Catheter-related infections

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Significance of Central Venous Catheters

The use of catheters has revolutionized the way cancer patients are treated and the advent of catheter technology is closely related to the improvement of the quality of cancer care and of the life of cancer patients.

The most common and life-threatening complication of catheters is infection. Catheter-related bloodstream infection (CRBSI) is the most common type of nosocomial infection, and it is associated with significant morbidity and mortality (1-6). Additionally, they contribute to the majority of nosocomial cases of septicemia caused by Staphylococcus epidermidis, Staphylococcus aureus, and Candida spp. (6-8). In cancer patients the risk of CRBSI is even higher than in other patients owing to a multitude of host factors (compromised skin due to radiation therapy or bioimmunotherapy such as interleukin-2, increased use of intensive chemotherapeutic regimens leading to profound and prolonged neutropenia, and aggressive surgery).

Microbiology

Vascular catheters within a short time after insertion become uniformly colonized with biofilm, an architecturally complex structure that is rich in exopolysaccharids. Following their attachment on the catheter surface, microorganisms, such as S. aureus, coagulase-negative Staphylococci and candida parapsilosis, undergo phenotypic and enzymatic changes resulting in the production of exopolysaccharide, a major component of the biofilm (9-19). Recent studies on S. epidermidis have described a polysaccharide adhesion (PS/A) that is crucial to the pathogenesis of CRBSI (20). Similar work on Saccharomyces cerevisia and a genomic from C. albicans lead to the identification of the ALA gene, whose product play a crucial role in adherence to fibronectin, laminin, type IV collagen, and epithelial cells (21). Recently, the genetic control of biofilm production begun to be elucidated in S. epidermidis, S. aureus, and C. albicans (16,17,22,23). Synthesis of the capsular polysaccharide in Staphylococcus spp. is mediated by the ica operon. The key event in biofilm formation is a phenomenon called quorum sensing (24). Quorum sensing is an intermicrobial communication system vital for the regulation of a diverse array of processes, such as plasmid transfer, the activation of virulence factors, and biofilm formation. This communication is accomplished via chemical messengers like acyl-homoserine-lactone (25) and other peptides. Quorum sensing been reported in all the major pathogens involved in CRBSI (S. aureus,
Staphylococcus epidermidis, and Candida spp.) (26-28). The microorganisms that are embedded in the biofilm layer become more resistant to different antibiotics (10,29,30), especially the glycopeptides (31), since they live in a microenvironment that acts as a barrier to circulating antibiotics.

The microorganisms most commonly implicated in CRBSI are predominantly skin organisms: S. aureus and coagulase-negative staphylococci (32). Staphylococcus aureus and coagulase-negative Staphylococci are considered to be introduced through the skin and contaminated hubs, whereas. C. albicans and C. parapsilosis are though to seed in the bloodstream from the gastrointestinal system (33), especially in cancer patients who receive cytotoxic immunosuppressive therapy. Other skin organisms such as Bacillus spp. and Corynebacterium spp. (especially the JK strains) have been reported frequently as the cause of CRBSI (34-36). Gram- negative microorganisms such as Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Acinetobacter spp. are frequent causes of CRBSI, since they can contaminate the hands of medical personnel, IV fluids, and other fomites of the hospital environment (37-39). Microorganisms emerging as CRBSI pathogens are Micrococcus spp. (40), Achromobacter spp. Rhodococcus spp. (41), Micrococcus chelonei (42), Mycobacterium fortuitum (43), and fungi such as Rhodotorula spp. (44), Fusarium spp. (45-47), and Hansenula anomala (48,49).

**Epidemiology**

The incidence of CRBSI with long-term silicone catheters ranges from 1.4 to 1.9 episodes per 1,000 catheter-days (50-54). Tunneled catheters have been shown to predispose less to CRBSI than non-tunneled catheters (54-61). However, two studies, one randomized, failed to demonstrate any difference in the infection rates among tunneled and non-tunneled catheters (62,63). Additional data, from a center that maintains an infusion therapy team, showed that tunneled catheters have comparable rates of infectious complications when compared to non-tunneled catheters or PICC (64,65). Totally implantable intravascular devices (ports), being totally covered by the skin, have been associated with the lowest rate of infection when compared to other long- term catheters (66-76).

