions, whereas most infections in the maximal sterile barrier precautions group were caused by Gram-negative bacteria most likely acquired from the gastrointestinal tract or the hospital environment. The projected cost savings with maximal sterile barriers was $167.30 per catheter insertion, and the projected annual cost savings was $1,172,104.

Microorganisms can be prevented from adhering to catheter surfaces by destroying the adhesive factors on the bacterial surface with subinhibitory concentrations of antibiotics, by blocking adhesion of bacteria to the catheter surface with monoclonal antibodies, and by using materials with antiadhesive and antiproliferative properties.[6] Catheters coated with antimicrobials act mainly as antiproliferative devices and prevent CVC infection with a limited period of use (such as prevention of early-onset catheter infections).[6] Problems with these devices include toxicity, development of resistance, and lack of effect with late-onset CVC infections. Coating of catheters with antimicrobials can prevent colonization and early CVC-related infection.

Although the management of CVC-related infection appears complex and the literature is contradictory at times, guidelines can direct the clinician in a stepwise fashion (Table 2). Knowledge of the pathogenesis of each organism and the immune status of the host is essential in deciding whether catheter removal or retention is indicated. For example, Gram-negative bacilli bacteremia usually would not prompt catheter removal in a neutropenic patient, but it would in a nonneutropenic host due to the gastrointestinal source of the former and a primary catheter source in the latter.

**Conclusions**

As more CVCs are used in patients undergoing chemotherapeutic, antimicrobial, transfusional, and nutritional supportive care, novel approaches are needed to prevent and to treat the associated infectious complications inherent with such devices. A multifaceted approach from impregnated catheters to local catheter site antisepsis has been presented. However, as simple handwashing between patient visits is crucial to infection control, so is a trained catheter care team using total barrier precautions and ensuring proper local catheter maintenance critical to preventing CVC-related infections.

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