Multilumen catheters have been associated with a higher risk of infection than single lumen catheters (77-81), although in more than 50% of the triple lumen catheters only a single port is being used (82).

The catheter insertion site is another factor influencing the rate of CRBSI. In general, the internal jugular vein is related to higher risk for infections than the subclavian vein (83-88).

The role of neutropenia as an independent risk for CRBSI is controversial. In a study in cancer patients with long-term tunneled CVCs (53) neutropenia (< 500 neutrophils/ mm³) was proven to be an independent risk factor for CRBSI, whereas a similar study conducted in M.D. Anderson Cancer Center (62), failed to show such an association. In the latter study (62) the only statistically significant risk factor for CRBSI was hematological malignancy, something that is supported by the study of Groeger et al. (66).

**Clinical Manifestations**

The clinical manifestations of CRBSI can be specific and nonspecific. Particularly in immunocompromised cancer patients, whose inability to launch an immune response to infectious stimuli obscures the signs and symptoms of any infectious process, the diagnosis of CRBSI can be a significant diagnostic challenge.

Nonspecific manifestations of CRCSI include fever, chills, and occasionally hypotension. Hypotension is often associated with CRBSIs caused by gram- negative bacilli or Canadida spp.

More specific signs, like inflammation and/ or purulence from the catheter site, palpable vessel
cord, and occasionally purulent secretions at the skin insertion site, indicate catheter exit site infection. A quantitative culture of the affected skin or of the excretions from the insertion site can help in distinguishing sterile inflammation from an exit site infection (89).

In tunneled catheters a greater than 2 cm inflammation extending proximally from the catheter exit site is an indication of tunnel infection. Pocket space abscess formation should be suspected in case of inflammation or cellulites overlying the catheter hub.

Although the majority of CRBSIs are uncomplicated, occasionally septic thrombophlebitis of deep-seated infections can occur (90). This is particularly true with virulent microorganisms like S. aureus, C. albicans, and Pseudomonas aeruginosa. Septic thrombosis is suspected in the presence of swelling above the site the thrombotic catheterized vein (swelling in the neck, shoulder or arm ipsilateral to the catheter insertion site). Imaging proof of the presence of thrombus (venography, or Doppler ultrasonography) in the vein with an indwelling catheter and positive blood cultures with clinical manifestations of septic or sepsis establish the diagnosis. Infrequently, deep-seated infections like endocarditis, osteomyelitis, septic pulmonary emboli, and retinitis (in case of candidemia) can complicate a CRBSI (90,91).

**Diagnosis**

Catheter-related bloodstream infection is to be suspected if a patient has; 1) clinical signs and symptoms of bloodstream infection (i.e., fever, chills, hypotension ), 2) blood culture (s) positive for an organism often associated with CRBSIs, such as S. aureus, Bacillus spp., or C. parapsilosis, 3) the absence of any other source for the bloodstream infection except the catheter, and 4) local catheter infection, such as exit site inflammation, tunnel tract inflammation, a port pocket abscess formation associated with bloodstream infection (table 1).

**Table 1. Diagnosis of long-term catheter-related infections**

<table>
<thead>
<tr>
<th>I. Criteria to suspect catheter-related infection</th>
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<tbody>
<tr>
<td>1. Clinical manifestations of infection (i.e., fever, chills)</td>
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<tr>
<td>2. Blood culture positive for likely organism (coagulase negative staphylococci, S. aureus, Bacillus spp., Corynebacterium spp., Candida spp.)</td>
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<tr>
<td>3. No apparent source of bacteremia other than the catheter</td>
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<th>II. Criteria to confirm the diagnosis of catheter-related infection</th>
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<tr>
<td>1. Clinical evidence of catheter site and/ or tunnel infection/inflammation (purulent discharge, erythema, tenderness, warmth)</td>
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<tr>
<td>2. Response to antibiotic therapy within 48 hours after catheter removal; after 48 hours without response</td>
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<td>3. 5:1 CFU(^*) ratio of the same organism from CVC-blood culture compared to simultaneously collected peripheral blood culture</td>
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<tr>
<td>4. &gt;15 CFU (roll plate) or &gt;1000 CFU (sonication) from CVC tip of the same organism as the one growing from peripheral blood culture</td>
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<td>5. CVC collected blood culture is positive &lt;2 hours prior to simultaneous peripheral blood culture</td>
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\(^*\)CFU: colony forming units

Culture of the catheter was considered to be the gold standard for the diagnosis of catheter infection, especially in the absence of local catheter site infection. Usually the distal tip of the catheter (3-5 cm) is cultured. Culturing the subcutaneous catheter segment does not add to the diagnostic yield of the currently used methods of catheter (92). A number of different methods are available for culturing vascular catheters (93-95). The roll plate semi quantitative culture method is the most widely used (95). This involves aseptic removal of the catheter, rolling it across agar plate several times and counting the number of colonies of microorganisms after overnight incubation. The limiting factor of this method is that it cultures only the external surface of the catheters and does not retrieve organisms that are well embedded in the biofilm layer that covers the internal lumen of the
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Consequently the roll-plate semi-quantitative technique is of limited usefulness in long-term catheters, in which the internal surface of the catheter is the predominant source of bloodstream infection (96).

Some laboratories use quantitative methods that are more labor intensive and more expensive. Such methods are 1) sonication (93), 2) vortexing a catheter segment (64), or 3) infusing the catheter lumen with a known volume of broth (94). The cutoff point differs between the various methods. It is greater than 15 colony-forming units (CFUs) for the semi-quantitative (95) or at least 100 CFUs for the quantitative methods (97). Quantitative methods have been proven to be of higher sensitivity than semi-quantitative methods (97,98). The limitation of the semi-quantitative and quantitative catheter culture methods is that they require removal of the catheter (99), often resulting in wasteful removal of non-colonized catheters, increased medical costs, and patient inconvenience.

Catheter-related bloodstream infections can be diagnosed using simultaneous quantitative blood cultures without removing the catheter (100). This involves drawing one set of blood cultures through the catheter and one from a percutaneous site. If both blood cultures are positive for the same microorganism and the number of CFUs in the catheter-drawn specimen is at least 5 times (>5:1 ratio) higher than the number of CFUs from the peripheral venipuncture blood, this strongly suggests catheter-related bloodstream infection. The sensitivity of this method is higher in long-term catheter, where intraluminal transmission of microbes to the bloodstream is more common (96). The limitation of the method is that it is costly and labor intensive, so not many hospitals use quantitative culture in their microbiology laboratory.

A way to bypass the above-mentioned restriction and preserve the catheter in place is to use the differential time to positivity method. This requires simultaneous collection of blood through the catheter and through a peripheral venipuncture. If growth is detected in the catheter-drawn blood at least 2 hours earlier than in the simultaneously collected peripheral blood, this suggests CRBSI (101,102). This is a simple technique and can be practiced worldwide, since many laboratories have adopted the use of automated continuously monitored blood systems. The value of this approach has been challenged by a recent study involving a small number of patients in medical/surgical ICUs (103). However, a large prospective clinical study at M.D. Anderson Cancer Center verified the value of this method in diagnosing CRBSI (104).

Catheter-related bloodstream infections can also be diagnosed using an endoluminal brush technique that involves brushing the lumen of the catheter and performing an acridine orange leukocyte cytospin (AOLC) test on blood drawn through colonized catheter (105). Although this approach has 95% specificity and 84% sensitivity, it has been associated with induction of transient bacteremia in 6% of the study patients. Staining catheter-drawn blood with AOLC was shown to be 96% specific and 92% sensitive when diagnosing CRBSI (106). Further larger studies are required to support such a finding.

Management

The optimal management of catheter-related infections requires taking many parameters into account, such as the condition of the host, the type of the infecting organism, and the site and severity of infection. Especially in cancer patients, a crucial question is added: Should we remove the catheter or not? The rationale for removing the catheter is to eliminate the nidus of infection that continuously sheds microorganisms in the bloodstream and possibly seeding other target organs. This action, however, may lead to increased morbidity and mortality, not to mention increased cost. Since the catheter is literally the lifeline of a cancer patient, removal of a long-term catheter usually
necessitates an insertion of a similar catheter at least at a different site, preferably after the infection is treated. In Hickman/Broviac or port-type catheters, this translates to another surgical procedure, which may be particularly hazardous in a patient who has thrombocytopenia or some other coagulopathy. An additional complication of insertion of new catheter is the possibility of pneumothorax.

Antibiotic lock therapy (ALT) is a new concept developed to reduce the need of catheter removal, when long-term catheters are infected. As stated earlier, the majority of these infections originate from microbes colonizing the internal lumen of the catheter. Recent studies have shown that many antibiotics are unable to kill microorganisms growing in biofilm, when used in therapeutic concentrations. Concentrations 100 to 1000 times greater are required in order to kill bacteria embedded in biofilm (sessile) than to kill planktonic (in solution) bacteria (107-110). ALT consists of installation and holding for hours or days pharmacological concentrations of antibiotics into the catheter lumen of the infected catheter. Antibiotic solutions that contain the desired antimicrobial agent are mixed with heparin or normal saline, in sufficient volume to fill the lumen (usually 2-5 ml) and are “locked” (installed) into the catheter lumen during periods when the catheter is not being used (e.g., during nighttime) (111,112). The volume of locked antibiotic is removed before infusion of the next dose of intravenous medication or fluids through the catheter. Although the duration of ALT varies, in the majority of clinical studies (112-119) it is most often done for 2 weeks. Antibiotics that are usually used in these solutions are vancomycin at a concentration of 1 to 5 mg/ml, gentamicin and amikacin (1 to 2 mg/ml), and ciprofloxacin (1 to 2 mg/ml) (120). Several trials of ALT on tunneled CRBSI, with or without concomitant intravenous antibiotic therapy, have reported response and catheter salvage rate in 82% of the episodes of CRBSI (120). Since the rationale behind ALT is to sterilize the lumen of the catheter, it should be used in cancer patients with long-term catheters, whose signs of catheter-related infection indicate an intraluminal source of infection.

Exit site infections can be cured by antibiotics locally and systemically, usually without removal of the catheter (54,121). If the infection persists for more than 48 hours, or if Pseudomonas spp. are cultured from the exit site, the removal of the catheter may be required for the eradication of the infection (54).

Tunnel infections and port pocket infections (abscesses) can sometimes be associated with significant local morbidity and even mortality. Catheter removal and 10 to 14 days of antibiotic therapy are required in order to cure the infection (120). In the treatment of Mycobacterium fortuitum and Mycobacterium chelonei infections, surgical excision of the infected tunnel may be required (122) in addition to CVC removal.

Managing catheter-related bloodstream infections means their categorization into three groups: low, moderate, and high risk. The risk stratification depends on the virulence of the organism involved and whether the CRBSI is complicated or uncomplicated. A CRBSI is characterized as complicated if: 1) the accompanying fever and/or positive blood culture(s) persist more than 48 hours despite appropriate antimicrobial therapy, 2) it is associated with hypotension, organ hypoperfusion, septic thrombosis, septic emboli, or deep-seated infections such as endocarditis (90,91) and 3) there is concurrent tunnel or port pocket infection.

A CRBSI is considered to be of low risk if it is uncomplicated and caused by a low-virulence microorganism, such as coagulase-negative staphylococci (123), the most frequent cause of bacteremia in neutropenic patients (124). These microorganisms are not usually associated with deep-seated infections, and their dramatic increase as pathogens parallels the use of long-term
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Catheters, accounting for the majority of CRBSI occurring annually (124-129). From the family of coagulase-negative staphylococci, S. epidermidis is most commonly isolated in bloodstream infections (124). In the case of a single positive blood culture for coagulase-negative staphylococci, the question arises if this represents a true bacteremia or just a catheter colonization or specimen contamination. Multiple positive blood cultures, isolation of the same microorganism from catheter and percutaneous blood cultures, as well as quantitative blood cultures collected through CVC, growing more than 100 CFU/ml, indicate true bloodstream infection (130). A low-risk CRBSI can be treated without removal of the long-term catheter (123,131), with systemic administration of appropriate antibiotics for usually 10 days (120). If the CVC is removed, appropriate systemic antibiotic therapy is recommended for 5 to 7 days (120). If the CVC is a high suspicion for intraluminal infection, patients should be treated with systemic antibiotics and antibiotic lock therapy for 10 to 14 days (120). Treatment failure manifesting as persistent fever, persistently positive blood cultures, or relapse of the infection after the antibiotic therapy has been completed is a clear indication for catheter removal (120). Vancomycin is the drug of choice in the case of methicillin resistant S. epidermidis. In patients who are either allergic to vancomycin or colonized with vancomycin-resistant enterococci, novel agents such as quinupristin-dalfopristin or linezolid can be used (132-136). In the absence of methicillin-resistant microorganisms, pencillinase-resistant penicillins (nafcillin, oxacillin) or a first-generation cephalosporin may be used if the patient is not allergic to β-lactam antibiotics. Staphylococcus haemolyticus is less frequently isolated from clinical specimens (125). Its resistance pattern to multiple antibiotics, including vancomycin (125), may impose catheter removal whenever S. haemolyticus is implicated in CRBSI.

A moderate-risk CRBSI is an uncomplicated CRBSI caused by moderate- to high-virulence microorganisms such as S. aureus and Candida spp. These microorganisms can be associated with serious complications such as deep-seated infection or fatal septic shock (90,137). In such cases the CRBSI is considered to be a high-risk one, especially if it occurs in an immunocompromised patient (138,139).

Owing to its high virulence and high rates of complications, S. aureus CRBSI requires prompt antibiotic therapy and in most cases catheter removal (90,140). Serious complications such as deep-seated infections (endocarditis, septic thrombophlebitis, and osteomyelitis) or fatal septic shock occur at a frequency of 20 to 30% following CRBSI caused by S. aureus (140). In the case of uncomplicated CRBSI, a 10 to 14 day course of antibiotic therapy is sufficient to treat the infection after the catheter is removed (120,140,141). Removal of non-tunneled catheter that are infected with S. aureus has been associated with more rapid response to therapy and higher cure rate (90,138,141,142). If a new catheter has to be inserted, a different site has to be chosen. Tunneled CVCs or ports should definitely be removed if there is evidence of tunnel, pocket, or exit-site infection (120). However, in the case of patients with long-term tunneled catheters or implantable ports, in the absence of tunnel, pocket, or exit-site infection, owing to the difficulty and expenses involved with the removal of such catheters, they may be preserved, and antibiotic lock therapy may be considered in addition to 14 days of systemic antibiotic therapy (120). For patients who remain febrile and/or have positive blood cultures >3 days after appropriate antibiotic therapy has been instituted and/or the catheter has been removed, the possibility of a deep-seated infection, especially endocarditis, should be investigated (143,144). In this case, transesophageal echocardiography (TEE) may help in the decision to remove the catheter and to guide therapy (145). Provided that TEE is
available, the use of transthoracic echocardiography for excluding a diagnosis of catheter-related endocarditis is not recommended (120) because of its low sensitivity (146). For patients with TEE negative results, and from whom the catheter has been removed, a 14-day systemic antibiotic therapy is recommended (120). Staphylococcus aureus CRBSI complicated by a deep-seated infection, such as septic thrombosis, endocarditis, osteomyelitis, septic emboli abscesses, and arthritis, should be treated for 4 to 6 weeks (90,120). Determining the duration of therapy based on findings provided by TEE is a cost-effective alternative to the administration of therapy for 1 month to all patients with S. aureus bacteremia (145). The first choice for antibiotic therapy, of CRBSI caused by methicillin-susceptible S. aureus, should be intravenously administered β-lactam antibiotics (penicillinase resistant penicillins, i.e., nafcillin or oxacillin (120). In case of penicillin allergy without anaphylaxis or angioedema, first- or second-generation cephalosporins such as cefazolin or cefuroxime can be used (120). The addition of aminoglycosides (gentamycin) for the first 5 to 7 days of therapy may improve eradication of the S. aureus infection (6). For patients who are allergic to β-lactam antibiotics, and for those with methicillin-resistant S. aureus, vancomycin is the drug of choice (120). In case of S. aureus isolates with reduced susceptibility to vancomycin, the use of linezolid or quinupristin/dalfopristin is a therapeutic alternative.

All patients with candidemia should be treated (120). Candidemia is the third or fourth most common cause of nosocomial bloodstream infections. It occurs usually in seriously ill patients with multiple catheters and is associated with high attributable mortality rate, as high as 38% (147). Hemodynamically stable patients could be treated with fluconazole provided that it has not been recently used either prophylactically or therapeutically (148,149). A 14-day regimen of fluconazole (400 mg/day) has been proven as effective as and less toxin than amphotericin B (0.5mg/kg/day) given for the same length of time (148). Amphotericin B is recommended in patients with catheter-related candidemia who are hemodynamically unstable. Additionally, infections caused by fluconazole-resistant Candida spp. such as C. krusei should be treated with high-dose amphotericin B (1.0 mg/kg/day) (150-152). Treatment should be provided for 14 days after the last positive culture result and when signs and symptoms of infection have resolved (120). Since C. albicans and other candida species adhere avidly to materials used in vascular catheters (153), the removal of all central catheters from all patients with candidemia is considered to be standard practice and reinforced by recent consensus guidelines (120,150). In neutropenic cancer patients who have mucositis (acute leukemia, bone marrow transplantation), independent of the vascular catheter, the gastrointestinal system is an important source of C. albicans infection (154-157). Vascular catheters may, however, be the primary source of fungemia (158-160). Predictors of catheter-related candidemia include: quantitative blood cultures suggestive of CRBSI (>5:1 CFU ratio from blood collected through the catheter, compared to blood collected from a peripheral vein); indicative differential time to positivity (>2 hours for blood collected from a percutaneous venipuncture, compared with the one drawn through the CVC); isolation of C. parapsilosis from blood samples candidemia in a non-neutropenic patient who has a CVC in place and no other apparent source of bloodstream infection candidemia in a patient who is receiving TPN through the catheter; and persistent fungemia in a patient with a CVC, who is not responding to systemic antifungal therapy (120). Several studies have evaluated the impact of CVC removal on the outcome of candidemia (139,161-173). In the majority of these studies, catheter removal was associated with decreased duration of fungemia,
recurrence of infection, and improved survival (139,161-172). In a prospective observational study, in 145 cases of candidemia in patients with different underlying conditions, catheter retention was the only variable associated with increased risk of death on multivariate analysis (172). However, when the same scientific team looked into the risk factors for death in cancer patients with fungemia, the variables associated with an increased risk for death in multivariate analysis were older age, persistent neutropenia, and low performance status (165). In a large multicenter prospective observational study of 427 consecutive patients with candidemia, CVC retention was an independent risk factor for persistence of candidemia after 72 hours of antifungal therapy and was associated with higher mortality (161). In a review of the existing literature, with the notable absence of a prospective randomized study whose primary endpoint is the evaluation of the effect of vascular catheter removal in patients with candidemia, the consensus of catheter removal in all patients with candidemia was not substantiated (173). Given the limitations of the studies published today, and based on our experience, we believe that early therapy with a parenteral agent is important, since sustained fungemia is associated with poor outcome (139). An organism as adherent as Candida spp. to a catheter can be more predictive of catheter-related candidemia (174), even in the setting of neutropenic cancer patients. Removal of the catheter is a common-sense therapeutic approach, especially if there is evidence implicating the catheter as the possible source of fungemia. Such predictors are: 1) no prior chemotherapy for the last month. Indicating the possible absence of gastrointestinal mucusitis that enhances the risk of gut originating candidemia (156), 2) no prior steroid therapy, which has been associated with breakthrough candidemia (175,176), and 3) no other apparent source of the candidemia. Additionally, evidence of septic thrombophlebitis (through angiography) and invasion of the vascular wall (177) is another indication for catheter removal, since it may further increase the difficulty of eradicating the infection with medical therapy only. If the catheter is retained, the parenteral antifungal agents should be administered through all the lumens of the catheter, and the patient should be very closely monitored. If the patient is severely ill or has 72 hours of fungemia or persistent fever while on appropriate antifungal therapy, then removal of all CVCs is advised. Fungemia with C. parapsilosis is strongly associated with direct catheter infection (178) and would indicate catheter removal.

Malassezia furfur is a lipophilic yeast that requires an exogenous lipid source to grow. Infection with this organism generally occurs in premature infants, but it has also been described in older children and adults, especially in critically ill patients hospitalized in ICU. Risk factors include the presence of a venous catheter and the administration of a lipid-enriched solution, like total parenteral nutrition. The basis of treatment is systemic administration of amphotericin B, discontinuation of the parenteral lipid supplements, and removal of the catheter, especially with non-tunneled catheter infections (120,179,180).

Although staphylococci and Candida spp. are the most frequent pathogens implicated in CRBSI, a number of other microorganisms have been reported as causing catheter-related bacteremia (181). The incidence of CRBSI due to gram-negative rods, including Pseudomonas spp., Acinetobacter spp., and Stenotrophomonas maltophilia is increasing, especially in cancer patients and immunocompromised hosts (182,183). They can cause infections associated with a high rate of failure when the catheter remains in place (37). There are no controlled trails evaluating the optimal antibiotics or the optimal duration of therapy for CRBSI caused by gram negatives. In addition, there is a similar lack of controlled trials encompassing the management of the catheter implicated in such infections. Catheter removal
within 48 to 72 hours of the onset of the CRBSI has been proven to prevent relapse of the infection (184). A course of 10 to 14 days of therapy with appropriate antibiotics is sufficient in the majority of cases (120). If the catheter cannot be removed and there is no evidence of tissue hypoperfusion, a combination of 14 days systemic therapy and antibiotic lock therapy is advised (120). In any case of persistence of and/or of positive blood cultures despite appropriate systemic antibiotic therapy, removal of the implicated catheter(s) should be seriously considered (120). Empirical antibiotic therapy, in cancer patients with gram-negative infections, should always cover P. aeruginosa (185).

Treatment of CRBSI caused by mycobacteria, notably M. fortuitum and M. chelonae, requires, in addition to systemic therapy with appropriate antibiotics, removal of the catheter (120,186).

Prevention

Most CVC infections are preventable. Several protective measures have been suggested to guard against long-term catheter CRBSI.

1- Precautions during catheter insertion

Careful hand washing and attention to aseptic technique during insertion is paramount for the prevention of infections in any type of catheter. For long-term central venous catheters, though, the level of precaution should be greater than just hand washing, wearing gloves, and using a small drape. The use of maximal sterile barriers (sterile gloves, mask, gown, cap, and a large drape) has been linked to a four-fold decrease in the rate of bacteremia related to pulmonary-artery catheters (187) and to a more than six-fold decrease in the rate of bacteremia related to CVCs (188).

2- Catheter-site care

The use of skin antiseptics at the insertion site is a very important measure for preventing CRBSI. The application of antimicrobial ointments to the catheter site at the time of catheter insertion or during routine dressing changes has been done to reduce the microbial burden at the skin insertion site. The use of a topical polyantibiotic regimen (polymyxin β, neomycin, bacitracin) is associated with a significantly lower rate of CRBSI (189); but the overall protective effect of the topical antibiotic regimen is offset by a higher risk of catheter colonization and infection with Candida spp. (189,190). The use of mupirocin, a non-systemic anti-staphylococcal agent with proven efficacy in reducing staphylococcal spp. nasal carriage, has been proven to reduce five-fold the colonization of internal jugular catheter in cardiac surgery patients (191).

3- Tunneled catheters

Tunneling of short-term polyurethane internal jugular catheters reduces significantly the risk for CRBSI compared to non-tunneled catheters (192).

4- Intraluminal antibiotic locks

The intraluminal antibiotic lock consists of flushing and filling the lumen of the CVC with a combination of anticoagulant and antimicrobial agents. This flushing solution is then locked into the catheter for the time period that the catheter is not being used. This procedure is particularly useful for long-term catheter where hub contamination leads to lumen colonization and ultimately to bloodstream infection (193-195). Vancomycin in combination with heparin has been used as a daily flush solution for tunneled CVCs in five prospective randomized studies (196-200). Four of them have demonstrated the benefit of heparin-vancomycin lock solution in preventing CRBSI caused by vancomycin-susceptible microorganisms (196-199).

The major drawback of this lock solution is that the use of vancomycin, even in minute quantities, could lead to the emergence of vancomycin-resistant gram-positive organisms. A different antimicrobial/anticoagulant combination as a lock solution is the combination of minocycline with edetic-acid (EDTA). EDTA is a potent calcium and
iron chelator with anti-staphylococcal and antifungal activity, in addition to its anticoagulant properties (201,202).

5- Antimicrobial coating of catheters

Microorganisms can be prevented from colonizing catheter surfaces by coating the external and/or internal surfaces of the catheter with antimicrobial agents.

Catheters coated with chlorhexidine and silver sulfadiazine (CHSS) were two less likely to become colonized and were at least four times less likely to cause bacteremia than non-coated catheters (203). The catheters used in this study were coated only in the external surface (first-generation CHSS catheters) and thus do not provide the luminal protection that is needed in long-term catheters (>2 weeks) (204,205). Additionally, these catheters have a short antimicrobial durability (205). Several clinical studies reflect these weaknesses of the first-generation CHSS catheters, especially when used for longer than 2 weeks (204,206-208). A meta-analysis of 12 studies did show a benefit in using the first-generation CHSS catheters as short-term catheters (209), as these catheters are associated with a decrease in CRBSI (210). A second generation CHSS polyurethane catheter has been tested in an animal model (211). The second-generation CHSS catheter (CS2) has both the external and internal surfaces coated and may retain antimicrobial activity longer than the first-generation CHSS catheters (211). Clinical trials of this catheter are pending. Given that only short-term polyurethane CVCs are coated with CHSS, these catheters may not be useful in cancer patients requiring long-term catheterization.

Catheters impregnated with minocycline and rifampin (MR) have both their external and internal surfaces coated. The MR catheters have broad-spectrum activity against the most common microorganisms implicated in CRBSI, including C. albicans. In addition, these catheters demonstrated superior inhibitory activity against these microorganisms over the CHSS catheters (212,213). Both an animal model and large-multicenter prospective randomized clinical trial demonstrated that the MR catheters are safe and efficacious in preventing CRBSI (213,214). A prospective randomized multicenter trial comparing the MR and the CHSS catheters concluded that the MR catheters were 12 times less likely to become colonized and three times less likely to be bacteremic than those coated only externally with CHSS (215). The MR catheters are coated both on the external surface and on their lumen, and the antimicrobial durability of these catheters extends to more than 4 weeks (216,217). No resistance thus far has been detected in the hundreds of MR catheters that have been studied. However the risk for development of such resistance still exists. Although an in vitro study suggests that the susceptibility of S. epidermidis to rifampin may decrease after repeated exposure of the organism to MR catheters (217), a surveillance study demonstrated that susceptibility patterns for minocycline and rifampin, among staphylococcal isolates from clinical service that uses the MR catheters, are comparable to those in patients not using antibiotic-coated catheters, in spite of a longer use of tetracyclines in the former group (218). The use of the MR catheters in the ICU of a cancer hospital resulted in a significant decrease in the frequency of nosocomial vancomycin-resistant enterococci-related bacteremia (219).

Antimicrobially coated catheters should be used when: 1) femoral or internal jugular vein insertion is desired (greater risk of infection than subclavian vein catheterization) (187), 2) catheterization expected to last longer than 4 days, 3) units with risk of CRBSI greater than 3% or 3.3/1000 catheter days, 4) patient with neutropenia or undergoing transplantation, 5) patients receiving TPN, 6) patients with burns, 7) patients undergoing hemodialysis, 8) patients with short bowel syndrome, 9) patients colonized with methicillin-resistant.
resistant S. aureus, 10) insertion or exchange in a patient with known infection or bacteremia.

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